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Challenges, techniques and pitfalls in surgery: How far can we push the boundaries?

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Challenges, techniques and pitfalls in surgery: How far can we push the boundaries?

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Editorial: Challenges, techniques and pitfalls in surgery: How far can we push the boundaries?

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Editorial on the Research Topic

Challenges, techniques and pitfalls in surgery: How far can we push the boundaries?

In the last decade, surgery to relevant was subjected to relevant improvement thanks technological innovations and consequent novel surgical techniques. The actual surgical panorama gained by the progress of minimally invasive surgery that has become the gold standard for several procedures historically performed with open access. This evolution involved different surgical fields, including general surgery, urology, gynaecology and many other specialities (1–3). Further evolution of minimally invasive surgery was represented by ultra-minimally invasive surgery, which is currently running through two different philosophies: the port size decreasing (3mm vs 5-10mm) (4) and the reduction of the incision numbers, represented by the single port approach (5). The latest innovations are represented by robotics. This technology allows for overcoming many limits of traditional endoscopy, even reducing the invasiveness.

Moreover, the different available platforms can actually allow for reduced costs (6). Furthermore, adjuvant therapies and new softwares can become fundamental in surgery. Therefore, these technologies could be useful even in different specialties as general surgery, surgical oncology, gynaecology, urology, etc. (7–12).

It was an very pleasure to serve as Guest Editors of the Research Topic of *Frontiers* entitled "*Challenges, Techniques and Pitfalls in Surgery: How Far Can We Push the Boundaries?*". This Research Topic provides an overview of the last innovation in surgery and contributes to the field's growth. All authors on the Research Topic contribute significantly to clinical and basic research advancements. Therefore, we present a collection of articles reported by authors from different specialities as general surgery to more specialistic surgical subspecialties. The article treated in this Research Topic could be useful for students, researchers and clinicians.

The Research Topic start with a case report by Wang et al. entitled "*Case Report: Gastric-Type Endocervical Adenocarcinoma Mimicking Submucosal Myoma Under Hysteroscopy*", reporting a rare case of endocervical carcinoma. Concluding that GAS could be subject to misdiiagnosis.

The second article by Bao et al., entitled "Endoscopic Endonasal Supraoptic and Infraoptic Approaches for Complex "Parasuprasellar" Lesions: Surgical Anatomy, Technique Nuances, and Case Series" evaluates the use of the endoscopic technique for parasuprasellar lesions and reporting that these approaches could be effective in selected cases.

The third article by Wei et al., entitled "Clinical Application of Indocyanine Green Fluorescence Technology in Laparoscopic Radical Gastrectomy", reports the outcomes of gastrectomy using new tracers reporting good outcomes in terms of operation time and intraoperative blood loss.

The fourth article by Xu et al., "Can a reresection be avoided after initial en bloc resection for high-risk non-muscle invasive bladder cancer? A systematic review and meta-analysis", was a meta-analysis related to the surgery options for bladder cancer that in coclusion reported good oncologic and post-operative outcomes. The fifth article by Campagna et al., entitled "Laparoscopic High Uterosacral Ligament Suspension vs Laparoscopic Sacral Colpopexy for Pelvic Organ Prolapse: A Case-Control Study" was focused on different surgical approaches for pelvic organ prolapse concluding that both techniques are safe, feasible, and effective. The sixth article by Peng et al., entitled "The Transumbilical Laparoendoscopic Single-Site Extraperitoneal Approach for Pelvic and Para-Aortic Lymphadenectomy: A Technique Note and Feasibility Study" investigated the use of single incision surgery for lymphadenectomy reporting the feasibility of the technique. The seventh article by Santullo et al. entitled "The Road to Technical Proficiency in Cytoreductive Surgery for Peritoneal Carcinomatosis: Risk-Adjusted Cumulative Summation Analysis" reported a model aimed to improve the surgical outcomes for cytoreductive surgery. The eighth article by Cianci et al., entitled "Different Surgical Approaches for Early-Stage Ovarian Cancer Staging. A Large Monocentric Experience", investigated advantages ans disadvantages of different surgical approaches for ovarian cancer treatment even from an oncological point of view. The ninth article by Li et al., "Toward Exempting from Sentinel Lymph Node Biopsy in T1 Breast Cancer Patients: A Retrospective Study", reported exciting data on the sentinel lymph node for breast cancer. The tenth article by Zhang et al., "A Scientometric Analysis and Visualization Discovery of Enhanced Recovery After Surgery", which applied the analysis to ERAS guidelines. The eleventh article by Zhao et al., entitled "Application Status and Prospects of Artificial Intelligence in Peptic Ulcers", reported an article related to the clinical use of artificial intelligence. The twelfth article by Spalthoff et al., "Time is crucial in malignant tumour cases: Speeding up the process of patient-specific implant creation, " focused on the time importance for patients implant creation affirming the importance of procedural standardization.

The thirteenth article by Zhu et al. entitled "Laparoscopic Subtotal Gastrectomy and Sigmoidectomy Combined With Natural Orifice Specimen Extraction Surgery (NOSES) for Synchronous Gastric Cancer and Sigmoid Colon Cancer: A Case Report" was a case report focused on the use of natural orifice used for specimen extraction reporting good outcomes.

The fourteenth article by Xiong et al., entitled "Partial Nephrectomy Versus Radical Nephrectomy for Endophytic Renal Tumors: Comparison of Operative, Functional, and Oncological Outcomes by Propensity Score Matching Analysis", studied the outcomes of different procedures for renal tumours surgery. The fifteenth article by Tang et al., entitled "Preliminary Analysis of Safety and Feasibility of a Single-Hole Laparoscopic Myomectomy via an Abdominal Scar Approach, " focused on a single port approach for gynecologic surgery demonstrating the feasibility.

The sixteenth article by Zuo et al., entitled "O-arm-guided percutaneous microwave ablation and cementoplasty for the treatment of pelvic acetabulum bone metastasis", reported exciting data on a new surgical strategy for bone surgery based on microwave instrument.

The seventeenth article by Abdullah et al., entitled "Laparoscopic retroperitoneal resection of the duodenal gastrointestinal stromal tumours in neurofibromatosis type 1; Case Report and literature review" reported an article focused on endoscopic treatment of gastrointestinal tumours reporting good surgical outcomes.

The eighteenth, by Wang et al., entitled "Effect of fetoscopic laser surgery on the placental characteristics and birth-weight discordance of twins with twin-to-twin transfusion syndrome", investigated the use of laser technology for fetal surgery.

The nineteenth article by Ishikawa and Shozu, entitled "Modified Leak-Proof Puncture Technique for the Aspiration of Giant Ovarian Cysts by Instantly Mounting a Plastic Wrap and Gauze with Cyanoacrylates: A Retrospective Observational Study", reported a technique for aspiration of giant cysts concluding the feasibility of the technique in selected cases.

The last article by Catena et al., entitled "Fertility-sparing treatment for endometrial cancer and atypical endometrial hyperplasia in patients with Lynch Syndrome: Molecular diagnosis after immunohistochemistry of MMR proteins" was focused on fertility sparing treatment for syndromic patients giving relevant indications for these cases.

We appreciated the effort of all authors put in their articles, which significantly contribute to the scientific panorama.

Author contributions

CS, GF, CG, EA contributed to conception and design of the study equally. CS wrote the first draft of the manuscript. GF, CG, EA contribute equally at the final version of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Clinical Application of Indocyanine Green Fluorescence Technology in Laparoscopic Radical Gastrectomy

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Background: This study aimed to observe the application and evaluate the feasibility and safety of indocyanine green (ICG) fluorescence technology in laparoscopic radical gastrectomy (LRG).

Methods: Patients who underwent LRG & D2 lymphadenectomy at Qilu Hospital of Shandong University were included between January 2018 and August 2019. According to whether endoscopic injection of ICG was performed, patients were assigned to the ICG group (n=107) and the control group (n=88). The clinicopathologic features, retrieved lymph nodes, postoperative recovery, and follow-up data were compared between the two groups.

Results: Baseline characteristics are comparable. The ICG group had a significantly larger number of lymph nodes retrieved (49.55 ± 12.72 vs. 44.44 ± 10.20, P<0.05), shorter total operation time (min) (198.22 ± 13.14 vs. 202.50 ± 9.91, P<0.05), shorter dissection time (min) (90.90 ± 5.34 vs. 93.74 ± 5.35, P<0.05) and less blood loss (ml) (27.51 ± 12.83 vs. 32.02 ± 17.99, P<0.05). The median follow-up time was 29.0 months (range 1.5-43.8 months), and there was no significant difference between the ICG group and the control group in 2-year OS (87.8% vs. 82.9%, P>0.05) or DFS (86.0% vs. 80.7%, P>0.05).

Conclusions: ICG fluorescence technology in laparoscopic radical gastrectomy has advantages in LN dissection, operation time, and intraoperative blood loss. The 2-year OS and 2-year DFS rates between the two groups were comparable. In conclusion, ICG fluorescence technology is feasible and safe.

Keywords: indocyanine green (ICG), fluorescence, gastric cancer, laparoscopic gastrectomy (LG), lymph node

INTRODUCTION

Gastric cancer is the fifth most frequently diagnosed cancer and the fourth leading cause of death from cancer worldwide (1). Composing complete removal of the tumor and systemic lymph node (LN) dissection, radical surgery remains the mainstay frontline treatment for resectable gastric cancer (2–4). Adequate assessment of the lymph nodes is essential for its role in the disease stage and its prognostic value (5–10), and D2 lymphadenectomy is recommended for advanced gastric cancer (2–4, 11–13).

Laparoscopic gastrectomy (LG) was first reported by Kitano (14) in 1994 and applied in the treatment of advanced gastric cancer by Goh (15) in 1997. Possessing the advantages of minimal invasion and quick postoperative recovery, LG is gradually replacing open surgery as the first choice (16–19). However, because of the lack of tactile feedback and direct observation compared with open surgery, precise tumor positioning under laparoscopy is relatively difficult, especially for patients with early gastric cancer not invading the serosa and those who need additional surgery after noncurative ESD. In addition, the complexity and vastness of the layout of blood and lymphatic vessels contribute to the difficulty and risk of effective LN dissection. Decision and evaluation making done only by the means of surgeons' experience is extremely subjective and poses a danger of false negativity, which may cause insufficient LN dissection and poor prognosis of patients.

As a new surgery technology, dye-mediated surgical navigation (including carbon nanoparticles, indocyanine green, etc.) proved to supply surgeons with improved inspection of the complex perigastric anatomy during laparoscopic surgery. Studies have shown that carbon nanoparticle lymphatic mapping technology increases the number of LNs harvested and realizes tumor localization (20–22). Drawbacks exist, however, that once the carbon nanoparticles leaked into the abdominal cavity, the whole surgical field would be dyed black, thus interfering with the vision of the surgery field and increasing operation difficulty.

Approved by the US Food and Drug Administration (FDA) in the 1960s, ICG was applied to assess cardiac output and hepatic function in the early stage (23–26). Possessing the advantages of not interfering with the surgical field and high tissue penetration (27, 28), ICG fluorescence-guided laparoscopic surgery is therefore the subject of numerous studies (29–34). At present, the application of ICG in LRG has achieved certain success (35, 36) (37, 38). When injected into the gastric tissue around the tumor with endoscopy and exposed to a specific wavelength of near-infrared light, fluorescence emitted from ICG displays the tumor and perigastric LNs (39), making them visible and facilitating the surgery.

To further investigate the feasibility and safety of ICG fluorescence technology in LRG and provide valuable medicine evidence for clinical decision-making in radical gastric cancer resection, we conducted this retrospective study by evaluating the role of ICG fluorescence technology in surgical procedures, lymph node dissection, short-term survival, etc.

Abbreviations: ICG, indocyanine green; LRG, laparoscopic radical gastrectomy.

MATERIALS AND METHODS

Patients and Study Design

Patients who underwent LRG in the Department of Gastrointestinal Surgery, Qilu Hospital of Shandong University from January 2018 to August 2019 were considered for inclusion. According to whether endoscopic injection of ICG was performed, patients were assigned to the ICG group and the control group. Endoscopic ICG injection is an invasive procedure and can only be performed with the patient's consent. Some patients refused the endoscopic ICG injection.

The inclusion criteria were as follows: (1) Primary gastric adenocarcinoma in T1-T4a confirmed by postoperative pathology. (2) Underwent LRG + D2 lymphadenectomy.

The exclusion criteria were as follows: (1) History of previous gastrectomy, endoscopic mucosal resection, or endoscopic submucosal dissection. (2) History of other malignant diseases within the past five years. (3) History of previous neoadjuvant chemotherapy or radiotherapy. (4) Requirement of simultaneous surgery for other diseases. (5) Conversion to laparotomy.

The analyzed data were as follows: (1) Demographic data: age, sex, body mass index (BMI), American Society of Anesthesiology (ASA) physical status scores, and Eastern Cooperative Oncology ECOG performance status. (2) Perioperative outcomes: surgical procedure, operation time, blood loss, first flatus, first liquid diet, postoperative hospital stay, and postoperative complications. (3) Pathological outcomes: tumor diameter, histology, pT, and pN stage. (4) Assessment of D1 station LNs, D2 station LNS, and overall LNs. (5) Overall survival time (OS) and disease-free survival time (DFS).

The study protocol was approved by the Medical Ethics Committee of Qilu Hospital of Shandong University. All procedures were conducted under the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.

Preoperative ICG Injection

Endoscopy was performed 1 day (12-24 hours) before surgery for patients in the ICG group. Four points in the stomach (proximal, distal, and bilateral to the tumor region) were selected, and "sandwich injection methods" were used. In other words, 0.5 ml normal saline + 0.5 mL of ICG solution + 0.5 ml normal saline were injected sequentially into the submucosa layer of each point (**Figure 1**). ICG (25 mg/dose, produced by Dandong Yichuang Pharmaceutical Co., Dandong, China) was diluted with distilled water at a dose of 0.625 mg/ml. Well-trained endoscopists performed all the injections in this study to ensure accurate injection.

Surgery Procedure

In this study, a NOVADAQ fluorescence surgical system (Stryker Co., Kalamazoo, MI, USA) was applied. All patients underwent laparoscopic radical gastrectomy + D2 lymphadenectomy.

FIGURE 1 | Endoscopic peritumoral ICG injection one day before surgery. A site adjacent to the tumor is selected. Slight swelling of the mucosa without ICG leakage is a sign of successful injection.

During the procedure, the surgeon viewed the surgical field with frequent switching between white light view and near-infrared mode to enable accurate tumor localization (**Figures 2A, B**) and adequate lymphadenectomy at each LN station.

The gastric resection extent and lymphadenectomy were determined based on the tumor location, as stated in the Japanese guidelines (2). Total gastrectomy was performed with Roux-en-Y esophagojejunostomy, and distal gastrectomy was performed with Billroth II gastrojejunostomy + Braun anastomosis.

If fluorescent LNs were detected outside the planned dissection areas (stations 10 and 14v), excessive dissection beyond the scope of D2 lymphadenectomy was performed. (**Figures 2C, D**) In some areas with complex anatomy, such as the spleen vessels and No. 11P LNs, surgery was performed with the assistance of ICG fluorescence. (**Figures 2E–G**) After dissection of LNs in all stations, the near-infrared mode was used to assess the completeness of the lymphadenectomy and remove remnant fluorescent LNs.

Specimen Management

A surgeon from the surgical team performed specimen management immediately after the surgery. LNs of different stations were separated from the specimen according to "the Japanese Classification of Gastric Carcinoma: 3rd English edition" (40) and separately sent to the pathology department. In addition, LNs in the ICG group were examined according to different stations and whether they were fluorescent. (**Figures 2H, I**).

Follow Up

A minimum follow-up of 24 months was required and achieved for each patient after surgery. All enrolled patients underwent physical examination, blood testing, computed tomography, and upper gastrointestinal endoscopy regularly (41–43). Disease-free survival (DFS) time and overall survival time (DFS) were calculated.

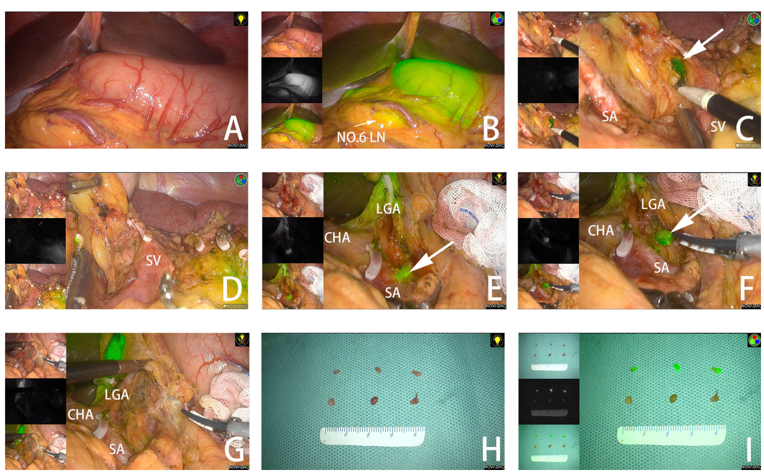

FIGURE 2 | **(A, B)** The tumor is observed under white light and fluorescent mode. **(C)** The fluorescent No.10 LNs are detected under fluorescent mode. **(D)** No remnant No.10 LNs are found after dissection. **(E)** Fluorescent No. 11P LNs are adjacent to splenic vessels. **(F)** No.11P LNs are separated from blood vessels. **(G)** No remnant No. 11P LNs are found after dissection. **(H)** LNs dissected from the specimen under white light. **(I)** LNs dissected from the specimen under fluorescent mode. The arrow points to the fluorescent LN. SA, spleen artery; SV, spleen vein; CHA, common hepatic artery; LGA, left gastric artery.

Statistical Analysis

The differences between the two groups were assessed using t tests, χ2 tests, or Fisher's exact tests as appropriate. The Kaplan–Meier method and the log-rank test were used for survival analysis. All tests were 2-sided with a significance level of $P < 0.05$. All data were analyzed using SPSS statistical software, version 24.0 (IBM Corp., Armonk, NY, USA). The data are presented as the mean ± standard deviation for continuous variables and as a number for categorical variables.

RESULTS

One hundred ninety-five patients (107 patients in the ICG group and 88 patients in the control group) were retrospectively analyzed. No significant differences were observed in sex, age, BMI, ASA score, or ECOG performance status between the two groups ($P > 0.05$), which indicates that the baseline characteristics of the two groups were comparable. (**Table 1**)

Clinicopathologic Characteristics

Clinicopathologic characteristics are listed in **Table 2**. No significant differences between the two groups were observed in tumor diameter, histology, pathological stage, or surgical procedure (P>0.05). Compared to the control group, the ICG group had a significantly shorter total operation time (min) (198.22 ± 13.14 vs 202.50 ± 9.91, P<0.05), shorter dissection time (min) (90.90 ± 5.34 vs 93.74 ± 5.35, P<0.05), and less blood loss (ml) (27.51 ± 12.83 vs 32.02 ± 17.99, P<0.05). There were no significant differences between the two groups in anastomosis time (min) (65.04 ± 3.89 vs 65.82 ± 4.39, P>0.05). The data were compared between the two groups, and no significant differences were observed in terms of first flatus (hours) (63.50 ± 27.345 vs 68.26 ± 28.83, P>0.05), first water intake (hours) (85.51 ± 29.03 vs 92.43 ± 28.48, P>0.05), or postoperative hospital stay (days) (9.22 ± 2.48 vs 9.26 ± 3.04, P>0.05).

Postoperative complications occurred in 15 patients (14%) in the ICG group (anastomotic bleeding in one patient, delayed gastric emptying in one, inflammatory bowel obstruction in two, pneumonia in eight, cholecystitis in two, and lymphatic leakage in one) and 12 patients (13.6%) in the control group (anastomotic leakage in one patient, delayed gastric emptying in two, pneumonia in seven, and cholecystitis in two), and there were no significant differences in the overall postoperative complication rate. (P > 0.05). According to the Clavien–Dindo classification of surgical complications, in the ICG group, 11 patients were classified as grade II or lower, 3 patients as grade IIIa, 1 patient as grade IIIb, and no patient as grade V or higher; in the control group, 7 patients were classified as grade II or lower, 4 patients as grade III a, 1 patient as grade IIIb, and no patient as grade V or higher. The distribution of severity was similar between the 2 groups. Furthermore, 1 patient in the ICG group and 1 patient in the control group experienced a repeat of surgery as a result of anastomotic leakage and bleeding. All patients with complications in both groups were discharged successfully after conservative treatment or surgical interventions. (**Table 3**)

TABLE 1 | Baseline characteristics of ICG and control group.

	ICG n=107	Control n=88	P Value
Sex			0.859
Male	57 (53.3%)	48 (54.5%)	
Female	50 (46.7%)	40 (45.5%)	
Age (Years)	59.27 ± 8.99	61.53 ± 10.30	0.103
BMI (kg/m²)	24.60 ± 3.41	24.95 ± 2.65	0.424
ASA Score			0.490
I	16 (15.0%)	16 (18.2%)	
II	83 (77.5%)	62 (70.5%)	
III	8 (7.5%)	10 (11.4%)	
ECOG performance status			0.076
0	94 (87.9%)	69 (78.4%)	
1	13 (12.1%)	19 (21.6%)	

Data are shown as the mean ± standard deviation or number (%).
ICG, indocyanine green; BMI, body mass index; ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group.

TABLE 2 | Perioperative outcomes of ICG and control group.

	ICG n=107	Control n=88	P Value
Tumor diameter (cm)	4.03 ± 2.48	4.09 ± 2.46	0.871
Histology			0.164
Poorly Differentiated	77 (72.0%)	52 (59.1%)	
Moderately Differentiated	21 (19.6%)	26 (29.5%)	
Well Differentiated	9 (8.4%)	10 (11.4%)	
pT stage			0.894
T1	35 (32.7%)	28 (31.8%)	
T2	18 (16.8%)	17 (19.3%)	
T3	37 (34.6%)	32 (36.4%)	
T4a	17 (15.9%)	11 (12.5%)	
pN stage			0.169
N0	50 (46.7%)	53 (60.2%)	
N1	13 (12.1%)	10 (11.4%)	
N2	11 (10.3%)	11 (12.5%)	
N3a	18 (16.8%)	7 (8.0%)	
N3b	15 (14.0%)	7 (8.0%)	
Surgical procedure			0.235
Distal gastrectomy	59 (55.1%)	41 (46.6%)	
Total gastrectomy	48 (44.9%)	47 (53.4%)	
Operation time (minute)	198.22 ± 13.14	202.50 ± 9.91	0.013
Dissection time	90.90 ± 5.34	93.74 ± 5.35	<0.001
Anastomosis time	65.04 ± 3.89	65.82 ± 4.39	0.190
Blood loss (ml)	27.51 ± 12.83	32.02 ± 17.99	0.043
First flatus (hour)	63.50 ± 27.35	68.26 ± 28.83	0.239
First water intake (hour)	85.51 ± 29.03	92.43 ± 28.48	0.096
Postoperative hospital stay (day)	9.22 ± 2.48	9.26 ± 3.04	0.931

Data are shown as the mean ± standard deviation or number (%).

Lymph Nodes Examination

The number of LNs harvested in the ICG group was significantly higher than that in the control group in terms of the overall LNs (49.55 ± 12.72 vs 44.44 ± 10.208, P<0.05) and the D1 station (28.54 ± 10.55 vs 24.13 ± 6.67, P<0.05), and no difference in the number of D2 station LNs was observed (21.05 ± 4.76 vs 20.38 ± 4.96, P>0.05).

The number of metastatic lymph nodes in the ICG group was significantly higher than that in the control group in terms of the overall LNs (6.45 ± 10.96 vs 3.33 ± 6.45, P<0.05) and the D1 station (5.06 ± 8.52 vs 2.40 ± 4.42, P<0.05), and no difference in

TABLE 3 | Postoperative complications of ICG and control group.

	ICG n=107	Control n=88	P Value
Postoperative complications	15 (14.0%)	12 (13.6%)	1.000
Anastomotic complication			
Bleeding	1 (0.9%)	0	1.000
Leakage	0	1 (1.1%)	1.000
Functional complication			
Delayed gastric emptying	1 (0.9%)	2 (2.3%)	1.000
Inflammatory bowel obstruction	2 (1.9%)	0	0.502
Others			
Respiratory infection	8 (7.5%)	7 (8.0%)	0.784
Cholecystitis	2 (1.9%)	2 (2.3%)	1.000
Lymphatic leakage	1 (0.9%)	0	1.000
In-hospital mortality	0	0	
Clavien–Dindo classification			0.678
I	2 (1.9%)	0	
II	9 (8.4%)	7 (8.0%)	
IIIa	3 (2.8%)	4 (4.5%)	
IIIb	1 (0.9%)	1 (1.1%)	
IV	0	0	
V	0	0	

Data are shown as number (%).

the number of metastatic D2 station LNs was observed (1.39 ± 2.93 vs 0.92 ± 2.32, P>0.05). No significant differences were found in the metastatic rate of LNs in any LN classification between the two groups.

In the ICG group, there was no significant difference in the positive rate of LNs between fluorescent and nonfluorescent LNs (**Table 4**).

Two Years Follow-Up

All patients were followed up, and data were collected: the median follow-up for all patients was 29.0 months (range 1.5-43.8 months). At the time of the last follow-up on August 31, 2021, 162 patients (83%) were alive without recurrence (90 in the ICG group and 72 in the control group), and 6 patients (3%) were alive with recurrence (4 in the ICG group and 2 in the control group). Twenty-seven of 195 patients (14%) had died; among them, 10 patients (5%) in the ICG group had recurrence at the time of death (2 patients with locoregional recurrence, 4 patients with local and distant recurrence, and 4 patients with distant recurrence) and 12 patients (6%) in the control group (2 patients with locoregional recurrence, 7 patients with local and distant recurrence, and 3 patients with distant recurrence), and 5 patients (3%) died due to other causes in the two groups (**Table 5**).

The long-term survival did not show differences between the ICG and control groups: the 2-year OS was 87.8% in the ICG group and 82.9% in the control group (log-rank p = 0.304). The 2-year DFS was 86.0% in the ICG group and 80.7% in the control group (log-rank p = 0.471). (**Figure 3**)

TABLE 4 | Number of retrieved lymph nodes in the ICG and control groups & Positive rate in the ICG group of fluorescent and nonfluorescent LNs.

	ICG n=107	Control n=88	P Value
Overall LNs			
Total LNs	49.55 ± 12.72	44.44 ± 10.20	0.002
Positive LNs	6.45 ± 10.96	3.33 ± 6.45	0.014
Positive rate	9.96 ± 17.83%	12.20 ± 22.38%	0.438
D1 Station LNs			
Total LNs	28.54 ± 10.55	24.13 ± 6.67	<0.001
Positive LNs	5.06 ± 8.52	2.40 ± 4.42	0.006
Positive rate	11.49 ± 18.84%	13.71 ± 21.74%	0.446
D2 Station LNs			
Total LNs	21.05 ± 4.76	20.38 ± 4.96	0.337
Positive LNs	1.39 ± 2.93	0.92 ± 2.32	0.221
Positive rate	5.07 ± 11.63%	5.55 ± 11.49%	0.774
	fluorescent LNs	**nonfluorescent LNs**	**P Value**
Positive rate	17.27 ± 27.58%	9.80 ± 21.39%	0.370

Data are shown as the mean ± standard deviation or number (%).

DISCUSSION

Recently, with the widespread application of laparoscopic surgery for patients with gastric cancer, ICG fluorescence-guided LRG has attracted much attention as a novel navigation technology. To evaluate the feasibility and safety of ICG in LRG, this study was conducted and indicated that compared with conventional LRG, ICG-guided LRG has the advantages of more lymph nodes dissected, less blood loss, and shorter operation time.

As a crucial step in gastric cancer surgery, adequate resection and assessment of LNs have been shown to be linked to disease staging, regional disease control, and long-term survival (6, 7, 44). Interestingly, fluorescence observation based on the absorption characteristics of ICG has been reported to make it possible to distinguish LNs containing ICG particles from surrounding tissue (45, 46), improving the chance of complete dissection. Kwon et al. (47) reported that ICG fluorescence-guided lymphography offered increased lymph node retrieval compared with conventional laparoscopic surgery. Chen et al.

TABLE 5 | Patients' status at last follow-up.

	ICG n=107	Control n=88	P Value
2-year OS	87.8%	82.9%	0.304
2-year DFS	86.0%	80.7%	0.471
2-year OS in T1	93.5%	92.0%	0.814
2-year DFS in T1	94.3%	92.9%	0.806
2-year OS in T2	94.4%	85.6%	0.472
2-year DFS in T2	94.4%	82.4%	0.275
2-year OS in T3	94.2%	85.0%	0.212
2-year DFS in T3	89.2%	87.5%	0.918
2-year OS in T4	52.9%	32.9%	0.191
2-year DFS in T4	52.9%	27.3%	0.175
Alive	94 (87.9%)	74 (84.1%)	
Alive without recurrence	90 (84.1%)	72 (81.8%)	
Alive with recurrence	4 (3.7%)	2 (2.3%)	
Death	13 (12.1%)	14 (15.9%)	
Death with other causes	3 (2.8%)	2 (2.3%)	
Death with recurrence	10 (9.3%)	12 (13.6%)	
Locoregional	2 (1.9%)	2 (2.3%)	
Local and distant	4 (3.7%)	7 (8.0%)	
Distant	4 (3.7%)	3 (3.4%)	

Data are shown as number (%).

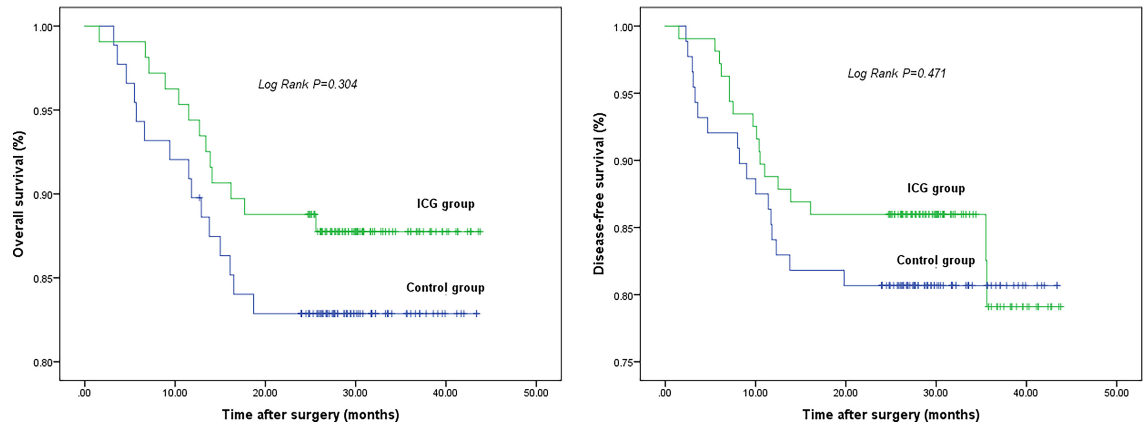

FIGURE 3 | 2-year overall survival (left) and 2-year disease-free survival (right). There is no difference in 2-year OS and 2-year DFS between two groups.

(48) suggested that more lymph nodes could be harvested during ICG-guided LRG with decreased lymph node noncompliance. Similar results are reported in this study; likewise, some new and interesting findings are yielded.

For example, the splenic artery may turn, twist, and become tortuous after originating from the celiac trunk, leading to the obscuration and difficulty of 11P LN dissection. However, possessing the property of strong tissue penetration, ICG fluorescence may highlight lymph nodes and enable the retrieval of a higher number of lymph nodes. In addition, because of the different diffusion and uptake rates of ICG in different tissues, perigastric blood vessels and associated lymphatic vessels can be accurately distinguished, making it possible to remove more lymph nodes adjacent to the blood vessel. Especially in the splenic hilum area, the relatively narrow operating space, the complexity of the vascular anatomy and the fragile texture of the spleen make ICG an indispensable tool to improve the safety and accuracy of surgery.

Since 1997, the Union for International Cancer Control (UICC) and American Joint Commission for Cancer (AJCC) have adopted the N stage of the tumor, node, metastasis (TNM) classification based on the number of metastatic lymph nodes (49). In our study, it seems that there were sufficient lymph nodes in the control group for positive lymph node status determination and more lymph nodes in the ICG group were unnecessary, but we should not ignore the fact that lymph node micrometastasis could not be exactly evaluated by routine H&E examination and is well associated with poor outcome in patients (50–54). Huang et al. (55) demonstrated that the number of dissected LNs is the only factor affecting negative lymph node counts. In other words, more lymph nodes dissected increases the number of positive lymph nodes and so-called negative nodes that may harbor micrometastases, thus leading to a better prognosis (56–58).

Although our study found that more overall LNs contributed to more positive LNs in the ICG group, we should take it into account that ICG is not a targeting marker for tumor cells (59) and is unable to trace positive LNs specifically. We also conducted a small sample (35 patients) study examining fluorescent and nonfluorescent LNs respectively in the ICG group, and no significant difference was found in the metastatic rate confirmed by pathology. Moreover, it is not uncommon to find discrepancies in which some obviously enlarged LNs are proven to be pathologically metastatic, but they are not fluorescent (60). This is considered to be partly because the lymphatic vessels were obstructed by a massive cancer embolus, the ICG cannot flow into these LNs (61). Therefore, ICG fluorescence technology can only be used to assist lymph node dissection, instead of being relied on to determine whether the lymph node is metastatic, which is consistent with the report of Cianchi et al. (62)

Another key step in curative gastric cancer surgery is the complete removal of the primary tumor with sufficient negative margins. Indeed, positive margins are associated with significantly worse survival (63–65). In fact, ICG fluorescence can improve the lack of visual inspection and palpation in traditional laparoscopic surgery and prove effective in the identification of tumors in our study. The surgeon can observe the tumor with frequent switching between white light view and near-infrared mode after endoscopic ICG injection around the tumor. As a consequence, it is possible to reduce the operation time and surgical invasion. In addition, the characteristics of ICG in distinguishing lymph nodes and surrounding tissues also enable prompt and accurate intraoperative decisions to speed up the surgical process and reduce the risk of blood vessel injury and bleeding.

It is reported that intraoperative blood loss and transfusion are associated with a higher risk of morbidity and mortality, although further investigation is needed (66–69). Yasuda et al. reported that not only the volume of blood loss, but the operation time is associated with morbidity after gastrectomy (70). In addition, cardiopulmonary adverse effects of general anesthesia and dioxide pneumoperitoneum are significant in laparoscopic surgery (71, 72). In this study, the ICG group was shown to provide the advantages of decreased intraoperative blood loss and shorter surgery time than the control group. The routine use of ICG fluorescence could potentially reduce the perioperative complications caused by blood loss and prolong dioxide pneumoperitoneum during LRG. In addition, the morbidity rates were 14.0% in the ICG group and 13.6% in the control group (P>0.05), which were similar to the rates reported in previous studies (73, 74). No intraoperative events or delayed complications during their hospital stay related to ICG were observed.

After a 2-year follow-up, there was no significant difference in long-term survival in each stage between the ICG group and the control group. This may be explained by the fact of the shorter follow up period of the present study. We also found that ICG-guided LRG obviously improved OS and DFS, because the number of harvested LNs in the ICG group was significantly larger and adequate numbers of LNs dissected in the standard lymphadenectomy region were necessary for accurate disease staging and avoiding LN micrometastasis, thus having a good impact on the prognosis of patients (75–77).

Currently, two ICG injection methods are used: preoperative endoscopic submucosal injection and intraoperative subserous injection. During the study, we found that the former is superior (61) since intraoperative injection may increase surgery risk caused by prolonged operation time and pneumoperitoneum time. In addition, the location of the tumor cannot be indicated accurately under laparoscopy if ICG was not injected around the tumor (78). There was also not sufficient time for ICG to diffuse from injection sites into the D2 station LNs. Of note, the concentration of ICG solution should not be too high; otherwise, the excessively strong fluorescence intensity may obstruct the observation of tissues. However, unlike carbon nanoparticles, low-dose of ICG is not visible in white light mode, so high concentrations or leakage of ICG do not interfere with the surgeon's vision.

There are some limitations to this study. First, compared with the control group, patients in ICG group had to bear more costs for indocyanine green and endoscopic injection. Second, there was no significant difference in long-term survival between the two groups due to the relatively short follow-up time, so a longer follow-up is necessary. Third, ICG is not a targeting tracer for tumor cells, so efforts to develop more targeted dyes are required. Fourth, this was not a strictly randomized controlled study, but patients almost randomly accept endoscopic ICG injections. The study was conducted at Qilu hospital of Shandong university that performs more than 1,000 gastrectomies for advanced gastric cancer each year. Considering the large number of patients, relatively few inpatient beds and the cost of hospitalization, the number of days in hospital before surgery was strictly controlled. In our hospital, gastroenterologists are also endoscopists, who are mainly responsible for the treatment of patients in addition to endoscopy. Inpatients waiting for surgery can receive endoscopic injection only after completing all preoperative examinations and making a successful appointment with an endoscopist. Those who do not meet these requirements cannot receive ICG injection.

In summary, a large randomized, multicenter trial is warranted to further evaluate the feasibility and safety of indocyanine green fluorescence technology in LRG for gastric cancer.

This study indicates that, with a shorter operation time, less blood loss, and no complications attributable to ICG, ICG fluorescence technology can guide surgeons to rapidly locate tumors and harvest more lymph nodes than conventional LRG. In addition, the two-year OS and DFS are comparable between two groups. In conclusion, ICG fluorescence technology in laparoscopic radical gastrectomy is safe and valuable.

AUTHORS CONTRIBUTIONS

WY is the corresponding author. MW and YZ are joint first authors. WY contributed to the study concept and design. WY, ZB and MW conducted the laparoscopic radical gastrectomy. LM and ZL conducted the endoscopy. MW and YZ wrote the manuscript. MW, YZ, LM, ZL, YY, ZB, DP, YD, XZ and PL conducted the data collection and analysis. WY revised and edited the manuscript. WY and YY are the guarantors of this study. All authors contributed to the article and approved the submitted version.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Qilu Hospital of Shandong University. The patients/participants provided their written informed consent to participate in this study.

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Laparoscopic High Uterosacral Ligament Suspension vs. Laparoscopic Sacral Colpopexy for Pelvic Organ Prolapse: A Case-Control Study

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Introduction: Laparoscopic sacral colpopexy is the gold standard technique for apical prolapse correction but it is a technically challenging procedure with rare but severe morbidity. Laparoscopic high uterosacral ligament suspension could be a valid technically easier alternative using native tissue.

Material and Methods: In the period from 2015 to 2018, 600 women were submitted to laparoscopic sacral colpopexy while 150 to laparoscopic high uterosacral ligament suspension in three Italian urogynecology referral centers. We enrolled women with apical prolapse stage ≥2 alone or multicompartment descensus. To reduce allocation bias, we performed a propensity matched analysis. Women undergoing laparoscopic high uterosacral ligament suspension surgery were matched 1:2 to women undergoing laparoscopic sacral colpopexy. The cumulative proportion of relapse-free women in time was analyzed by the Kaplan–Meier method. The primary objective of this multicenter case-control retrospective study was to compare the recurrence rate while the secondary objectives were to compare feasibility, safety, and efficacy of laparoscopic sacral colpopexy and laparoscopic high uterosacral ligament suspension in surgical treatment of pelvic organ prolapse.

Results: Three hundred and nine women were enrolled (103 laparoscopic high uterosacral ligament suspension; 206 laparoscopic sacral colpopexy). Median operatory time was significantly shorter in the laparoscopic high uterosacral ligament suspension group ($P = 0.0001$). No statistically significative difference was found in terms of estimated blood loss, admission time, intraoperative, and major early postoperative complications, postoperative pelvic pain, dyspareunia and *de novo* stress urinary incontinence. Surgical approach was the only independent risk factor for prolapse recurrence (RR = 6.013 [2.965–12.193], $P = 0.0001$). The objective cure rate was higher in the laparoscopic sacral colpopexy group (93.7 vs. 68%, 193/206 vs. 70/103, $P = 0.0001$) with a highly reduced risk of recurrence (RR = 5.430 [1.660–17.765]). Median follow up was 22 months.

Conclusion: Both techniques are safe, feasible, and effective. Laparoscopic sacral colpopexy remains the best choice in treatment of multicompartment and advanced pelvic organ prolapse while laparoscopic high uterosacral ligament suspension could be appropriate for moderate and isolated apical prolapse when laparoscopic sacral colpopexy is not suitable for the patient or to prevent prolapse in women at high risk at the time of the hysterectomy.

Keywords: laparoscopic high uterosacral ligament suspension, laparoscopic sacral colpopexy, pelvic organ prolapse, laparoscopic surgery, urogynecology

INTRODUCTION

Pelvic organ prolapse (POP) is a common female condition which involves the descent alone or in combination of the bladder, the rectum, the uterus (cervix) or the apex of the vagina (in case of previous hysterectomy) from their normal position in the pelvis with a consequent bulge into the vagina (1, 2). Although rarely resulting in severe morbidity or mortality, POP with is lower genital, urinary, and gastrointestinal tracts symptoms, affects the quality of life up to 40% of all women influencing daily activities, sexual function, and exercise (3). Its presence can have a negative impact on body image and sexuality (4, 5). Both the incidence and prevalence of POP surgery tend to increase with age. The estimated incidence of POP surgery ranges from 1.5 to 1.8 per 1,000 women year with the incidence peaking in women between 60 and 69 years (6).

Even though the vaginal approach continues to be the most common contributing up to 90% of surgical intervention (7), the know high rate of POP recurrence after transvaginal surgery with native tissue and the increasingly frequent reports on mesh-related complications with the consequent FDA transvaginal mesh-related litigation, have caused a decrease in the practice of this type of surgery in favor of laparoscopic abdominal procedures (8–10).

Nowadays, laparoscopic sacral colpopexy (LSCP) can be considered the gold standard technique for apical prolapse correction because of its lower recurrence and reoperation rates than a variety of vaginal procedures (vaginal sacrospinous colpopexy, uterosacral colpopexy, and transvaginal mesh) with a longer operating time as the only disadvantage (7). However, LSCP is a technically challenging procedure, because of the need of deep pelvic dissections and high skill in suturing and it is associated with rare but severe morbidity, with documented cases of vascular injuries and sacral nerve roots damage and consequent chronic constipation and pain (11, 12). For these reasons, new strategies were investigated to suspend vaginal apex in a technically easier way avoiding the most difficult and dangerous steps of LSCP.

Laparoscopic high uterosacral ligament suspension (L-HUSLS) is an alternative surgical intervention for apical prolapse correction using native tissue with feasibility, safety, and efficacy already demonstrated by several studies (13–18). When compared with the conventional vaginal approach, the laparoscopic procedure has similar objective success rates and a small number of ureteral injuries (13–16).

Despite the current state of affairs, the previously published studies able to compare the two techniques are few and characterized by a small sample of size (13, 19). For these reasons, our case-control study aimed to compare feasibility, safety, efficacy, and prolapse recurrence rates of LSCP and L-HUSLS in a high-volume urogynecology practice.

MATERIALS AND METHODS

This is a multicenter retrospective case control study including patients with apical POP (ICS) stage ≥ 2 (1) alone or in association with anterior and/or posterior descensus who underwent to L-HUSLS (Cases) and LSCP (Controls). The study was conducted at urogynecology referral centers of Fondazione Policlinico Universitario A. Gemelli IRCCS of Rome, Azienda Ospedaliera Universitaria Gaetano Martino of Messina and Clinica Polispecialistica Convenzionata Pederzoli of Peschiera d/G. In the period from 2015 to 2018, we enrolled 600 patients in the Control group and 150 patients in the Case Group (**Figure 1**). Both types of surgical techniques were performed in all the hospitals involved in the study.

Inclusion and Exclusion Criteria

Inclusion criteria were the following: postmenopausal patients with POP (ICS) stage ≥ 2 for the apical compartment; age < 80 years; no uterine cervix dysplasia or endometrial disorders; no uterine size larger than conform 12 weeks' gestation; no previous longitudinal major abdominal surgery.

We excluded patients with anesthesiologic contraindications for minimally invasive approach. Cases were retrieved from our institutional database.

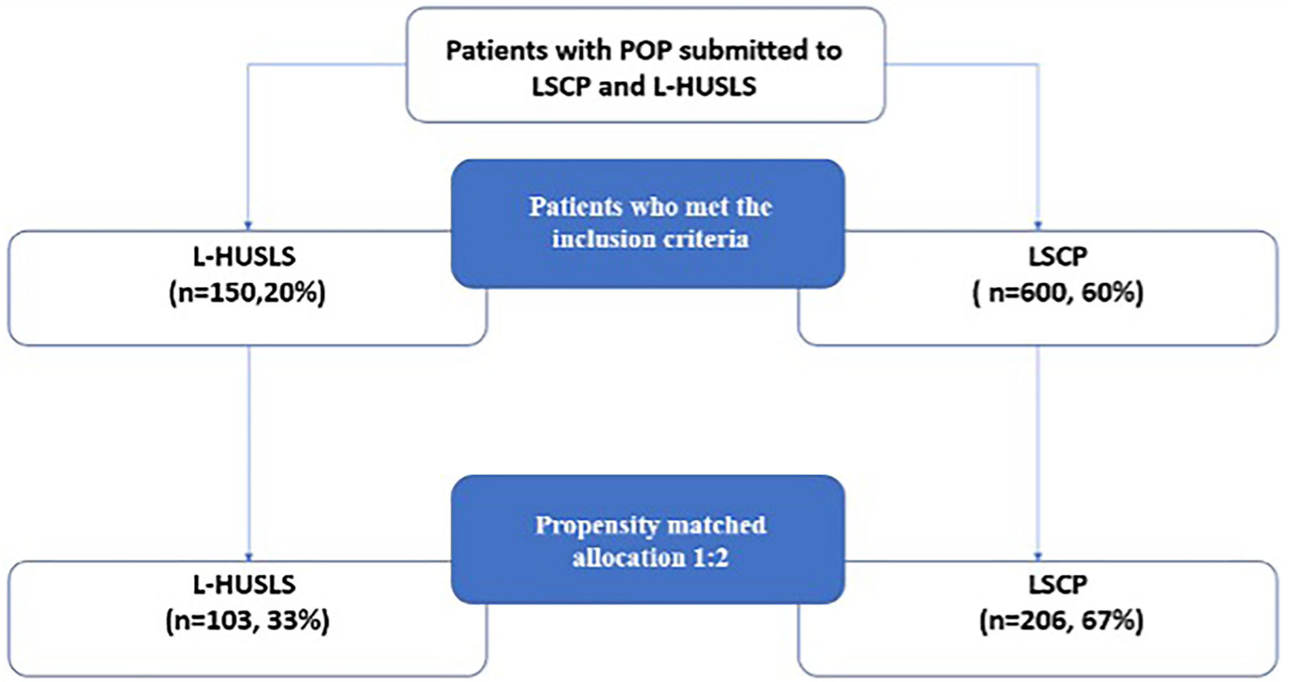

FIGURE 1 | Study design and selection process. In the period from 2015 to 2018, patients in the Control group and 150 patients in the Case Group were enrolled. Because of the nonrandomized nature of the study design and the possible allocation biases arising from the retrospective comparison between groups, we performed a propensity matched analysis. LSCP, laparoscopic sacral colpopexy; L-HUSLS, laparoscopic high uterosacral ligament suspension.

Four expert uro-gynecological surgeons (GC, GP, AE, and RZ) with a minimum of 30 LSCP and 30 L-HUSLS per year, prior to this study, performed all procedures.

The surgical selection was based on prolapse type and grade, surgeon preference, risk factors, and women history of previous surgery and preference. Additional procedures performed when indicated include total or supracervical hysterectomy, anterior colporrhaphy, and suburethral sling.

All patients received an upfront explanation of the surgical approach. Women signed written consent to undergo the described procedure and to permit data use.

The study was approved by the three hospitals institutional review boards and has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Preoperative and Perioperative Assessment

Preoperative assessment involving exhaustive history, physical examination, urodynamic testing, smear test and ultrasound scan was performed by an urogynecologist of each surgical team. When urogenital or ano-rectal malignant pathologies were suspected, supplementary exams and/or imaging were executed. POP was classified according to the Pelvic organ prolapse quantification (POP-Q) system published by the International Continence Society (1). Preoperatively women were questioned about urinary, bowel, and sexual function.

Surgical Technique

The three surgical teams performed all procedures using a standard technique in accordance with what we previously published (20–23).

In case of LSCP two adequately shaped polypropylene type 1 mesh fixed with non-absorbable sutures were used to correct the POP. Finally, the anterior mesh was fixed to the longitudinal vertebral ligament at L5-S1 level with 1–0 non absorbable suture on a noncutting needle.

When L-HUSLS was performed two polydioxanone 1 suture stitch (PDS®; Ethicon, Somerville, NJ, USA) were used to suspend vaginal apex. During the procedure, we mobilized and lateralized the ureters and hypogastric nerves to avoid injuries.

Follow-Up

We used Clavien–Dindo's (CD Grade) classification for grading postoperative complications during the first 30 days after surgery (24) and the ICS/IUGA joint report on the terminology for pelvic floor dysfunction (25) to describe surgical results.

We considered as an anatomic surgical failure a POP stage $\geq$ 2 in any compartment.

Patients underwent postoperative routine follow up at 1, 3, 6, and 12 months after the intervention and then yearly which were performed by an urogynecologist of each group. Urodynamic testing was repeated 12 months after the surgical treatment in all women without problems.

The Patient Global Impression of Improvement (PGI-I) questionnaire administered at 3 and 12 months (26) was used to evaluate the overall postoperative patient satisfaction. Women were asked about the changing of urinary and/or bowel and/or sexual function after the surgical procedure. During medical interview, sexually active patients were asked if they were affected by dyspareunia, defined as a perceived pain or discomfort during sexual intercourse.

Statistical Analysis

Because of the non-randomized nature of the study design and the possible allocation biases arising from the retrospective comparison between groups, we performed a propensity matched analysis (**Figure 1**). Propensity-matched comparison attempts to estimate the effect of a treatment by accounting for possible factors (e.g., constitutional variables) that predict receiving the treatment. Propensity-matched comparison aims to reduce biases arising from different covariates (27–29). A propensity score was developed through a multivariable logistic regression model. Age, body mass index, the preoperative stage of apical prolapse, were included in the model. Patients undergoing L-HUSLS surgery were matched 1:2 to patients undergoing LSCP using a caliper width $\leq$ 0.1 standard deviations of the logit odds of the estimated propensity score. Univariate analysis was performed to verify any difference between the two groups. The χ^2 analysis or Fisher's exact test were used, when appropriate, for categorical variables and the Student *t*-test and Mann–Whitney test, when appropriate, for continuous variables. Differences between the groups were considered statistically significant at $p < 0.05$ (95% confidence interval). The Kaplan–Meier method was used to analyze the cumulative proportion of relapse-free patients in time. The NCSS statistical software program, version 11.0 (NCSS Statistical Software, Kaysville, UT), was used.

RESULTS

After propensity matching, 103 patients were in the case cohort and 206 patients were in the control cohort. Patient characteristics of the two cohorts are shown in **Table 1**. No difference between groups was found in terms of age, BMI, comorbidities, previous POP surgery, parity, prior hysterectomy. Smokers were prevalent in the control group.

Even though the distribution of apical POP Q stage was similar among two groups there was a trend toward more severe (stage III/IV) anterior and posterior prolapse in the sacral colpopexy cohort (83.0 vs. 61.2% $p = 0.0001$ for the anterior descensus and 0 vs. 9% for the posterior one) Perioperative parameters are summarized in **Table 2**.

Median OT was significantly shorter in the L-HUSLS group 120 min vs. 190 min ($p = 0.0001$). No statistically significative difference was found in terms of estimated blood loss, admission time, intraoperative complication and major early postoperative complication. We registered 1 (0.5%) intraoperative complication: a bladder injury in LSCP group.

All women with uterus underwent total hysterectomy in the case group and subtotal hysterectomy in the control group.

There were no significant differences between the two cohorts in terms of postoperative pelvic pain (1% in the case group vs. 2.4% in the control group, $p = 0.382$), dyspareunia (2% in the case group vs. 6% in the control group, $p = 0.612$) and *de novo* stress urinary incontinence (6.8% in the case group vs. 13.1% in the control group, $p = 0.123$).

There was one case of LSCP mesh erosion (0.5%) managed conservatively with vaginal estrogen. There were four cases

TABLE 1 | Baseline patients characteristics.

Variables	L-HUSLS+ (*N*) (%)	LSCP[a] (*N*) (%)	*p*-value
All cases	103	206	–
Age			
<65 years	74 (71.8)	147 (71.4)	0.929
≥65 years	29 (28.2)	59 (28.6)	
Body mass index (Kg/m^2)			
<25	44 (42.7)	94 (45.6)	0.716
≥25	59 (57.3)	112 (54.4)	
Diabetes			
Yes	7 (6.8)	13 (6.3)	0.870
No	96 (93.2)	193 (93.7)	
COPD°			
Yes	4 (3.9)	4 (1.9)	0.448
No	99 (96.1)	202 (98.1)	
Parity			
Yes	102 (99.0)	199 (96.6)	0.277
No	1 (1.0)	7 (3.4)	
Prior POP* surgery			
Yes	7 (6.8)	25 (12.1)	0.169
No	96 (93.2)	181 (87.9)	
Prior hysterectomy			
Yes	11 (10.7)	40 (19.4)	0.053
No	92 (89.3)	166 (80.6)	
Smoking			
Yes	5 (4.9)	28 (13.6)	**0.01**
No	98 (95.1)	178 (86.4)	
Preoperative SUI**			
Yes	25 (24.3)	55 (26.7)	0.681
No	78 (75.7)	151 (73.3)	
POP Q stage anterior			
1–2	40 (38.8)	35 (17.0)	**0.0001**
3–4	63 (61.2)	171 (83.0)	
POP Q stage apical			
2	48 (46.6)	91 (44.2)	0.717
3–4	55 (53.4)	115 (55.8)	
POP Q stage posterior			
1–2	103 (100)	187 (90.8)	**0.001**
3–4	0	19 (9.2)	

+*Laparoscopic sacral colpopexy.*
[a]*Laparoscopic high uterosacral ligament suspension (L-HUSLS).*
°*Chronic obstructive pulmonary disease.*
[*]*Pelvic organ prolapse.*
[**]*Stress urinary incontinence.*
LSCPa, aLaparoscopic sacral colpopexy; L-HUSLS+, +Laparoscopic high uterosacral ligament suspension.

TABLE 2 | Perioperative data.

Variables	L-HUSLS (*N*) (%)	LSCP (*N*) (%)	*p*-value
All cases	103	206	–
Operative time (minimum) (median) (range)	120 (60–270)	190 (110–290)	**0.0001**
Estimated blood loss (mL) (median) (range)	70 (0–130)	50 (0–110)	0.965
Concomitant procedures			
Anterior colporrhaphy	66 (64.1)	0	**0.0001**
Sub-urethral sling	12 (11.7)	1 (0.5)	**0.0001**
Intraoperative complications	–	1 (0.5)	0.479
Early (<30 days) major postoperative complications*	–	–	n.a.**
Hospital stay (days) (median) (range)	2 (1–4)	2 (1–4)	0.186

*≥3 according to Clavien-Dindo scale (xx); **n.a., not applicable.

TABLE 3 | Patient global Impression of Improvement (PGI-I).

	Very much better Much better Score 1–2	A little better No change Score 3–4
L-HUSLS (*N*) (%)	74 (72%)	29 (28%)
LSCP (*N*) (%)	194 (94%)	12 (6%)
***p*-value**	**0.0001**	**0.0001**

of urinary retention in the L-HUSLS group which all resolved spontaneously within 1 week, two cases of urinary infection in the LSCP group treated successfully with antibiotics and 1 case of Deep vein thrombosis cured with anticoagulant therapy.

PGI-I score for both groups is summarized in **Table 3**.

In the univariate and multivariate analysis surgical approach was the only independent risk factor for POP recurrence (RR = 6.013; CI: 2.965–12.193, $p = 0.0001$; **Table 4**).

Anatomic outcomes are presented in **Table 5**. The objective cure rate was higher in the LSCP group (93.7 vs. 68%, $p = 0.0001$) with a highly reduced risk of prolapse recurrence (RR = 5.430, CI: 1.660–17.765). The length of follow-up was similar with a median of 22 months in both groups.

Kaplan–Meier curves of objective recurrence in the whole population are shown in **Figure 2**.

DISCUSSION

Our study demonstrates that both laparoscopic procedures are safe with rare and minor perioperative complications and a superimposable admission time in accordance with the main principles of the mini-invasive approach. In addition, L-HUSLS showed significative lower OT than LSCP. The absence of ureteral injuries further emphasizes the safety of the L-HUSLS techniques if compared to the 11% of the ureteral damaging rate described in previous studies on V-USLS (30). One of the perceived benefits of the laparoscopic approach includes the magnified view of the operative field allowing an easier dissection, a more precise suture placement and a better visualization of vital structures. This may help to reduce the possible damage to the ureter which could be further protected by a prophylactic ureterolysis before the apical suspension. This confirms what already published studied demonstrated about the minimal ureteric injury rates during this laparoscopic procedure (14, 15, 31, 32). Mesh erosion rate in LSCP group with only in 1 case (0.5%) was lower compared to data already reported in literature (7, 12, 33, 34). This may be related to the surgical technique, to the prothesis material (polypropylene type 1 with mesh weight ranging from 16 to 65 g/m^2) (35) and to time of follow up. The use of a standard subtotal hysterectomy avoids the communication between the vaginal and the abdominal cavities and the consequent exposition of the surgical bed to the vaginal microbiota. This element, combined with the devascularization of the vaginal cuff caused by uterus removal, may play a significative role in the evolution of subsequent erosion. Even though the length of the follow up in the study is enough to detect mesh related complications, it's still too short to compare our results with those included in the study by Nygaard et al. (33) which report a rate of mesh erosion of 10.5% at 7 years. The incidence of *de novo* SUI was higher in the LSCP group but not in a significative manner. Our data don't differ from those already published in literature (13, 36).

The present study founded that LSCP has higher objective success rate than L-HUSLS in multicompartment advanced pelvic organ prolapse. Regarding LSCP our anatomic outcome was similar to those already described in literature (33, 34). The recurrence rate in patients underwent L-HUSLS were higher than those previously published (13, 15, 37, 38). This may be related to the larger sample size investigated, the longer follow up time and the highest grade of preoperative pelvic organ prolapse. Filmar et al. (13) reported an anatomic success rate for L-HUSLS of 89.7 % in only 29 patients with a preoperative POP stage 2 and a follow up of 6 months. Haj Yahya et al. reported with the same procedure an anatomic success rate of 91.3% but 54% of the population had a preoperative apical prolapse of grade I, and 22.9% of grade II with a FUP of 17.5 months (38). The PGI-I reflects the anatomical outcome with a significative higher percentage of women in the LSCP group with a score of 1–2.

TABLE 4 | Risk factors for prolapse recurrence.

Variable	Univariate analysis		Multivariate analysis*	
	Risk ratio (95% CI)	***p*-value****	**Risk ratio (95% CI)**	***p*-value****
Age				
≤65§	0.497 (0.222–1.116)	0.107	2.110 (0.897–4.964)	0.087
>65				
Body mass index (BMI)				
≤25 Kg/m²	1.123 (0.593–2.128)	0.748	–	–
>25 Kg/m²§				
Surgical approach				
L-HUSLS§	6.691 (3.324–13.470)	**0.0001**	6.013 (2.965–12.193)	**0.0001**
LSCP				
COPD				
Yes§	0.850 (0.811–0.892)	0.237	–	–
No				
Prior POP surgery				
Yes§	0.363 (0.084–1.574)	0.159	1.586 (0.336–7.491)	0.560
No				
Prior hysterectomy				
Yes§	0.921 (0.386–2.196)	0.853	–	–
No				
POP Q stage anterior				
1–2	1.333 (0.610–2.914)	0.574	–	–
3–4§				
POP Q stage apical				
2	0.924 (0.490 – 1.741)	0.872	–	–
3–4§				
POP Q stage posterior				
1–2	0.845 (0.804–0.888)	0.063	1.198 (0.01–8.493)	0.998
3–4§				

Multivariate analysis with method backward stepwise was performed for variable with $p < 0.2$ at univariate analysis.
**Bold cases are statistically significant: $p < 0.05$.*

TABLE 5 | Pattern of recurrent prolapse according to surgical approach.

Variable	*N* (%)	L-HUSLS (%)	LSCP (%)	*p*-value	Risk ratio (95% CI)
All cases	309	103	206	–	–
Recurrences	46 (14.9)	33 (32)	13 (6.3)	0.0001	5.430 (1.660–17.765)
Anterior	26 (56.5)	18 (54.5)	8 (61.6)	0.0001	5.743 (2.768–11.917)
Apical	4 (8.7)	4 (12.1)	0	0.0001	7.944 (2.544–24. 809)
Posterior	2 (4.3)	1 (3.0)	1 (7.7)	0.011	6.309 (1.251–31.832)
Multicompartmental	14 (30.5)	10 (30.4)	4 (30.7)	0.002	5.430 (1.660–17.765)

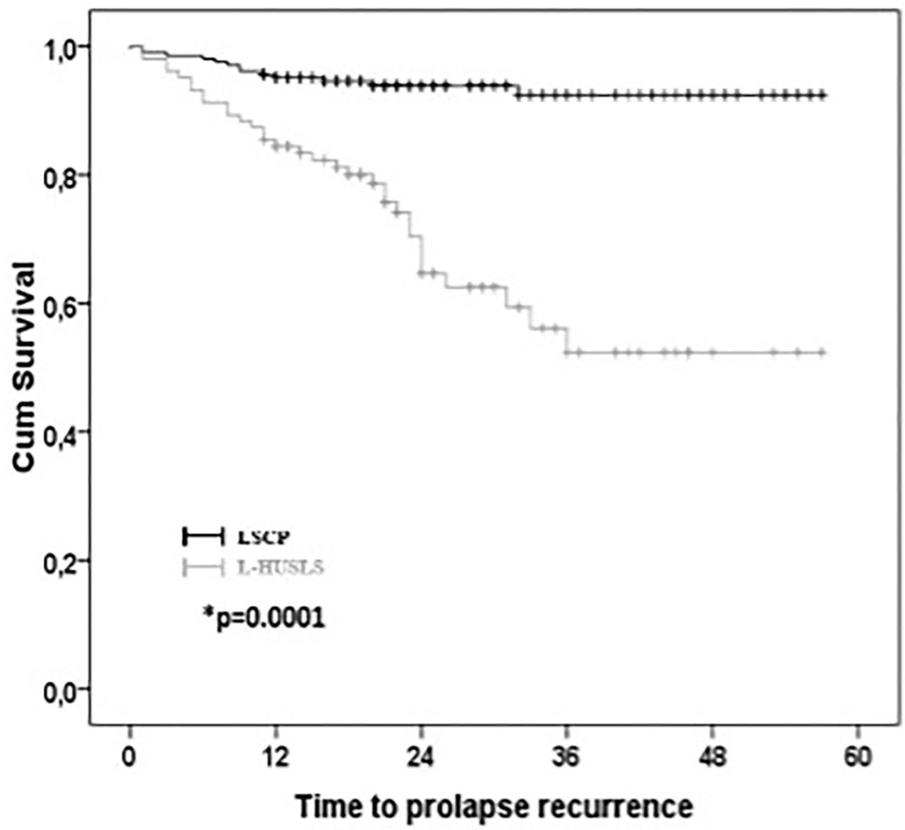

FIGURE 2 | Kaplan–Meier survival curves for anatomical recurrence. Kaplan–Meier curves of objective recurrence in the whole population.

To better evaluate the effectiveness of the two techniques, the univariate and multivariate analysis was performed to understand which could be possible confounding risk factors for surgical failure. However, none of the tested independent variables, including preoperative POP Q stage, had an influence on anatomic recurrence except for the type of surgical procedures. This may be related to the characteristics of our population characterized by multicompartmental POP. L-HUSLS is a fascial technique indicated for the correction of apical prolapse. Higher grade of apical prolapse is often associated with anterior or posterior descensus. While LSCP is often able to correct the defects in all the compartments in this clinical situation, L-HUSLS often requires an additional vaginal native tissue repair. This exposes the women to the augmented risk of surgical failure of fascial surgery. Significantly we observed that 85% of prolapse recurrence in L-HUSLS group involved the anterior compartment even though the procedure was associated with anterior colporrhaphy in 66 cases (64.1 %). The anatomical failure rate in the anterior compartment (28/103, 27%) is similar to those described by Maher's Cochrane indicating that 27–42% of women would have a recurrence after native tissue repair (39). Taking in consideration only the apical compartment we observed that, even if the LSCP remains the referral treatment with an objective success rate of 98% (202/206), the anatomical success rate for the L-HUSLS technique increases up to 87% (89/103). This demonstrates that although L-HUSLS is significantly less effective than LSCP in advanced multi- component prolapses, it remains an effective treatment for isolated and mild apical prolapses bypassing the limits of the vaginal routes (such as chronic pelvic pain, dyspareunia, ureteral obstruction) (14, 15). There are particular clinical situations such as the need for a total hysterectomy (in case of cervical pathology) and the presence of contraindications to the positioning of the prosthetic material (patients at high risk of mesh infection) in which the L-HUSLS may play a significative role. Moreover, results showed a significative shorter operative time of L-HUSLS. This would be an advantage for patients who, due to their comorbidities, cannot sustain a long surgical procedure. Thanks to its demonstrated safety and feasibility this technique should take in consideration for POP prevention in patients undergoing total hysterectomy for benign indication in which risk factors for future descensus have been recognized.

This was a pilot study before planning a multicentric prospective study with a larger sample. In the absence of specific questionnaires, women completed the PGI-I questionnaire and expressed their satisfaction with the surgical treatment in terms of sexual function and bulge symptom resolution.

In our prospective study, we plan to evaluate additional subjective outcomes.

Strengths of our study include large sample size, the multicentric setting in high volume hospitals, all participating surgeon performing both techniques and the long follow up.

Limitations of our study include those inherent to cohort studies. Because of the possibility of selection bias due to the absence of randomization we balanced the differences in patient characteristics between groups by using propensity score-matching. Although differences remained between the matched groups related to the preoperative POP Q stage anterior and posterior, we have attempted to address this discrepancy using the regression modeling.

CONCLUSION

In conclusion, both presented techniques suggest safety, feasible, and efficacy in the treatment POP. LSCP still remains (remove the extra space) to be the best choice in the treatment of multicompartment and advanced pelvic organ prolapse while L-HUSLS appears to be well-appropriate for moderate and isolated apical prolapse when LSCP is not suitable for the patient or to prevent prolapse in patients at high risk at the time of the hysterectomy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Policlinico Universitario A. Gemelli—Largo Agostino Gemelli 8, 00168 Roma—Prot. ID 3487. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GC, AE, LV, and RZ: conception and design. LV, RZ, and MM: acquisition of data. GV, SC, and GP: analysis and interpretation of data. LV, GP, MA, and DC: drafting of the manuscript. AE, GC, RG, and GS: critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.853694/full#supplementary-material

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frontiers in Medicine

CASE REPORT
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Case Report: Gastric-Type Endocervical Adenocarcinoma Mimicking Submucosal Myoma Under Hysteroscopy

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Gastric-type endocervical adenocarcinoma (GAS) is considered a distinct and clinically important entity because it is unrelated to human papillomavirus infection and has aggressive behavior and worse clinical outcomes than the usual type of endocervical adenocarcinoma (ECA). The preoperative diagnosis of GAS is often difficult because of its nonspecific clinical manifestations and special lesion location. We report the case of a 50-year-old Chinese woman who presented with intermittent left lower abdominal pain for 1 year. Preoperative images showed left hydrosalpinx and a lesion that was mainly located in the lower part of the uterine cavity. We considered the lesion to be a polyp before surgery. During hysteroscopic surgery, we suspected that it may be a submucosal myoma. However, pathology revealed that it was a GAS. GAS may be located in the upper endocervix or even reach the uterine cavity. The appearance is occasionally similar to that of submucosal myoma, resulting in difficult preoperative diagnosis and even misdiagnosis.

Keywords: endocervical adenocarcinoma, gastric-type, human papillomavirus, submucosal myoma, diagnosis

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INTRODUCTION

Cervical cancer is the fourth most common gynecological malignancy worldwide (1). Most cervical cancers are related to the continuous infection of high-risk human papillomavirus (HPV). However, a few are not, such as some endocervical adenocarcinoma (ECA). ECA accounts for 20–25% of invasive cervical cancers, and its incidence is gradually increasing (2). In the 2020 World Health Organization (WHO) classification of female genital tumors, ECAs are subclassified into human papillomavirus (HPV)-associated (HPVA) and HPV-independent (HPVI) groups based on their distinct etiology and clinical behavior (3). The most common histological type of the HPVI group is gastric-type ECA (GAS) (4), which has a worse prognosis than HPVA (5). The clinical manifestations are not specific, the focus is hidden, and the positive rate of screening and biopsy is low, which brings great challenges to timely and correct diagnosis. Here, we present a patient with GAS with lower uterine cavity involvement, which was misdiagnosed as submucosal myoma during hysteroscopic surgery. However, pathology confirmed the diagnosis of GAS.

CASE REPORT

The patient was a 50-year-old premenopausal female, gravida 2, para 1. Cesarean section followed by right adnexectomy, which was performed due to a right ovarian cyst, was performed in 1995. On June 15, 2021, the patient visited our hospital for "intermittent left lower abdominal pain for 1 year." In May 2020, pelvic ultrasound was performed in another hospital because of left lower abdominal pain and fever. The results showed a cystic mass in the left adnexa, about 7.6 × 1.4 cm, with a high possibility of hydrosalpinx; an intrauterine device (IUD) and liquid dark area in the uterine cavity, and Nabothian cysts in the cervix. Her symptoms were relieved after anti-inflammatory treatment, but slight intermittent pain persisted in the lower abdomen. The patient underwent pelvic ultrasound again on May 26, 2021. The results showed left hydrosalpinx, about 7.5 × 3.4 cm, and in addition to the IUD and cervical Nabothian cysts, a slightly strong echo mass was seen in the uterine cavity. Then the patient was referred to our hospital. On gynecological examination, the vulva and vagina were normal, a small amount of secretion could be seen, the cervix was of normal size with a smooth surface, the uterus was normal, the left adnexa were thickened and accompanied by slight tenderness. Pelvic ultrasound revealed that a mass around 2.3 × 1.8 × 1.7 cm was seen in the lower part of uterine cavity. The internal echo was uneven, and the boundary was clear (**Figures 1A,B**). Color Doppler flow imaging detected blood flow signals. The size of the left ovary was normal, and a 7.7 × 3.6 × 1.6 cm cystic mass was seen in the left adnexal area, which was tortuous and tubular, with liquid inside and a clear boundary. Thinprep cytology test (TCT) revealed atypical squamous cells of undetermined significance (ASCUS); HPV: negative. The serum carbohydrate antigen (CA)-199, carcinoembryonic antigen (CEA), CA-125, and CA-724 levels were normal. Preoperative diagnoses included left hydrosalpinx and endometrial polyp. Laparoscopic left salpingectomy, removal of the IUD, and resection of the mass under hysteroscopy were performed on June 22, 2021. Laparoscopic exploration revealed a thickened left fallopian tube, with a size of about 7.0 × 2.0 cm, which surrounded the left ovary. The right adnexa were absent. The uterus was normal in size and regular in shape. After removing the left fallopian tube, the left ovary was exposed and appeared normal, and hysteroscopic surgery was subsequently performed. We first removed the T-shaped IUD. A mass with a size of about 2.5 × 2.0 cm was seen at the left anterior wall close to the internal os (**Figures 1C,D**). The texture was tough, the local shape was irregular, the surface contained thickened blood vessels (**Figure 1E**), and the mucosa of the cervical canal was smooth. The lesion was removed using a circular electrode (**Figure 1F**). All resected tissues were sent for pathology examination. The patient recovered and was discharged on the fourth postoperative day. Paraffin pathology results were as follows: well-differentiated GAS and left hydrosalpinx. We contacted the patient and asked her to return to our hospital for further treatment.

After the second admission, the patient's medical history was recorded. The patient said that she began having intermittent watery vaginal fluid approximately 1 year prior. She did not care for it or inform the doctors because she thought it was vaginitis. Gynecological examination showed that the cardinal and uterosacral ligaments were not thickened. Pelvic contrast-enhanced magnetic resonance imaging (MRI) showed that the cervix was plump, with an uneven equal T1 and slightly higher T2 signal shadow, which was mainly located in the posterior lip of the cervix. Weak enhancement was seen on contrast-enhanced scan, with a range of about 3.5 × 2.7 cm, in which there were many small circular long T1 and long T2 signal shadows (**Figures 2A,B**). No definite abnormality was found in the left ovary. Abdominal contrast-enhanced computed tomography (CT) showed that the cervix was slightly plump, and multiple low-density small nodules could be seen in it (overall range of about 2.8 × 2.5 cm), and the enhancement was not obvious (**Figures 2C,D**). Therefore, the diagnosis of stage IB2 GAS was made. Open operation was performed on July 26, 2021. During the operation, we found that the cervix was slightly plump (**Figure 2E**), the parauterine tissue was not thickened, and the appearance of the left ovary, peritoneal surface, greater omentum, and appendix were normal. First, the left ovary was removed and a tumor of approximately 1.5 × 1.3 cm was seen inside. The cut surface was yellowish white. Multiple cystic cavities were seen around (**Figure 2F**). The left ovary was subjected to frozen pathology, which suggested heterotypic glands and metastases. Therefore, radical hysterectomy, pelvic and paraaortic lymph node resection, greater omentum resection, and appendectomy were performed. There were no untoward events intraoperatively and postoperatively, and the patient was discharged on the eighth postoperative day. The paraffin pathological results were reported as follows: well-differentiated GAS, infiltrating the outer 1/3 of the cervical stroma; metastatic carcinoma of the left ovary; and no cancer at the surgical margin, parauterine, greater omentum, appendix, and lymph nodes. Microscopic examination revealed GAS (**Figures 3A,B**) and metastatic carcinoma of the left ovary (**Figure 3C**). Immunohistochemical analysis showed that the tumor was focally positive for CEA (**Figure 3D**), about 5% positive for Ki-67 (**Figure 3E**), and negative for P16, ER, and PR (**Figures 3F–H**). Four weeks after the second operation, the patient was referred to the gynecological tumor center for concurrent chemoradiotherapy (CCRT): pelvic intensity-modulated radiotherapy 50.4 Gy/28f + cisplatin concurrent chemotherapy. The patient completed the treatment, and there was no recurrence or metastasis during outpatient follow-up.

DISCUSSION

GAS, first described by Kojima et al. (6), was included as a subtype of HPVI group in the latest 2020 WHO classification of female genital tumors (3). It is an aggressive type of ECA characterized by mucinous morphology, gastric-type mucin, lack of association with HPV, and resistance to chemo/radiotherapy (7).

The incidence of GAS has obvious regional differences; GAS accounts for 10% of all ECA in an international population (4) and 20–25% of cases in Japanese women (8). Precursor lesions are essential for the prevention and early detection of cancer. Some findings suggest that atypical lobular endocervical

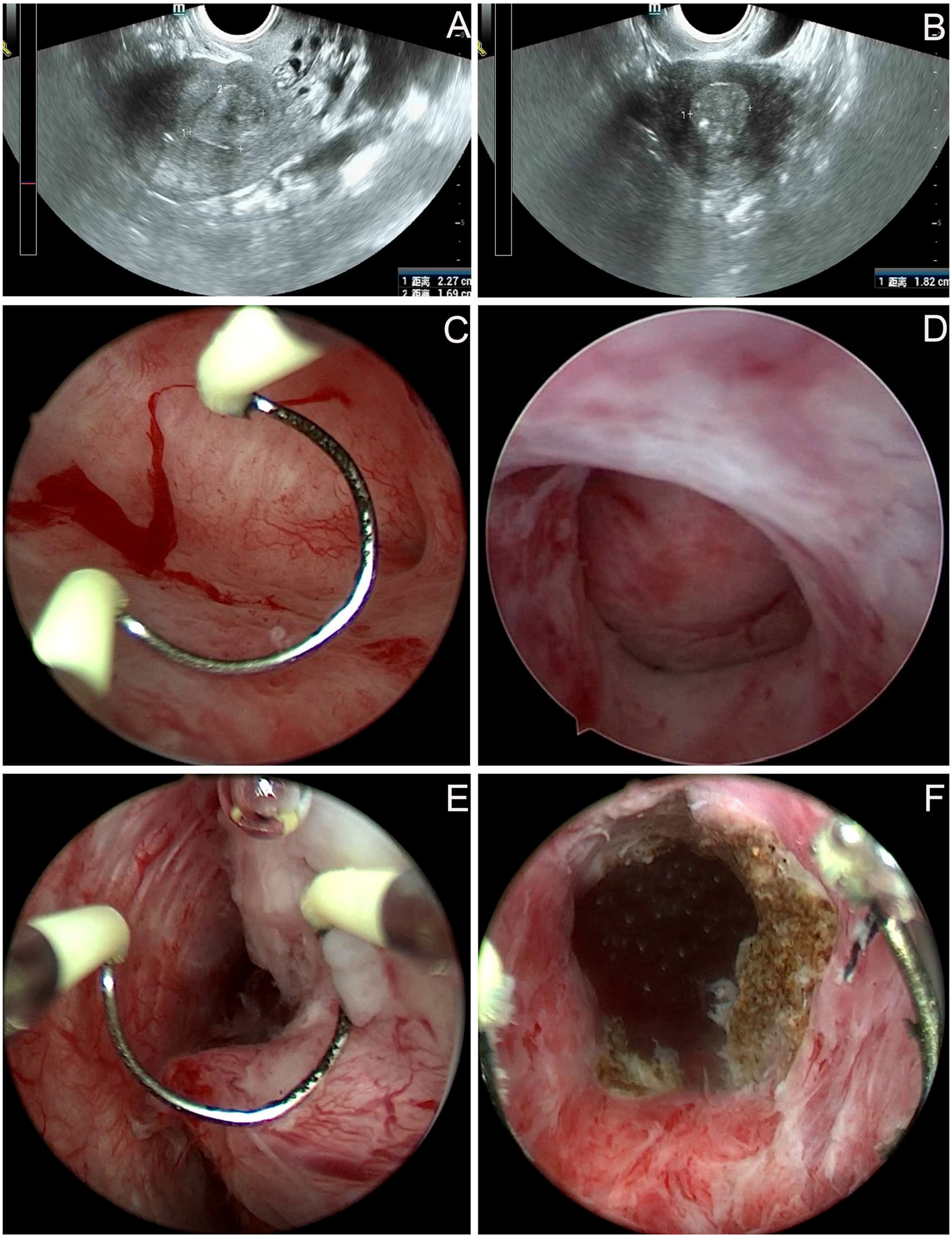

FIGURE 1 | Imaging findings of the patient before and during the first operation. **(A,B)** Pelvic ultrasound: a mass around 2.3 × 1.8 × 1.7 cm was seen in the lower part of uterine cavity. The internal echo was uneven, and the boundary was clear. **(C–F)** Hysteroscopy: a mass with a size of about 2.5 × 2.0 cm was seen at the left anterior wall close to the internal os. The local shape was irregular, the surface contained thickened blood vessels. The tumor was removed using a circular electrode, the boundary between the attachment position of tumor and cervical tissue was unclear.

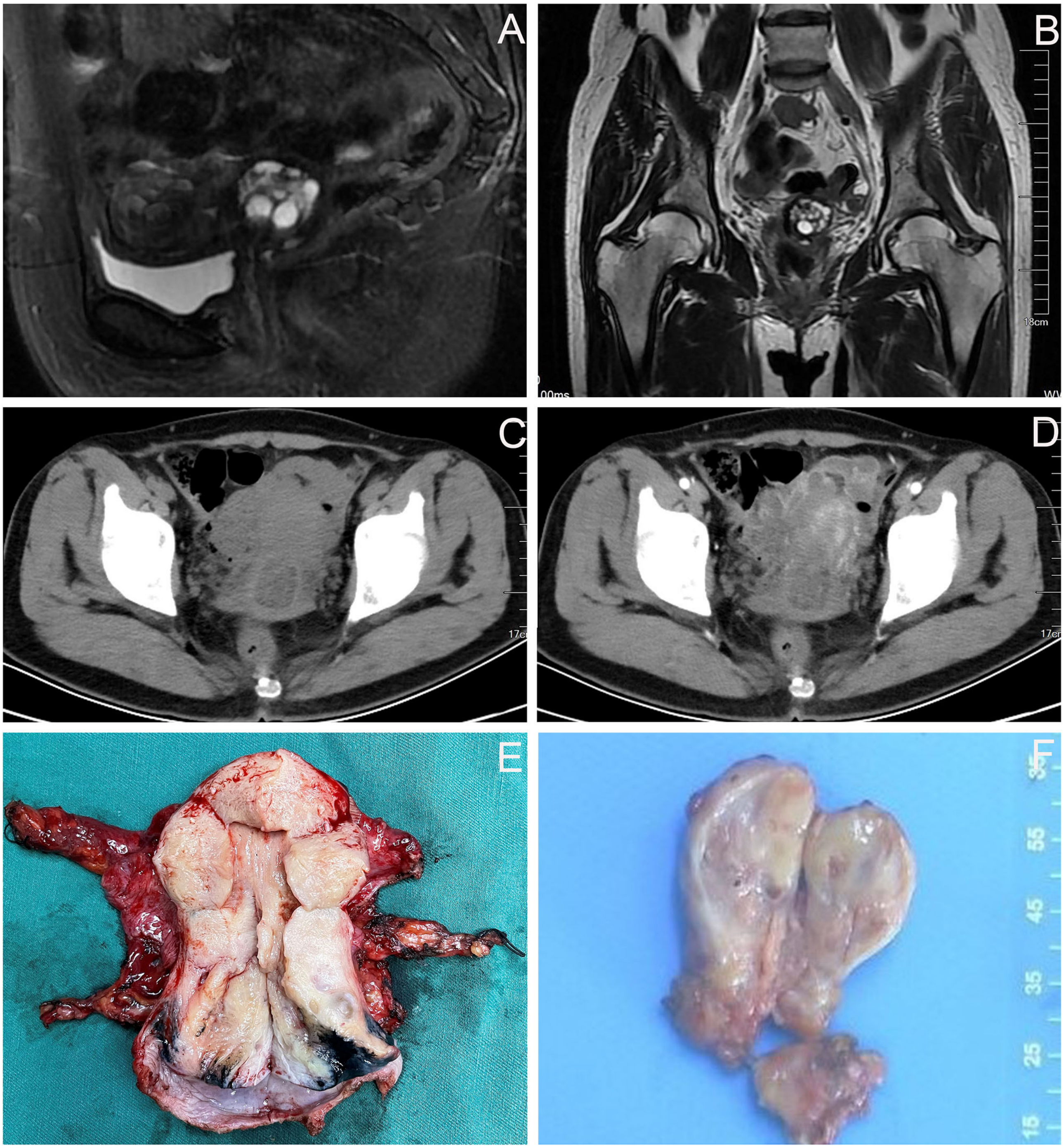

FIGURE 2 | Imaging findings of the patient before and during the second operation. **(A,B)** Pelvic MRI: the cervix was plump, with an uneven equal T1 and slightly higher T2 signal shadow, which was mainly located in the posterior lip of the cervix, about 3.5 × 2.7 cm, in which there were many small circular long T1 and long T2 signal shadows. **(C,D)** Abdominal CT: the cervical was slightly plump, and multiple low-density small nodules could be seen in it (overall range of about 2.8 × 2.5 cm), and the enhancement was not obvious. **(E)** The cervix was slightly plump. **(F)** The appearance of the left ovary was normal, a tumor of approximately 1.5 × 1.3 cm was seen inside, the cut surface was yellowish white, multiple cystic cavities were seen around.

glandular hyperplasia (LEGH) and gastric-type adenocarcinoma in *situ* are the precursors of GAS (9). D'Alessandro et al. (10) reported a case of GAS in presence of Nabothian cysts. They thought it would be interesting to evaluate the role of Nabothian cysts in the pathogenesis of GAS. The genetic underpinnings of GAS are beginning to be elucidated, as

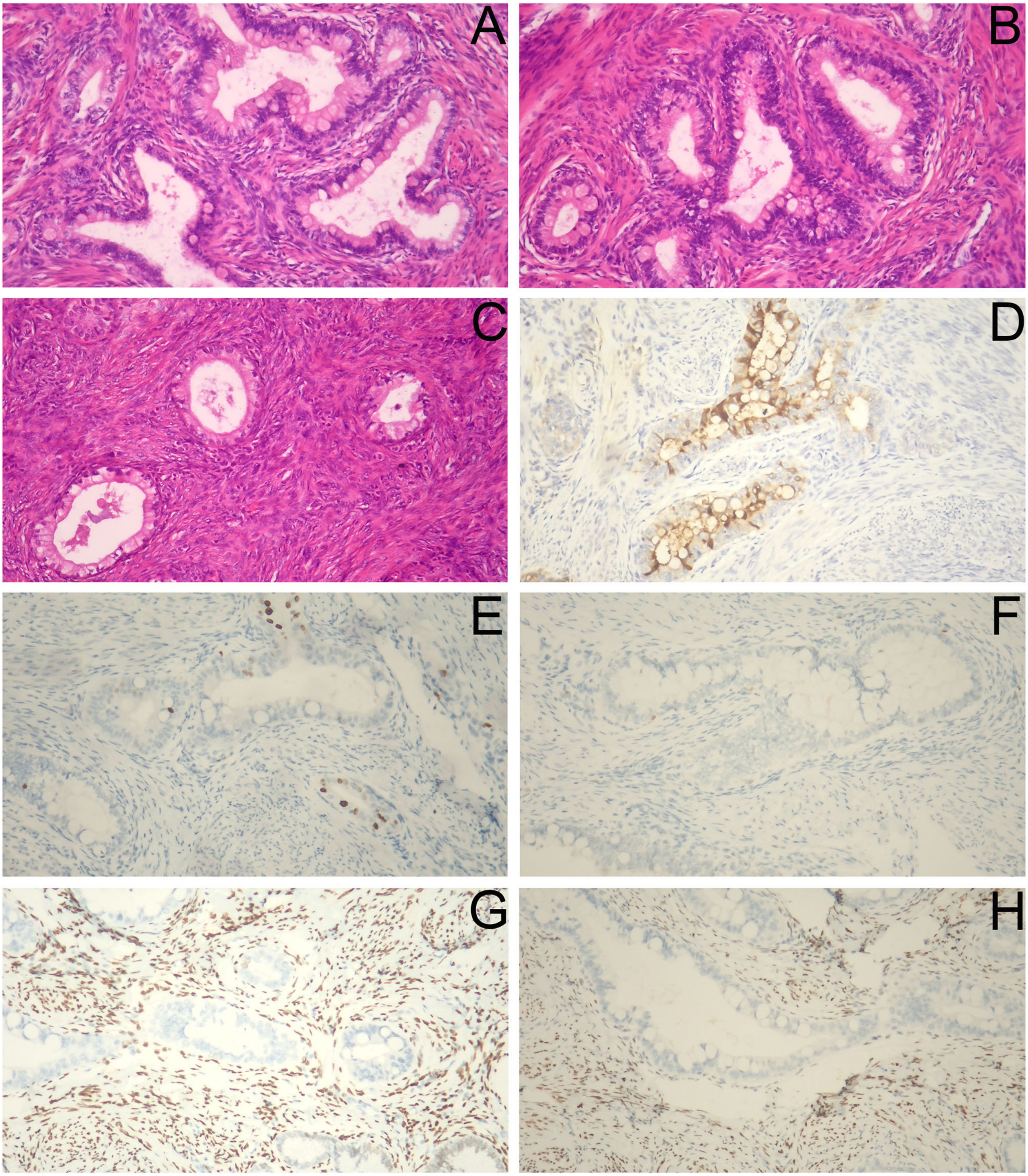

FIGURE 3 | Histopathological and immunohistochemical staining findings. **(A,B)** The cancer cells were columnar and arranged in irregular glandular tubes, some nuclei were large and deeply stained, cytoplasm was empty and bright, and intracellular mucus were seen (H&E staining, ×40). **(C)** Heterotypic glands were seen in the left ovary (H&E staining, ×40). **(D)** CEA (focally +). **(E)** Ki-67 (about 5% +). **(F)** P16 (–). **(G)** ER (–). **(H)** PR (–) (**D–H**, ×100).

illustrated by the following recent studies. In the study by Park et al. (11) next-generation sequencing was performed in 21 GAS cases, and a total of 54 nonsynonymous somatic mutations were detected, with an average mutation rate of 2.6 per lesion. The mutated genes, of which TP53 was the most frequent, were mostly involved in signal transduction, DNA damage repair, and epithelial-mesenchymal transition. Another study showed that GAS most frequently harbored somatic mutations in TP53, CDKN2A, KRAS, and STK11, and potentially targetable mutations were identified in ERBB3, ERBB2, and BRAF (7).

The average age of patients with GAS is 49–51 years (6, 12). The symptoms of patients with GAS are diverse and non-specific. They are often situated in the upper endocervix, present with bleeding or profuse watery discharge, and are associated with a clinically bulky cervix without a well-defined mass due to an infiltrative growth pattern (13). Patients with GAS often have no specific signs of cervical cancer, and the surfaces of the cervix are mostly smooth. Most patients with GAS present at an advanced stage, and pelvic, abdominal, and distant metastases are not uncommon (5). Patients with ovarian and pelvic-abdominal metastases may have signs similar to those of ovarian cancer.

Screening methods for the usual cervical cancer are ineffective for GAS, which may result in a probable delay in diagnosis. Our case was initially treated in another hospital because of lower abdominal pain and fever. Ultrasound showed a hydrosalpinx, dark area in the uterine cavity, and cervical Nabothian cysts. Considering the abdominal pain and fever caused by hydrosalpinx, the patient was given anti-inflammatory treatment, while ignoring the performance of the dark area in the uterine cavity. Until this year, the patient did not undergo pelvic ultrasound again. In addition to hydrosalpinx, an abnormal mass in the uterine cavity was observed. Although TCT showed ASCUS, all high-risk HPVs were negative, and the possibility of an endometrial polyp was considered. During hysteroscopic surgery, we found that the tumor was located in the lower part of the uterine cavity near the internal os and considered that the possibility of submucosal myoma. However, the local shape of the tumor was irregular and like a fingertip; secondly, there was local vascular proliferation of the tumor; thirdly, multiple glandular cavities were seen on the section of the tumor; fourthly, after tumor resection, the capsule of myoma was not seen, and the boundary between the attachment position of tumor and cervical tissue was unclear. Hence, the diagnosis of GAS was accidentally determined based on the pathology. The diagnosis of GAS is primarily based on pathological morphology, combined with immunohistochemical examination if necessary (8). GAS is characterized by tumor cells showing clear, foamy, or pale eosinophilic cytoplasm and well-defined cytoplasmic borders, spanning the spectrum from well-differentiated to poorly differentiated tumors (7). Hysteroscopy is of great significance in the diagnosis of endometrial lesions. Ianieri et al. (14) developed a hysteroscopic scoring system according to some morphological and hysteroscopic parameters, which helps physicians, especially those less experienced, to make a differential diagnosis among normal endometrium, endometrial hyperplasia, and endometrial carcinoma. We believe that hysteroscopy also plays an important role in the diagnosis of cervical canal lesions because we can clearly observe the atypical vessels on the lesion in addition to the location of lesions, which can be useful in suspecting malignant lesions, as described in the report by Ianieri et al. and shown in our hysteroscopic images.

Patients with GAS may have elevated tumor markers, especially serum CA19-9 levels (15). However, the results of serum tumor markers in our case were all normal. Pelvic MRI features of "cosmos pattern" (CP), which means some small cysts or solid components are present in the central part of the lesion surrounded by relatively large cysts, can help to distinguish gastric-type mucin-positive lesions (GMPL) such as LEGH and GAS from gastric-type mucin-negative lesions (GMNL) such as cervical Nabothian cyst. If CP is observed as a hypointense area compared with the cervical stroma on T1WI, GMPL should be strongly suspected (16). A combination of cytology and MRI and an assay for gastric-type mucin have been suggested to be effective for the early detection and preoperative diagnosis of GAS (17). The differential diagnosis of GAS requires the inclusion of both benign and malignant lesions because of its complex and diverse morphologic features (12).

Clinical management can be challenging due to its rare incidence rate, cognitive limitations, diagnostic dilemmas, and aggressive behavior. Currently, there are no specific treatment guideline recommendations for GAS. Surgical removal of the uterus, adnexa, pelvic and/or paraaortic lymph nodes, omentum, appendix, and gross tumor might be considered because of its tendency to spread along surfaces throughout the peritoneal cavity and the higher likelihood of presenting with advanced stage (5). Our case confirmed the diagnosis of stage IB2 GAS after the second admission. Because GAS is prone to ovarian metastasis, we first removed the left ovary and sent it to intraoperative frozen pathology. The results suggested that heterotypic glands were observed, and metastasis was considered. During the first laparoscopic surgery, we did not find any abnormalities in the appearance of the left ovary. Radiologists also did not report any left ovarian abnormalities. This suggested that the ovarian metastatic lesions were insidious, and ovarian preservation was not recommended. Combined with the preoperative staging and intraoperative pathology, we performed radical hysterectomy and removed the paraaortic lymph nodes, greater omentum, and appendix. Postoperative paraffin pathology also revealed metastatic cancer of the left ovary. Although there were no high-risk factors for positive lymph nodes, positive margins, or positive parauterine status after surgical resection, CCRT was still recommended according to pathologic moderate risk factors of adenocarcinoma and invasion of the outer 1/3 cervical stroma.

GAS prognosis is significantly worse than that of UEA: the overall 5-year disease-specific survival rate of GAS is reportedly 30–42% compared to 74–91% for UEA (18). Progression-free survival and overall survival are poorer in patients with GAS than in those with UEA (8). The prognosis is related to tumor stage, parametrial invasion, surgical margin, metastasis, and treatment. Our patient completed the treatment and is in good condition without recurrence or metastasis.

There were some deficiencies in the diagnosis and treatment of our case. Although the patient's TCT suggested ASCUS, it did not attract enough attention because all high-risk HPVs were negative. Although some differences were found between the tumor and submucosal myoma during hysteroscopic surgery, the possibility of GAS was not considered, which led to another operation and increased the physical and economic burden. Due to economic reasons, the patient did not agree to undergo genetic testing.

CONCLUSIONS

GAS is a type of HPV-independent ECA, which may be located in the upper endocervix or even reach the uterine cavity, resulting in a difficult preoperative diagnosis. Sometimes, the appearance is similar to submucosal myoma under hysteroscopy, which is easily misdiagnosed. MRI can show some characteristic changes and hysteroscopy can be used as a method to obtain pathological tissues for patients with GAS. Timely diagnosis is of great significance for the formulation of treatment plan and improving the prognosis of patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Shengjing Hospital of China Medical University (approval number: 2021PS849K). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JW was responsible for the data collection and drafting of the manuscript. QY and DW participated in providing knowledge of the disease. ML analyzed the literature. NZ was responsible for critical revision of the manuscript. All authors read and approved the final manuscript.

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METHODS
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The Transumbilical Laparoendoscopic Single-Site Extraperitoneal Approach for Pelvic and Para-Aortic Lymphadenectomy: A Technique Note and Feasibility Study

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Background: Nowadays, lymphadenectomy could be performed by the transperitoneal or extraperitoneal approach. Nevertheless, each approach has its own advantages and disadvantages. Under these circumstances, we developed a transumbilical laparoendoscopic single-site (TU-LESS) extraperitoneal approach for lymphadenectomy. In this research, the primary goal is to demonstrate the feasibility of the novel approach in systematic lymphadenectomy and present the surgical process step-by-step.

Methods: Between May 2020 and June 2021, patients who had the indications of systematic lymphadenectomy underwent lymphadenectomy via the TU-LESS extraperitoneal approach. This new approach was described in detail, and the clinical characteristics and surgical outcomes were collected and analyzed.

Results: Eight patients with gynecological carcinoma were included in the research, including four with high-risk endometrial cancer and four with early-stage ovarian cancer. The TU-LESS extraperitoneal approach for pelvic and para-aortic lymphadenectomy was successfully performed in all patients without conversion. In all, a median of 26.5 pelvic lymph nodes (range 18–35) and 18.0 para-aortic lymph nodes (range 7–43) were retrieved. There was a median of 166.5 min of surgical time (range 123–205). Patients had speedy recoveries without complications. All patients had positive pain responses after surgery, as well as satisfactory cosmetic and body image outcomes.

Conclusion: Our initial experience showed that it is feasible to perform systematic lymphadenectomy with the TU-LESS extraperitoneal approach. And this new approach may provide a new measure or a beneficial supplement for lymphadenectomy in gynecologic cancer.

Keywords: extraperitoneal approach, pelvic lymphadenectomy, para-aortic lymphadenectomy, laparoendoscopic single-site (LESS) surgery, ovarian cancer, endometrial cancer

INTRODUCTION

Lymphadenectomy is paramount for precise staging and tailoring treatment of gynecological malignancies. Compared to laparotomy, laparoscopic surgery caused less surgical trauma and fewer wound complications. The feasibility and safety of minimally invasive surgery for lymphadenectomy has been well-investigated and proved (1, 2). Currently, laparoscopic lymphadenectomy is performed either trans- or extraperitoneally. Dissection of the pelvic lymph nodes (LNs) is easier with the transperitoneal approach; however, the intestinal disruption is a major barrier for para-aortic lymphadenectomy (PALN) (**Figure 1**). The extraperitoneal approach has been described as a solution to resolve this problem. Without the interference of bowels, the extraperitoneal approach provides an easier access to the infrarenal para-aortic LNs with lower risk of intestinal and urinary injuries (3). The full exposure of surgical field achieved a higher para-aortic LN yield compared to the transperitoneal route (4, 5).

Laparoendoscopic single-site (LESS) surgery has emerged as a minimal invasive surgical approach, which could further minimize the surgical trauma compared to multi-port laparoscopy surgery (6). LESS is as safe and effective as the traditional laparoscopy in the gynecologic surgery (7). Compared to patients in the multi-port laparoscopy group, patients in the single-port laparoscopy group attained mild pain with less analgesic consumption and shorter hospital stay (8–11). The single-port left iliac extraperitoneal PALN was first described by Guoy et al. (12). Subsequently, Lambaudie et al. (13) and Beytout et al. (14) introduced similar single-port lateral approaches. These results indicated that the number of para-aortic LNs retrieved by the single-port lateral extraperitoneal approach was compatible with that of the multi-port extraperitoneal route (3, 10, 13). In spite of this, the most common lateral extraperitoneal technique restraints access to the obturator fossa which impedes pelvic lymphadenectomy (PLN) (15) (**Figure 2**). Under these circumstances, PLN and other staging procedures sometimes need extra incisions, which increases the amount of trauma experienced throughout the operation. Thus, the TU-LESS extraperitoneal approach, which combines the strengths of LESS with that of extraperitoneal approach was developed to achieve PLN and PALN in a minimal invasive way. This study aims to describe the details of surgical procedures and present our preliminary experience with the TU-LESS extraperitoneal approach for PLN and PALN in order to further evaluate its feasibility.

METHODS

Patients

This study included eight patients from May 2020 to June 2021. Patients who had indications of systematic lymphadenectomy and were candidates for LESS surgery were eligible for inclusion. Clinical data were collected, including demographics, pathological features, and perioperative outcomes of patients who had the surgery. The study was approved by the institutional review board of the West China Second Hospital, Sichuan University, and all participants provided their written informed consent to participate in this study. The duration of lymphadenectomy time was defined as the interval from the first incision of skin to completion of lymphadenectomy, excluding subsequent procedures such as hysterectomy. The failure of the TU-LESS extraperitoneal approach was defined as the conversion to a transperitoneal approach *via* laparoscopy or open surgery; and intraoperative complications included peritoneal rupture and damage to intestines, bladder, ureters, nerves, or blood vessels. Postoperative complications included any adverse event that occurred within 30 days after surgery, including lymphocysts, thrombosis, infection, and chyle leakage. Visual analog scoring was used to assess the degree of postoperative pain of umbilical incision 24 h after surgery in the range of 0–10, 0 for no pain, 1–3 for mild pain, 4–6 for moderate pain, and 7–10 for severe pain (16). The body image questionnaire (BIQ) was administered 7 and 30 days after the surgery to assess patient satisfaction with the surgical intervention (17). The BIQ consists of two subscales: body image scale and cosmetic scale (**Supplementary Data Sheet 1**). With a score from 5 to 20, the body image scale measures perception of patients and their attitude to physical condition. The cosmetic scale evaluates the satisfaction of patients to their umbilical scars with a score from 3 to 24. The higher the score, the more satisfied the patient was with body image and cosmetic effect.

Lymphadenectomy Indications

Dissection of LNs should be recommended for endometrial cancer (EC) patients who are at high risk of recurrence, including those with deep myometrial invasion, high-grade histology, lymphatic vascular invasion, or type II tumors (2). For early-stage EC, the biopsy of sentinel lymph node (SLN) has been proved to be an accurate and effective alternative to lymphadenectomy. However, the use of SLN in high-risk group is controversial, lacking adequate high-level evidences to prove its safety. As a result, systematic lymphadenectomy was nevertheless conducted in this trial on individuals who were considered to be at high risk. In addition, systematic lymphadenectomy was indicated in patients with stage IA-IIA epithelial ovarian carcinoma (OC), except for the mucinous type without suspicious LNs), including those who wished to preserve fertility. Laparoscopy could be employed for patients with early-stage OC by an experienced surgeon (1).

Surgical Technique

All surgical procedures were performed by an experienced gynecologic oncologist. The patient was placed in trendelenburg position with the primary surgeon on the left and the assistant on the opposite sides. First, the primary surgeon made a 2 cm umbilical incision and a multichannel single port (Kangji, Hangzhou, China) was inserted into the intraperitoneal space (**Figure 3**). Careful transperitoneal exploration was conducted to exclude intra-abdominal carcinomatosis and collect peritoneal washing for cytologic evaluation.

Second, we had to identify the posterior peritoneum above the aortic bifurcation at first and execute a figure-of-eight suture subsequently. The surgeon pulled the thread and the sutured

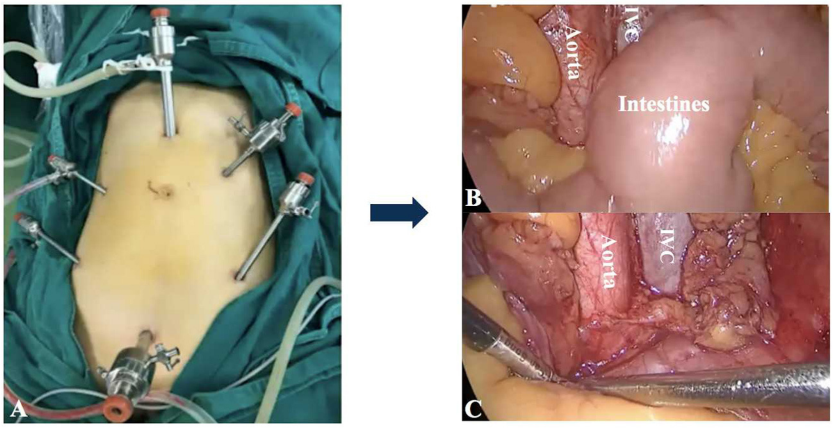

FIGURE 1 | The transperitoneal approach for PALN. **(A)** The placement of trocars. It was difficult to achieve adequate exposure of para-aortic regions for PALN because of the interference of intestines **(B,C)**. IVC: Inferior vena cava.

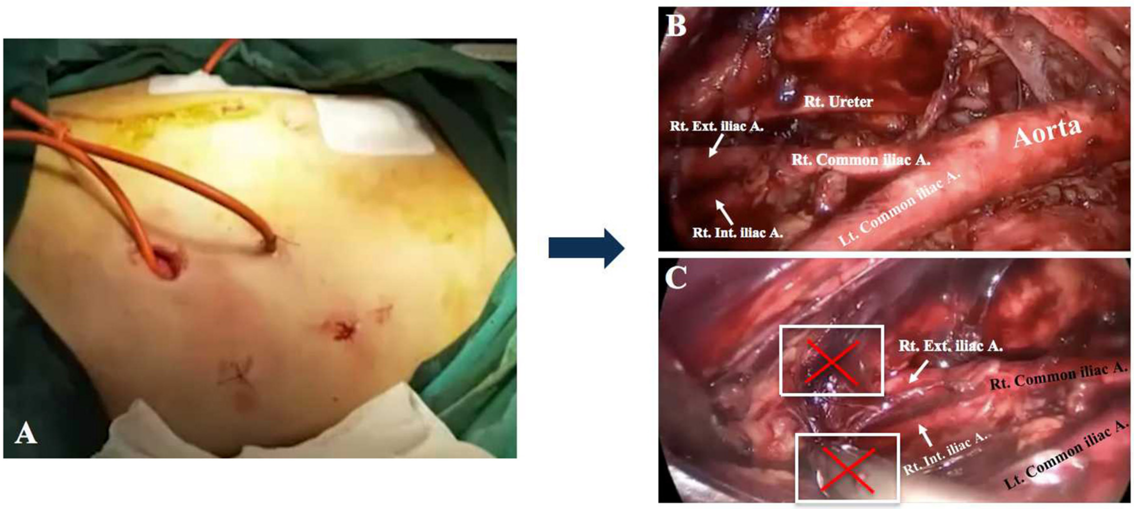

FIGURE 2 | The lateral extraperitoneal approach for lymphadenectomy. **(A)** The lateral incisions. **(B)** Para-aortic LN dissection. Bilateral obturator fossae were challenging to reach when performing pelvic lymphadenectomy **(C)**.

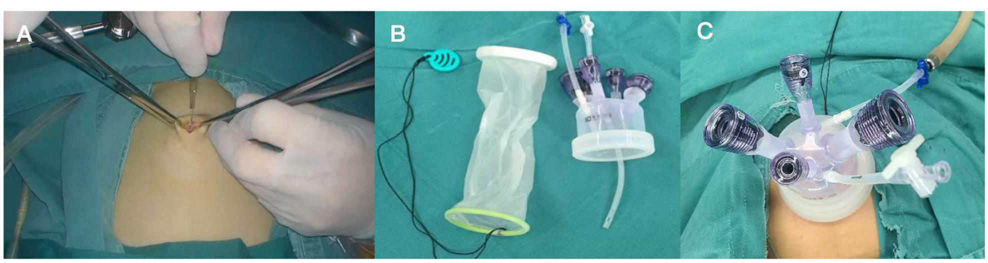

FIGURE 3 | (A) Make a 2-cm umbilical incision. **(B)** The multichannel single port (Kangji). **(C)** Set up the port into the intraperitoneal space.

posterior peritoneum was gently raised toward the umbilical incision. Using a purse-string suture, the suspended posterior peritoneum was held in place and marked. Afterwards, the center portion of the suspended posterior peritoneum was gently sliced open (**Figure 4**, **Supplementary Video 1**). The third step was to separate the extraperitoneal soft tissues that attached to the

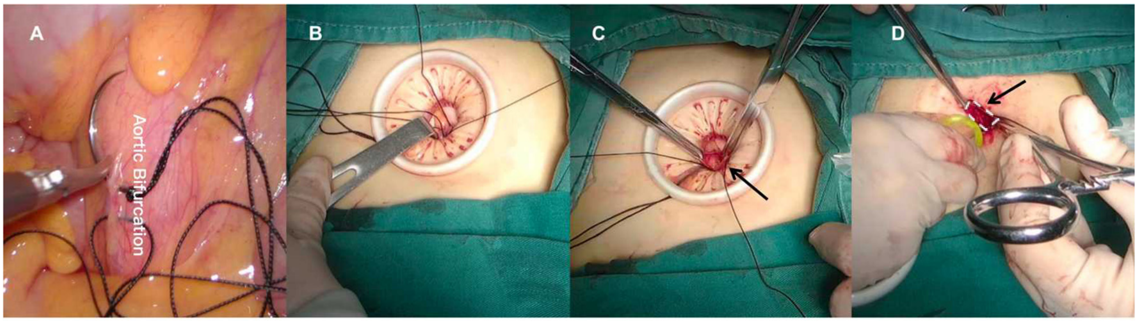

FIGURE 4 | (A) Make a figure-of-eight on the posterior peritoneum above the aortic bifurcation. **(B)** Raise the sutured posterior peritoneum to the umbilical incision. **(C)** Cut open the suspended posterior peritoneum. **(D)** Reset the port into the retroperitoneal space.

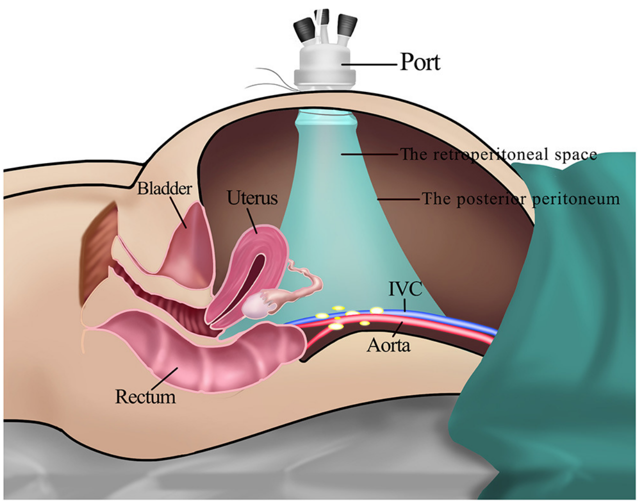

FIGURE 5 | The establishment of the retroperitoneal space. IVC, inferior vena cava.

anterior peritoneum with blunt-finger dissection in order to expand the extraperitoneal space. Subsequently, the port was repositioned into the retroperitoneal space with the purse-string suture tightened and secured. The microvessels were coagulated by a harmonic scalpel (HARMONIC, Ethicon, America), and carbon dioxide was insufflated at the maximum pressure of 14–20 mmHg to establish the retropneumoperitoneum (**Figure 5**, **Supplementary Video 1**).

Procedures were carried out for systematic PLN that included removal of the common iliac, external iliac, internal iliac, obturator, and deep inguinal nodes (**Figure 6**, **Supplementary Video 1**). During PALN operations, the surgeon stood between the legs of the patient and the assistant on the right. Para-aortic LNs were dissected from the aortic bifurcation to the left renal vein (RV) (**Figure 7**, **Supplementary Video 1**). All surgical specimens were taken out in bags in time to prevent the spillage of tumor cells. And the surgeon sprayed the porcine fibrin sealant kit (Bioseal, Guangzhou, China) onto the surgical field to prevent lymphatic leakage and lymphocyst (18).

After the extraperitoneal surgery, the port was reset into the intraperitoneal space for other transperitoneal procedures (i.e., hysterectomy, omentectomy, or salpinx oophorectomy) according to the different types of tumor.

RESULTS

Patient Information

A total of eight patients underwent lymphadenectomy via the TU-LESS extraperitoneal approach. Half of patients were suffering from high-risk EC (one dedifferentiated carcinoma, two grade 3 serous carcinoma with deep myometrial infiltration, and one clear cell carcinoma). The other four patients were diagnosed with early-stage epithelial OC (two serous carcinoma, one clear cell carcinoma, and one endometrioid carcinoma), and three of them opted for fertility-sparing surgery (i.e., preservation of the uterus and contralateral adnexa). The median age was 44 years (range 22–64), and the median BMI was 23.1 kg/m^2 (range 20.7–28.4). According to the Chinese criteria, two patients were classified as obese (BMI = 28.2 and 28.4 kg/m^2) (19). In this group, half had a history of abdominal surgery, and one even had undergone four surgeries. The clinical characteristics of patients are summarized in **Table 1**.

Surgical Outcomes

Table 2 displays the operative outcomes. The upper limit of PALN for all patients was at the renal vascular level. The median time of LN dissection was 166.5 min (range 123–205). During the procedure, no intraoperative complications were observed and no conversion to transperitoneal approach or multiport laparoscopic surgery occurred. The median blood loss was 100 ml (range 100–300) and no patient required blood transfusion. Concerning the LN yields, the median count of para-aortic LNs was 18 (range of 7–30), and the retrieved pelvic LNs was 26.5 (range 18–35). Three EC patients had positive LNs, two with pelvic nodal metastasis and one with para-aortic nodal involvement. Furthermore, there was no evidence of LN metastasis in OC patients. The median flatus time was 23.0 h (range 16.0–38.0) and the median hospital duration was 3 days (range of 2–4). All patients felt mild pain for 24 h after surgery with a median score of 2

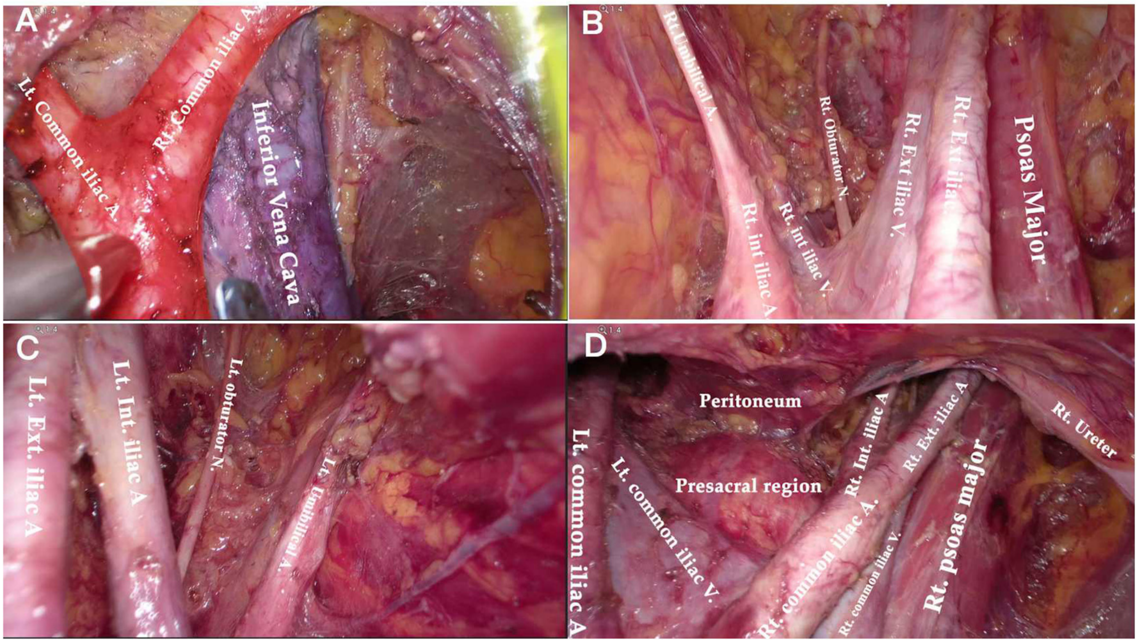

FIGURE 6 | Anatomical overview of pelvic area after PLN. **(A)** The aortic bifurcation and inferior vena cava. **(B)** The right obturator fossa. **(C)** The left obturator fossa. **(D)** The view of presacral area.

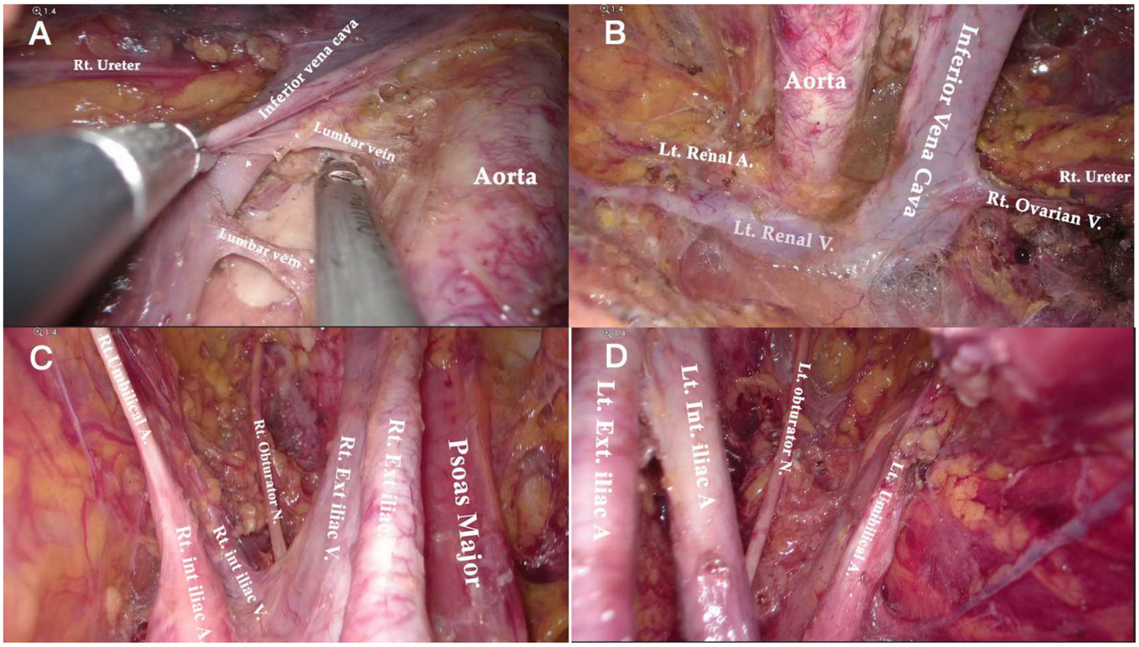

FIGURE 7 | Anatomical overview of para-aortic area. **(A)** Lymphadenectomy up to the left renal vein. **(B)** The right para-aortic region. **(C)** Dissection of the interaortocaval and retrocaval lymph nodes. **(D)** The infrarenal region after PALN.

(range 1–3). The median satisfaction value for body image was 17 (range 16–19) 7 days after surgery and increased to 19.5 (range 18–20) a month after surgery; while the median score of cosmetic effects was 18 (range 15–19) 1 week after surgery and improved to 22.5 (range 21–23) after 30 days (**Figure 8**).

TABLE 1 | Patient characteristics.

Case	Age, y	BMI, kg/m^2	Histologic type	FIGO staging	Number of previous abdominal surgeries	Conversion
1	48	21.0	Dedifferentiated EC	IIIC	0	N
2	54	23.0	Serous EC	IB	0	N
3	29	28.2	Serous OC	IC	1	N
4	50	26.0	Serous EC	IB	1	N
5	22	22.5	Endometrioid OC	IA	1	N
6	64	28.4	Clear cell EC	IIIC	0	N
7	40	20.7	Serous OC	IA	4	N
8	28	23.1	Clear cell OC	IC	0	N

TABLE 2 | Surgical and postoperative information.

Case	Operative time, min	Aortic dissection level	Para-aortic LNs, *n*	Pelvic LNs, *n*	Blood loss, ml	Complications	Flatus time, h	Postoperative pain score, 24 h	Body image scale (range 5–20) 7/30 days	Cosmetic scale (range 3–24), 7/30 days	Hospital duration, days
1	205	Infrarenal	14	33	100	N	38	2	16/18	18/22	4
2	173	Infrarenal	43	18	100	N	21	2	17/20	17/23	2
3	163	Infrarenal	12	35	200	N	22	2	18/20	19/23	3
4	165	Infrarenal	19	27	100	N	18	1	19/20	17/23	4
5	175	Infrarenal	30	20	300	N	16	3	16/19	15/22	4
6	168	Infrarenal	17	23	100	N	27	1	16/20	18/22	3
7	158	Infrarenal	21	28	200	N	24	2	17/19	19/21	2
8	123	Infrarenal	7	26	100	N	26	2	18/19	18/23	3
Median	166.5	/	18.0	26.5	100	/	23	2	17/19.5	18/22.5	3

DISCUSSION

Lymph node status evaluation is a critical component of thorough surgical staging for ovarian and EC (20–22). Laparoscopic lymphadenectomy has been proven safe for surgical staging in EC and early-stage OC patients with less complications and faster recovery (1, 2, 23). Previous studies have shown that extraperitoneal lymphadenectomy is superior to the transperitoneal approach for PALN, because it could avoid intestinal interference and allow an easier access to supramesenteric LNs (5, 24, 25). We initially attempted to employ the TU-LESS extraperitoneal approach in the surgical staging procedures for a patient with advanced cervical cancer in order to accurately delineate the radiographic field. The PALN and right enlarged obturator LN biopsy were performed easily via this novel technique (26). Further exploration and practice of this technique were conducted, and the primary findings of our study confirmed that the TU-LESS extraperitoneal approach is feasible for systematic PLN and PALN.

Compared to the node counts of laparoscopic transperitoneal procedure (range 14–22) (11, 13, 27–29), our method yielded a comparable number of pelvic LNs. The median count of para-aortic LNs (18, range 7–30) in our investigation was equivalent to that of the largest case series of single-port lateral extraperitoneal approach reported by Guoy (median 18, range 2–47) (3), but was higher than that of left-sided extraperitoneal approach using multiport laparoscopy (range 9.5–15) (3, 5, 14, 30). Despite the left extraperitoneal approach being viable for completing the aortic nodal dissection, Dargent asserted that the number of right-sided aortic sampling had reduced compared to bilateral extraperitoneal approach ($p < 0.01$) (31). Furthermore, being limited in access to the deep obturator fossae was one of major technical difficulties of the left-sided approach, which was mainly due to the poor angle of view (13, 15, 32) (as **Figure 2C** shows). Some technique modifications were made to overcome this difficulty, such as addition of different incisions. Querleu added two incisions on the basis of the left-sided extraperitoneal approach in order to achieve obturator node sampling for patients with locally advanced cervical cancer (32). However, whether this technique could be applied in systematic PLN remains to be verified, and the authors further noted that right obturator fossa was obviously difficult to reach with this technique. Other methods for pelvic LN dissection were also reported, such as combining a right extraperitoneal approach (33). Nonetheless, these modifications would increase surgical trauma, and there were few studies that investigated the feasibility for systematic PLN. One of the greatest merits of the TU-LESS extraperitoneal approach is that it allows equal access to the bilateral pelvic and para-aortic areas through the same extraperitoneal approach because the umbilical

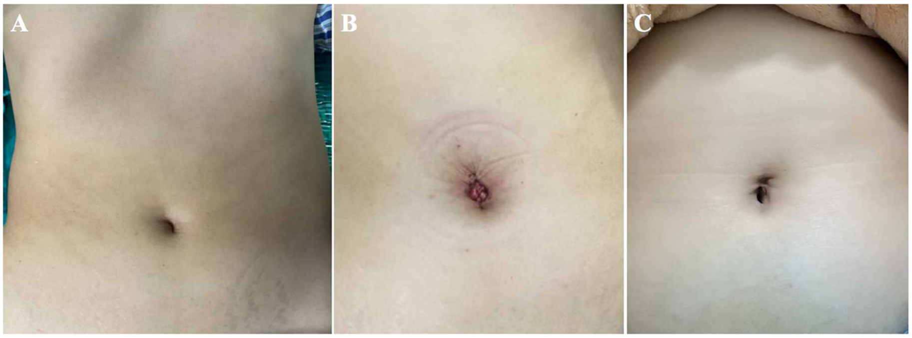

FIGURE 8 | The umbilical incisions of the TU-LESS extraperitoneal approach. **(A)** The preoperative appearance. **(B)** The postoperative appearance. **(C)** The appearance 3 months after surgery.

incision is centrally located, which facilitates the obturator and infrarenal LN dissection (**Figures 6**, **7**). Additionally, careful contrast of **Figures 2C**, **6**, **7** showed that the anatomic angles during the lateral extraperitoneal procedures were altered, adding to identification complexity for surgeons. However, surgeons did not need to readapt to the changing anatomic angles with the TU-LESS extraperitoneal approach, since the angle of view was the same as the transperitoneal approach or laparotomy which many surgeons have been accustomed to.

Reducing intraperitoneal adhesion is another significant advantage of the extraperitoneal approach. Occelli et al. compared the adhesion rate of laparoscopic transperitoneal vs. extraperitoneal PALN on pigs. The results showed that the extraperitoneal group had a lower adhesion formation rate than the transperitoneal group ($p = 0.04$) (15). Abdominal adhesion is likely to increase the morbidity associated with radiotherapy and may result in adnexal adhesion or even infertility (34, 35). The TU-LESS extraperitoneal approach also theoretically has this advantage, because it could minimize peritoneal injury and leave the peritoneal cavity intact after surgery. For these reasons, in our research, the TU-LESS extraperitoneal approach was considered to be an optimal treatment for young patients who wish to preserve their fertility. Three patients with epithelial OC received the fertility preservation surgery. All of them completed the comprehensive assessment of LNs and dissected lesions with little peritoneal damage. While peritoneal cavity could remain intact with our technique, however, the fertility outcomes ought to be followed. Additionally, patients who underwent abdominal surgeries might potentially benefit from the TU-LESS extraperitoneal approach since it avoids adhesiolysis, and thus it could reduce the risk of intra-abdominal organ injury. In our analysis, half of the patients had surgical history, and none of them had intraperitoneal complications. To sum up, different approaches for lymphadenectomy have their own strengths and limitations; and the concerned summarization from our current exploration and prior studies are presented in **Table 3**.

In previous studies, the lymphadenectomy time of the lateral extraperitoneal approach was varied (range 125–339.5 min) (3, 25, 30, 36). The time required for lymphadenectomy in this study was in concordance with the prior findings, but it was less than the time of early practice of the single-port extraperitoneal approach for PALN (average 240 min, range 180–270 min) described by Guoy et al. (37). However, our lymphadenectomy time was somewhat longer than the single-port transperitoneal approach for PLN and PALN (range 60–185 min) (13), which might be explained by the extra time needed to establish the retropneumoperitoneum. The operation time may decrease when the learning curve climbs.

TABLE 3 | Advantages and limitations of three approaches for lymphadenectomy.

	Transperitoneal approach	Lateral extraperitoneal approach	TU-LESS extraperitoneal approach (current work)
PLN	Easy	Difficult	Easy
PALN(RV level)	Difficult	Easy	Easy
Risk of abdominal adhesion	Increase	Decrease	Decrease
Changes in anatomic recognition	No change	Change	No change
Surgical trauma	Small	Small	Minimal

RV, renal vein.

In our research, there were no complications during or after surgery, nor was there a conversion to the transperitoneal route. The procedural failure of the extraperitoneal approach was attributed to the peritoneal rupture (38). Peritoneal rupture occurred in seven patients (16%) during the lateral single-port extraperitoneal lymphadenectomy according to Beytout (14). Neither a peritoneal rupture nor any other technical problems have ever caused abortion of extraperitoneal operation in our series.

Additionally, some studies indicated that the extraperitoneal approach may be an optimal option for patients with a high

BMI. Dowdy et al. (39) and Pakish et al. (25) confirmed that patients with BMI >35 kg/m^2, who had extraperitoneal PALN, harvested more para-aortic nodes than those who underwent abdominal or transperitoneal PALN. BMI had no effect on the duration of surgery, and the area of visceral adipose tissues did not affect the extraperitoneal approach of PALN (40). According to earlier studies, the maximum BMI of patients who underwent the extraperitoneal lymphadenectomy was ranging from 31 to 40 kg/m^2 (1, 3, 9, 11, 20). Nonetheless, we successfully performed the TU-LESS extraperitoneal technique on two obese patients who satisfied Chinese diagnostic criteria (BMI $\geq$28 kg/m^2). However, since this was a primary exploration with a limited number of patients, we did not try to use this measure for systematic lymphadenectomy in patients with BMI more than 30 kg/m^2. We were exploring an easier method for establishing extraperitoneal space in obese patients. The feasibility and safety of robotic technology for lymphadenectomy in gynecologic cancer have been validated, with the benefits of a three-dimensional vision, scaled movement, and short learning curves (41). Gallotta demonstrated that the robotic technology is conducive for PALN. The results showed that aortic LN yields were comparable when patients with BMI >30 kg/m^2 were compared with those with BMI <30 kg/m^2 (42).The robotic surgery was likely to be a preferable approach for obese patients, and the node counts were not affected by increasing BMI (43). Combining robotic technology and the TU-LESS extraperitoneal approach for lymphadenectomy may provide a potential and feasible option for obese patients. Robotic technology may facilitate in shortening the learning curve of the TU- LESS extraperitoneal approach and implementing it.

CONCLUSION

In conclusion, the TU-LESS extraperitoneal approach for pelvic and PALN is feasible with a practical application. It significantly improves the exposure and visualization for PLN and PALN, while causing minimal surgical trauma. Depending on the results of our study, this innovative approach may become an effective alternative measure to the transperitoneal and lateral extraperitoneal approach. However, further studies are required to compare the surgical outcomes like LN yields, surgical trauma, cosmesis, and other index among three approaches. Additionally, based on the current research, a long-term clinical application on a larger sample would be required to evaluate the effects in a more objective manner.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Institutional Review Board of West China Second Hospital of Sichuan University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SP contributed to writing the manuscript and drawing pictures. YZ designed the study and revised the manuscript. FY and KW analyzed and interpreted the data. SC and YW made the video and collected the data. All authors contributed to the manuscript and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.863078/full#supplementary-material

Supplementary Video 1 | The TU-LESS extraperitoneal approach for systematic lymphadenectomy.

Supplementary Data Sheet 1 | The Body Image Questionnaire (BIQ).

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Different Surgical Approaches for Early-Stage Ovarian Cancer Staging. A Large Monocentric Experience

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Introduction: Ovarian cancer is the third most frequent gynecological cancer. In early stage ovarian cancer (ESOC) comprehensive surgical staging is recommended. Surgical staging is traditionally approached by laparotomy, although minimally invasive surgery can be a valid alternative in selected patients. This study aims to analyze the surgical and oncological outcomes of three different surgical approaches in a large series of patients.

Methods: We retrospectively included all histologically proven ESOC cases treated between January 2014 and December 2017. ESOC was defined as stage IA to IIB according to the 2018 FIGO staging system. Subjects were divided into groups 1, 2, and 3, based on the surgical approach (open abdominal, laparoscopic, or robotic, respectively).

Results: Within patients enrolled during the study period, 455 met the inclusion criteria. No difference in intraoperative complications was recorded in the three groups ($p = 0.709$). Conversely, a significant difference occurred in postoperative complications (16.2 vs. 3.8 vs. 11.1%, in groups 1, 2, and 3 respectively, $p = 0.004$). No difference was found in overall survival (OS) (32 vs. 31 vs. 25 months, $p = 0.481$) and disease-free survival (DFS) (26 vs. 29 vs. 24 months, $p = 0.178$) in groups 1, 2, and 3, respectively. At univariate analysis FIGO stage I ($p = 0.004$) showed a lower recurrence rate compared to FIGO stage II.

Conclusion: No significant difference was found in OS and DFS among the three groups (open, laparoscopic, and robotic). The minimally invasive approach showed lower rate of complications than the laparotomic approach.

Keywords: laparoscopy, robotic, laparotomy, ovarian cancer (OC), early-stage

INTRODUCTION

Ovarian cancer (OC) is the third most frequent gynecological cancer worldwide (1). More than 70% of patients are diagnosed at an advanced stage because of the disease aggressiveness and the absence of early symptoms and adequate screening (2, 3).

The diagnosis of early-stage ovarian cancer (ESOC) (stage I-II disease) is usually incidental and associated with better survival, compared to advanced stages (4). In patients with ESOC, a radical surgical staging (RSS) including total abdominal hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic and para-aortic lymphadenectomy, and radical omentectomy is recommended (4). RSS is traditionally performed by large midline laparotomies; however, due to the progressive technological improvements, minimally invasive surgery (MIS) has been increasingly adopted in the setting of ESOC (5, 6). Different studies showed that the MIS approach is associated with reduced hospitalization, fewer intra and post-operative complications, better cosmetic results, and superimposable oncological outcomes when compared to open surgery (7–12).

Given the rarity of ESOC, only few studies comparing laparotomy, laparoscopy, and robotics are currently available in the literature (13, 14). These studies have the major bias represented by small sample size, inadequate follow-up, and wide patient heterogeneity thus reducing the generalizability of the reported results.

The present study aims to analyze the surgical and oncological outcomes of the three different surgical approaches (open abdominal, laparoscopic, and robotic) for ESOC treatment in a large series of patients with a long-term follow-up.

MATERIALS AND METHODS

This is a retrospective monocentric study conducted at the "Dipartimento Scienze della Salute della Donna e del Bambino, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy" between January 2014 and December 2017. The IRB n. CICOG-31-10-18/212 was obtained. All patients provided written informed consent for their data to be collected and analyzed for scientific purposes. Data were extracted from the Research Electronic Data Capture (REDcap) database (Vanderbilt University in Nashville, Tennessee, USA) (15).

All ESOC cases, from IA to IIB International Federation of Gynecology and Obstetrics (FIGO) stage 2018 (2), were included. Age, FIGO stage, histologic subtype, American Society of Anesthesiologists (ASA) performance status, intra and postoperative complications, operative time, rate of conversion to standard laparoscopy or laparotomy, hospital stay, disease-free survival (DFS), overall survival (OS), recurrence rate, and time to chemotherapy, were collected for all patients. Histological slides were evaluated by dedicated pathologists with an extensive background in ovarian malignancies. The surgical approach was chosen based on patient BMI, previous surgery, ovarian lesion diameter, surgeon skill, and preoperative apparent FIGO stage. In the case of MIS approach, a laparoscopic endobag was used for ovarian lesion removal avoiding abdominal tumor spillage. Postoperative complications were categorized according to the Clavien-Dindo classification (16). Operative time was recorded from skin incision to skin closure. In the robotic group, the docking time was excluded. DFS was considered from the date of the histological diagnosis to the date of recurrence. OS was considered from the day of the diagnosis to death or last follow-up. Relapse and response to chemotherapy were evaluated following the response evaluation criteria in solid tumors (RECIST) (17).

Patients with FIGO stage> IIB, with missing pathological data, and those who did not provide informed consent for the enrollment in the present study were excluded.

All patients included in the analysis were divided into group 1, group 2, and group 3, based on the surgical approach as open abdominal, laparoscopic, and robotic, respectively. In addition, a comparative subanalysis between open abdominal and minimally invasive surgery (MIS) (robotic plus laparoscopic) was performed. All patients underwent RSS or fertility-sparing surgery (FSS). RSS was defined as standard staging surgery including (hysterectomy, bilateral salpingo-oophorectomy, omentectomy, systematic pelvic and para-aortic lymphadenectomy, and random peritoneal biopsies); FSS was performed in young women with IA stage disease and strong, motivated wish of conceiving, in accordance to international guidelines (4). Restaging surgery (i.e. complete lymphadenectomy, omentectomy, and possibly hysterectomy/salpingo-oophorectomy) was accomplished in all cases in which the diagnosis of ESOC was not performed intraoperatively and the malignancy was discovered only at final pathological examination.

Statistical Analysis

Continuous variables were initially described using mean and standard deviation (SD), while categorical ones were reported as absolute numbers (%). The distribution of the variables by the surgical approach was initially assessed through a chi-squared test or analysis of variance (ANOVA) when appropriate, according to the surgical approach (open abdominal, laparoscopy, robot) and eventual relapses (yes/no). Survival analyses (i.e. overall survival and disease-free survival) were initially assessed through Kaplan Meier statistics, including overall survival/disease-free survival by eventual status (death/relapse) with and without the stratum of the surgical approach (Tarone-Ware for comparisons). Next, the exact log-rank test to standardize the follow-up medians in the survival analysis was used.

RESULTS

Among patients who had access to the Department of gynecology oncology at the University Hospital Fondazione Policlinico Gemelli, IRCCS during the study period, 455 met the inclusion criteria. Patients' characteristics are summarized in **Table 1**. Specifically, 197 (43.3%), 213 (46.8%), and 45 (9.9%) patients have been allocated to group 1 (open abdominal), group 2 (laparoscopy), and group 3 (robotic surgery), respectively, according to the surgical approach. Of the overall population

TABLE 1 | Patients' characteristics.

	Total series (*n*;%) 455;100	Open abdominal (*n*;%) 197;43.3	Laparoscopy (*n*;%) 213; 46.8	Robot (*n*;%) 45, 9.9	*p* value
Age (years, mean ± sd)	52.8 ± 13.1	55.4 ± 12.8	51.0 ± 13.4	50.0 ± 10.7	**0.001**
BMI (kg/m^2, mean ± sd)	24.9 ± 5.8	25.5 ± 5.5	24.5 ± 5.8	24.8 ± 6.6	0.303
ASA status > 2	9, 5.6%	6, 9.0%	2, 2.7%	1, 5.0%	**0.030**
FIGO Stage					
IA	210; 46.2	78; 17.1	108; 23.7	24; 5.3	**0.042**
IB	53; 11.6	23; 11.7	25; 11.7	5; 11.1	0.993
IC	53; 11.6	20; 10.2	24; 11.3	9; 20.0	0.199
II	139; 30.5	76; 38.6	56; 26.3	7; 15.6	**0.002**
IIA	51; 11.2	30; 15.2	21; 9.9	-	**0.014**
IIB	88; 19.3	46; 23.4	35; 16.4	7; 15.6	0.174
Histology					
Serous carcinoma, high grade	144; 31.6	69; 35.0	59; 27.7	16; 35.6	0.248
Serous carcinoma, low grade	23; 5.1	6; 3.0%	16; 7.5	1; 2.2	0.077
Mucinous carcinoma	54; 1.9	25; 12.7	22; 10.3	7; 15.6	0.513
Clear cell carcinoma	82; 18.0	38; 19.3	38; 17.8	6; 13.3	0.651
Endometroid carcinoma	142; 31.2	53; 26.9	74; 34.7	15; 33.3	0.207
Other	10; 2.2	6; 3.0	4; 1.9	0; -	0.416
Grading					
G1	76; 16.9	24; 12.2	45; 21.4	7; 16.3	**0.041**
G2	94; 20.9	40; 20.3	46; 21.9	8; 18.6	0.925
G3	272; 60.4	131; 66.5	116; 55.2	25; 58.1	0.083
N/A	8; 1.8	2; 1.0	3; 1.4	3; 7.0	-
Chemotherapy	341, 74.9	157, 79.7	153, 71.8	31, 68.9	0.114
Time to chemotherapy (days; mean ± sd)	41.1 ± 14.0	41.8 ± 11.7	41.1 ± 16.6	36.4 ± 7.4	0.352

BMI, Body Mass Index; ASA, American Society of Anesthesiologists; SD, Standard deviation. Significant values were reported in bold.

of 455 patients, 316 (69.5%) subjects were diagnosed at stage I, and 139 (30.5%) at stage II. Within the group of FIGO stage II patients, 38.6% underwent open abdominal surgery while 26.3 and 15.6% of cases respectively underwent laparoscopic and robotic approaches ($p = 0.002$).

Seventy-six patients showed a grade 1 tumor (16.9%), 95 (20.9%) a grade 2, and 272 (60.4%) a grade 3. The most frequent histotype was high-grade serous (31.6%), followed by endometrioid (31.1%), clear cells (18.0%), low-grade serous (5.1%), and mucinous (1.9%).

No difference in adjuvant chemotherapy (79.7 vs. 71.8 vs. 68.9%, in group 1, 2, and 3, respectively, $p = 0.114$) or mean time to chemotherapy (41.8 days ± 11.7 vs. 41.1 days ± 16.6 vs. 36.4 days ± 7.4, in group 1, 2, and 3, respectively, $p = 0.352$) was observed in the three different groups.

The median age at diagnosis was 52.8 years. Patients in the open abdominal group showed a higher mean age (55.4 years) than in the laparoscopic (51.0) and robotic (50.0) groups. Most of FIGO stage IA patients were clustered in group 2 (108 cases, $p = 0.042$), while FIGO stage II patients were more represented in group 1 (76 cases, $p = 0.002$).

Surgical Outcomes

Ninety-seven (21.3%) patients underwent FSS, 358 (78.7%) underwent RSS, and 171 (37.6%) were subjected to restaging surgery after accidental OC diagnosis during previous salpingo-oophorectomy or cystectomy.

As shown in **Table 2**, no difference in intraoperative complications was recorded in the three groups ($p = 0.709$); conversely, a significant difference occurred in postoperative complications (16.2% in group 1 vs. 3.8% group 2 vs. 11.1% group 3, $p = 0.004$). In particular, postoperative anemia (9 cases vs. 0 vs. 0, $p = 0.002$), and abdominal effusion (5 cases vs. 0 vs. 0, $p = 0.036$), occurred more often in the open abdominal group, while lymphocele (3 cases vs. 0 vs. 2, $p = 0.026$) was more frequent in the robotic one. Finally, grade 1/2 Claiven-Dindo complications were more often reported in group 1 than in group 2 or 3 (28 cases vs. 8 cases vs. 5 cases, $p = 0.008$). Complications according to Claiven-Dindo classification in the different surgical approaches are shown in **Table 3**. No statistically significant difference compared to the other groups ($p = 0.112$) was observed, but four (2%) patients required reintervention for postoperative bowel perforation in the open abdominal group. Furthermore, these differences remained even when grouping laparoscopic and robotic patients into the MIS vs. the laparotomic approach.

As shown in **Table 4**, a higher estimated blood loss (EBL) (274.5 vs. 142.2 vs. 79.3 ml, $p < 0.001$), longer hospital stay (5.8 vs. 2.6 vs. 2.8 days, $p < 0.001$), and longer operative time (243.0 vs. 224.1 vs. 197.2 min, $p = 0.004$) were recorded in group 1 vs.

TABLE 2 | Intraoperative and postoperative complications.

	Total (n;%) 455;100	Open abdominal (n;%) 197;43.3	Laparoscopy (n;%) 213; 46.8	Robot (n;%) 45, 9.9	*p* value	MIS (*n*;%) 258, 56.7	*p* value LPT vs. MIS
Intraoperative	8;1.8	5;2.5	2;0.9	1; 2.2	0.709	3; 1.2	0.338
Pleural effusion	0;-	0;-	0;-	0;-	-	-	-
Pulmonary embolism	0;-	0;-	0;-	0;-	-	-	-
Hemorrhage	0;-	0;-	0;-	0;-	-	-	-
Vascular lesions	2; 0.4	1; 0.5	1; 0.5	0; -	0.894	1; 0.4	0.679
Ureteral lesions	4; 0.9	2; 1.0	1; 0.5	1; 2.2	0.501	2; 0.8	0.581
Intestinal lesions	2; 0.4	2; 1.0	0; -	0; -	0.621	-	0.268
Laparotomic conversions	-	-	8; 3.8	1; 2.2	0.358	9; 3.5	-
Postoperative	45;8.9	32;16.2	8;3.8	5;11.1	**0.004**	**13; 5.0**	**0.022**
Ureteral lesions	4; 0.9	2; 1.0	1; 0.5	1; 2.2	0.501	2; 0.8	0.723
Intestinal lesions	2; 0.4	2; 1.0	0; -	0; -	0.621		
Pleural effusion	1; 0.2	1; 0.5	0; -	0; -	0.519	0;-	0.433
Pulmonary embolism	1; 0.2	1; 0.5	0; -	0; -	0.519	0;-	0.433
Hemorrhage	1; 0.2	0; -	1; 0.5	0; -	0.566	1; 0.4	0.567
Pneumonia	3;0.7	2; 1.0	0; -	1; 2.2	0.176	1; 0.4	0.400
Sepsis	7;1.5	5;2.5	2;0.9	0; -	0.285	2; 0.8	0.130
Anemia	9	9; 4.6	0; -	0; -	**0.002**	**0;-**	**<0.001**
Abdominal effusion	5	5;2.5	0; -	0; -	**0.036**	**0;-**	**0.015**
Urinary tract infections	1; 0.2	0; -	1; 0.5	0; -	0.566	1; 0.4	0.567
Intestinal Pseudo-Obstruction	3;0.7	0; -	2;0.9	1; 2.2	0.198	3; 1.2	0.181
Lymphocele	5;1.1	3;1.5	0; -	2;4.4	**0.026**	2; 0.8	0.375
Fistula	1; 0.2	0; -	1; 0.5	0; -	0.566	1; 0.4	0.567
Wound infection	2; 0.4	2; 1.0	0; -	0; -	0.268	0; -	0.187

LPS, Laparoscopy; LPT, Laparotomy; MIS, Minimally invasive. Significant values were reported in bold.

TABLE 3 | Complications according to Claiven-Dindo classification in the different kinds of surgeries.

General population	Total	Open abdominal	Laparoscopy	Robot	*p* value	MIS	*p* value (LPT vs. MIS)
G1-G2 *	41	28	8	5	**$p = 0.008$**	**13**	**<0.001**
G3-G4**	4	4	0	0	$p = 0.112$	**0**	**0.035**
Fertility sparing							
G1-G2	6	2	2	2	$p = 0.318$	4	0.264
G3-G4**	1	2	0	0	$p = 0.139$	0	0.607
Radical surgical staging							
G1-G2	35	26	6	3	$p = 0.076$	9	0.190
G3-G4**	3	2	1	0	$p = 0.156$	1	0.072

**Vascular lesions, ureteral lesions, pulmonary embolism, pneumonia, sepsis, anemia, urinary tract infection, ileus, lymphocele, fistula, surgical site infection. ** Intestinal lesions requiring reintervention. LPS, Laparoscopy; LPT, Laparotomy; MIS, Minimally invasive. Significant values were reported in bold.*

group 2 vs. group 3, respectively. Conversely, these differences were nullified by pooling MIS patients vs. the laparotomic group (**Table 4**).

Finally, no significant difference in the number of pelvic ($p = 0.197$) and lumboortic ($p = 0.195$) lymph nodes removed was observed among the three groups.

Survival Analysis

Twenty total deaths occurred in the entire population, 12 (2.6%) in group 1, 6 (1.3%) in group 2, and 2 (0.4%) in group 3 ($p = 0.267$). Sixty total relapses (13.2%) were found in the whole series; of them, 54 occurred in patients who underwent RSS, and 24 were patients at FIGO stage II.

In the entire population, after applying the exact log-rank test, to smooth out the follow-up discrepancies, no statistically significant differences in median OS (32 months in group 1 vs. 31 in group 2 vs. 25 in group 3, $p = 0.481$) and DFS (26 months in group 1 vs. 29 in group 2 vs. 24 in group 3, $p = 0.178$) were found in the three groups. Oncological outcomes are displayed in **Table 5** and Kaplan-Meier analysis after the exact log-rank

TABLE 4 | Surgical outcomes.

	Total (*n*;%) 455;100	Open abdominal (*n*;%) 197;43.3	Laparoscopy (*n*;%) 213; 46.8	Robot (*n*;%) 45, 9.9	*p* value	MIS (n;%)	*p* value LPT vs. LPS
Type of surgery							
Fertility sparing	97; 21.3	19; 9.6	62; 29.1	16; 35.6	**<0.001**	78; 17.1	**<0.001**
Radical surgical staging	358; 78.7	178; 39.1	151; 33.2	29; 6.4	**<0.001**	**180; 39.6**	**<0.001**
Restaging	171; 37.6	19; 0.2	110; 24.2	42; 9.2	**<0.001**	**152; 33.4**	**0.374**
Aortic lymph nodes removed Number (mean ± sd)	9 ± 8.4	8 ± 9.9	8.5 ± 7.3	9 ± 6.9	0.197	10.8 ± 7.2	0.735
Pelvic lymph nodes removed Number (mean ± sd)	10 ± 8.0	10 ± 8.3	9 ± 7.5	12.5 ± 8.6	0.195	12.7 ± 9.1	0.930
Estimated blood loss (mL; mean ± sd)	179.0 ± 209.8	274.5 ± 229.3	142.2 ± 201.6	79.3 ± 47.3	**<0.001**	127.3 ±178.5	0.632
Operative time (minutes; mean ± sd)	227.5 ± 81.7	243.0 ± 83.6	224.1 ± 78.9	197.2 ± 79.4	**0.004**	245 ± 79.1	0.842
Hospital stay (days; mean ± sd)	3.9 ± 5.3	5.8 ± 7.8	2.6 ± 1.1	2.8 ± 1.7	**<0.001**	2.6± 1.2	0.610

LPS, Laparoscopy; LPT, Laparotomy; MIS, Minimally invasive. Significant values were reported in bold.

TABLE 5 | Survival analysis.

	Total median (range) 455;100%	Open abdominal median (range) 197;43.3%	Laparoscopy median (range) 213; 46.8%	Robot median (range) 45, 9.9%	*p* value	MIS	*p* value (LPT vs. MIS)
General population							
DFS (months)	28 (10–44)	26 (8–43.5)	29 (10.8–48)	24 (12–31.5)	0.178	28 (10.8–31.5)	0.067
OS (months)	30 (12–47)	32 (11.5–52.5)	31 (13–48)	25 (12–33)	0.481	29 (12–33)	0.441
Relapse (*n*; %)	60; 13.2	39; 19.8	19; 8.9	2; 4.4	0.072	21; 8.1	0.064

DFS, Disease-Free Survival; OS, Overall survival; LPS, Laparoscopy; LPT, Laparotomy; MIS, Minimally invasive.

test is shown in **Figures 1**, **2**. Furthermore, these differences remained non-statistically significant even when comparing MIS with laparotomic group (DFS 28 vs. 26 months, $p = 0.067$, and, OS 29 vs. 32 months, $p = 0.441$, respectively). Kaplan Meier analysis showed 1-year OS of 100 vs. 100%, 3-years OS of 100 vs. 100%, and 5-years OS of 99.2 vs. 99.5% in the laparotomic vs. MIS approach (95% Confidence Interval 26.37–31.75).

As reported in **Table 6**, at univariate analysis FIGO stage I patients ($p = 0.004$) showed lower recurrence rates when compared to FIGO stage II patients. Furthermore, the subanalysis of patients undergoing complete surgical staging showed a higher relapse rate in the laparotomic than the MIS group, 68.5 vs. 31.5% ($p = 0.002$).

DISCUSSION

The present study showed that minimally invasive comprehensive surgical staging for ESOC was safe and associated with a lower rate of postoperative morbidity, compared to the traditional open abdominal approach. Furthermore, there was no statistically significant difference in patients' survival among the laparotomic, laparoscopic, and robotic groups.

In line with our results, Magrina et al. (14) reported an overlapping OS between these three different surgical approaches in a series of both early and advanced epithelial ovarian cancer. In the sub-analysis of early-stage cases, the same authors reported superimposable results in terms of oncological outcomes with fewer surgical complications in the MIS group (laparoscopic and robotic) when compared to the traditional open abdominal surgery. Several authors confirmed these findings: in particular, Liu et al. (18), analyzing the most relevant studies in the literature, demonstrated a comparable survival between the minimally invasive and the open approach in both early and advanced FIGO stage (19–21).

An important hurdle we faced to obtain a meaningful survival analysis was related to the wide heterogeneity of the population enrolled. As recently reported by Shi et al. (13), the heterogeneity of OC population in the different trials can afflict survival outcomes making comparisons unreliable. Furthermore, Falcetta et al. (22) stressed that trouble for data analysis of ESOC patients was related to the variety of the treatments proposed, ranging from fertility-sparing to radical surgery. Trying to overcome these limitations, we enrolled a large single-center series and we focused the survival analysis on the comprehensive surgically staged patients. Furthermore, an exact log-rank test for survival

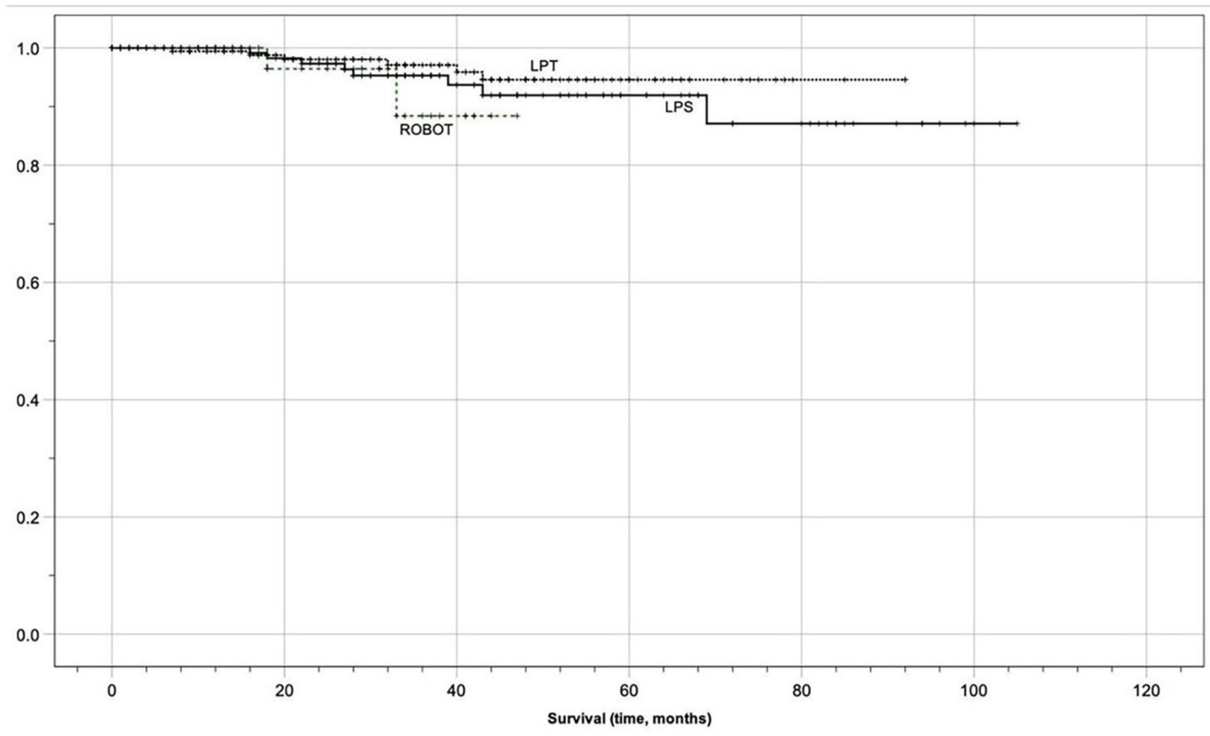

FIGURE 1 | Kaplan meier survival analysis (overall survival).

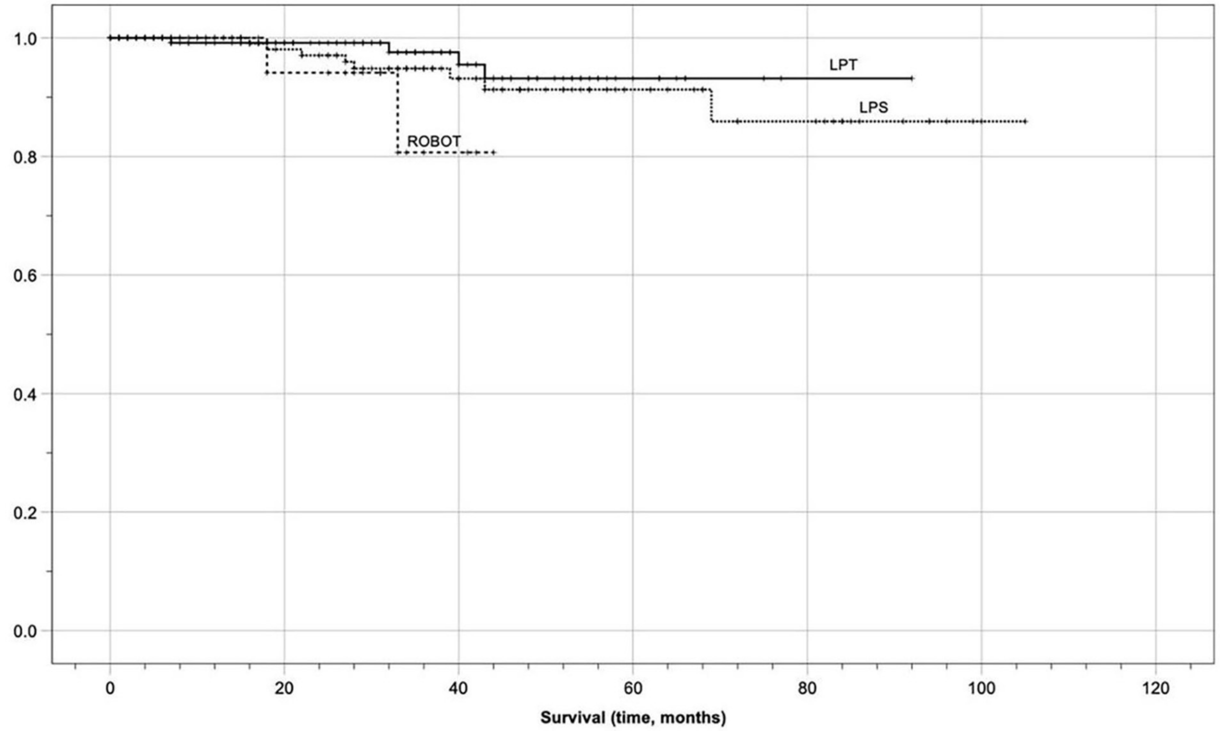

FIGURE 2 | Kaplan meier survival analysis (disease-free survival).

TABLE 6 | Univariate analysis.

Patients underwent complete surgical staging	Recurrence 54 number %		No recurrence 304 number %		*p* value
Age > 50 years	36	66.7%	200	65.8%	0.9
BMI > 30 kg/m^2	7	13.0%	36	11.8%	0.815
ASA > 2	2	3.7%	7	2.3%	0.544
Hystotype					0.178
Serous. high grade	24	44.4%	105	34.5%	
Serous. low grade	1	1.9%	16	5.3%	
Mucinous	3	5.6%	33	10.9%	
Clear cells	14	25.9%	50	16.4%	
Endometrioid	11	20.4%	92	30.3%	
Others	1	1.9%	8	2.6%	
Grading					0.053
G1	4	7.4%	48	15.8%	
G2	6	11.1%	62	20.4%	
G3	44	81.5%	188	61.8%	
FIGO stage					0.156
I	13	24.1%	115	37.8%	
IA	2	3.7%	24	7.9%	
IB	6	11.1%	34	11.2%	
IC	9	16.7%	38	12.5%	
IIA	7	13.0%	37	12.2%	
IIB	17	31.5%	56	18.4%	
II vs. I	24	44.4%	93	30.6%	**0.046**
Surgical approach					**0.002**
Laparotomy	37	68.5%	141	46.4%	
MIS	17	31.5%	163	53.6%	
Introperative complication	3	5.6%	5	1.6%	0.073
Postoperative complication	3	5.6%	30	9.9%	0.293
Chemiotherapy	47	87.0%	227	74.7%	0.072

G, Grading; LPT, Laparotomy; LPS, Laparoscopy; ASA, American Society of Anesthesiologists; MIS, Minimally invasive surgery. Significant values were reported in bold.

analysis was used to reduce the consequent bias and to adequately match the patients.

It is well established that the main prognostic factor affecting OC recurrence is the FIGO stage (23). In our series, group 1 showed a greater proportion of FIGO stage II cases ($p = 0.014$) than the two minimally invasive groups and, as expected, the relapse rate appeared higher in this group when compared to the other approaches. However, after standardization of follow-up with exact log-rank test, no significant difference was found in DFS within the three approaches ($p = 0.178$). In line with our results, Zhang et al. (24), in a meta-analysis including 8 studies, reported no significant difference in DFS of ESOC patients subjected to laparotomy vs. laparoscopy with fewer complication rates and shorter hospital stay in the latter group.

In contrast with previously reported studies, we found that patients undergoing robotic surgery had a shorter operative time (8, 25). This finding may be due to the very precise three-dimensional movement of the robotic arms that could be useful and time-saving, especially when facing complex procedures such as lumboortic lymphadenectomy (26). Furthermore, the greater number of complete surgical staging procedures in the open abdominal and laparoscopic groups compared to the robotic one could justify this result.

Compared to previous retrospective studies and clinical trials, our series showed a higher rate of mild complications (G1-G2 according to Claiven Dindo classification) in the open abdominal group (27, 28). In addition, these differences in G1-G2 complications not only remained when comparing the MIS group with the laparotomic approach but also included the G3-G4 complications. This finding could be related to the mean age ($p = 0.001$), ASA status ($p = 0.030$), and FIGO stage II ($p = 0.002$) which were higher in group 1. As reported by Patankar et al., all these demographic factors are associated with worse surgical outcomes (29).

We know that this study has several possible limitations due to its retrospective nature. Given the rarity and the good prognosis of ESOC, only 20 death events were observed in the entire population, and this may have influenced the survival analysis.

Furthermore, the different complications rate reported could be influenced by the heterogeneity of the interventions performed in the three groups. Therefore, prospective studies with standardization of interventions performed in the various approaches are needed to confirm our results.

On the other hand, we emphasize that this study has important strengths such as the size of the sample analyzed, the long follow-up time, the close selection of the patients analyzed, and the single oncological tertiary center experience reported.

CONCLUSIONS

After follow-up standardization, we observed no statistically significant difference in OS and DFS among the three groups analyzed (open abdominal, laparoscopic, and robotic).

The open abdominal approach in ESOC was associated with a higher mild complication rate than the laparoscopic and robotic ones. Based on these findings, the minimally invasive approach should be preferred in selected patients and in tertiary cancer centers.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Dipartimento Scienze della Salute della Donna e del Bambino, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy. IRB code n. CICOG-31-10-18/212. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SC, VC, and AR: conceptualization, methodology, and writing-original draft preparation. MR and VR: software and data curation. SU, GC, and SG: visualization and investigation. AF, GS, and FC: supervision, validation, reviewing, and editing. All authors contributed to the article and approved the submitted version.

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The Road to Technical Proficiency in Cytoreductive Surgery for Peritoneal Carcinomatosis: Risk-Adjusted Cumulative Summation Analysis

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Background: Cytoreductive surgery (CRS) is a technically demanding procedure, and there is considerable debate about its safe application. This study investigated the learning curve for CRS and the clinical outcomes of consecutive patients treated by a single surgeon at a single institution.

Methods: We collected 251 consecutive patients who underwent CRS for peritoneal metastases by a single surgeon at Fondazione Policlinico Universitario A. Gemelli IRCCS, between January 2016 and December 2020. The learning curve was estimated using the cumulative summation analysis (CUSUM) for operative time (OT). Risk-adjusted CUSUM (RA-CUSUM) charts were developed using a composite variable (surgical failure), defined as the occurrence of at least one of the following events: major postoperative complications (Clavien–Dindo grade ≥3), blood loss ≥500 mL, incomplete cytoreduction. Three learning phases were thus derived from the RA-CUSUM analysis, and were compared in terms of perioperative outcomes.

Results: CUSUM-OT showed that the operation time improved significantly after the 161th case. RA-CUSUM analysis allowed to break the CRS learning curve into three different phases: phase 1, "the learning phase" (cases 1–99), phase 2 "the experienced phase" (cases 100–188), and phase 3, "the mastership phase" (cases 189–251). The rate of major postoperative complications decreased significantly over the three phases ($p = 0.019$). Operative time decreased significantly as well ($p = 0.031$) and was significantly shorter in phase 3 with respect to the other two phases (phase 3 vs phase 2: 420 min vs 500 min, $p = 0.017$; phase 3 vs phase 1: 420 min vs 503 min, $p = 0.021$). Blood loss consistently decreased throughout the three phases ($p = 0.001$). The rate of incomplete cytoreduction was significantly lower in phase 3 than in phase 2 (4.8% vs 14.6%, $p = 0.043$).

Conclusion: The CRS failure rate stabilized after the first 99 cases, and the complete surgical proficiency was achieved after 189 cases. A standardised and mentored learning model is a safer strategy to shorten the learning process, to reduce morbidity and mortality, to improve oncologic outcomes.

Keywords: peritoneal metastases, cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (hipec), peritonectomy, learning curve, CUSUM, RA-CUSUM

INTRODUCTION

The peritoneal of gastrointestinal and gynaecological malignancies is usually associated with poor prognosis (1). Also, peritoneal carcinomatosis (PC) has been marginally affected by systemic chemotherapy and previously considered by the oncologists as an end-of-life condition, not amenable for surgery (2–4). Nowadays, the treatment of PC is radically changing thanks to a better understanding of tumours biology and their dissemination pattern. Therefore, PC is considered a form of loco-regional disease that could benefit from a multimodal approach combining aggressive surgery and chemotherapy (5).

Cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) is currently the standard of care in selected patients with PC from various abdominal malignancies (6, 7). CRS aims to remove every macroscopically visible tumour implant within the peritoneal cavity, and then a heated chemotherapy local infusion eradicates any residual microscopic disease (8). Therefore, CRS plus HIPEC results in a highly complex and lengthy surgical procedure involving multi-visceral resection, burdened by high morbidity due to the synergistic effect of cytoreduction, hyperthermia, and local chemotherapy cytotoxicity (9).

Over the years, CRS and HIPEC have improved the selection of more suitable patients and is now considered safe and comparable to other high-risk surgical oncology procedures in terms of complications rate (9).

In spite of this, the learning curve for CRS plus HIPEC is not standardised yet, because the surgical procedures required to clear the peritoneal metastasis are often complex and heterogenous, and the caseload is limited, even in high-volume cancer centres (10).

In our tertiary referral hospital, the surgical treatment of PC from colorectal cancer (CRC) (11) and pseudomyxoma peritonei (PMP) (12) has reached an acceptable perioperative outcome and long-term survival, with respectively a 3-year OS of 43% for CRC and a 5-year OS of 91% for PMP.

This study aimed to generate learning curves for CRS based on the performance of a single surgeon at a single institution performing cytoreductive surgery for PC from various abdominal malignancies.

METHODS

Study design

We retrieved clinical data for 251 consecutive patients who underwent CRS for peritoneal carcinomatosis (regardless of the origin) by a single surgeon at Fondazione Policlinico Universitario A. Gemelli IRCCS between January 2016 and December 2020. All CRS were performed by a single experienced general surgeon (AD) with no previous experience in cytoreductive surgery for carcinomatosis. AD completed the European School of Peritoneal Surface Oncology (ESPO) training during the study time-period. He was mentored along the process by another experienced general surgeon (FP), who also had already experience with peritoneal surgery and HIPEC.

We analysed the learning curve for CRS using the cumulative summation (CUSUM) and the risk-adjusted cumulative summation (RA-CUSUM) methods (13). The operation time was assessed with the CUSUM method. The RA-CUSUM was calculated using a composite variable (surgical failure) that merges all the variables presumably involved into the learning process and creates a curve plotting change in the success rate over an increasing number of cases. Surgical failure was defined as the occurrence of at least one of the following events: major post-operative complications (Clavien–Dindo grade ≥3), blood loss ≥500 mL, incomplete cytoreduction. Three learning phases were thus derived from the RA-CUSUM analysis, and were compared in terms of perioperative outcomes.

All patients provided written informed consent and entered a follow-up program. Data were collected and stored in a prospectively maintained database. The study was approved by the local Institutional Review Board (IRB). We use the STROBE statement checklist (v 4.0) for our research.

Preoperative evaluation

After a complete preoperative workup, all patients were reviewed at our institutional peritoneal disease multidisciplinary team (MDT). The extent of peritoneal disease was subsequently assessed by diagnostic laparoscopy, and the peritoneal carcinomatosis index (PCI) scoring system was recorded for each patient. The decision of the multidisciplinary team in offering cytoreductive surgery depends on the primary oncological disease:

- *Pseudomixoma Peritoneii:* CRS and HIPEC were offered to all medically fit patients with PMP. The main goal was to achieve a complete cytoreduction; however, if this was not possible due to the extension of the disease, maximal tumour debulking was performed.
- *Colorectal and gastric peritoneal metastasis:* CRS and HIPEC was offered in case of potentially complete cytoreduction of peritoneal disease without extra-abdominal metastases.

Patients not eligible for cytoreductive surgery were referred for systemic chemotherapy.

- *Ovarian cancer, mesothelioma, and other less common histology:* before progressing to CRS and HIPEC, these cases were discussed by the institutional MDT.

Cytoreductive surgery with HIPEC

Following the laparotomy, a revaluation of PCI was performed. The surgical intent was to obtain a maximal cytoreduction and perform the HIPEC. Patients who could not achieve a complete cytoreduction, generally due to the extent of disease or their general conditions, underwent a maximal tumour debulking without HIPEC. Cytoreductive surgery was performed using the Sugarbaker technique (10). When the disease was limited, patients underwent selective peritonectomy. The surgical purpose was to remove all visible peritoneal metastases through diaphragmatic, parietal anterior, and pelvic peritonectomy with greater and lesser omentectomy. In addition, multiple organ resections were performed depending on disease involvement if an CC-0/1 resection could be achieved. Organ resections included segmental colectomy, proctectomy, small bowel resections, gastrectomy (partial or rarely total), segmental liver resection, cholecystectomy, splenectomy, and hysterectomy with bilateral salpingo-oophorectomy in females. The HIPEC procedure was then performed using the closed technique. In 8 cases, the HIPEC procedure was performed using CO_2 technology (14).

HIPEC regimens varied according to histology: oxaliplatin were used for colorectal cancer, mitomycin for colorectal cancer, pseudomixoma peritoneii and gastric cancer, whereas cisplatin for gastric cancer, ovarian cancer and mesothelioma. The target temperature, likewise, was set between 40–42 °C and the time duration was 60 or 90 min. Glucose 5% solution was used for oxaliplatin and physiologic solution 0.9% for other drugs. An adequate intra-abdominal patient filling volume was 2–2.5 L/mq.

Data

The clinical and pathological variables for each patient were retrospectively reviewed. The following clinical variables were recorded: age, sex, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary tumour location, operative time, PCI score, completeness of cytoreduction (CC score), blood loss and post-operative complications, which were divided into minor (Clavien-Dindo I-II), and major (Clavien-Dindo ≥III3) (15).

Intraoperative blood loss was calculated, at the end of the procedure, by the combination of absorbent materials (number of used gauzes) and volume of blood in canisters. The 500 mL cut-off was choice considering previous literature data (16) and present NICE guidelines (17, 18). The completeness of the cytoreduction (CC) score was determined at the end of each procedure. CC-0 reflected no remaining visible disease. CC-1, 2, and 3 implied remaining diseases less than 2.5 mm, 2.5 to 2.5 cm, and greater than 2.5 cm. The procedures were divided into “complete cytoreduction” and “incomplete cytoreduction” based on the primary tumour histology. Colon cancer, gastric cancer, and mesothelioma CC-0 were deemed complete cytoreduction, while CC-1/2/3 cases were considered incomplete (19). CC-0/1 were considered a complete cytoreduction in PMP and mesothelioma (20, 21).

Statistics

Descriptive statistics were used to describe the patients’ surgical and pathological characteristics. Continuous variables are reported as medians and ranges, and categorical variables are reported as numbers and percentages of the overall group.

We examined the learning curve for CRS using CUSUM and RA-CUSUM analyses. The patients were ordered chronologically. The CUSUM analysis for operation time (CUSUMOT) was defined as:

$$CUSUM_{OT} = \sum_{i=1}^{n} (x_i - \mu)$$

where x_i is the single patient’s operation time, and μ is the mean operation time. The RA-CUSUM analysis was defined as

$$RACUSUM = \sum_{i=1}^{n} (x_i - \tau) + (-1)^{xi} P_i$$

where $x_i = 1$ indicates the presence of surgical failure, otherwise, $x_i = 0$; τ represents the event rate, and P_i is the expected surgical failure rate derived from a logistic regression model with a backward stepwise selection of the variable procedure. The entire series is plotted from left to right on the horizontal axis. The curve moves down for each success and up for each failure. We delineated the end of the learning process as the point where the curve reached the steady state (13, 22).

Based on the trend displayed by the curve, the whole sample was divided into three phases: phase 1, “the learning phase”, phase 2, “the experienced phase”, and phase 3, “the mastership phase”. The different phases were compared using the χ^2 test and Student *t*-tests for parametric estimations and Wilcoxon Mann-Whitney U test for nonparametric estimations. $p \leq 0.050$ was considered statistically significant. Statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, New York, USA) software for Windows.

RESULTS

Two hundred fifty-one patients underwent CRS for peritoneal carcinosis from various origins during the study period. Patient characteristics are shown in **Table 1**. The median age was 59 years (range: 26–86 years). One hundred and forty-five patients were females (57.8%), and 106 were males (42.2%). Considering the primary cancer sites, 115 (45.8%) were colorectal cancer, 19 (7.6%) were gastric cancer, 48 (19.1%) were PMP, 16 (6.4%) were mesothelioma, 42 (16.7%) were ovarian cancer, and 11 were from various origin (pancreatic, biliary) and were grouped as other. The median PCI score calculated after laparotomy was 12 (range 3–30). Two hundred and twenty-three (88.8%) patients received a complete cytoreduction, while 28 (11.2%) received an incomplete cytoreduction. The median operating time was 502 (140–900) min. The complete operative details are shown in **Table 2**.

TABLE 1 | Baseline characteristics and operative details.

Variable	*N* (%)
Gender	
Female	145 (57.8)
Male	106 (42.2)
Age, years [median (range)]	59 (26–86)
BMI [median (range)]	24.2 (17–41.7)
ECOG PS	
0	139 (55.4)
≥1	112 (44.6)
Primary tumor histotype	
Colorectal	115 (45.8)
Gastric	19 (7.6)
PMP	48 (19.1)
Mesothelioma	16 (6.4)
Ovarian	42 (16.7)
Other	11 (4.4)
Operative time, min [median (range)]	500 (140–900)
PCI [median (range)]	12 (3–30)
Surgical Procedures	
Right colectomy	91 (36.3)
Left colectomy	18 (7.2)
Rectal resection	122 (48.6)
Pelvic peritonectomy	163 (64.9)
Hysterectomy/oophorectomy	122 (48.6)
Diaphragmatic peritonectomy	134 (53.4)
Mesenteric cytoreduction	54 (21.5)
Omentectomy	181 (72.1)
Gastric resection	19 (7.6)
Small bowel resection	65 (25.9)
Segmental liver resection	6 (2.4)
Splenectomy	65 (25.9)
Ostomy	93 (37.1)
Completeness of Cytoreduction (CCR)	
Complete	223 (88.8)
Incomplete	28 (11.2)
HIPEC	
No	41 (16.3)
Yes	210 (83.7)
Blood loss >500 mL	
No	182 (72.5)
Yes	69 (27.5)

All patients were managed in the intensive care unit for at least one night in the post-operative period. No major intraoperative complications occurred. There were 3 (1.2%) post-operative in-hospital deaths.

One-hundred and six (42.2%) patients developed post-operative complications: grade I/II complications occurred in 64 (25.5%) patients, and grade III/IV complications occurred in 42 (16.7%) patients. Considering major complications, 9 (3.5%) patients experience post-operative bleeding, 20 (7.9%) abdominal collections, and 13 (3.9%) anastomotic leaks (AL). Among the 9 patients with post-operative bleeding, 7 needed surgeries with relaparotomy and surgical hemostasis, while the remaining 2 patients were treated with angioembolisation.

The percentage of AL was analysed considering all the 334 anastomoses. Two (15.4%) ALs were from an ileocolic anastomosis, 1 (7.7%) from a colo-colic anastomosis and 10 (76.9%) from a colorectal anastomosis. Seven (53.8%) of the 13 patients with AL received a protective ileostomy during the first surgery. Among all the ALs, 3 of them were treated conservatively (percutaneous drainage plus broad-spectrum antibiotic therapy), while 10 patients underwent re-operation with resection of the anastomotic complex and colostomy or ileostomy, depending on the leak. The leading cause of abdominal collection was pancreatic fistula (10 patients; 3.9%). Among the 20 patients with abdominal collections, 12 were treated with percutaneous drainage plus antibiotic therapy, while the rest (8 patients) underwent relaparotomy and surgical drainage. The complete description of post-operative complications is shown in **Table 2**.

The learning curve for CRS was assessed using the CUSUM and RA-CUSUM methods. The CUSUM-OT curve shows an initial long plateau, with the first downward slope only after 161 cases (**Figure 1**). Afterwards, the reduction appears slow and inconstant, as documented by the multiple peaks and throughs in the plot (**Figure 1**). In the RA-CUSUM graph,

TABLE 2 | Postoperative complications.

Variable	*N* (%)
Complications	
No	145 (57.8)
Yes	106 (42.2)
Complication grade (Clavien-Dindo)	
Grade I–II	64 (25.5)
Grade III–IV	42 (16.7)
Postoperative mortality	3 (1.2)
Postoperative ileus	10 (3.9)
Pulmonary complications	21 (8.4)
Postoperative bleeding	9 (3.5)
Abdominal collection	20 (7.9)
Genitourinary infection	11 (4.4)
Anastomotic leak[a]	13 (3.9)[a]
Surgical site infection	18 (7.2)
Renal failure	4 (1.6)

[a]*Analyzed considering all the 334 anastomosis.*

the curve moved upwards for surgical failure and downwards for surgical success. The RA-CUSUM analysis revealed that the surgical failure rate was significant in the initial phase until case 99. Next, the slope remained stable until case 198 and then gradually decreased (**Figure 2**). Consequently, according to the RA-CUSUM curve, the CRS learning curve breaks into three different phases: phase 1, "the learning phase" (cases 1–99), phase 2 "the experienced phase" (cases 100–188), and phase 3, "the mastership phase" (cases 189–251).

Perioperative outcomes throughout the three learning phases are shown in **Table 3**. There were no significant differences in age, sex, BMI, ECOG grade, and primary tumour histotype among the three phases.

PCI constantly increased over the different phases and was significantly higher in phase 3 than in the other two phases (phase 3 vs phase 2: 16 vs 12, $p = 0.029$; phase 3 vs phase 1: 16 vs 10, $p = 0.001$).

Concerning the completeness of cytoreduction, even though there was no consistently significant reduction among all three phases, the rate of incomplete CCR was significantly lower in phase 3 with respect to phase 2 (4.8% vs 14.6%, $p = 0.043$). Moreover, a trend of lower incomplete CCR was observed in phase 3 than in phase 1, though not significant (4.8% vs 12.1%, $p = 0.094$). Consequently, the HIPEC administration rate increased across the three phases ($p = 0.001$) but was significantly higher in phase 3 than in the other two phases

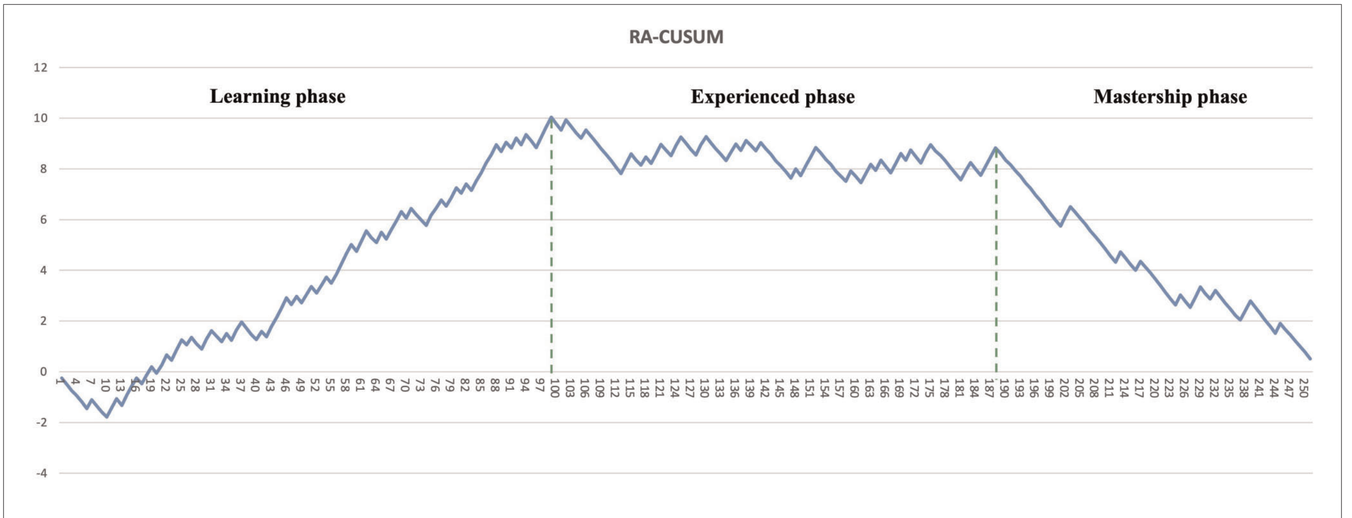

FIGURE 1 | CUSUM curve of operation time (CUSUMOT).

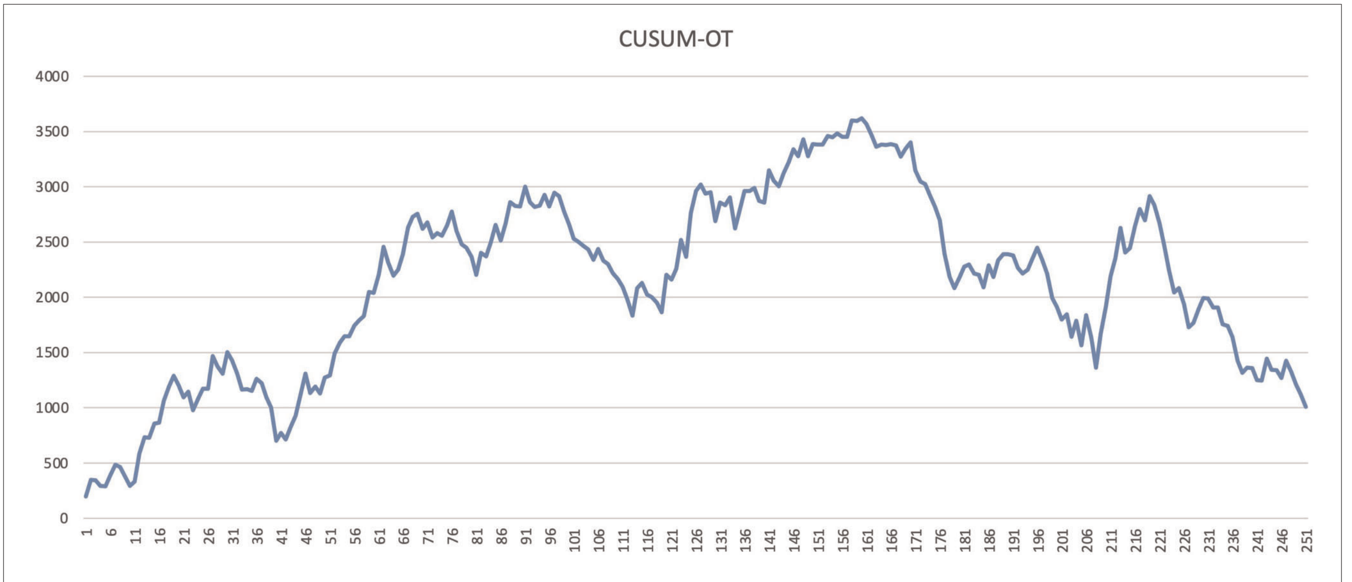

FIGURE 2 | Risk-adjusted CUSUM curve (RA-CUSUM).

TABLE 3 | Comparison of baseline characteristics and perioperative outcomes among the three phases defined by the RA-CUSUM analysis.

Parameters	Phase 1 ($n = 99$)	Phase 2 ($n = 89$)	Phase 3 ($n = 63$)	p-value	Phase 1 vs 2	Phase 2 vs 3	Phase 1 vs 3
Age (years)	55 (26–80)	60 (35–86)	61 (34–79)	0.138	0.178	0.382	0.068
Gender							
Male	39 (39.4)	45 (50.6)	22 (34.9)	0.120	0.082	0.056	0.567
BMI (Kg/m^2)	23.9 (17–34.6)	24.7 (17–31.3)	24.6 (18–41.7)	0.080	0.469	0.101	0.031
ECOG							
≥1	47 (47.5)	36 (40.4)	29 (46)	0.605	0.333	0.493	0.858
PCI	10 (3–27)	12 (3–30)	16 (3–27)	0.001	0.096	0.029	0.001
Primary tumor histotype							
Colon	44 (44.4)	41 (46.1)	30 (47.6)	0.894	0.689	0.963	0.689
Gastric	9 (9.1)	7 (7.9)	3 (4.8)				
PMP	17 (17.2)	17 (19.1)	14 (22.2)				
Mesotelioma	5 (5.1)	7 (7.9)	4 (6.3)				
Ovarian	17 (17.2)	15 (16.9)	10 (15.9)				
Other	7 (7.1)	2 (2.2)	2 (3.2)				
Completeness of cytoreduction							
Incomplete	12 (12.1)	13 (14.6)	3 (4.8)	0.152	0.616	0.043	0.094
HIPEC							
Yes	78 (78.8)	70 (78.7)	62 (98.4)	0.001	0.561	0.001	0.001
Operative time (min)	503 (140–800)	500 (200–900)	420 (200–808)	0.031	0.963	0.017	0.021
Major complications							
Clavien-Dindo 3–5	22 (22.2)	15 (16.9)	5 (7.9)	0.019	0.230	0.085	0.013
Blood loss							
>500 mL	43 (43.4)	21 (23.6)	5 (7.9)	0.001	0.002	0.012	0.001

(phase 3 vs. phase 2: 98% vs. 78.8%, $p = 0.001$; phase 3 vs. phase 1: 98% vs. 78.8%, $p = 0.001$).

The rates of major post-operative complications decreased significantly over the three phases ($p = 0.019$). Despite the rates of post-operative complications not being significantly different among phases 1 and 2 and phases 2 and 3, there was a significant reduction in complication rates in phase 3 compared to phase 1 (phase 3 vs phase 1: 7.9% vs 22.2%, $p = 0.013$).

Operative time decreased significantly over the three phases ($p = 0.031$) and was significantly lower in phase 3 than in the other two phases (phase 3 vs phase 2: 420 min vs 500 min, $p = 0.017$; phase 3 vs phase 1: 420 min vs 503 min, $p = 0.021$). Blood loss constantly and significantly decreased among the three phases ($p = 0.001$).

DISCUSSION

Considering the results of the case series published in the literature, the number of operations necessary to overcome the learning curve varies from 130 to 220 cases (23–26). The first report was in 2007 when Smeenk et al. (23) showed a significant increase in complete cytoreduction from 35.6% to 65.1% after 130 cases. A similar learning curve of 140 cases based on completeness of cytoreduction and severe morbidity was reported by Kusamura et al. in 2012 (24). In two other series, the operative outcomes are improved following 220 (25) and 180 (26) cases, respectively.

In our understanding, such heterogeneity could be due to the use of different analytical methods and outcomes to evaluate surgical proficiency in CRS. In other complex surgical procedures, such as pancreaticoduodenectomy (22), the operation time is frequently used as a primary outcome to measure the surgical skill improvement and it decreases with the surgeons' experience. However, especially in CRS, operation time is affected by several factors, such as PCI, location of PM, primary disease, regardless of the surgeon's skill and experience. In addition, the relationship between operative time and post-operative complications is not well defined yet. Furthermore, CUSUMOT plot shows a rather steady trend in our paper, and only after 161 cases a late and slow reduction is visible. Additionally, several inconstant peaks were visible in the late period after the 161 cases (**Figure 1**), suggesting an inconsistent reduction in the operative time.

To overcome this limitation, we outline a composite variable (surgical failure) that merges all the parameters supposedly entailing the learning process.

Among the three phases defined by the RA-CUSUM curve, we found no difference in the rate of incomplete cytoreduction, but there was a significant reduction in the rate of severe postoperative complications.

During the first 99 cases, we found a complication rate of 22.2%, comparable with the one reported in the literature (27). Moreover, this value is higher than 16.7%, which is the median value of the major complication rate of our whole series (**Table 3**). Furthermore, the rate of incomplete cytoreduction in this phase is 12%, comparable with the value reported by other papers (24, 27, 28).

This means that our results are within acceptable limits (i.e. minimal level of proficiency) in terms of morbidity, mortality, and completeness of cytoreduction, also during the initial phase, when surgeries are performed without having gained the highest level of expertise.

After the 99th case, the RA-CUSUM curve reaches a steady-state until the 188^{th} case (i.e. the experienced phase). A possible explanation for this "deadlock period" without any apparent improvement in surgical skills could be that we implemented our surgical indications after gaining experience and autonomy, including patients with a higher disease burden. As a matter of fact, in our series, the PCI and the consequent surgical challenge gradually increases during the study period (**Table 3**). Hence, the improved skills acquired in this phase were partially hidden by the significant surgical abilities required to manage a more significant disease load. Moreover, the results obtained in this phase (major complication rate 16.9%, incomplete cytoreduction rate of 14.6%) are acceptable and widely comparable with other data reported from other series (27, 29). Hence, a relatively long period is necessary to improve these results considering the advanced technical skills needed to face a more extensive disease.

Following a relatively long period of stability, the RA-CUSUM slope takes a gradual decrease after the 189th case (i.e. the mastership phase), with a clear improvement of all the surgical outcomes. In this phase, the achieved surgical abilities allow dealing with a more extensive and challenging disease (median PCI = 16), achieving a remarkably low rate of incomplete cytoreduction (4.8%) and complication rate (7.9%). Moreover, our major complication rate is lower than other series reported in the literature (27–31). The improvement of the rate of incomplete cytoreduction accounts for the significantly higher rate of HIPEC administration in the last phase compared with the other two (**Table 3**).

Additionally, to highlight further the surgical proficiency acquired in the mastership phase, we found a significant reduction in operative time compared with the learning phase ($p = 0.021$) and the experienced phase ($p = 0.017$).

Pondering on our results, the achievement of the technical proficiency required 189 cases, which is comparable with the 130–220 cases reported in the literature. Before achieving the complete proficiency and after the first 99 cases, the surgeon could safely perform CRS in patients with a moderate extension of the disease, obtaining a complication rate and an incomplete cytoreduction rate widely comparable to other series in the literature.

In this study of an experienced surgeon without prior experience of CRS and HIPEC, the incidence of major post-operative complications and the rate of incomplete cytoreduction, even in phase 1, were comparable with the incidence in prior studies (24, 27, 28). The reason for these results could be the accurate and targeted selection of patients with a low tumour burden in the early phase, performed under the direct supervision of the mentor and in a multidisciplinary context. In this way, the surgeon could deal with the type of disease most suited to his surgical skills at every stage of his learning process. Therefore, the mentorship by another experienced general surgeon with previous experience with peritoneal surgery and HIPEC and a well-defined multidisciplinary team is crucial to expedite an otherwise long and steep learning curve, decrease its untoward outcomes in the early period, and ameliorate oncological outcomes.

As shown in this study and earlier studies, the long and insidious learning curve before achieving surgical proficiency is the main obstacle to the safe diffusion of CRS and HIPEC. Estimating that the average amount of CRS and HIPEC at reference high-volume centres varies from 24 to 123 cases per year, achieving technical competency can take several years (32).

This study has some limitations. First, our analyses did not investigate whether the initial training period has some impact on oncological outcomes. However, the incomplete cytoreduction rate, which represents a surrogate marker for oncologic outcomes, was not inferior to the historical data from previous reports (27–31). And secondly, it is unclear which technical aspect of CRS or HIPEC provided the most outstanding contribution to the long learning curve. Identifying the crucial steps in the learning process could shorten the achievement of surgical proficiency.

In conclusion, a long learning curve was necessary even for an experienced general surgeon to achieve technical proficiency. Moreover, the technical aspect of CRS is relatively unfamiliar to most general surgeons. Hence, a mentorship model in high-volume centres by surgeons with experience and knowledge of this disease should be paramount to reduce the learning curve. Therefore, considering a possible future direction, it is crucial to develop standardised training programs to shorten the learning process reduce morbidity and mortality, and improve oncologic outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FS, FF, AD and CA contributed to study conception and design. CA, MAEH, and LB contributed to the acquisition of data. FS, CA, and FG contributed to writing the manuscript. FP, FG, and CL contributed to the drafting of the manuscript. FS, AD, and FP contributed to critical revision. All authors contributed to the article and approved the submitted version.

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Endoscopic Endonasal Supraoptic and Infraoptic Approaches for Complex "Parasuprasellar" Lesions: Surgical Anatomy, Technique Nuances, and Case Series

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Objective: The surgical management of lesions involving the lateral area of the suprasellar region, including the lateral aspect of the planum sphenoidale and the tight junction region of the optic canal (OC), anterior clinoid process (ACP), and internal carotid artery (ICA) and its dural rings, is extremely challenging. Here, these regions, namely, the "parasuprasellar" area, are described from the endonasal perspective. Moreover, the authors introduce two novels endoscopic endonasal supraoptic (EESO) and endoscopic endonasal infraoptic (EEIO) approaches to access the parasuprasellar area.

Methods: Surgical simulation of the EESO and EEIO approaches to the parasuprasellar area was conducted in 5 silicon-injected specimens. The same techniques were applied in 12 patients with lesions involving the parasuprasellar area.

Results: The EESO approach provided excellent surgical access to the lateral region of the planum sphenoidale, which corresponds to the orbital gyrus of the frontal lobe. With stepwise bone (OC, optic strut and ACP) removal, dissociation of the ophthalmic artery (OA) and optic nerve (ON), the EEIO approach enables access to the lateral region of the supraclinoidal ICA. These approaches can be used independently or in combination, but are more often employed as a complement to the endoscopic endonasal midline and transcavernous approaches. In clinical application, the EESO and EEIO approaches were successfully performed in 12 patients harboring tumors as well as multiple aneurysms involving the parasuprasellar area. Gross total and subtotal tumor resection were achieved in 9 patients and 1 patient, respectively. For two patients with multiple aneurysms, the lesions were clipped selectively according to location and size. Visual acuity improved in 7 patients, remained stable in 4, and deteriorated in only 1. No postoperative intracranial infection or ICA injury occurred in this series.

Conclusions: The EESO and EEIO approaches offer original treatment options for well-selected lesions involving the parasuprasellar area. They can be combined with the endoscopic endonasal midline and transcavernous approaches to remove extensive pathologies involving the intrasellar, suprasellar, sphenoid, and cavernous sinuses and even the bifurcation of the ICA. This work for the first time pushes the boundary of the endoscopic endonasal approach lateral to the supraclinoidal ICA and ON.

Keywords: endoscopic endonasal approach, parasuprasellar area, anterior clinoid process, optic canal, internal carotid artery, surgical technique

INTRODUCTION

With advances in surgical anatomy and endoscopic technology, the endoscopic endonasal approach (EEA) has been widely applied for ventral skull base lesions over the last several decades (1–3). Furthermore, this approach has been expanded to the lateral skull base, accompanied by the introduction of endoscopic transpterygoid route, such as the cavernous sinus (CS), pterygopalatine fossa and infratemporal fossa (4–9). The anatomy and related surgical nuances of these complex skull base areas have been well documented in a considerable amount of literature. Nevertheless, few reports exist on the detailed anatomy of the lateral area of the suprasellar region, including the lateral aspect of the planum sphenoidale and the tight junction region of the optic canal (OC), the anterior clinoid process (ACP), and the internal carotid artery (ICA) and its dural rings that fix its course (10, 11). There are essentially two reasons for such limited data: 1) limited access to these regions due to obstruction of vital neurovascular structures such as the optic nerve (ON) and ICA; 2) consideration of these regions as off-limits due to the lateral-seated location and intrinsic anatomical complexity. In fact, it is difficult to imagine the existence of such a high density of neurovascular and osseous as well as dural structures in such a narrow anatomical space.

Although not common, some different pathologies can afflict these regions, including primary lesions, such as ACP meningiomas and paraclinoid aneurysms, but more secondary tumors spread, such as tuberculum sellae meningiomas, invasive pituitary adenomas and craniopharyngiomas, from nearby regions. Pathologies encountered in these areas are typically intra- and extracranially. Moreover, these lesions tend to displace the ON from above and/or below, erode osseous and dural structures, and even encase the ICA and its bifurcation. Therefore, effective resection of these lesions poses a considerable challenge, even for skilled and experienced neurosurgeons.

Several traditional transcranial approaches (TCAs), including the standard or extended pterional approach (12, 13), orbital-zygomatic approach (14) and supraorbital approach (15), for accessing lesions in these areas have been described. Although TCAs can be good alternatives for subdural lesions, extradural lesions involving the intrasellar, sphenoid sinus and even CS are extremely difficult to manage because surgical corridors are inconsistent with the axis of tumor growth. In addition, inevitable brain retraction, extensive bone removal, and easy damage to important neurovascular elements make TCAs less favorable options.

In contrast, the EEA provides a direct corridor to access extradural lesions, with the advantage of easy removal of extensively involved osseous architectures and dural attachments. Additionally, a corridor to the subdural lesion is established when the lesion is removed. Most importantly, EEA allows for early identification and control of the paraclinoidal ICA, which is the main structure that must be crossed to expand laterally into these regions. These advantages are particularly promising for treating lesions involving these areas. Nevertheless, there are few reports regarding the endoscopic anatomy and how to effectively manage lesions involved these areas (10, 11).

For this reason, we sought to undertake a thorough anatomical description of the lateral aspect of the planum sphenoidale and the tight junction region of the OC, ACP, and ICA and its dural rings. These regions are located in the lateral area of the suprasellar region, the "parasuprasellar" area. Building on our detailed dissection, we introduce two novels endoscopic endonasal supraoptic (EESO) and endoscopic endonasal infraoptic (EEIO) approaches to access the parasuprasellar area. Indications and nuances of these approaches in treating 12 patients with tumors and aneurysms involving this area are also presented.

METHODS

Anatomical Dissection

Five embalmed and injected adult cadaveric heads were used for endoscopic and microsurgical dissection. The anatomy research was approved by our institutional ethics committee. Endoscopic endonasal anatomical dissections were performed using rod lens endoscopes (4-mm diameter, 18-cm length, 0° and 30°, Karl Storz). An extended EEA to the sella, parasellar and suprasellar areas, involving wide sphenoidotomy, posterior ethmoidectomy, and posterior septectomy, followed by a transpterygoid approach, was performed for all cadaveric heads in a stepwise manner, as previously described (2, 3, 16). All intrasphenoidal landmarks were exposed, including the sella, tuberculum sellae, optic protuberances, carotid protuberances, medial opticocarotid recesses (MOCRs) and lateral opticocarotid recesses (LOCRs). The posterior ethmoidal artery (PEA) was also skeletonized.

We defined the parasuprasellar area as a quadrangular space, and its main contents included the ON, the ICA and its proximal and distal dural rings, the ophthalmic artery (OA), and the ACP. The PEA is defined as the upper boundary of the parasuprasellar area. The inferior boundary is formed by the horizontal connection between the inferior edge of the LOCR and MOCR. The medial boundary is the vertical connection between the medial edge of the MOCR and the PEA, and the lateral boundary is the vertical connection between the lateral edge of the LOCR and the PEA. In addition, we divided the parasuprasellar area into 2 compartments based upon the ON: supraoptic and infraoptic compartments (**Figure 1A**). The EESO and EEIO approaches were performed to access the supraoptic and infraoptic regions, respectively.

Particular attention should be paid to the anatomy of the parasuprasellar area and its vicinity from an endoscopic perspective as well as to the stepwise surgical techniques related to the safe dissociation of the ON and OA. After completing the endonasal procedures, the extent of bone and dural removal from the parasuprasellar area was further evaluated from the intracranial superior view (**Figures 1E,F**). Several anatomical parameter measurements were also measured and recorded.

Patient Population

From January 2016 to March 2020, we retrospectively reviewed 12 patients with lesions invading the parasuprasellar area and for whom the EESO and EEIO approaches were performed either alone or in combination. T1/T2WI and Gd-enhanced T1WI were performed in 10 patients with tumors, and contrast-enhanced postoperative MRI was performed as follow-up on postoperative day 1 and at 3 months after surgery. The remaining two patients with multiple aneurysms underwent pre- and postoperative cerebrovascular examinations, including CT angiography and digital subtraction angiography (DSA). All patients also underwent preoperative thin-slice CT scans to evaluate the extent of OC and ACP involvement. Preoperative BOT was performed to evaluate whether collateral circulation could be compensated; if poor, an endovascular stent or bypass

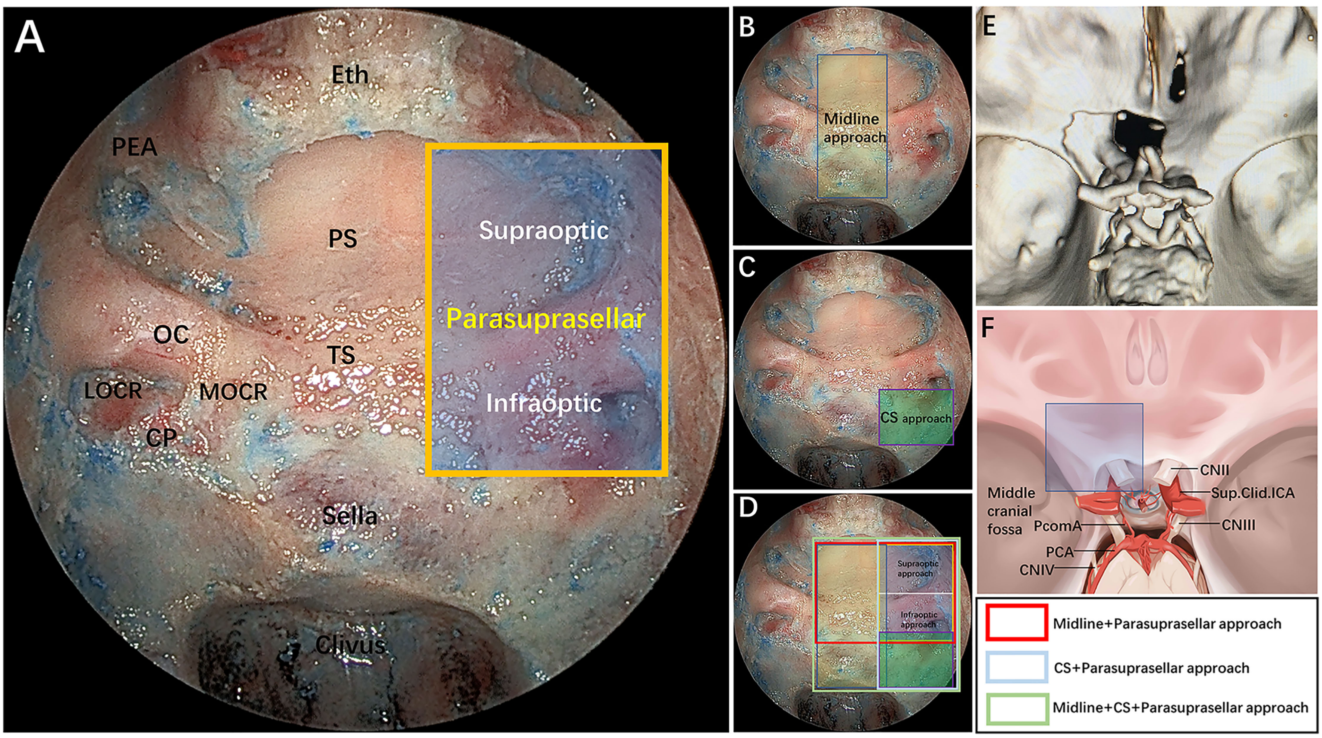

FIGURE 1 | **(A)** Endoscopic endonasal view of our proposed parasuprasellar area and its surrounding essential anatomical structures. The parasuprasellar area is delineated by the yellow quadrangular space, which is limited medially by the medial edge of the MOCR, laterally by the lateral edge of the LOCR, superiorly by the PEA, and inferiorly by the inferior edge of the MOCR and LOCR. In addition, as bounded by the optic nerve, it can be divided into supraoptic and infraoptic regions. **(B–D)** Illustration showing different combinations of surgical modules in both midline (transsellar/transtuberculum/transplanum approach) and/or lateral (transcavernous and parasuprasellar approach) planes. Note that the parasuprasellar approach includes supraoptic and infraoptic approaches. The various combinations of endoscopic corridors are indicated with different quadrangular colors (figure in the lower right corner). Red marks the combination of the endoscopic endonasal midline approach and parasuprasellar approach; blue represents the combination of the transcavernous approach and parasuprasellar approach; green shows the combination of the midline approach, transcavernous approach and parasuprasellar approach. **(E)** Three-dimensional (3D) reconstruction of a postoperative fine-slice CT scan showing the extent of bone removal through the supraoptic and infraoptic approaches. **(F)** Artistic illustration demonstrating maximum bone removal (blue square) in the parasuprasellar area *via* the supraoptic and infraoptic approach. Eth, cribriform plate of the ethmoid; PEA, posterior ethmoidal artery; PS, planum sphenoidale; OC, optic canal; TS, tuberculum sellae; MOCR, medial optocarotid recess; LOCR, lateral optocarotid recess; CP, carotid protuberance; CS, cavernous sinus; CN II, optic nerve; CN III, oculomotor nerve; CN IV, trochlear nerve; PcomA, posterior communication artery; Sup.Clid. ICA, supraclinoidal internal carotid artery; PCA, posterior cerebral artery. The figure is available in color only online.

would be prepared. Intraoperative electrophysiological monitoring, particularly visual evoked potentials (VEP), was used routinely throughout the procedure. Intraoperative neuronavigation and Doppler ultrasound were also applied to determine the exact course of the ICA. Additionally, the paraclival ICA was exposed in advance for proximal control. Special attention was given to the ophthalmological evaluation, including visual acuity and visual field, and limitations of ocular motility were observed by an ophthalmologist for all patients preoperatively and 3 to 6 months postoperatively. All medical records, including symptoms, neuroimaging, intraoperative videos, technical nuances, and surgical outcomes, were reviewed and analyzed retrospectively (**Table 1**).

RESULTS

EESO Approach to the Supraoptic Region

Stage 1: Recognition and Exposure of the Supraoptic Recess

After undergoing an initial extended EEA, the PEA located in its osseous canal is identified and serves as the upper boundary of the supraoptic region; the artery can be ligated and transected to facilitate lateral mobilization. The supraoptic recess is pyramid-shaped, with its base abutting the sphenoid sinus and apex corresponding intracranially to the body of the lesser sphenoid wing (**Figure 2A**) (11). The supraoptic recess needs to be identified and sufficiently delineated because its removal is one of the key steps to achieve further lateral extension over the planum sphenoidale.

Stage 2: Removal of the Medial Portion of the Lesser Sphenoid Wing and OC Unroofing

During this stage, the base of the supraoptic recess is drilled with a small diamond burr, proceeding deeply in a medial-to-lateral direction toward the body of the lesser sphenoid wing. As a consequence, the most medial portion of the lesser sphenoid wing overlying the orbit is exposed and progressively drilled out. However, removal of the lateral portion of the lesser sphenoid wing is limited inferiorly by the intracanalicular portion of the ON and the superior aspect of the medial orbital walls, which serves as the main anatomical landmark of the superolateral boundary of this exposure (**Figure 2B**). Afterward, the roof wall of the OC is drilled.

Stage 3: Resection of the Lateral Dura of the Planum Sphenoidale and Exposure of the Orbital Gyrus

The dura mater of the planum sphenoidale is opened in a posterior-to-anterior direction, after which the gyrus rectus of the frontal lobe and the olfactory nerve are visible at this level. The residual lateral part of the dura mater of the planum sphenoidale can be safely removed using an outward-facing Kerrison rongeur. This maneuver permits visualization of the medial orbital gyrus, anterior orbital gyrus and post orbital gyrus of the frontal lobe (**Figures 2C,D**). At this time, the distance from the lateral edge of the olfactory nerve to the outermost edge of the orbital gyrus is measured with a ruler (**Table 2**).

EEIO Approach to the Infraoptic Region

Stage 1: Removal of the Anterior Wall of the OC and Exposure of the Intracranial ON

After the bone of the anterior wall of the OC is removed in a medial-lateral direction up to the orbital apex, the dura overlying the intracranial ON is incised longitudinally to expose the origin of the OA (**Figures 3A–C**). Of note, the most common relationship of the origin of the OA to the intracranial ON is an inferomedial location; thus, opening the dura through a cut parallel to the ON in its upper half reduces the risk of damaging the artery (17, 18). To gain working space in the medial region of the paraclinoidal ICA, the diaphragm is incised toward the medial part of the distal dural ring (DDR). Following this, intradural exploration of the main neurovascular structures is performed. The pituitary stalk, superior hypophyseal artery (SHA) and its branches are exposed by gently lifting the ipsilateral ON (**Figure 3C**). Sliding deeper, the posterior communicating artery (PcomA) and the A1 segment of the anterior cerebral artery are identified using the space between the SHA and the ON (**Figure 3D**).

Stage 2: Drilling of the Optic Strut and Dissociation of the OA

Surgery in the lateral compartment of the paraclinoidal ICA requires removal of the optic strut, which corresponds to the LOCR from the endonasal perspective (19). Three vertices of this recess (resembling a triangle in shape) are identified: the superomedial, superolateral, and inferior vertices. The distance between each vertex of the LOCR is measured (**Table 2**). With regard to safe removal of the three vertices in turn to the base of the ACP, we have specifically discussed the relevant anatomical details and surgical nuances in a previous publication (20). Once drilling of the optic strut is concluded (**Figure 3E**), the DDR is opened to further safely dissociate the OA. Next, proper exposure of the ON and OA surrounded by the dural sheath is performed. At this stage, the courses of the precanalicular ON and OA are entirely exposed (**Figure 3F**). This maneuver aims to separate the ON from the OA, thus widening the surgical corridor of the infraoptic approach. The main structures are identified, including the PcomA, the anterior choroidal artery and its branches into the anterior perforating substance, the oculomotor nerve passing between the posterior cerebral artery and superior cerebellar artery into the CS, and the bifurcation of the ICA (**Figures 3G, H**).

Stage 3: Removal of the ACP and Severing of the OA

The ACP is now only connected to part of the lesser sphenoid wing. By using this ACP triangle space and following gentle medial mobilization of the paraclinoidal ICA, drilling and curettage of the base and tip of the ACP becomes feasible (**Figures 3I,J**). However, this step is performed with extreme care to avoid injury to the ICA, OA, ON and oculomotor nerve, and tailored bone drilling is strongly suggested according to disease-specific management. Once removal of the ACP tip is achieved, the dura of the inferior surface of the ACP is incised with angled scissors or coagulated. At this moment, the sylvian cistern is visible, and M1 is exposed between the frontal and temporal lobes; more laterally, the middle cerebral artery

TABLE 1 | Summary characteristics and outcomes of all 12 clinical cases.

Case No.	Age/ Sex	Size(cm)	Diagnosis	Preop		Other Symptoms	ICA, ACA, MCA Involvement	Previous Treatment	Surgical Approach	Anterior Clinoidectomy	EOR	Postop		Complications	Follow-Up (months)
				Visual Acuity	Visual Field							Visual Acuity	Visual Field		
1	56/F	2.1×1.9×1.7	Lt ACP meningioma	Visual loss (lt)	Upper hemianopsia	Dizzy	No	None	TPA+SOA	No	GTR	Improvement	Normal	None	56
2	25/F	2.5×1.9×1.4	Rt ACP meningioma	Visual loss (rt)	Rt temporal hemianopsia	Headache	Yes, all attached	Pterional approach	TMA*+IOA	Yes	GTR	Worse (rt), unchanged (lt)	Rt temporal hemianopsia	None	50
3	56/F	2.1×1.8×1.7	Lt ACP meningioma	Normal	Normal	Dizzy	Yes, all attached	None	TMA+SOA +IOA	No	GTR	Stable	Normal	None	36
4	37/F	3.0×1.7×1.4	Lt ACP meningioma	Visual loss (lt)	Lt temporal hemianopsia	None	Yes, all encased	Pterional approach	TMA+TPA +TCA +SOA +IOA	Yes	STR	Stable	Lt temporal hemianopsia	CNIII pasly	45
5	12/ M	2.8×3.1×3.9	Osteogenic meningioma	Visual loss	Lt amaurosis	None	No	None	TMA+TPA +SOA +IOA	Yes	GTR	Marked improvement	Lt temporal hemianopsia	Transient DI	18
6	45/F	3.7×4.0×3.9	Pituitary adenoma	Visual loss	Lt temporal hemianopsia	Headache	Yes, ICA and ACA encased	None	TMA+TPA +TCA +SOA +IOA	No	GTR	Stable	Lt temporal hemianopsia	CSF leak	30
7	52/F	3.5×2.7×2.9	Pituitary adenoma	Visual loss	Rt temporal hemianopsia	None	Yes, ICA encased, ACA and MCA attached	Endonasal endoscopic approach	TMA+TPA +TCA +SOA +IOA	Yes	GTR	Improvement	Normal	Panhypopituitarism Transient DI	22
8	56/ M	4.5×2.7×3.0	Pituitary adenoma	Visual loss (rt)	Bitemporal hemianopsia	Headache, hypomnesis	Yes, ICA encased, ACA attached	Endonasal microscope approach	TMA+TPA +TCA +SOA +IOA	No	GTR	Marked Improvement	Normal	None	29
9	47/F	lt paraclinoid: 0.7×0.8 lt ophthalmic: 0.4×0.3 lt cav-ICA: 0.5×0.4	Multiple aneurysms: lt paraclinoid, lt ophthalmic, lt cav-ICA	Normal	Normal	Headache	NA	None	TMA+TPA +IOA	Yes	Clipping of lt paraclinoid, lt ophthalmic aneurysms	Stable	Normal	None	58
10	62/F	lt paraclinoid: 0.75×0.42 rt paraclinoid:2.26×2.17 Acom: 0.4×0.3	Multiple aneurysms: lt paraclinoid, rt paraclinoid, Acom	Visual loss	Normal	Dizzy	NA	None	TMA+IOA	No	Clipping of lt paraclinoid, Acom aneurysms	Marked improvement	Normal	None	44
11	30/ M	2.3×2.2×1.9	Craniopharyngioma	Visual loss(rt)	Lower marginal field	None	Yes, all encased	Subfrontal approach, V-P shunting	TMA+SOA +IOA	No	GTR	Improvement	Rt hemianopsia	Hypothyroidism DI	26
12	37/F	1.8×1.4×1.0	Meningeal IgG4-related disease	Visual loss(rt)	Rt temporal hemianopsia	None	No	None	TMA+SOA +IOA	Yes	GTR	Improvement	Normal	CNIII pasly	52

*ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; EOR, extent of resection; ACP, anterior clinoid process; TPA, transpterygoid approach; TMA, transmidline approach;TCA, transcavernous approach; SOA, supraoptic approach; IOA, infraoptic approach; GTR, gross-total resection; STR, subtotal resection; DI, diabetes insipidus; NA, not applicable; Acom, anterior communicating;Cav-ICA=cavernous segment of ICA; * including endoscopic endonasal transsellar, transtuberculum, transplanumh and transclivus approaches.*

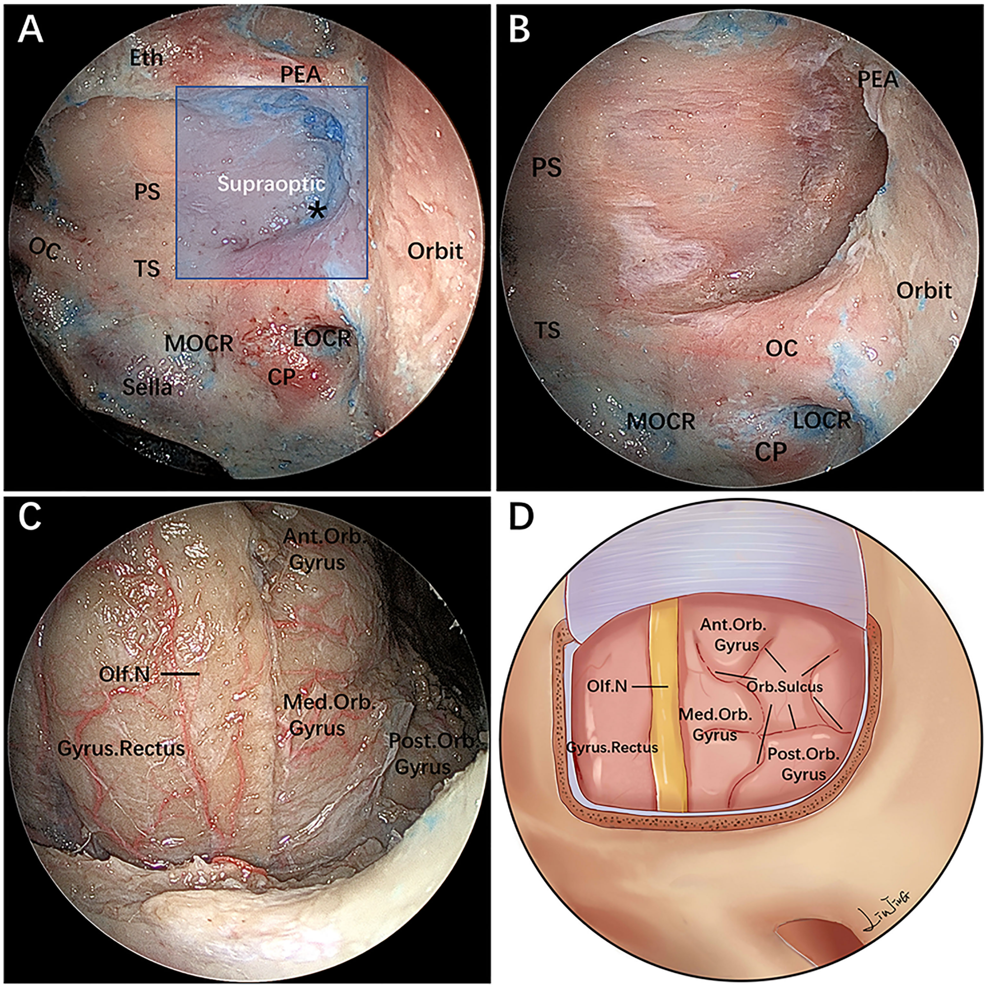

FIGURE 2 | Endoscopic endonasal supraoptic (EESO) approach: stepwise dissection to the supraoptic region in a colored silicone-injected cadaveric specimen. **(A)** Panoramic view of the sphenoid sinus floor with its anatomical landmarks. The blue quadrangular zone marks the supraoptic region, and the black asterisk represents the supraoptic recess. **(B)** A closer view of the supraoptic region after removal of the medial portion of the lesser sphenoid wing and OC unroofing. **(C)** After removing the bone and dura mater lateral to the planum sphenoidale, the gyrus rectus, olfactory nerve, medial orbital gyrus, anterior orbital gyrus and post orbital gyrus of the frontal lobes were exposed, viewed with a 0° endoscope. **(D)** Artistic illustration demonstrating the contents of the supraoptic region that can be reached *via* the EESO approach. Olf. N, olfactory nerve; Med.Orb. Gyrus, medial orbital gyrus; Ant.Orb. Gyrus, anterior orbital gyrus; Post.Orb. Gyrus, post orbital gyrus. The figure is available in color only online.

TABLE 2 | Relevant measurements.

Measurement	Mean ± SD, mm (right, n=5)	Mean ± SD, mm (left, n=5)	Mean ± SD, mm (total, n=10)
The length of the three sides of the ACP triangle:			
superomedial to superolateral vertices	4.30 ± 0.57	4.40 ± 0.65	4.35 ± 0.58
superomedial to inferior vertices	4.10 ± 0.55	4.20 ± 0.45	4.15 ± 0.47
superolateral to inferior vertices	3.80 ± 0.27	3.90 ± 0.42	3.85 ± 0.34
The lateral edge of the olfactory nerve to the outermost edge of the orbital gyrus	10.40 ± 0.65	10.30 ± 0.84	10.35 ± 0.71

bifurcation is observed at the level of its insular portion (**Figure 3K**). Some perforating vessels from M1 are also identified. Finally, the OA is transected, and the operating space of the infraoptic approach is further enlarged (**Figures 3L,M**).

Combined EESO and EEIO Approaches for the Parasuprasellar Area

After completing the above step-by-step dissection, combined EESO and EEIO approaches for accessing the parasuprasellar area were performed, as shown in **Figure 4**. It should be

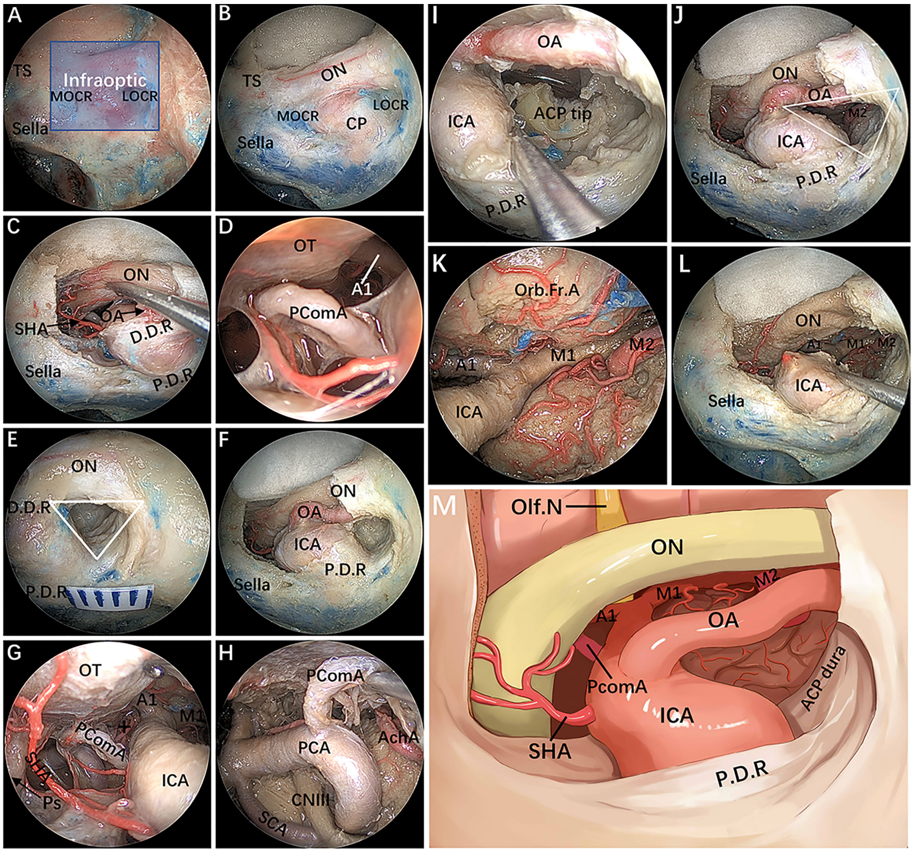

FIGURE 3 | Endoscopic endonasal infraraoptic (EEIO) approach: stepwise dissection to the infraoptic region in a colored silicone-injected cadaveric specimen. **(A)** The main anatomical landmarks in the infraoptic region (blue zone) are shown. **(B)** Removal of the anterior wall of the OC in a medial-lateral direction up the orbit apex. **(C)** The dura overlying the intracranial ON was incised longitudinally to expose the origin of the OA; the diaphragm was incised toward the medial part of the DDR, and SHA and its branches were exposed. **(D)** A closer view shows more subdural contents, including the PcomA, OT and A1 segments of the anterior cerebral artery. **(E)** Drilling of the optic strut and showing the ACP triangle. **(F)** The DDR and ON sheath are opened to further safely dissociate the OA and ON. **(G, H)** The subdural neurovascular structures were explored again by gently lifting of the ipsilateral ON. The main structures are identified, including the PcomA, pituitary stalk, AchA and its branches (black plus sign) into the anterior perforating substance in the crural cistern, the CNIII passing between the PCA and SCA into the cavernous sinus, and the bifurcation of the ICA. **(I)** The base and tip of the ACP can be further removed by gentle lifting of the OA or medial mobilization of the paraclinoidal ICA. **(J)** The ACP triangular is further enlarged. **(K)** The sylvian cistern was visible, and the ICA bifurcation was exposed between the frontal and temporal lobes; more laterally, the middle cerebral artery (MCA) bifurcation was observed at the level of its insular portion. **(L)** The OA was transected, and the operation space of the EEIO corridor was further enlarged. **(M)** Artistic illustration showing the main contents of the infraoptic region that can be reached *via* the EEIO approach. Note the ON has been slightly elevated. ON = optic nerve; OA = ophthalmic artery; SHA = superior hypophyseal artery; D.D.R, distal dural ring; P.D.R, proximal dural ring; ICA, internal carotid artery; OT, optic tract; AchA, anterior choroidal artery; SCA, superior cerebellar artery; Orb.Fr.A, orbital frontal artery; ACP, anterior clinoid process; M1, sphenoidal segment of the middle cerebral artery; M2, insular segment of the middle cerebral artery. The figure is available in color only online.

emphasized that the EESO and EEIO approaches can be used either alone or in combination; they can also be combined with the endoscopic endonasal midline approach (transsellar/transtuberculum/transplanum) and transcavernous approach according to the disease-specific location (**Figures 1B–D**).

EESO and EEIO Approaches: Case Series

The EESO and EEIO approaches were successfully performed either alone or in combination for 12 patients harboring tumors and aneurysms involving the parasuprasellar area (**Table 1**). The mean patient age was 42.9 years (range 12–62 years); there were 3 males and 9 females. The most common presenting symptom was visual deficit, including visual loss and visual field defects. Other symptoms were headache, dizziness, and hypomnesis. Three patients had previously undergone TCA, and 2 patients underwent an endonasal (microscope or endoscopic) approach at other institutions. The final diagnoses were meningiomas in 5 patients, pituitary adenoma in 3 patients, multiple aneurysms in 2 patients, and meningeal IgG4-related disease and craniopharyngioma in 1 patient each. Gross total tumor resection was achieved in 9 patients; subtotal resection was achieved in 1 patient. There were 2 patients with multiple aneurysms. One case of anterior communication and paraclinoid aneurysms were clipped *via* a pure EEIO approach; a contralateral giant paraclinoid aneurysm was secondarily

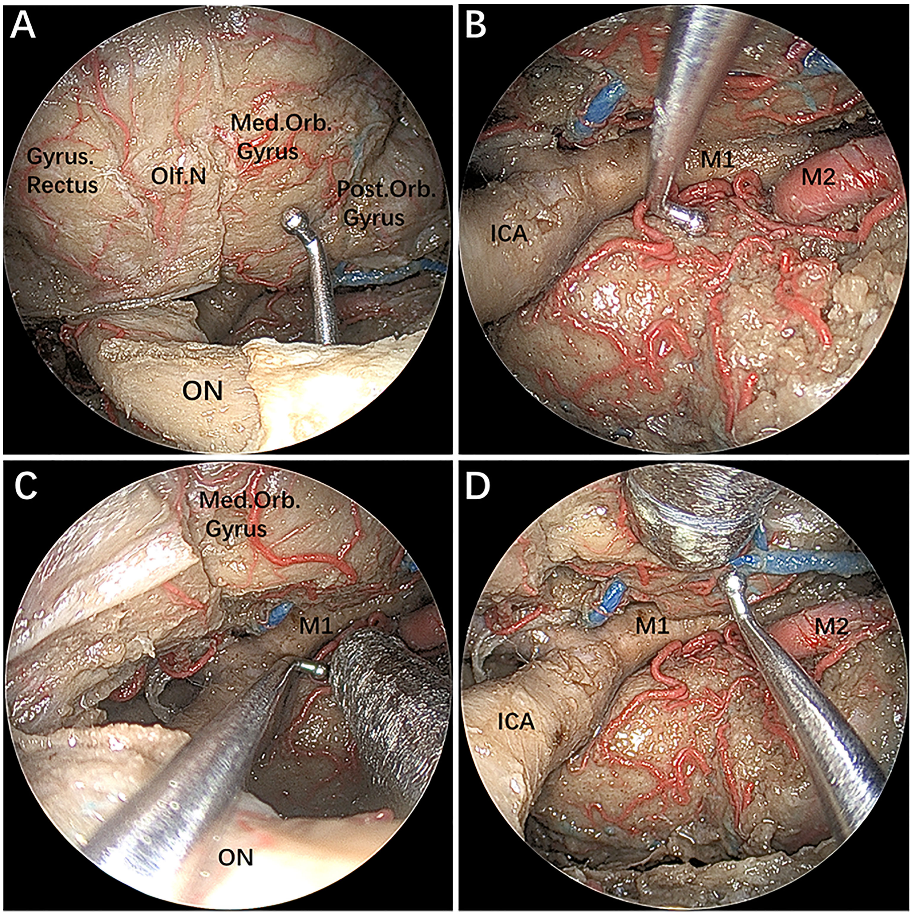

FIGURE 4 | **(A–D)** The instruments demonstrating a combined supraoptic and infraoptic approach to access the parasuprasellar area. The figure is available in color only online.

embolized at 2 months after the operation. The other patient harbored ophthalmic and paraclinoid aneurysms that were also clipped through the EEIO approach, although an intracavernous aneurysm was left untreated due to its location and size. Postoperative visual acuity improved in 7 patients, remained unchanged in 4 patients, and deteriorated in 1 patient in the right eye. The postoperative visual field was normal in 7 patients, whereas 5 still had unilateral temporal hemianopsia. Two patients experienced transient diabetes insipidus (DI), and 1 patient developed postoperative panhypopituitarism, which normalized by the 3-month follow-up. One patient experienced permanent DI and hypothyroidism, and postoperative hormone replacement therapy was required in the follow-up period. Postoperative cerebrospinal fluid (CSF) leakage occurred in 1 patient, and endoscopic endonasal repair was performed. Postoperative oculomotor nerve palsy developed in 2 patients; fortunately, it resolved completely in one patient by the 1-month follow-up, and significantly improved in the other patient by the 6-month follow-up. No postoperative intracranial infection or ICA injury occurred in this series.

DISCUSSION

Skull base pathologies encompassing the suprasellar lateral area, including the lateral aspect of the planum sphenoidale and the tight junction region of the OC, ACP, and ICA and its dural rings, still pose unique surgical challenges for neurosurgeons in terms of subsequent morbidity and gross total resection (10, 12, 20–22). These pathologies typically involve intra- and extracranially, tend to displace the ON from above and/or below, erode osseous and dural structures, and even involve the ICA bifurcation. Hence, TCAs for complete resection of these lesions have a high potential morbidity, even for skilled and experienced neurosurgeons. Today, endoscopy, which offers a wider, close-up view of the surgical field, is used broadly in skull base surgery. Although it has the disadvantage of increasing the rate of CSF leakage, the potential advantages of the EEA compared to conventional TCAs include avoiding brain retraction, improved visualization, better protection of surrounding neurovascular structures, and shorter hospital stay (1–3, 23–25). These advantages are similar when comparing the EEA and different TCAs for lesions involving the lateral area of the suprasellar region. The EEA not only provides the most straightforward surgical route parallel to the growth axis of the tumor but also, most importantly, allows for better control of the paraclinoidal ICA, which constitutes a lateral barrier to directly approaching these regions through the sphenoid sinus. However, the intricate anatomical complexity and lack of anatomical detail suitable for surgical exploration make these regions among the most challenging areas to approach.

In this paper, we describe the surgical anatomy of the lateral area of the suprasellar region, termed the "parasuprasellar" area, from the endoscopic perspective. Moreover, we introduce the EESO and EEIO approaches to access this complex area. The same techniques were applied in 12 consecutive patients harboring tumors and aneurysms involving the parasuprasellar area. To the best of our knowledge, this is the first report on the EESO and EEIO approaches.

Approach Selection and Technical Considerations

Our results validate the efficacy of the EESO and EEIO approaches in managing lesions involving the parasuprasellar area, as well demonstrated in our illustrations (**Figures 5–11**). In our experience, when tumors simultaneously invade the intrasellar, suprasellar and lateral to the parasuprasellar area, such as pituitary adenomas or craniopharyngiomas, the EEIO approach should be considered first. If the tumor is not safely exposed or still has an invisible portion, even after pulling it downward, the EESO approach should be selected to allow for additional exposure of the lateral tumor. When the lesion originates in the parasuprasellar area, such as ACP meningiomas or paraclinoid aneurysms, the EEIO approach can also be considered first to remove the lesion on the medial or lateral side of the paraclinoidal ICA. Similarly, if the lesion cannot be completely removed through the corridor below the ON, a combined EESO approach can be applied in most cases. It must be emphasized, however, that not all lesions involving this area are indications for EESO and EEIO approaches. Indeed, a primary TCA or staged operation may be indicated when the lesion involves the intracranial to the parasuprasellar area and is mainly located subdurally.

Of note, the use of the EESO or EEIO approach alone is rather rare and most often requires combination with the endoscopic endonasal midline approach and/or transcavernous approach. Different combinations of approaches can be selected according to the size and location of the lesion(s). For example, the transtuberculum/transplanum approach can be conveniently combined with the single EESO approach to provide better access to anterior cranial fossa meningiomas with lateral extension (case 1). Similarly, the combination of the transcavernous approach and EEIO approach has the potential for achieving complete resection of ACP meningiomas or pituitary adenomas involving the CS (cases 4, 6, 7 and 8). The EESO and EEIO approaches can be used as a complement to the midline approach and transcavernous approach and are

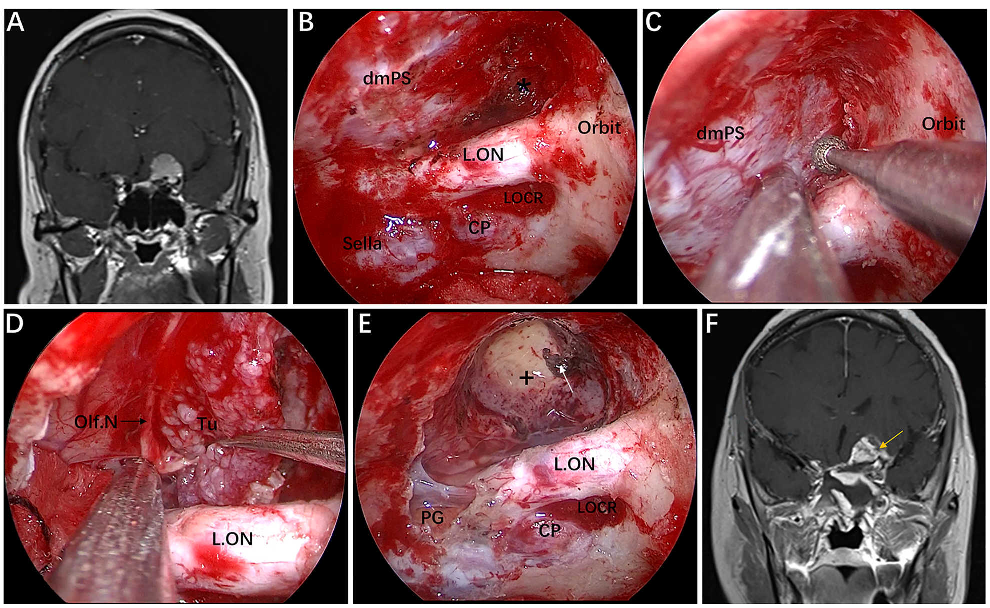

FIGURE 5 | Case 1, a 56-year-old woman, presented with a 1-year history of dizziness and progressive left visual loss for more than 1 month. **(A)** Preoperative coronal Gd-enhanced MRI showing a left ACP meningioma. **(B–E)** Intraoperative images. **(B)** Exposure of the lateral dura of the planum sphenoidale and supraoptic recess (black asterisk). **(C)** Drilling the roof wall of the optic canal and supraoptic recess in a medial-to-lateral direction toward the body of the lesser sphenoid wing. **(D)** Separation of the tumor from the olfactory nerve through the supraoptic approach. **(E)** Final endoscopic view after complete tumor removal. The white arrow represents the severed posterior ethmoidal artery. **(F)** Postoperative coronal MRI showing total tumor removal. The yellow arrow represents the autologous fat used during the operation. + = tumor cavity. The figure is available in color only online.

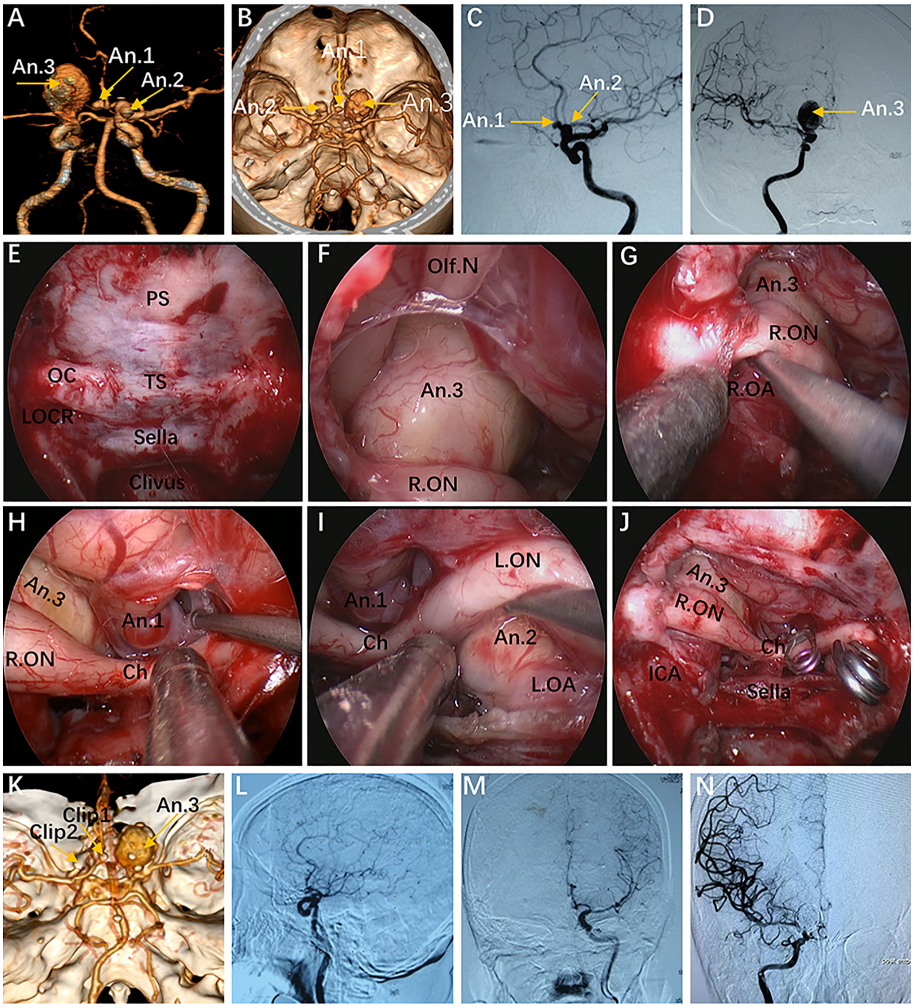

FIGURE 6 | Case 10, a 62-year-old woman, presented with visual loss for 2 months. **(A, B)** Preoperative CT angiography **(A)** and a 3-D reconstruction image **(B)** showing an Acom aneurysm (An1), a left praclinoid aneurysm (An2), and a large right paraclinoid aneurysm (An3). **(C, D)** Anteroposterior view **(C)** and lateral view **(D)** of bilateral internal carotid artery (ICA) injection of digital subtraction angiography (DSA) confirming an Acom aneurysm, a left praclinoid aneurysm, and a large right paraclinoid aneurysm. **(E–J)** Intraoperative images. **(E)** Endoscopic view of the skull base showing important bony landmarks. **(F, G)** Intraoperative image demonstrating an aneurysm body with a thrombus above the right optic nerve that cannot be clipped through an endonasal approach. **(H, I)** Exposure to the Acom aneurysm **(H)** and left paraclinoid aneurysm **(I)**. **(J)** Intraoperative picture showing that both aneurysms were clipped successfully after proximal control. **(K)** Postoperative CT angiography confirmed the patency of the bilateral A2 and distal ICA. **(L, M)** Postoperative lateral view **(L)** and anteroposterior view **(M)** of left ICA injection of DSA, revealing complete obliteration of An1 and An2. **(N)** Postoperative anteroposterior view of right ICA injection of DSA, showing complete obliteration of the An3 after second-stage coiling. An, aneurysm; R.OA, right ophthalmic artery; L.OA, left ophthalmic artery; Ch, optic chiasm. The figure is available in color only online.

extremely useful to access extensive pathologies for more complete resection while limiting morbidity.

Since the EESO and EEIO approaches require extensive removal of the skull base, strict cranial base reconstruction techniques for closure of the osteodural defect should be discussed. In our institution, we first use small pieces of autologous fat for intradural closure to eliminate the dead space. Then, we adopted the so-called sandwich technique, that is, two pieces of fascia lata or artificial dura were placed between the dura and bone as inlay substitutions and outside the bone as outlay substitutions, respectively. Finally, a vascularized pedicle nasoseptal flap harvested at the beginning of the procedure was positioned to cover the cranial defect, and each of the above layers was fixed with biological fibrin glue. However, it must be emphasized that, in the most lateral region of the cranial defect (where the ON stands), an inlay-overlay of dural substitutes will be difficult due to the irregularity of the osteodural defect. Therefore, autologous fat pieces should be placed across the intraextradural space.

Graduated, Stepwise EEIO Approach

In our practice, the EEIO is a graduated, stepwise approach based largely on the lesion location, size and extent. Our anatomical study and clinical cases demonstrate how to assemble multiple surgical

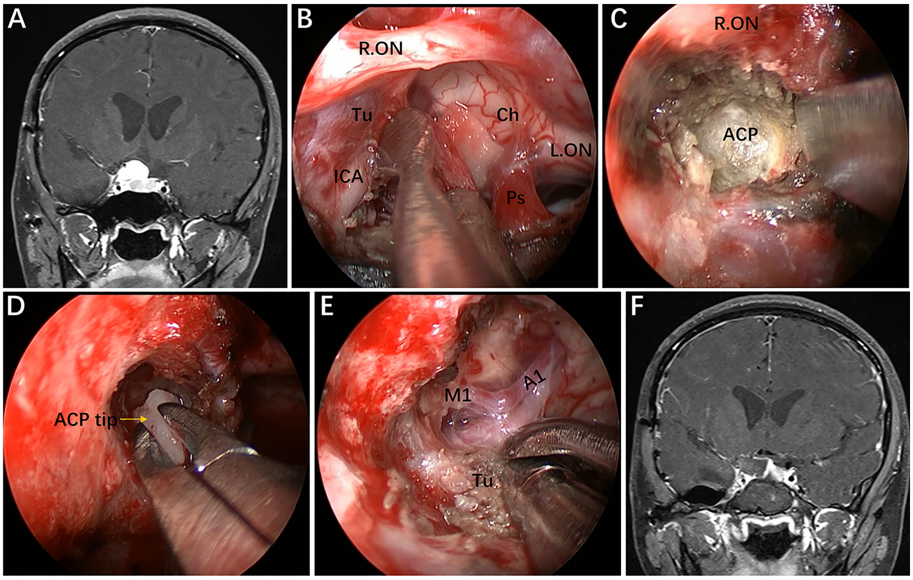

FIGURE 7 | Case 2, A 25-year-old woman presented with headache and decreased vision in her right eye for 6 months. **(A)** Preoperative coronal Gd-enhanced MRI demonstrating a right recurrent ACP meningioma. **(B)** Removal of the tumor on the medial and upper parts of the supraclinoidal ICA. **(C, D)** Removal of the ACP invaded by the tumor. **(E)** Separation of tumor adhering to the bifurcation of the ICA through the infraoptic corridor. **(F)** Postoperative MRI showing total tumor removal. Tu = tumor; Ps = pituitary stalk; ACP = anterior clinoid process. Some panels **(7A, D, F**) of the figure have been published in *Journal of Neurosurgery*. Published with permission. The figure is available in color only online.

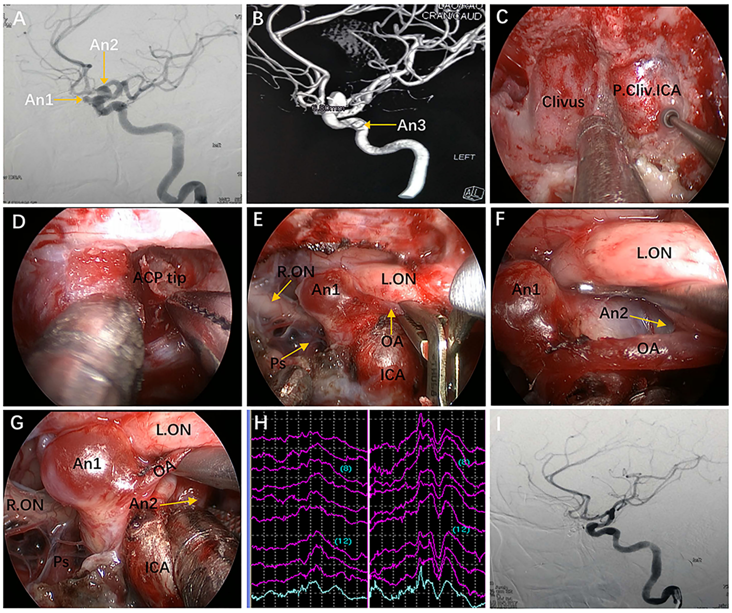

FIGURE 8 | Case 9, a 47-year-old woman, presented with headache for 3 months. **(A)** Preoperative lateral view of left internal carotid artery (ICA) injection for digital subtraction angiography (DSA) showing an ophthalmic aneurysm (An1) and a paraclinoid aneurysm (An2). **(B)** anteroposterior view of the 3D reconstruction images showing another aneurysm (An3) located in the cavernous segment of the ICA. C-G: Intraoperative images. **(C)** Exposure of the paraclival ICA for proximal control in advance. **(D)** Removal of the ACP tip. **(E)** Temporary occlusion of the OA. **(F)** Exposure of the An2 neck by lifting the ipsilateral optic nerve. **(G)** Clip application to the An2 neck after proximal control. **(H)** Intraoperative visual evoked potential monitoring changed after temporary occlusion of the OA. **(I)** Postoperative lateral view of DSA showing complete obliteration of An1 and An2. Some panels **(8A, B, G, I)** of the figure have been published in *Journal of Neurosurgery*. Published with permission. The figure is available in color only online.

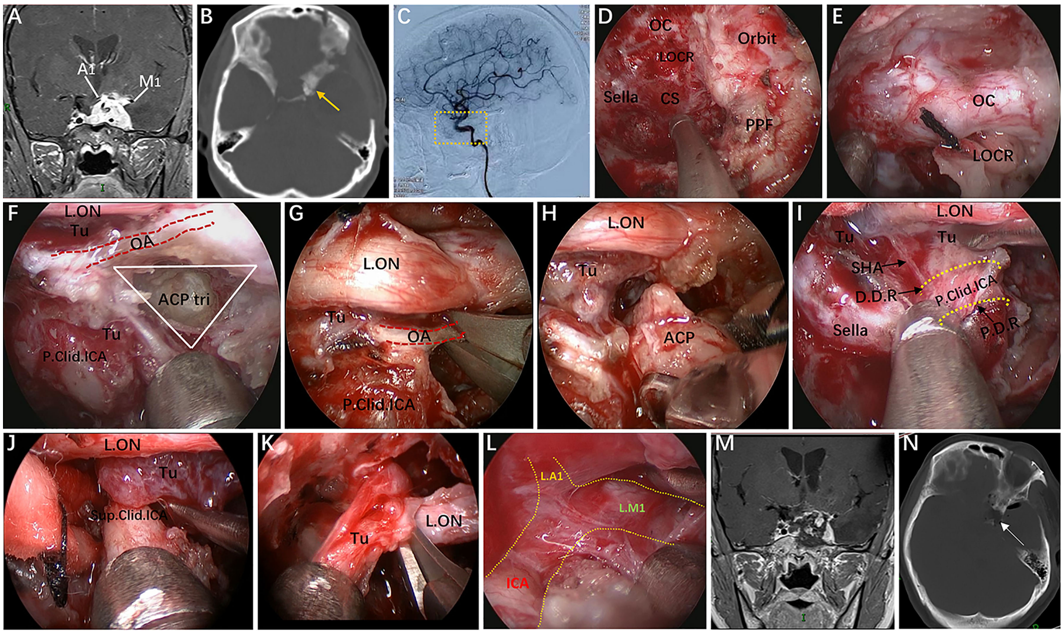

FIGURE 9 | Case 4, a 37-year-old woman, presented with progressive visual loss in the left eye for 2 years. **(A)** Preoperative coronal Gd-enhanced MRI showing a left recurrent ACP meningioma involving the right cavernous sinus and encasement of the ICA and its bifurcation. **(B)** Preoperative CT scans. The yellow arrow indicates the hyperplastic ACP. **(C)** Preoperative lateral view of left ICA injection of digital subtraction angiography (DSA) showing that the ophthalmic artery was not visible. **(D–L)** Intraoperative images. **(D)** Endoscopic view of important bony landmarks after the initial transpterygoid approach. **(E)** Exposure of the thickened OC and drilling of its roof and anterior walls. **(F)** Endoscopic exposure of the ACP triangle. The red dotted line indicates the course of the imaginary occluded OA. **(G)** Sacrifice of the OA surrounded by tumors and involving the dura. **(H)** Removal of the hyperplastic ACP. **(I–K)** Resection of the tumor on the medial and lateral sides of the supraclinoidal ICA through the combined supraoptic and infraoptic approaches. **(L)** Endoscopic exposure of the bifurcation of the ICA covered by arachnoid membrane. **(M)** Corresponding postoperative coronal MRI showing subtotal tumor resection, with part of the tumor remaining in the lateral wall of the left CS. **(N)** Postoperative CT scan showing ACP resection. The white arrow represents the removed ACP. Some panels **(9A, B, M, N)** of the figure have been published in *Journal of Neurosurgery*. Published with permission. The figure is available in color only online.

corridors to provide personalized access to complex parasuprasellar lesions. In Case 10, in which the left paraclinoid aneurysm was located just below the ON, successful clipping of the aneurysm was achieved using a pure EEIO approach (**Figure 6**).

Regarding Case 2, we found during the operation that a recurrent ACP meningioma was severely adhered to the ON and ICA and extended into the right OC. Thus, anterior clinoidectomy was applied, and the tumor, which was tightly attached to the ACP and the ICA bifurcation, was completely removed (**Figure 7**). It should be noted, however, that complete anterior clinoidectomy is not mandatory and that the extent of bony removal should be tailored to each case based on intraoperative need. If only the lateral region of the paraclinoidal ICA needs to be exposed or to obtain distal vascular control, partial anterior clinoidectomy should be considered; however, complete anterior clinoidectomy should be performed if the tumor involves the ACP and causes evident hyperplasia or the lesion has extended to involve the ICA bifurcation or even further. Such resection can reduce the risk of tumor recurrence. Most importantly, a corridor for accessing the lateral region of the supraclinoidal ICA is established while removing the involved ACP and the dura that envelops it. Nonetheless, this technique can only be implemented by experienced surgeons due to the complicated procedures and potential risks.

In Case 9, a lateral projecting paraclinoid aneurysm was encountered. In view of its position and orientation, we first performed anterior clinoidectomy to expose the lateral region of the paraclinoidal ICA. Then, the OA was dissociated and temporarily clipped, but the VEP changed, indicating that severing the OA would lead to serious visual impairment (**Figures 8E, H**). Finally, we attempted to expose the aneurysm neck between the OA and ON and successfully clipped the aneurysm through the ACP triangle (created by anterior clinoidectomy) (**Figures 8F, G**).

In Case 4, the tumor involved the intrasellar, suprasellar, CS, and encased the ICA and its bifurcation. The optic strut was drilled first, and the OA completely wrapped by the tumor was selectively dissected to further remove the hyperplastic ACP (**Figures 9F–H**). Thus, the tumor on the medial and lateral regions of the supraclinoidal ICA could be completely removed *via* an enlarged EEIO corridor (**Figures 9I, J**). This is the only case in our series, which preoperative DSA showed that the OA was not visible and the patient's intraoperative VEP stabilized,

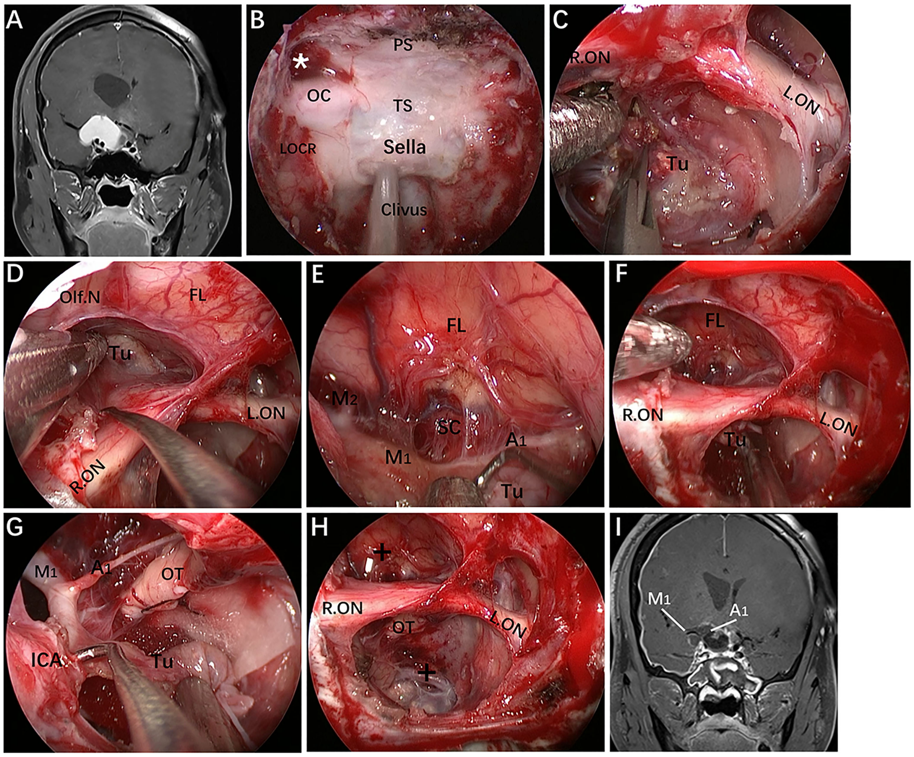

FIGURE 10 | Case 11, a 30-year-old man, presented with progressive loss of vision for 6 months. **(A)** Preoperative coronal Gd-enhanced MRI demonstrating a recurrent intra- and suprasellar craniopharyngioma with right sylvian fissure extension. **(B–H)** Intraoperative images. **(B)** Endoscopic view of the skull base showing important bony landmarks. The white asterisk marks the supraoptic recess. **(C)** Removal of intrasellar tumor. **(D)** Extracapsular separation of the tumor adhering to the frontal lobe through the supraoptic corridor. **(E)** Endoscopic view of the sylvian fissure during tumor removal. **(F, G)** Sharp dissection of the tumor away from the neurovascular structures by the infraoptic corridor. **(H)** Final endoscopic view after complete tumor removal. **(I)** Postoperative coronal MRI showing total tumor removal. The figure is available in color only online.

the OA was sacrificed. As expected, the patient's vision remained stable after surgery.

Visual Outcomes

The special location of such lesions is often responsible for vision loss related to intracranial and/or intracanalicular ON involvement. Ten patients in our series presented with varying degrees of vision loss; thus, improvement and preservation of visual function is a priority for this surgery. Remarkably, in our series, visual improvement occurred in 7 patients but was unchanged in 4 patients, and only 1 patient with recurrent ACP meningioma developed visual deterioration. This demonstrates that gentle pulling of the ON during resection will hardly affect visual function under VEP monitoring. Postoperative visual deterioration has been mainly related to injury of the subchiasmatic perforators, providing the main blood supply to the optic chiasma (26). Accordingly, the potential risk of injuring visual acuity may not be increased by extra manipulation in the supraoptic region. Furthermore, while applying the EEIO approach, endoscopy provides early and direct visualization of the subchiasmatic perforators, allowing for adequate dissection and protection. Last but most importantly, this approach allows for direct 270° decompression of the intracanalicular ON (10) and prompt removal of the involved dura and hyperostotic bone. Nevertheless, as mentioned above, these procedures must be carried out in an extremely delicate and careful manner. When removing bone, the egg-shelling technique with continuous saline irrigation must be followed to prevent thermal injury to the ON. We believe that if sufficient decompression is performed without the risk of further injury, vision problems may be reversed.

Limitations of the Study

The current study has several limitations that need to be considered. First, although no ICA or ON injury occurred in our series, these events are still our primary concern when managing parasuprasellar lesions. Second, cadaveric specimens are useful models to investigate surgical approaches, but they do not fully capture the clinical environment. Indeed, these corridors are relatively narrow in individuals who do not harbor such lesions. Finally, the learning curve is extremely steep and requires a high level of expertise in comprehensive skull base surgery, including both microsurgical cerebrovascular and endoscopic skills. Consequently, practice in the cadaver laboratory is mandatory to develop familiarity with these

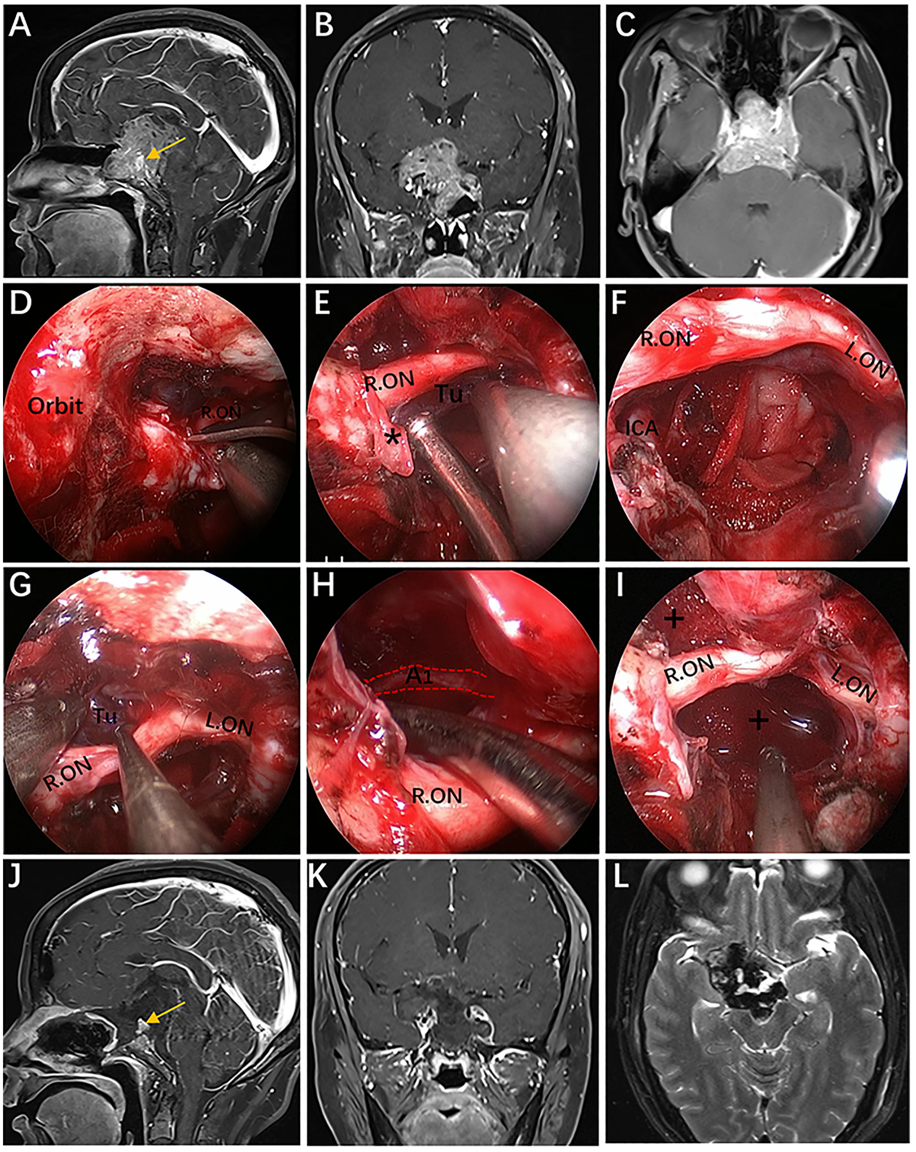

FIGURE 11 | Case 6, a 45-year-old woman presented with visual loss and headache for 2 years. **(A–C)** Preoperative Gd-enhanced MRI showing a multilobulated pituitary adenoma with bilateral cavernous sinus invasion, inferior extension into the clivus, superior compressed the third ventricle, and significantly encasement of the ICA and its bifurcation. **(D–I)** Intraoperative images. **(D)** Opening of the optic nerve sheath. **(E, F)** Removal of the tumor below the right optic nerve using a bimanual microsurgical technique and endoscopic view after resection. **(G)** Expose the tumor above the optic nerve. **(H)** Removal of the tumor using angled suction instruments through the supraoptic corridor. The red dotted line indicates the course of the A1 segments of the anterior cerebral artery. **(I)** Endoscopic view after tumor resection. **(J–L)** Postoperative MRI showing total tumor removal. The yellow arrow represents the normal pituitary gland. * = optic nerve sheath; + = tumor cavity. The figure is available in color only online.

precise and meticulous operations before they are applied clinically.

CONCLUSIONS

Based on our anatomical and surgical results, the EESO and EEIO approaches offer unique treatment options for well-selected lesions involving the parasuprasellar area. The approaches can be combined with the endoscopic endonasal midline approach and the transcavernous approach to remove extensive pathologies involving the intrasellar, suprasellar, sphenoid, and cavernous sinuses and even the bifurcation of the ICA. Our work for the first time pushes the boundary of the EEA lateral to the supraclinoidal ICA and ON.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Ethics Committee of the First Affiliated Hospital of Nanchang University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TH contributed to the study conception and design. Material preparation and data collection were performed by YB, YY and LZ. Analysis of the data was performed by TH, YB, YY, LZ, SX, XW, HD, JW, LX, LY and BT. The first draft of the manuscript was written by YB. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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ORIGINAL RESEARCH
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A Scientometric Analysis and Visualization Discovery of Enhanced Recovery After Surgery

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Background: Enhanced recovery after surgery (ERAS), a new clinical surgical concept, has been applied in many surgical disciplines with good clinical results for the past 20 years. Bibliometric analysis is an effective method to quantitatively evaluate the academic productivity. This report aimed to perform a scientometric analysis of the ERAS research status and research hotspots.

Methods: Comprehensive scientific mapping analysis of a wide range of literature metadata using the scientometric tools, including the Bibliometrix R Package, Biblioshiny, and CiteSpace. Data were retrieved from the Web of Science Core Collection database of original articles from 2001 to 2020. Specific indicators and maps were analyzed to show the co-authorship, co-institute, co-country, co-citation, and international cooperation. Automatic literature screening, unsupervised cluster filtering, and topic cluster identification methods were used to display the conceptual framework and thematic evolution.

Results: A total of 1,403 research projects drafted by 6,966 authors and published in 413 sources were found. There was an exponential growth in the number of publications on ERAS. There were 709 collaborations between authors from different countries, and the US, China, and the UK had the greatest number of publications. The WORLD JOURNAL OF SURGERY, located in Bradford's Law 1, had the highest number of published articles ($n = 1{,}276$; total citations = 3,193). CiteSpace network analysis revealed 15 highly correlated cluster ERAS studies, and the earliest study was on colonic surgery, and ERAS was recently applied in cardiac surgery. The etiology of ERAS is constantly evolving, with surgery and length of hospital as the main topics. Meta-analyses and perioperative care have tended to decline.

Conclusion: This is the first scientometric analysis of ERAS to provide descriptive quantitative indicators. This can provide a better understanding of how the field has evolved over the past 20 years, help identify research trends, and provide insights and

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Abbreviations: ERAS, Enhanced recovery after surgery; TC, total citations; NP, Net output; FTS, Fast-track surgery.

research directions for academic researchers, policymakers, and medical practitioners who want to collaborate in these areas in the future.

Keywords: enhanced recovery after surgery, fast-track surgery , bibliometrics, bibliometrix, citespace

INTRODUCTION

Enhanced recovery after surgery (ERAS) was first proposed by Kehlet et al. at the University of Copenhagen in Denmark in the late 1990s and has been applied clinically (1, 2). ERAS was initially used primarily in Europe and North America to study the effects of surgical stress response on open colorectal surgery in terms of rapid recovery. ERAS represents the idea of synergy through a combination of effective measures, with the central aim of reducing trauma and stress. ERAS is the best result of multidisciplinary collaboration that perfectly blends the latest research findings from surgery, anesthesia, and nursing into an integrated innovative concept that represents an optimized clinical pathway. This optimized clinical pathway involves the whole process of patient diagnosis and treatment, emphasis on the patient-centered concept. The implementation of the ERAS pathway can improve perioperative safety and the satisfaction in surgical patients, shorten the postoperative hospital stay, and help reduce the incidence of postoperative complications (3). Using the ERAS, patients can be identified, compartmentalized, and accommodated at every step throughout the perioperative period to facilitate an effective and safe process from preoperative evaluation through discharge to recovery. The advantages of ERAS have been recognized by operators and specialists worldwide, and its application in the medical field has been actively promoted. The ERAS Society has developed numerous perioperative guidelines for ERAS for various specialties and disciplines since 2005 (4–11).

The postoperative rehabilitation of patients undergoing surgery is affected by various factors, such as stress response, pain, and postoperative intestinal paralysis (12). stress response after surgery is a physiological and pathological process in the body, including changes in the nerve, endocrine, metabolic, and immune functions. Similarly, pain can adversely affect patient recovery. Postoperative intestinal paralysis aggravates postoperative discomfort, especially in patients undergoing abdominal surgery, affecting oral feeding and delaying the recovery of patients. Therefore, the combination of new techniques in anesthesiology, pain control, and surgical methods with the improvement of the traditional postoperative nursing methods can reduce the postoperative stress reaction, incidence of postoperative complications and mortality, postoperative hospital stay, and hospitalization cost. This finding is consistent with the concept of minimally invasive surgery. ERAS generally includes the following: (1) Preoperative patient education. (2) better anesthesia, analgesia, and surgical techniques can reduce surgical stress, pain, and discomfort. (3) enhanced postoperative rehabilitation including early ambulation and enteral nutrition. Several surgical studies have shown that ERAS can significantly shorten the postoperative hospitalization time, reduce hospitalization costs, and maximize the use of limited hospital resources without increasing the incidence of complications and mortality, which will become the trend of surgery (13, 14).

ERAS has been applied and supplemented for 20 years since it was first proposed in 2001, and is now being developed in a more refined direction. Its research direction is not limited to the surgical field, and future research directions and current research hotspots need to be clarified. Bibliometric analysis is the application of statistical and mathematical tools to books and media communications (15). Bibliometric analysis is a transparent, systematic, and repeatable review process that significantly improves the quality of literature review. This provides a means of mapping research fields and influential work without subjective bias.

This study aimed to identify research flows and topics by analyzing the citation dynamics in ERAS studies from to 2001–2020 to measure their impact on the scientific community (qualitative indicators). These topics and streams of research can guide scholars to find directions for future research and to find answers to current questions.

MATERIALS & METHOD

Study Design/Ethics Statement

This was a bibliometric network study using metadata from the Web of Science Core Collection on July 12, 2021. This is described in accordance with the STROBE guidelines (16). This was not a human-focused study and, as such, neither the institutional review board approval nor informed consent was required. This study was divided into five steps, known as the document metering workflow proposed by Zupic and Ater (17). **Figure 1** represents the five steps used to complete the bibliometric analysis of ERAS.

Data Sources

The original data for this article were obtained from the Web of Science core collection database, including SCI-EXPAND and SSCI. This following titles were used for the selection: "enhanced recovery after surgery" or "enhanced postsurgical recovery" or "enhanced recovery program" or "enhanced recovery pathways" or "accelerated rehabilitation" or "fast track surgery." The publication date was restricted from January 1, 2001 to December 31, 2020. The manuscript type was "article" and the target results were filtered. The file format recorded content was set to "plain text" and was exported as "full record".

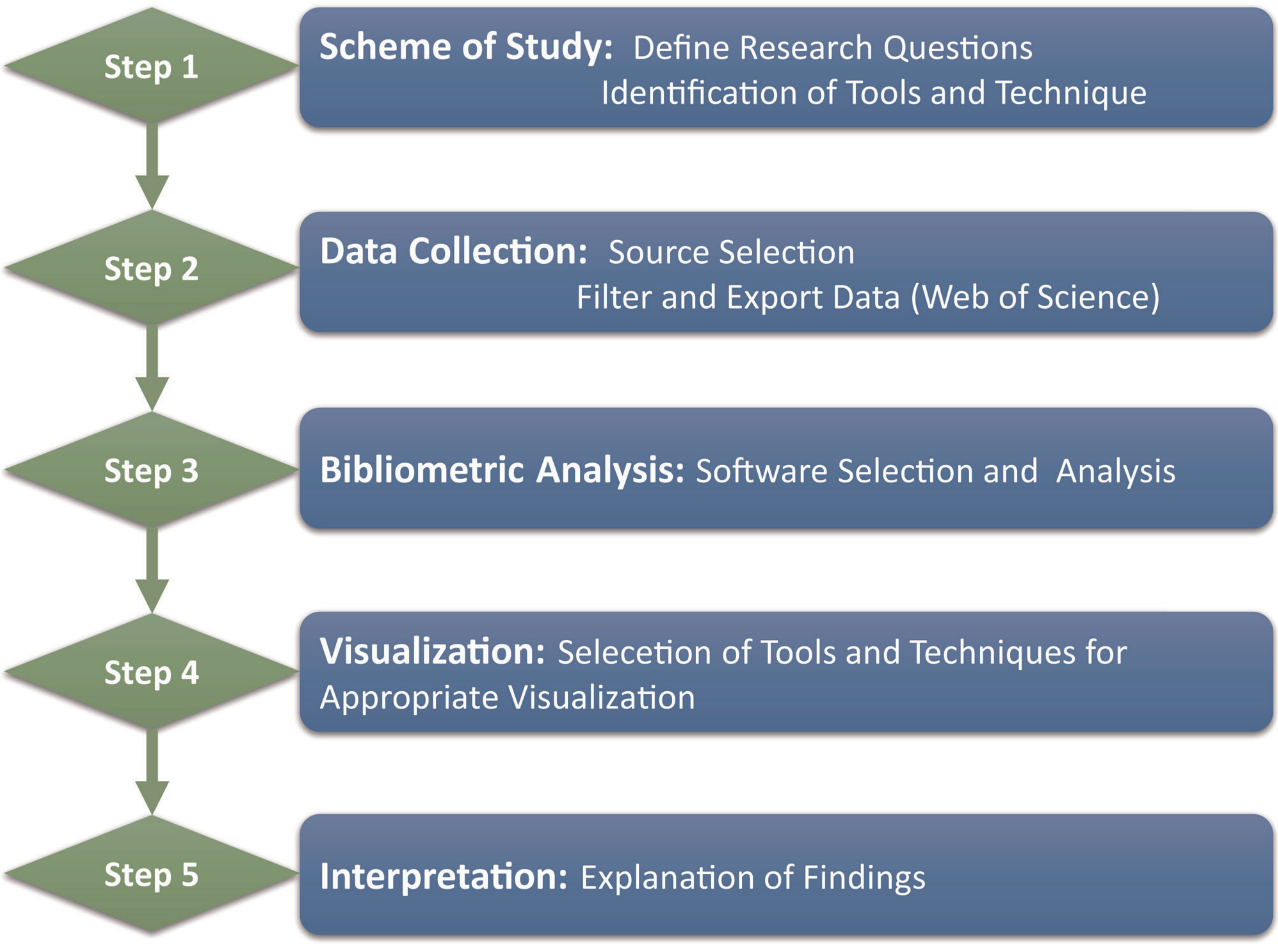

FIGURE 1 | The Procedure of Bibliometric Analysis.

Analysis Tool

Bibliometrix is an R language based bibliometric software with multiple toolkits for full-process bibliometrics and visual presentation of scientific documents, which was developed by Aria (18). Based on the data exported from the WOS database and then completed by the team researchers (XX Wang and ZX Song), the bibliometric analysis was conducted using the R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org) through the Bibliometrix R package.

CiteSpace is a visual tool for bibliometric analysis developed by Chaomei Chen, based on the Java platform (19). As an interactive analysis tool, it combines bibliometrics and data-mining algorithms to complete scientific mapping through the visualization of results. CiteSpace can be used to analyze cooperative networks and co-citations (20). Version 5.8.3 was used in this study for the analysis of the co-authorship, co-institute, co-country, and document co-citation of the articles published from 2001 to 2020. The time slice was two years, and the selection criterion was the first 50% of each time period. In collaborative networks, the size of the circles represents the number of studies published; the shorter the distance between the circles, the greater the collaboration between the two authors/institutions/countries. The blue-purple nodes represented earlier studies, whereas the yellow-red nodes represented more recent studies. In the co-citation analysis, the size of the nodes represented the frequency of citations, nodes with different colors represented different years, the line between the nodes represented the relationship between the co-citations, and the thickness of the line represented the strength of the relationship. The color corresponds to the time of the node's first co-citation, and the color from cold to warm represented early to recent co-citation. The thickness of the tree-ring was proportional to the number of citations in a given time zone. Modularity (Q) and weighted mean silhouette (S) were the two indicators used to evaluate clustering in the co-citation analysis. A Q value >0.3 meant very important network and an S value >0.5 meant reasonable clustering results.

Measurement

Descriptive analysis was used to explain the core sources, authors, countries, publications, and affiliations of publications. Price's law was used to assess whether the growing trend in the ERAS was scientific. Simultaneously, we identified the core sources using the Bradford's law (21). According to the Bradford's law, the data was divided into three regions. Zone 1 was highly productive and was considered a nuclear zone.

The author/publication-level metrics, such as the h-, m-, and g indices were determined (22, 23). In addition, we used keyword plus for the analysis, which was provided by the database to describe the knowledge structure of the study more concisely and standardized. The core research areas and key themes were essential for determining the direction of future research, therefore, thematic maps and thematic evolution were used.

In the thematic maps, each quadrant could be separated by centrality and density to form a two-dimensional graph. Centrality was the importance of a topic in the research field, and the density was used to measure the development of the topic. Quadrant I, located in the upper-right quadrant, named motor themes, suggested that the themes of the region have developed and formed important pillars that shape the field of research. Quadrant II, located in the upper left quadrant, named niche themes, reflected highly developed but isolated themes. Quadrant III, located in the lower-left quadrant and named emerging or declining themes, suggested weak development and marginalization of the research field. Quadrant IV, located in the lower-right quadrant, was named as basic themes. Although these topics are less developed, they are important to the field of study.

RESULTS

Overall Publication Performance and Growth Rate

Table 1 presents the descriptive features of the ERAS literature. A total of 1,403 studies were selected according to the search strategy. We identified 1,320 articles and 81 articles and proceedings papers. A total of 2,098 keywords plus 1,991 author keywords were used. Furthermore, 6,966 authors wrote the documents; among them, only 26 articles were written by one author. The collaboration index was 5.07, which showed the highly collaborative nature of ERAS publications. The document-per-author ratio was 0.201, implying that, on average, approximately five authors wrote a document.

By summarizing the number of papers published over the years, **Figure 2A** shows the overall trend of ERAS studies published worldwide from 2001 to 2020. ERAS research has an overall upward trend, and according to the curves analyzed from the data, it was found to be more suitable for exponential adjustment than linear adjustment, thus satisfying the Price's law. The correlation coefficient (r) after mathematical adjustment of the exponential curve was 0.9804, while the linear adjustment of the measured values, R, was 0.8051. Therefore, the percentage of unexplained variation was 19.49%.

Figure 2B shows three sets of data: simple-country authors, multicountry authors, and the citation rate of each country. The USA was at the top with several publications, China was ranked second, and the UK was ranked third, but concerning citations, China's total citations were worse than those of the UK. In contrast, although Sweden has a relatively small number of publications, it was at the top four the most cited countries, after the USA, the UK, and Canada. The country with the highest international cooperation was the USA, followed by Canada and the France. The most relevant affiliations are reported in **Figure 2C**. The McGill University was the first, and provided a strong basis for ERAS. The University of Texas MD Anderson Cancer Center and Maastricht University were the second and third affiliations of most publications, respectively.

In addition to the annual production, major topics, locations, and affiliations of ERAS-related publications were viewed. **Figure 2D** shows a threefold analysis of the ERAS publications, with keywords plus on the left, affiliations on the right, and relevant countries in the middle. The chart shows that the USA was working with most of the top agencies to focus on ERAS-related topics. In addition, China, Canada, and

TABLE 1 | Descriptive characteristics of ERAS literature.

Description	Results
Main information about data	
Timespan	2001:2021
Sources (Journals, Books, etc)	413
Documents	1,403
Average years from publication	5.27
Average citations per documents	26.72
Average citations per year per doc	3.939
References	21,902
Document types	
article	1,320
article; proceedings paper	81
Document contents	
Keywords Plus (ID)	2,098
Author's Keywords (DE)	1,991
Authors	
Authors	6,966
Author Appearances	9,558
Authors of single-authored documents	26
Authors of multi-authored documents	6,940
Authors collaboration	
Single-authored documents	33
Documents per Author	0.201
Authors per Document	4.97
Co-Authors per Documents	6.82
Collaboration Index	5.07

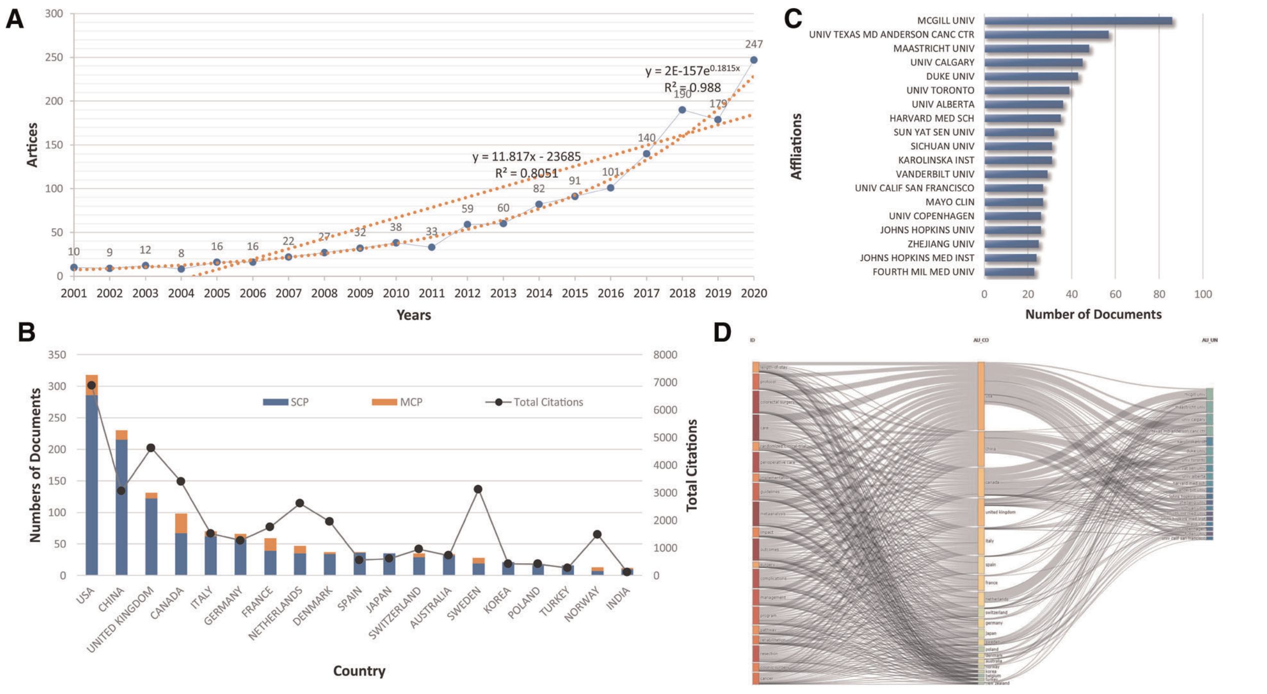

FIGURE 2 | (**A**) Growth of scientific production on ERAS from 2001 to 2020. A linear adjustment of the data and an adjustment to the exponential curve were made, in order to assess whether the production fulfilled the Price's Law. Linear adjustment: $y = 11.8176x - 23685$, $R^2 = 0.8051$; Exponential adjustment: $y = 2E\text{-}157e0.1815x$, $R^2 = 0.9804$. (**B**) The countries of the top 20 most relevant corresponding authors of the articles on ERAS. MCP, Multi-country publications; SCP, simple-country publications. (**C**) Top 20 of the Most Relevant Affiliations. (**D**) R Studio - Three-fields plot: left – keywords plus from the data records, middle – countries, right – authors affiliations.

the UK have made significant contributions to ERAS science topics. Issues related to outcomes and care are the most widely studied in most countries.

Core Journals, Core Journal Articles and Core Words of ERAS

We used source impact and Bradford's Law to find publications on ERAS in the core journals in the scientific literature. **Table 2** ranks the articles by h, M, G-index, total citations (TC), net output (NP), and pub year of publication (PYstart), and represents the Bradford's Law (**Figure 3A**), which divides journals into three regions. We found that 24 of the 413 journals were in core zone 1, and the top 24 journals were the core publishing sources for corona literature in the social sciences.

Table 3 lists the top 20 most-cited articles in the database along with their global citations. **Figure 3B** shows the local and global citations for highly cited papers. **Table 4** provides the most frequent words used in the ERAS literature, which is divided into four parts: keywords plus, authors' keywords, abstracts, and titles. **Figure 3C** shows the word cloud created using keyword plus. Words with a high frequency in the literature were larger in size.

Co-authorship, Co-institute, Co-country and Document Co-citation Analysis

The results of the generating collaborator mappings using CiteSpace were 676 nodes and 1,440 links (**Figure 4A**), which means that 1,401 articles were published by 676 authors. As shown in **Figure 4A**, many authors preferred to combine with relatively stable collaborators, resulting in a relatively large cluster of authors. In earlier studies, only a few core authors cooperated less with the central clusters. The most representative author was LJUNGQVIST O, who published 33 studies, followed by DEMARTINES N and KEHLET H. The top-ranked item by centrality was O LJUNGQVIST (2005) with a centrality of 30, and the second one was OLLE LJUNGQVIST (2010) with a centrality of 28. The third was H KEHLET (2002) and GREGG NELSON (2016), with centralities of 25.

The institute of the two authors appeared in the same article as a cooperative organization, namely, the co-institute. The Citesapce software was used to calculate the co-occurrence frequency matrix to determine the degree of cooperation. **Figure 4B** shows the collaborative institutes in the era domain, with an institution map of 367 nodes and 848 links. Generally, the institutions were concentrated in universities and a few in hospitals.

TABLE 2 | Zone 1 journals according Bradford's law and the source impact.

Element	Source impact							Bradford's law			
	Articles	h_index	g_index	m_index	TC	NP	PY_start	Rank	Freq	cumFreq	Zone
World journal of surgery	1,276	26	44	1.857143	3,193	44	2008	1	44	44	Zone 1
Surgical endoscopy and other interventional techniques	714	15	24	1.363636	666	37	2011	2	38	82	Zone 1
Colorectal disease	792	18	31	1.125	990	33	2006	3	34	116	Zone 1
International journal of colorectal disease	480	16	26	1.066667	693	31	2007	4	32	148	Zone 1
Journal of cardiothoracic and vascular anesthesia	260	16	22	0.761905	513	23	2001	5	24	172	Zone 1
Obesity surgery	398	13	22	0.8125	517	22	2006	6	23	195	Zone 1
Journal of laparoendoscopic & advanced surgical techniques	73	9	15	0.692308	255	17	2009	7	20	215	Zone 1
Journal of gastrointestinal surgery	530	14	18	0.933333	706	18	2007	8	19	234	Zone 1
Surgical clinics of North America	68	9	13	1	192	19	2013	9	19	253	Zone 1
British journal of surgery	2,355	17	18	0.809524	1,912	18	2001	10	18	271	Zone 1
Diseases of the colon & rectum	951	13	17	0.722222	1,171	17	2004	11	17	288	Zone 1
International journal of clinical and experimental medicine	20	1	2	0.142857	11	6	2015	12	16	304	Zone 1
International journal of surgery	253	11	16	1.375	383	16	2014	13	16	320	Zone 1
American surgeon	91	6	11	0.3	127	13	2002	14	15	335	Zone 1
Anesthesia and analgesia	1,102	11	15	0.52381	680	15	2001	15	15	350	Zone 1
Journal of the american college of surgeons	694	12	15	1.333333	645	15	2013	16	15	365	Zone 1
BMJ open	94	10	14	1	311	14	2012	17	14	379	Zone 1
American journal of surgery	474	7	13	0.538462	202	13	2009	18	13	392	Zone 1
Gynecologic oncology	385	9	13	1.5	601	13	2016	19	13	405	Zone 1
Annals of surgery	2,424	10	12	0.5	1,291	12	2002	20	12	417	Zone 1
Journal of surgical research	150	7	11	0.538462	172	11	2009	21	12	429	Zone 1
Medicine	98	7	11	1.166667	133	11	2016	22	12	441	Zone 1
American journal of obstetrics and gynecology	173	9	11	2.25	395	11	2018	23	11	452	Zone 1
Clinical nutrition	1,031	10	11	0.588235	3,219	11	2005	24	11	463	Zone 1

Authors from two different countries appear in the same article; that is, a co-country. **Figure 4C** shows the results for co-countries in the era domain. As shown in **Figure 4C**, although the United States was ranks first worldwide in terms of publication volume, European countries had a relatively close cooperative relationship.

After analysis using CiteSpace, **Figure 4D** shows a document co-citation network diagram containing 832 nodes, 3,503 links, and 15 main clusters. The modularity Q value was 0.7918, and the weighted mean silhouette S was 0.9004.

A literature co-citation analysis of ERAS studies yielded 15 co-citation categories, marked by their citation index terms. To obtain the key cluster of the cited references, log-likelihood tests (LLR) were used to select the noun phrase from the title of the article in Citespace. The contour value of each cluster was >0.9, indicating reliable and meaningful results. **Figure 4E** summarizes the details of the 15 clusters using a timeline view to reflect the research patterns and emerging trends in the network map. Articles with the strongest citation bursts showed a significant increase in interest in ERAS. **Figure 4F** shows the 25 strongest references from 2008 to 2020.

Collaborative World Map as a Measure of the Social Structure: There were 709 collaborations between authors from different countries. The world map (**Figure 4G** and **Supplementary material**) shows that the most frequent cooperation was between the United States and Canada (24), followed by the United Kingdom and Canada (25), Canada and Sweden, and the United Kingdom and Sweden (23).

Conceptual Framework and Thematic Evolution

Based on the relationship between the keywords plus, the research content was roughly divided into several topics. The identified topics were categorized into a strategic map to analyze the importance and development of the research topic. The strategy map was based on the full-time span from

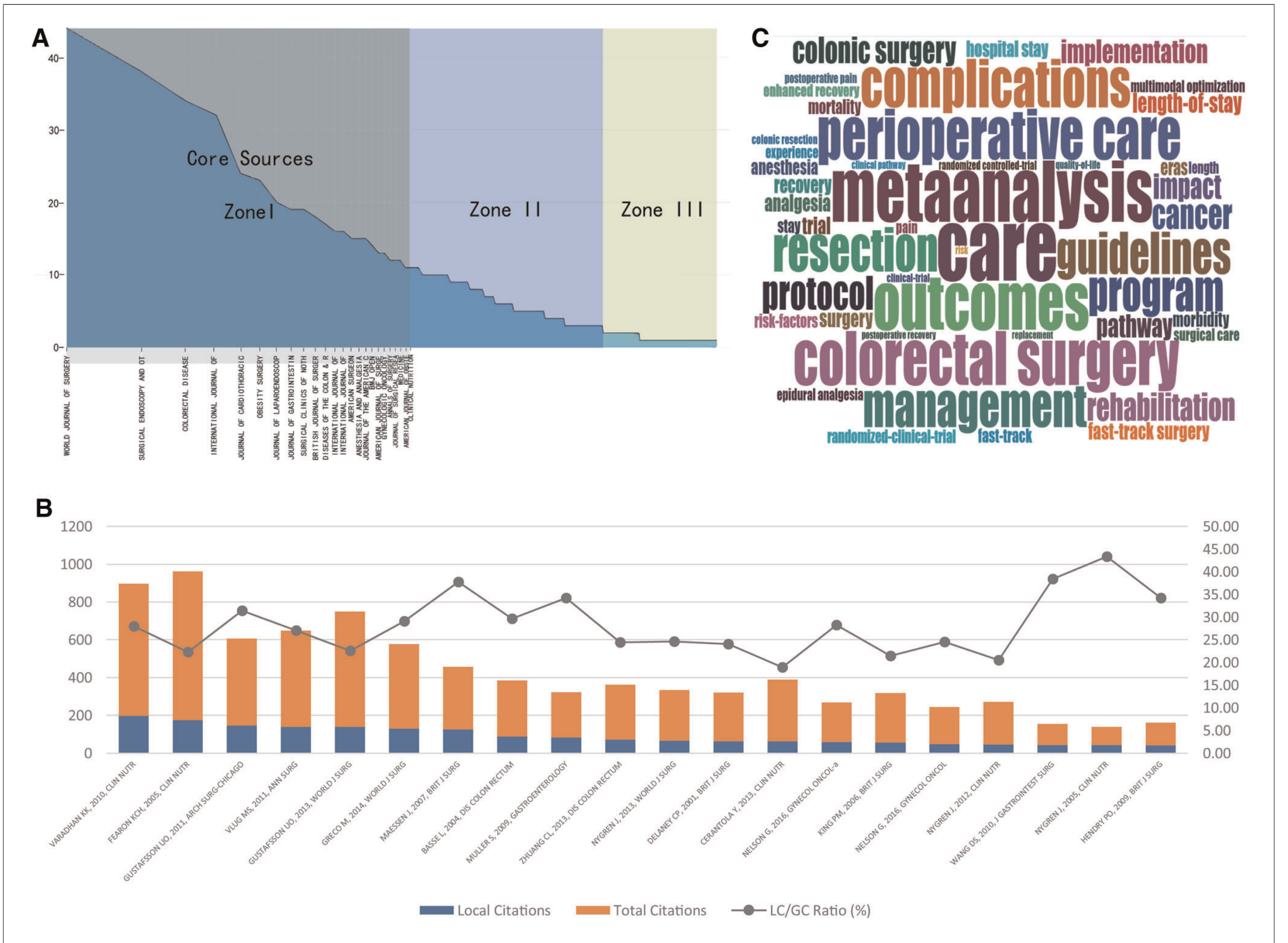

FIGURE 3 | (**A**) Journal Rankings According to the Bradford Law. (**B**) Top 20 of the Most Globally Cited Article and their located cited. (**C**) Word cloud based on the most frequent words (Keywords Plus) used in the articles on ERAS.

2001 to 2020. We used the first 400 keywords, but the items displayed in the cluster were set to a minimum frequency of 40. The number of representative labels in each theme was set to three so that the thematic map based on density (Y-axis) and centrality (X-axis) could be obtained, as shown in **Figure 5**. The centrality measured the importance of a topic, and density measured the development of the topic. The topics appearing in the lower left were the emerging or declining topics, which are new topics that can emerge better or decline from the research field. The upper right panel represented high density and high centrality. The developed theme of this section was the motor theme, and was necessary.

Thematic evolution showed the historical development of the ERAS literature. The use of keywords and topic evolution described the history and evolution of the topics. This time division was based on the author's subjective judgment while allowing for a better representation of the evolution of the subject. The first part was from 2001 to 2006, the second from 2007 to 2011, the third from 2012 to 2016, and the last from 2017 to 2021. **Figure 6** shows the topic evolution of the keyword plus (**Supplementary material**).

DISCUSSION

Fast-track surgery (FTS) or ERAS is the inevitable result of the development of medical theory and technology, "Pain and Risk "Free" was the goal of surgery (26). The connotation of ERAS was to reduce the body's stress response to trauma, promote rapid functional recovery, reduce the incidence of clinical complications, and shorten the length of hospital stay. A large number of clinical studies have proven that perioperative process optimization and multidisciplinary collaboration of minimally invasive techniques can improve the treatment effects, reduce medical interventions (over-treatment), and promote patient recovery (27). For ERAS to be practiced clinically, its philosophy and associated pathways must be based on evidence-based medicine and multidisciplinary

TABLE 3 | Top 20 most cited articles.

Paper	Most local cited				Most global cited			
	Local citations	Normalized local citations	Normalized global citations	Total citations	TC per year	Normalized TC	LC/GC ratio (%)	Year
The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials	196	16.44	12.87	701	58.4167	12.8686	27.96	2010
Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection	175	11.72	10.48	787	46.2941	10.4846	22.24	2005
Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery	145	10.22	7.83	462	42	7.8345	31.39	2011
Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study)	138	9.73	8.67	511	46.4545	8.6655	27.01	2011
Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS(®)) Society recommendations	138	12.12	10.15	611	67.8889	10.1523	22.59	2013
Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials	130	15.23	11.71	447	55.875	11.7105	29.08	2014
A protocol is not enough to implement an enhanced recovery programme for colorectal resection	125	10.11	5.33	331	22.0667	5.327	37.76	2007
Colonic surgery with accelerated rehabilitation or conventional care	88	5.46	3.56	297	16.5	3.5569	29.63	2004
A fast-track program reduces complications and length of hospital stay after open colonic surgery	82	7.09	5.13	240	18.4615	5.1268	34.17	2009
Enhanced recovery after surgery programs versus traditional care for colorectal surgery: a meta-analysis of randomized controlled trials	71	6.24	4.84	291	32.3333	4.8352	24.40	2013
Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS(®)) Society recommendations	66	5.80	4.45	268	29.7778	4.4531	24.63	2013
'Fast track' postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvic colorectal surgery	62	6.89	4.34	258	12.2857	4.3361	24.03	2001
Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS(®)) society recommendations	62	5.45	5.45	328	36.4444	5.45	18.90	2013
Guidelines for pre- and intra-operative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations–Part I	59	10.44	8.00	209	34.8333	8.0019	28.23	2016
Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme	56	5.37	5.95	261	16.3125	5.9487	21.46	2006
Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations–Part II	48	8.49	7.50	196	32.6667	7.5042	24.49	2016
Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations	46	4.61	3.55	224	22.4	3.5527	20.54	2012

(*continued*)

TABLE 3 | Continued

Paper	Most local cited				Most global cited			
	Local citations	Normalized local citations	Normalized global citations	Total citations	TC per year	Normalized TC	LC/GC ratio (%)	Year
Fast-track surgery improves postoperative recovery in patients with gastric cancer: a randomized comparison with conventional postoperative care	43	3.61	2.06	112	9.3333	2.056	38.39	2010
A comparison in five European Centres of case mix, clinical management and outcomes following either conventional or fast-track perioperative care in colorectal surgery	42	2.81	1.29	97	5.7059	1.2923	43.30	2005
Determinants of outcome after colorectal resection within an enhanced recovery programme	41	3.55	2.56	120	9.2308	2.5634	34.17	2009

collaboration. It should not only reflect the core concept of accelerating recovery, but should consider the patient's underlying diseases, types of surgery, perioperative complications, and other specific conditions. Moreover, in-depth clinical studies are required to demonstrate the safety, feasibility, and necessity of ERAS-related pathways.

According to a bibliometric analysis, the United States has the largest number of ERAS-related articles published followed by China. Despite the large number of published reports in China, there were fewer citations. Most of the top 20 most-cited articles were published in the early period of ERAS in Europe and the United States because ERAS originated in Europe and the United States, and were the first to carry out relevant research on ERAS (28, 29). In contrast, as a North American country, Canada was ranks fourth in the total number of articles published; however, the proportion of multi-country publications was high, and most of the articles were from the McGill University, which reflects the high concentration of research. The university with the second highest research focus was the MD Anderson Cancer Center in the United States, which may be due to the fact that the previous studies on ERAS were on radical surgery for patients with tumor.

Earlier researches on ERAS were mainly related to surgery, therefore, the most cited journals in zone 1 of the Bradford's Law were journals of the surgery discipline, such as the WORLD JOURNAL OF SURGERY, SURGICAL ENDOSCOPY AND OTHER INTERVENTIONAL TECHNIQUES, and COLORECTAL DISEASE. According to the Word Cloud, "colorectal surgery" and "resection" played important roles in surgery and colorectal surgery was the most mature surgical method that used ERAS. With ERAS, the hospital stay and complications in patients who underwent colorectal surgery effectively reduced without an increase in the readmission rates (30).

The ERAS Society was founded in 2001, and in 2005, the first worldwide expert consensus on accelerated recovery for colon resection was developed (29). In addition, relevant studies on ERAS mainly focused on research directions, such as meta-analysis and perioperative care. Randomized controlled trials and meta-analyses have been used in ERAS studies, and a large number of high-quality clinical studies are important for further evidence-based practice and guidelines development. Meta-analysis and clinical research have mainly focused on perioperative nursing, postoperative complications, length of hospital stay, final results, and process management (25, 31). In addition to the ERAS, perioperative care was very important in the implementation to surgical management. Currently, the relevant care specifications are clearly specified in the guidelines for various specialties (7–9). Clinical evidence has shown that perioperative FTS care can promote postoperative rehabilitation and shorten the hospitalization time of patients with gynecological diseases (32). Magheli provided FTS care to 50 patients undergoing laparoscopic radical prostatectomy, which significantly improved the recovery time of the bowel function and defecation time, shortened the postoperative hospital stay, and improved the overall satisfaction rate of patients (33).

Among the 15 clusters obtained through CiteSpace cluster analysis, most studies on ERAS were still related to surgery, but were developed from colorectal surgery in the early stages of cardiac surgery, neurosurgery, and other surgical disciplines. Guidelines are emerging for other general surgery procedures (pancreaticoduodenectomy, elective colon surgery, and elective rectal and pelvic surgery) (10, 11, 24). ERAS has gained acceptance worldwide over time and is widely used in a range of surgical specialties, such as urology, orthopaedics, and obstetrics and gynecology. Although a study on FTS was published in cardiac surgery as early as 1994 (34), it was not until 2015 that Zaouter from France first reported the systematic application of ERAS in cardiac surgery (35). In 2018, Noss systematically reviewed the relevant issues of ERAS in cardiac surgery and provided an in-depth consideration of the existing problems (36). Many urological studies have

TABLE 4 | Most frequent words.

Keywords plus		Author keywords	
Words	**Occurrences**	**Words**	**Occurrences**
care	285	enhanced recovery after surgery	301
metaanalysis	254	eras	159
outcomes	231	enhanced recovery	149
colorectal surgery	222	colorectal surgery	117
perioperative care	209	fast-track surgery	85
complications	200	length of stay	84
resection	183	fast track	71
management	180	perioperative care	70
guidelines	174	laparoscopy	60
program	168	fast-track	52
protocol	141	surgery	49
cancer	122	enhanced recovery after surgery (eras)	46
rehabilitation	115	rehabilitation	38
colonic surgery	111	colorectal cancer	36
impact	104	complications	34
implementation	98	fast track surgery	33
pathway	96	outcomes	31
randomized clinical-trial	96	postoperative complications	31
length-of-stay	83	bariatric surgery	30
surgery	73	colorectal	29
Titles		**Abstracts**	
Words	**Occurrences**	**Words**	**Occurrences**
surgery	1,363	patients	5,596
recovery	1,092	surgery	3,898
enhanced	981	eras	3,540
patients	316	recovery	2,527
fast_track	241	postoperative	2,454
colorectal	237	stay	1,859
program	226	hospital	1,726
Eras	185	study	1,515
protocol	178	enhanced	1,507
Study	167	days	1,467
pathway	163	care	1,291
cancer	156	protocol	1,254
laparoscopic	153	complications	1,226
undergoing	140	length	1,221
postoperative	124	results	1,169
randomized	122	compared	1,028
implementation	120	outcomes	999
Trial	120	time	969
Care	119	undergoing	950
perioperative	109	significantly	932

reported the use of ERAS in the perioperative period of laparoscopic nephrectomy (37), open partial nephrectomy (38), laparoscopic radical prostatectomy (39), and TVT or TVT-O (40). Compared to the control group, the duration of hospital-stay in the patients who underwent ERAS was significantly shorter, with better pain control and patient satisfaction. Similarly, to promote and regulate the use of ERAS in gynecology, the International ERAS Society in 2016 proposed guidelines for the use of ERAS in gynecology/gynecological oncology (41, 42).

After more than 20 years of research, evidence-based medicine demonstrated the effectiveness of ERAS in a rational manner, and ERAS models have demonstrated unprecedented advantages in the recovery of patients undergoing surgery (28). From the thematic maps, studies on complications, impact, length of hospital stay, resection, and cancer were mature, and several of the research directions were supported by evidence-based evidence in the guide. However, research topics such as meta-analyses, colorectal surgery, and perioperative care are declining despite the current large number of studies. Similarly, the thematic evolution of ERAS research in the past 20 years showed that ERAS application and anesthesiology research in tumor surgery were prominent in 2006–2010, while in the next five years, more attention will be paid to the comprehensive management of the perioperative period and the emergence of large randomized controlled clinical trials. Simultaneously, ERAS-related meta-analyses began to appear (43). After 2015, patient-reported outcomes were the purpose of ERAS. More attention has been paid to the comfort and safety of patients in hospitals, as well as the reduction of surgical complications, rather than the reduction of hospital days and cost alone (44–47).

ERAS is not a new technology but an integrated and innovative management mode. Its theoretical system has been relatively well-developed after more than 20 years of development. ERAS concepts and models in different disciplines need to consider the characteristics of their respective disciplines; therefore, there are some differences. Despite the success of the ERAS concept, it still has several challenges. The implementation of the ERAS protocol requires good patient and doctor compliance. A multicenter study found that a reduction in the complications was positively correlated with ERAS compliance ($OR = 0.69$, $P < 0.001$) (48, 49). At the same time, team cooperation and continuous quality improvement plans are required. The team will formulate the ERAS plan and target management, such as the length of stay, and continue to adhere to and learn the summarized strategies (50). For example, many hospitals in Canada have continuously improved and perfected the clinical practice guideline (CPG) with the application of the "Knowledge-to-Action Cycle" (51), thus slimming the ERAS protocol and increasing the clinical application compliance. Preoperative assessment, preparation, and treatment of patients with high-risk factors and reduction in the failure rate of the ERAS protocols are the major measures to increase

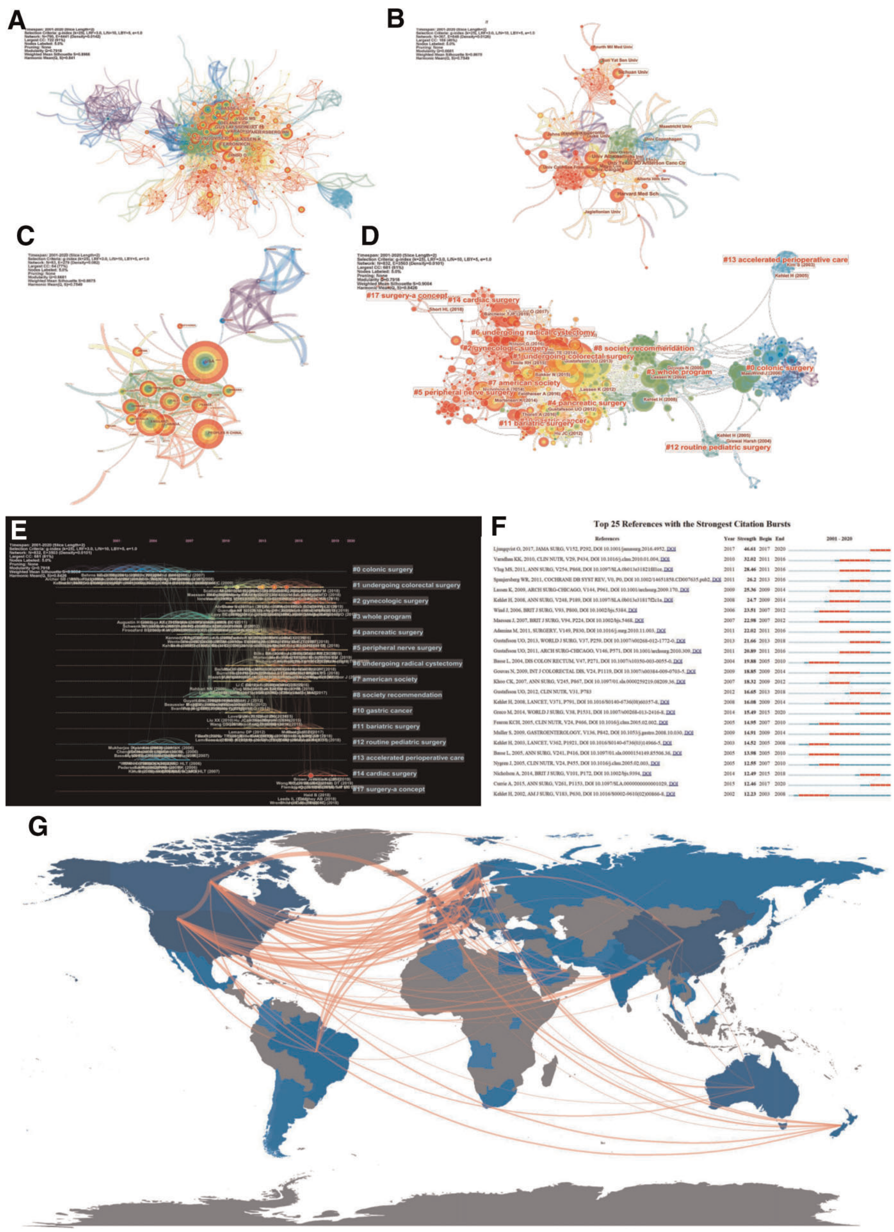

FIGURE 4 | (**A**) An author cooperation map related to ERAS research from 2001 to 2020. (**B**) An institution cooperation map related to ERAS research from 2001 to 2020. (**C**) A country cooperation map related to ERAS research from 2001 to 2020. (**D**) Reference co-citation map related to ERAS research from 2001 to 2020. (**E**) The timeline view of cited reference related to ERAS. (**F**) Top 25 references with the strongest citation bursts. (**G**) The country collaboration map of the global authors of the ERAS research.

patient compliance (52–54). Based on multimodal or multidisciplinary collaboration, the preoperative emphasis on patient education, communication, and collaboration underpins the success of ERAS (55, 56).

Although ERAS has many advantages and is accepted by doctors, there may be limitations to its future use. ① Firstly, the doctors and patients rely on "traditional practices" and "safety considerations." ② Secondly, from the different systemic conditions, diseases, surgical procedures and hospitals, it was concluded that the ERAS protocols must be "diversified and individualized," which makes them less evidence-based. ③ Thirdly, the combination of different disciplines may make ERAS processes too convoluted, impeding accelerated recovery. The payment system of medical insurance and cultural background influence the promotion of ERAS programs.

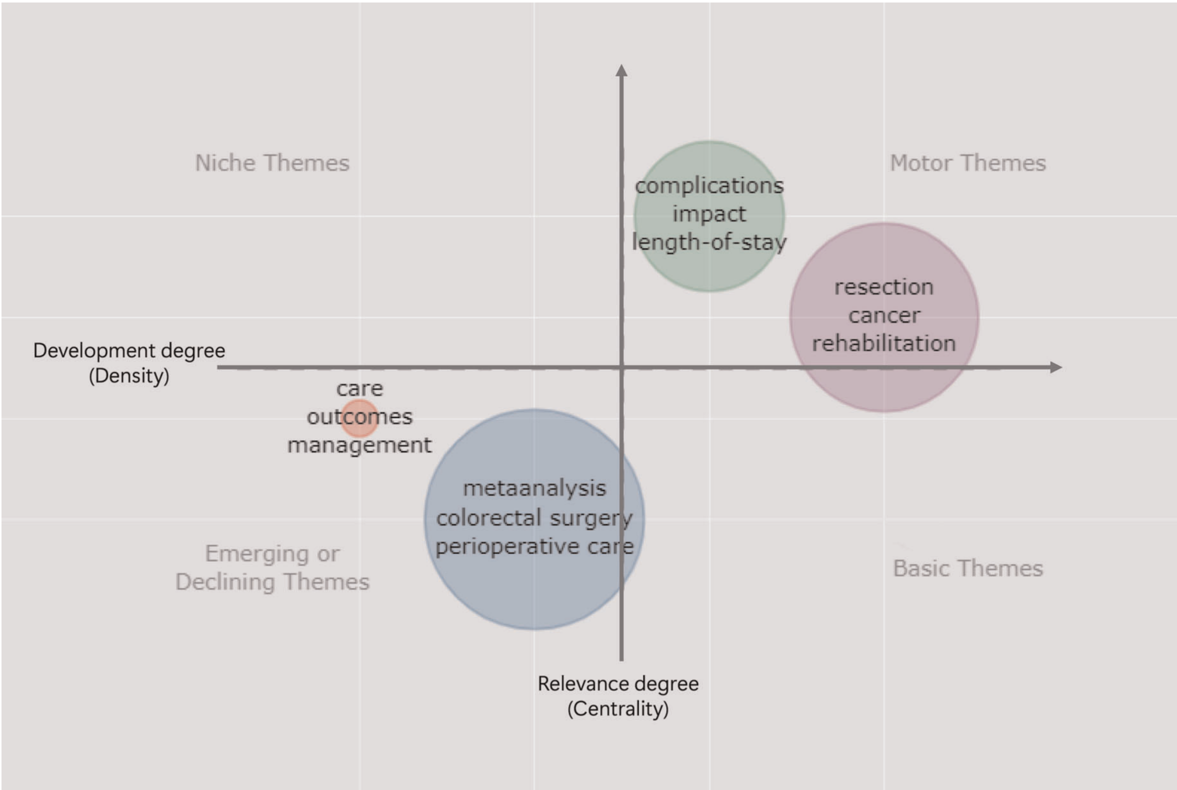

FIGURE 5 | The strategy map of identified topics clustered by keywords plus.

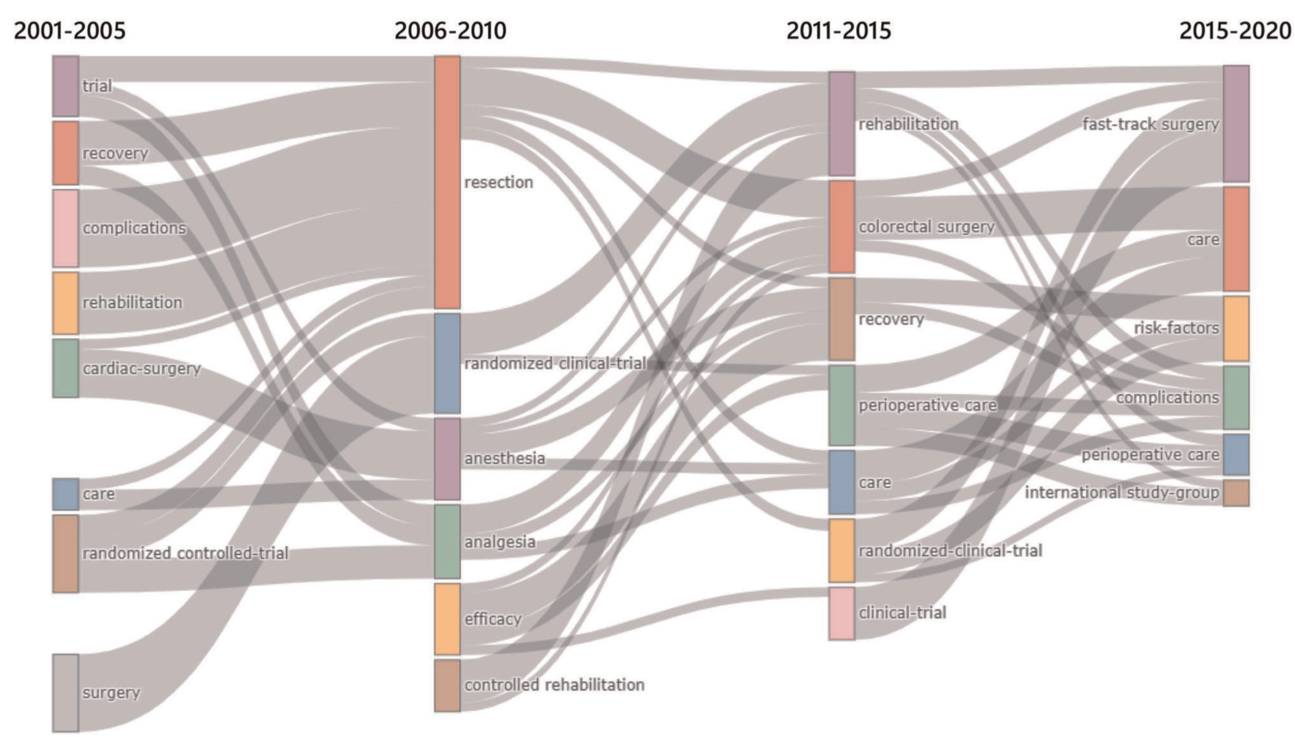

FIGURE 6 | Thematic Evolution of ERAS research from 2001 to 2020.

The literature included in this study is from the core collection database of WOS, which has high quality studies, but selection bias cannot be avoided. It is well known that various databases have their advantages and disadvantages, but we chose the WoS over PubMed because PubMed does not store reference metadata, and references were an important part of the research output indicators. In addition, according to the bibliometric research principles, there is a potential length time-lapse bias that puts newer articles at a disadvantage in receiving citations. Of course, bibliometric analyses of the same topic will be used by other authors, and our results may be compared with those of others in the future.

CONCLUSION

In this study, Bibliometrix and Citespace were used to analyze ERAS literature over the past 20 years. Despite the rapid development of ERAS in various disciplines, the effective coordination of multidisciplinary physicians and the change in patients' deeply rooted traditional views were the major obstacles to its further development. The bibliometric analysis conducted in this study is expected to provide a reference for the development of ERAS.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

DATA SHARING STATEMENT

The data are available from the authors upon request. Because of the policies of Clarivate, data cannot be shared openly.

AUTHOR CONTRIBUTIONS

MZ and DZ designed the study and drafted the manuscript. XW, XC, YW and YZ designed the statistical analysis plan. ZS and DZ reviewed the manuscript. All authors take responsibility for the appropriateness of the content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.894083/full#supplementary-material.

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CASE REPORT
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Laparoscopic Subtotal Gastrectomy and Sigmoidectomy Combined With Natural Orifice Specimen Extraction Surgery (NOSES) for Synchronous Gastric Cancer and Sigmoid Colon Cancer: A Case Report

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Background: Gastric cancer and colon cancer are rarely seen in clinic, but there are still related reports. For gastric cancer and simultaneous colon cancer, surgical resection is the main treatment. Traditional surgery requires an incision from xiphoid process to pubic symphysis. With the progress of minimally invasive technology, laparoscopic surgery is also used in the treatment of gastric cancer, but also in the abdominal incision to remove specimens and in vitro anastomosis of digestive tract. Taking specimens through the natural cavity as a new surgical method can not only reduce the abdominal incision, but also reduce the occurrence of wound-related complications. Here, we report a patient with gastric cancer and colon cancer who was treated in our hospital.

Case Summary: We report a series of patients with gastric cancer and colon cancer. upper abdominal pain was treated in our hospital for 6 months. electronic gastroscopy showed large irregular ulcers on the lesser curvature of the gastric antrum and biopsy showed poorly differentiated adenocarcinoma of the gastric antrum. The enhanced CT of abdomen and pelvis showed irregular thickening of gastric antrum wall, irregular thickening of sigmoid colon wall and no obvious enlarged lymph nodes around. Further electronic enteroscopy showed that the sigmoid colon showed cauliflower protuberance, the intestinal cavity was slightly narrow, the intestinal wall was stiff, and the biopsy pathology showed moderately differentiated adenocarcinoma of the sigmoid colon. No obvious abnormality was found in serological tumor indexes. We diagnosed gastric cancer with sigmoid colon cancer and the patient received Laparoscopic subtotal gastrectomy and sigmoidectomy combined with natural orifice specimen extraction surgery. At present, 12 months after operation, no clear tumor recurrence was found in the metastasis.

Conclusion: We should improve the understanding of gastric cancer and sigmoid cancer and combine examination with pathology to avoid misdiagnosis as metastatic cancer. Laparoscopic subtotal gastrectomy should be performed for tumors with no serosa invasion, body mass index <30 and tumor diameter <6.5 cm. Sigmoidectomy combined with natural nostril sampling is feasible.

Keywords: gastric cancer, sigmoid colon cancer, natural orifice specimen extraction surgery, laparoscopic surgery, case report

INTRODUCTION

With the popularity of gastroscopy and colonoscopy, gastric cancer and sigmoid colon cancer are often diagnosed at the same time. Surgical resection is still the main treatment method for gastric synchronous sigmoid colon cancer. Studies have shown that laparoscopic surgery is similar to open surgery in terms of safety, efficacy, and completeness of tumor resection (1–3). In recent years, specimen collection through the natural orifice has gradually been used in clinical practice as a new surgical method, which can reduce the incidence of wound-related complications while reducing abdominal incisions (4). For gastric cancer with sigmoid colon cancer, there have been reports of laparoscopic synchronous resection (5), but laparoscopic radical gastrectomy combined with radical sigmoid resection for sigmoid cancer combined with natural orifice specimens for the treatment of gastric cancer with sigmoid colon cancer is rarely reported. Recently, we treated a patient with gastric cancer with sigmoid colon cancer, and performed laparoscopic radical operation for gastric cancer and sigmoid colon cancer with specimens taken from the natural orifice. The report is as follows.

CASE PRESENTATION

Clinical History and Diagnosis

A 73-year-old male patient was admitted to our hospital for 6 months with epigastric pain. Physical examination revealed a soft abdomen, mild upper abdominal tenderness without rebound tenderness, and no obvious mass palpable throughout the abdomen. There was tympanic sound on percussion, negative mobile dullness, no percussion pain in the liver and kidney areas, and no enlarged lymph nodes were palpated in the bilateral supraclavicular areas. Laboratory tests showed no significant increase in tumor markers. Electronic gastroscopy: Huge irregular ulcers with irregular hyperplasia around the lesser curvature of the gastric antrum, surface erosions, and a little oozing blood were seen (**Supplementary Figure S1A**). Gastric biopsy pathology: poorly differentiated adenocarcinoma. Electronic colonoscopy showed that the sigmoid colon was 20–26 cm away from the anus with a cauliflower-like bulge, with hyperemia, edema and erosion on the surface, around the circumference, the intestinal lumen was slightly narrow, and the intestinal wall was rigid (**Supplementary Figure S1B**). Enhanced computed tomography (CT) of the abdomen showed irregular thickening of the gastric antrum wall, enhanced enhancement, no obvious surrounding lymph nodes (**Supplementary Figure S1C**), and the sigmoid colon had local wall thickness and no obvious surrounding swelling. Lymph nodes (**Supplementary Figure S1D**). Because the patients and their families requested surgical treatment, they signed the informed consent form for surgery. We conducted a multidisciplinary oncology consultation for the patient. After evaluating the patient's cardiopulmonary function and no obvious surgical contraindications, we decided to perform Laparoscopic subtotal gastrectomy and sigmoidectomy combined with natural orifice specimen extraction (NOSE) under general anesthesia with tracheal intubation.

Treatment

After successful anesthesia, take the lithotomy position, routinely sterilize the drape, take an incision of about 1 cm above the umbilicus, incision on the skin and all layers of the abdominal wall, insert a 10 mm trocar, establish a pneumoperitoneum, and the carbon dioxide pneumoperitoneum pressure is 10–12 mmHg, and then enter the abdominal cavity. Microscopic examination: no ascites, no metastasis to liver, peritoneum and pelvis. According to the results of preoperative examination and intraoperative exploration, we decided to perform complete laparoscopic radical resection of gastric cancer and sigmoid colon cancer with specimens taken through the natural orifice. We first underwent subtotal gastrectomy. 12 mm trocar was placed as the main operation hole above the midline of the right clavicle and below the costal edge of the left anterior axillary line, and 5 mm trocar was placed above the midline of the left clavicle and below the costal edge of the right anterior axillary line as an auxiliary operation hole. Distal subtotal gastrectomy and standard lymph node dissection were performed under laparoscopy. Digestive tract reconstruction was performed with Billroth II + Braun anastomosis.

To perform sigmoidectomy, 12 mm trocar was placed as the main operating hole at the medial 2 cm of the right anterior superior iliac spine and 5 mm trocar was placed at the left lower abdominal McDonnell's point (**Supplementary Figure S2**). Cut the sigmoid colon at the upper and lower 5 cm of the tumor, Cut open the distal intestine, disinfect with iodophor gauze, and remove the gauze through the rectum to prevent abdominal infection. Put the sterile protective bag into the abdominal cavity from the right 12 mm trocar, put the oval forceps through the anus, pull out one end of the sterile protective bag from the anus, and first put the nail head of the tubular stapler into the abdominal cavity by aseptic protective bag. Then the oval forceps were used to remove the stomach and sigmoid colon specimens successively through the anus. After the specimen was removed, the aseptic protective bag was closed and protruded through the anus (**Supplementary Figure S3**). Close the broken end of the rectum, insert the nail anvil head of the tubular stapler in the proximal colon by reverse puncture, and insert the tubular anastomosis through the anus for end-to-side anastomosis of the rectosigmoid colon, and the anastomosis can be strengthened with absorbable sutures. The abdominal cavity and pelvic cavity were washed, no active bleeding was examined. Abdominal drainage was placed in the splenic fossa, under the gallbladder and in the pelvis and suture the abdominal incision (**Supplementary Figure S4A**).

The operation time was 365 min, the blood loss was 50 mL, specimens of subtotal gastrectomy and sigmoid colon in **Supplementary Figure S4B**. The patient got out of bed 36 h after the operation and was discharged from the hospital 10 days later. Postoperative pathology: (1) Gastric poorly differentiated adenocarcinoma, with an area of 4.5 cm × 3.5 cm, invading the full thickness of the gastric wall, no clear nerve invasion and intravascular tumor thrombus, positive serosal surface, and 48 lymph nodes were detected, none of which were found. See cancer metastasis, no cancer metastasis in omentum tissue, mouth, anus clean margins. (2) Moderately differentiated adenocarcinoma of the sigmoid colon, with an area of 3.5 cm × 2 cm, invading the entire thickness of the intestinal wall and reaching the fat, with tumor thrombi in the vessels, no clear nerve invasion, clean serosa, and 17 lymph nodes were detected around the intestine, all of which were No cancer metastasis was found, the mesenteric resection margin and the surrounding near incision margin were clean, and the mouth and anal incision margins were clean.

Outcome and Follow-Up

There were no complications after the operation, and the patient was discharged smoothly. As of 12 months after operation, no tumor recurrence or metastasis was found.

DISCUSSION

Multiple primary cancer (MPC), also known as compound cancer or repeat cancer, refers to the occurrence of two or more independent primary cancers in the same individual at the same time or in succession. We can understand that (1) every tumor is malignant; (2) the tumor is not the recurrence or metastasis of other tumors; for multiple primary cancers of the digestive system, with the popularization of endoscopy and CT examination, its detection The incidence rate continues to increase, and pathological diagnosis is still the gold standard for the diagnosis of multiple primary cancers. In this case, gastric cancer was first diagnosed by electronic gastroscopy, and sigmoid colon was found to occupy the sigmoid colon during preoperative CT examination, and sigmoid colon cancer was confirmed by colonoscopy. It was a double primary cancer of gastric cancer combined with sigmoid colon cancer. Pre-evaluation is particularly important for the diagnosis of multiple primary cancers. If this patient was misdiagnosed as gastric cancer with colonic metastases, the opportunity for surgery may be missed. Although gastric cancer with colon cancer is rare in clinical practice, there are still 1.3%–3.9% of patients with gastric cancer and colon cancer at the same time. Therefore, it is necessary to use colonoscopy as a routine preoperative examination item for gastric cancer (6–8).

In laparoscopic surgery, whether the placement of trocar is reasonable or not is an important factor affecting the operation. The basic principle is that the operation is convenient, the instruments do not interfere with each other, generally the focus as the center into a fan or diamond distribution is the best. In this case, we first selected the umbilical 1 cm to place the first trocar as the observation hole. In gastric surgery, placing the observation hole above the navel can obtain a good surgical field of vision and is more conducive to the clearance of the upper edge of the pancreas. In sigmoid surgery, because the inferior mesenteric blood vessel is located at the umbilical level, if the observation hole is placed in the umbilical part or too close to the operation site, it is easy to cause lens contamination. Placing the observation hole above the umbilical can avoid this problem. At the same time, the auxiliary operation hole during subtotal gastrectomy can be used as an auxiliary operation hole for sigmoidectomy without additional incision, which reduces the postoperative pain and reduces the incidence of postoperative complications such as trocar hole infection and incision hernia.

For gastric cancer with colon cancer, the conventional surgical method requires an incision from the xiphoid process to the pubic symphysis, because such an incision can ensure thorough lymph node dissection at the same time as tumor resection, severe postoperative pain, and many wound complications. With the advancement of minimally invasive technology, laparoscopy can obtain clearer images and dissect more lymph nodes, but for gastric cancer with colon cancer, laparoscopic surgery also requires a small incision in the abdominal wall to facilitate removal of specimens and anastomosis outside the body. In this case, no additional abdominal incision is required, and rectosigmoid anastomosis can be performed through the anus. Yamamot et al. (9) believe that rectosigmoid end-to-side anastomosis is simple and convenient, and does not increase the risk of anastomotic leakage, and the stool is not in the rectosigmoid blind pouch, which indicates that the channel is well preserved. Pironi et al.

(10) believe that the use of tubular stapler for colorectal anastomosis is a valuable choice. Ikeda et al. (11) believe that manual suture can increase the strength of the anastomosis and reduce the incidence of anastomotic leakage. The operation of rectosigmoid double purse end-to-side anastomosis is simple and economical, and the anastomosis can be strengthened under laparoscope, but it should be noted that if the distal intestinal tube is too long and thin, it is difficult for the stapler to reach the closed end. Violent operation will cause intestinal wall tear or bleeding, resulting in postoperative anastomotic leakage, abdominal infection and other complications. Before anastomosis, we should dilate the anus properly, and then wipe the tubular stapler with iodophor, which can not only prevent infection but also increase the degree of lubrication. This tip can better deal with this problem. Secondly, after the completion of the anastomosis, it is necessary to check the patency of the distal and proximal intestines.

At present, NOSES is gradually used in clinical practice because of its few wound complications and quick postoperative recovery, especially in sigmoid resection. Sumer et al. (12) reported for the first time NOSES total laparoscopic palliative subtotal gastrectomy with colon cancer. The patient had advanced gastric cancer combined with colon cancer, gastrointestinal bleeding and obstruction occurred before surgery, and died of cachexia 3 months after surgery. After the patient was diagnosed with dual primary cancers, after multidisciplinary oncology consultation, it was decided to undergo complete laparoscopic radical resection of gastric cancer and sigmoid colon cancer with specimens taken through the natural orifice. Laparoscopic surgery on the stomach and colon is performed at the same time, both specimens can be pulled out through the rectum, no additional abdominal incision is required, avoiding incision-related complications (incision infection, fat liquefaction, incisional hernia), reducing pain and bringing better Beauty results, faster return to normal work and life. At present, the patient is still alive and healthy 12 months after the operation, and the weight has increased by 2 Kg compared with that before the operation.

However, not all patients are suitable for NOSES, and Izquierdo et al. (13) suggested that the tumor diameter <6.5 cm and the body mass index <30 could improve the prognosis of patients by implementing NOSES. In addition, the aseptic principle and the tumor-free principle are the basic principles that must be adhered to in all gastrointestinal surgical operations. At present, some scholars worry that NOSES will increase the probability of abdominal infection. In this case, the specimen was first placed in the rectal cavity before the specimen was pulled out through the natural orifice. Put the sterile plastic protective sleeve into the protective sleeve, first put the stapler into the abdominal cavity through the protective sleeve, and then drag the specimen out of the body through the protective sleeve, the tumor tissue does not fall off due to extrusion. Up to now, no tumor recurrence or metastasis has been found in the patient.

CONCLUSION

We should improve our understanding of MPC, and combine the examination and pathology to avoid misdiagnosing it as metastatic cancer. Secondly, for tumors that do not invade the serosa, body mass index <30, and tumor diameter <6.5 cm, laparoscopic subtotal gastrectomy should be performed. and sigmoidectomy combined with natural orifice specimen extraction surgery (NOSES) is feasible.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Research Ethics Committee of Weifang people's Hospital. The patients/participants provided their written informed consent to participate in this study.

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JQ: guarantees the integrity of the entire study and edited the manuscript. QZ and LY: prepared and edited the manuscript. GZ, XJ, and BL: performed the literature research, data analysis, and text proofreading. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Application Status and Prospects of Artificial Intelligence in Peptic Ulcers

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Peptic ulcer (PU) is a common and frequently occurring disease. Although PU seriously threatens the lives and health of global residents, the applications of artificial intelligence (AI) have strongly promoted diversification and modernization in the diagnosis and treatment of PU. This minireview elaborates on the research progress of AI in the field of PU, from PU's pathogenic factor *Helicobacter pylori (Hp)* infection, diagnosis and differential diagnosis, to its management and complications (bleeding, obstruction, perforation and canceration). Finally, the challenges and prospects of AI application in PU are prospected and expounded. With the in-depth understanding of modern medical technology, AI remains a promising option in the management of PU patients and plays a more indispensable role. How to realize the robustness, versatility and diversity of multifunctional AI systems in PU and conduct multicenter prospective clinical research as soon as possible are the top priorities in the future.

Keywords: peptic ulcer, artificial intelligence, gastric ulcer, complications, convolutional neural network

INTRODUCTION

Peptic ulcer (PU) is an inflammatory reaction and necrotizing lesion of the mucosa or submucosa under the action of various pathogenic factors. It often occurs in the gastrointestinal mucosa that performs the function of gastric acid secretion, of which the stomach and duodenum are the most common. It is estimated that the incidence of PU is 0.1%–0.3% per year, while its lifetime prevalence reaches as high as 5%–10% in the general population (1). Therefore, early diagnosis and prevention of PU is crucial to reduce the economic burden on global health.

Artificial intelligence (AI) refers to a modern technology that imitates human behavior and thinking through computer networks and is an interdisciplinary subject developed on the basis of computer science, information theory, determinism, neuropsychology, philosophy, linguistics, etc. (2). With the advent of the era of big data, AI has achieved rapid development in the field

Abbreviations: PU, peptic ulcer; GU, gastric ulcer; DU, duodenal ulcer; AI, artificial intelligence; ML, machine learning; DL, deep learning; CNNs, convolutional neural networks; DBNs, deep belief networks; *HP, Helicobacter pylori;* RFSNN, refined feature selection with neural network; RMIS, robot-assisted minimally invasive surgery; GI, gastrointestinal; AUC, area under the curve; GBS, glasgow–blatchford score; eiPDLA, end-to-end importance perception personalized DL method; LSTM, long short-term memory; NSAIDs, non-steroidal anti-inflammatory drugs; IPU-ML, idiopathic peptic ulcer ML mode; ANN, artificial neural network; CI, confidence interval; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy.

of image and speech recognition with the help of technological innovations such as machine learning (ML) and deep learning (DL). Among them, the most advanced and common one is the DL technology represented by convolutional neural network (CNN), which is currently widely used in many fields (3).

The concept of DL is inspired by the synaptic system of the human brain's neural network. It is composed of multiple layers of simple computing nodes that simulate the activities of the human visual cortex through complex connections. In terms of specific research content, DL mainly includes CNNs, self-coding neural networks and deep belief networks (DBNs) (4). DL can identify important features from a large database of images through a repeated learning process. The larger the data volume given to it, the more obvious the advantages of DL, namely, the faster and higher accuracy of recognition. In the medical field, DL-based intelligent systems can automatically extract and learn clinical data, which can not only help doctors diagnose diseases but also accurately predict prognosis. Currently, DL has been prominent in the diagnosis of lung cancer, breast cancer, brain cancer, prostate cancer, Alzheimer's disease and Parkinson's disease, and has also been widely reported in the clinical diagnosis and treatment of digestive diseases (5, 6).

The differential diagnosis of benign and malignant ulcers of the digestive tract is significantly important for subsequent treatment. However, macroscopic endoscopic diagnosis is sometimes very burdensome, since the accuracy of endoscopic diagnosis largely depends on the technical level and clinical experience of endoscopists. Moreover, massive image data also require considerable time and efforts. Fortunately, the emergence of AI can solve the above problems. This minireview elaborated on the research progress of AI in the field of PU, from its pathogenic factors, diagnosis, to management and complications (**Figure 1**). Moreover, the challenges and prospects in this field were also elaborated.

APPLICATION OF AI IN PU

AI in the Pathogenic Factors of PU

Helicobacter pylori (Hp) infection is one of the important pathogenic factors of PU. Statistics show that the positive rates of *Hp* in gastric ulcer (GU) and duodenal ulcer (DU) patients are 60%–80% and 90%, respectively (7, 8). In terms of pathogenesis, on the one hand, *Hp* can release urease to break down urea to produce NH_3, which destroys the acidic environment of the gastrointestinal tract. However, *Hp* can generate numerous toxin proteins that destroy the barrier system of the gastric mucosa. Therefore, early identification of *Hp* infection is essential in preventing PU. At present, noninvasive tests, such as urea breath and stool antigen tests, are still the first choice for the exclusion of *Hp* infection, while elderly people over 60 can select direct gastroscopy for

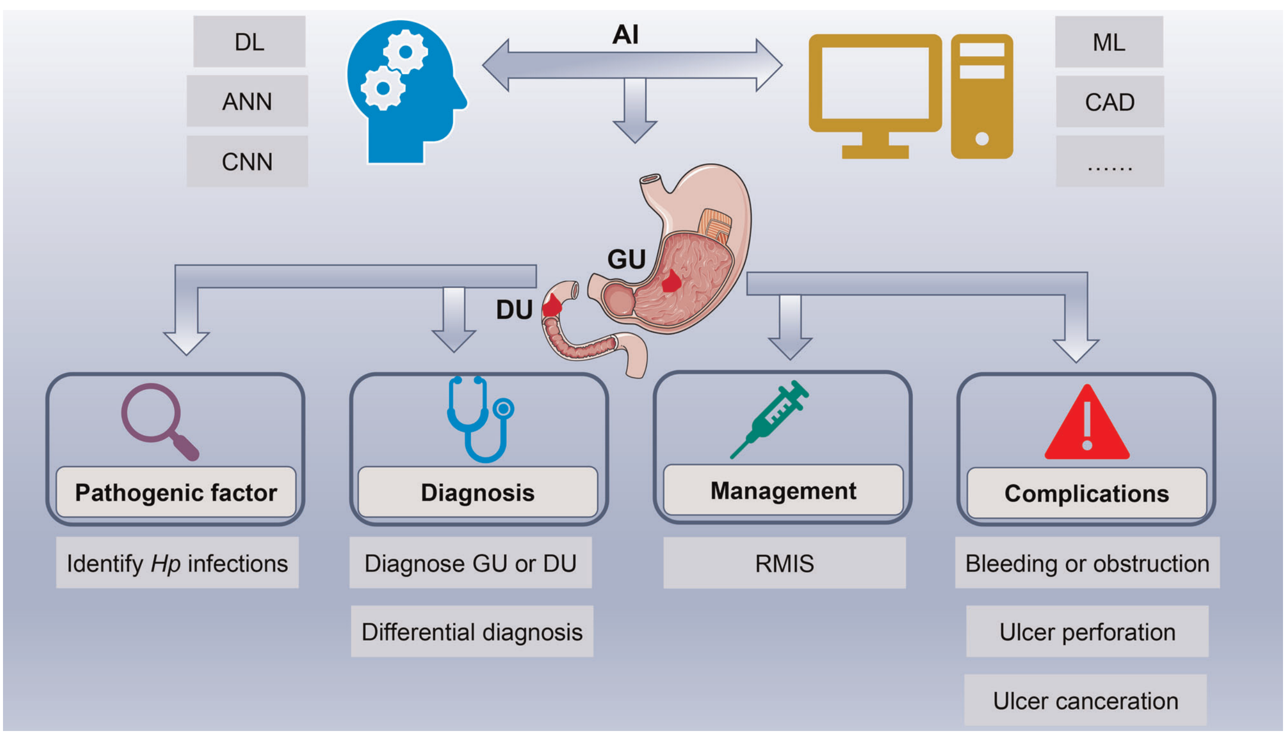

FIGURE 1 | Application of artificial intelligence in peptic ulcers. AI has achieved rapid development in the field of PU with the help of technological innovations such as ML, DL, and CNN. AI is widely applied in the field of PU, ranging from its pathogenic factors, diagnosis and differential diagnosis to management and complications. Abbreviations: AI, artificial intelligence; PU, peptic ulcer; ML, machine learning; DL, deep learning; CNN, convolutional neural network.

exclusion (9). However, most cases of subclinical *Hp* infection still rely on invasive biopsy, which takes time to avoid misdiagnosis. In addition, the severity of *Hp* infection needs to be measured by the inspector with the naked eye. This method is a subjective judgment, and there will inevitably be bias. Fortunately, the emergence of AI may shed light on the current dilemma.

The earliest application of AI technology in *Hp* infection recognition was in 2004. Huang et al. (10) first trained AI by using endoscopic images of 30 dyspeptic patients (15 *Hp* infections and 15 non-*Hp* infections) and established a refined feature selection with neural network (RFSNN) algorithm. Then, a verification test was performed on the images of the remaining 74 patients with dyspepsia. The sensitivity, specificity, and accuracy of the algorithm for identifying *Hp* infection reached 78.8%, 90.2%, and 85.1%, respectively. Since then, AI technology has developed rapidly, and CNNs have also emerged and quickly become an absolute leader in the field of medical image processing. In 2017, Shichijo et al. (11) adopted 32,208 photos from 1750 patients (735 *Hp* positive and 1,015 *Hp* negative) as a discovery cohort to train a CNN model, followed by validation of its diagnostic performance in an independent dataset. Finally, it was verified on a new data set to compare the difference between CNN and endoscopists in identifying *Hp* infections. The results showed that the sensitivity, specificity, accuracy, and diagnosis time of the CNN were 88.9%, 87.4%, 87.7% and 194 s, respectively, and these indicators were 79.0%, 83.2%, 82.4%, and 230 ± 65 min among 23 endoscopists. This showed that using a CNN to diagnose *Hp* infection has higher accuracy and costs less time than manual diagnosis by endoscopists.

There are many similar studies on AI in predicting *Hp* infection (12–16), all of which demonstrate AI's superior accuracy and sensitivity (**Supplementary Table S1**). However, AI's ability to recognize *Hp* infection still has some limitations that need to be overcome in the future. For example, the training and test sets of the above studies were all from one medical center or one country, and more continuous and rigorous external validation from various sources is necessary to ensure the credibility of conclusions.

AI in the Diagnosis and Differential Diagnosis of PU

Typical GU is more common in the gastric angle or lesser curvature. The lesions are mostly round or oval and generally solitary but can also be multiple. Most benign GUs are small in diameter and have regular edges. The surrounding mucosa often has hyperemia and edema, and the surface is mostly covered with white or yellow exudate. The morphology of DU is similar to that of GU. DU mostly occurs in the duodenal bulb, especially near the anterior or posterior wall of the gastric pylorus. Under normal circumstances, gastroscopy physicians can make corresponding clinical diagnoses based on the subject's gastrointestinal morphology or histological abnormalities, but if the situation is more complicated or the endoscopists are not fully sure, then they will take some specimens from around the lesion for pathological examination and give the final pathological diagnosis.

However, gastroscopy has two limitations: first, the sensitivity and specificity of diagnosis are closely related to the level of the examiner; if the examiner lacks clinical experience, misdiagnosis and missed diagnosis of PU can easily occur. Second, gastroenterologists need to check the abnormalities of numerous images or videos to detect the patient's lesions. However, considering the limited time and energy of clinicians, such a large number of images or videos will undoubtedly increase their workload.

The application of AI in PU diagnosis can be traced back to 2002. Saenz Bajo et al. (17) used the Neurone network to differentiate between PU and functional or idiopathic dyspepsia on the basis of clinical notes. The researchers classified and verified 81 patients who were clinically diagnosed with dyspepsia according to the presence of determined symptoms and finally found that the Neurone network successfully classified 81% of patients with negative and positive predictive values of 90% and 80%, respectively. To improve the diagnostic efficiency of GU, Al-Kasasbeh et al. (18) constructed a fuzzy logic decision-making system based on the variations in electrical resistance of acupuncture points, and the result was encouraging. The prediction error level of this decision-making system was not higher than 0.18, which once again proved the feasibility of AI application in PU.

In the past three years, with the increasingly widespread application of DL and CNN in the medical field, a body of researches on AI in PU diagnosis and differential diagnosis have emerged. To explore the ability of deep CNN to identify ulcers in wireless capsule endoscopic images, Wang et al. (19) first used 15,781 ulcer frames to train deep CNN, then used 2040 ulcer and 2,319 normal frames for verification, and finally performed it on 4,917 ulcer and 5,007 normal frames for testing. The results showed that the overall sensitivity of deep CNN in diagnosing ulcers was 89.7%, and the overall specificity and accuracy were both higher than 90%. Similarly, Alaskar et al. (20) built a CNN to detect its effect in diagnosing gastrointestinal ulcers. They trained and tested 336 and 105 photos respectively. Finally, the sensitivity, specificity and accuracy of the CNN in diagnosing gastrointestinal ulcers all reached an astonishing 100%.

In addition to its extraordinary performance in the diagnosis of PU, AI also plays an indispensable role in the discrimination of PU from other gastrointestinal diseases. To differentially diagnose the two most common stomach deformities (ulcers and bleeding), Khan et al. (21) constructed a rank-based deep features selection system that was verified by 4,000 video frames of ulcers, 4,000 video frames of bleeding and 4,000 normal ones, and found that the system only took 21.15 sec to identify all these video frames with an accuracy of 99.5%. This will undoubtedly greatly improve the work efficiency of gastroenterology clinicians. Majid et al. (22) and Xia et al. (23) established a CNN model to explore its differential diagnostic ability of four types of stomach infections (ulcer, polyp, esophagitis, and bleeding) and seven types of gastric lesions (erosion, polyp, ulcer, submucosal tumor, xanthoma, normal mucosa, and bleeding), respectively. The research results all proved the excellent differential diagnosis ability of CNN. The accuracy of the former reached 96.5%, while the sensitivity, specificity and accuracy of the latter were 96.2%, 76.2% and 77.1%, respectively. There are many similar studies (24–26), and detailed information can be seen in **Supplementary Table S2**.

AI in the Management of PU

In addition to ML and CNN, robots are also an outstanding representative of the development and application of AI in medicine. For example, the Da Vinci robot has played a crucial and irreplaceable role in multiple surgical disciplines, becoming the most representative achievement of minimally invasive surgery and intelligent medicine. The progress of robots in the field of PU is relatively slow, mainly because the proportion of surgical intervention in the treatment of PU is inherently small.

Sutures are one of the most difficult tasks in robot-assisted minimally invasive surgery (RMIS), because the surgeon needs to coordinate and control three or four tools, which will distract and consume the surgeon's energy and prolong the operation time. Gao et al. (27) proposed a robot autonomous suture task allocation method, and conducted a suture repair experiment for DU under the guidance of a surgeon. The results showed that this method obtained an optimal suture task allocation plan, which was beneficial to improve the intelligent degree of robot operation. Brungardt et al. (28) explored the feasibility of right-side robot-assisted transthoracic vagotomy for the treatment of marginal ulcers after gastric bypass surgery for the first time. The patient was a 43-year-old white female who underwent Roux-en-Y gastric bypass surgery at the age of 29. The author's team successfully ligated two vagus nerves through right-side robot-assisted thoracoscopic surgery, and the patient had a good prognosis. This successful case provides a new idea for expanding the application of robotic surgery in highly selective transabdominal vagotomy.

AI in the Complications of PU

Bleeding

When the mucosal damage of peptic ulcer has exceeded the basal layer of the mucosa, if it is further deepened, it may impair the blood vessels under the mucosa and cause bleeding. Bleeding in the digestive tract is the most common complication of PU. Nearly 20% of ulcer-related bleeding cases had no obvious alarm symptoms or signs before onset. Early recognition of the risk of bleeding and its related adverse outcomes can help doctors provide timely intervention, which may improve the prognosis.

Traditional prediction methods based on electronic health records usually do not take the correlation between static and dynamic data into consideration, but these data contain important information about the interaction effects which are important to fit the association between clinical materials and outcomes. Tan et al. paid attention to this point and developed a novel end-to-end importance perception personalized DL method (eiPDLA), which improved the accuracy of early bleeding risk at 1 year ahead with an AUC of 0.944 (29). The team also made relevant improvements in predicting mortality in patients with PU bleeding (30). The fatality rate of PU bleeding was greatly related to age, complications, severity of bleeding and recurrence of bleeding. Through the multiconvolution deep residual network (ResNet), deep fusion and long short-term memory (LSTM) methods, the AUC of the mortality prediction model for patients with PU bleeding reached 0.9353. ML models were also used to predict the risk of recurrent bleeding in idiopathic ulcers (31), which was characterized by occurring without *Hp* infection or the use of non-steroidal anti-inflammatory drugs (NSAIDs) and a high risk of recurrent bleeding and death. The idiopathic peptic ulcer ML (IPU-ML) model built in this study was trained by 22 854 patients with a diagnosis of PU disease and tested by 1,265 patients who were diagnosed with GI bleeding. It could identify patients who had 1-year recurrent ulcer bleeding, with an overall accuracy of 84.3% and an AUC of 0.775, especially idiopathic ulcer patients who were at low risk of recurrent ulcer bleeding.

AI also plays a role in guiding the practice of endoscopy. It could help identify the risk of PU bleeding under endoscopy according to the Forrest classification (32). After training on 2,378 static endoscopic images from 1,694 PU patients, the DL model had moderate to substantial consistency with advanced endoscopists on the test data set, which was higher than that of novice endoscopy. Therefore, this had certain application value for training young doctors and helping to make decisions in emergency endoscopy.

Perforation

PU perforation refers to the deep development of GU or DU, which penetrates the serosal layer and causes local flatulence and perforation. It is a severe clinical complication and a leading cause of operation-related death. Early identification of patients with perforated ulcers with poor prognosis is of great importance to patient risk stratification and identification of potential treatment. An artificial neural network (ANN) model was constructed to identify risk factors (increasing age, the presence of an active cancer, a delay from admission to surgery >24 h, hypoalbuminemia, hyperbilirubinemia and increasing creatinine values) of the 30-day mortality after surgery and their complex interactions with the mortality among patients with PU perforation (33). Among the 168 patients included in the study, the data of 117 patients were used to train the model, and 51 patients were used to test it. The mortality predicted by ANN showed an AUC of 0.90 (95% confidence interval [CI], 0.85–0.95). However, the study was restricted by its small sample size, and relied on predictor variables that were previously defined rather than extensive screening to build the model. Moreover, this research lacked true, secondary and external verification queues. Therefore, it is still necessary to enhance the accuracy of prediction to generate a more reliable model for future risk projection and clinical decision making of PU treatment.

Karargyris's team (34) developed a wireless capsule endoscope that could identify small intestinal perforated ulcers and polyps, but no similar identification method had been seen to assist in identifying PU perforations in endoscopy.

Pyloric Obstruction

Obstruction is often seen in DU and pyloric duct ulcers. The pylorus is the narrowest part of the digestive tract, with a normal diameter of approximately 1.5 cm, so it is prone to obstruction. PU may cause inflammation and swelling of the tissues around the pylorus, leading to obstruction. Temporary obstruction can be resolved after the ulcer has healed. However, pyloric ulcer scars can also cause intractable mechanical obstruction, which requires an endoscopic or surgical operation to relieve the obstruction. Unfortunately, to our knowledge, there is no relevant research report on the application of AI in pyloric obstruction.

Cancerization

DU rarely become cancerous, while GU may become cancerous, especially in those with *Hp* infection. More than 70% of early gastric cancer (EGC) patients have no obvious symptoms (35). As the disease progresses, symptoms of gastritis or gastric ulcer may gradually appear, including loss of appetite, nausea, indigestion, weight loss, upper abdominal discomfort or dull pain, and occasionally vomiting, fecal occult blood or melena, pantothenic acid deficiency, unexplained fatigue or progressive anemia. As an important basis for choosing treatment options for EGC, tumor classification and microscopic staging are very important. Esophagogastroduodenoscopy (EGD) biopsy is considered the current standard method for identifying gastric mucosal lesions. Endoscopists must have considerable experience and knowledge to correctly diagnose malignant ulcers, but this often requires long-term technical training and experience accumulation. Machines have fewer variations within and between observers, and the results are generally better than those of human endoscopists (36). The advancement of AI technology can provide higher sensitivity and specificity for the recognition and diagnosis of EGC under endoscopy.

The work of Ken Namikawa et al. proved that after training the AI-based diagnostic system with a large amount of data, the diagnostic accuracy of gastric cancer and GU classification reached a very high level, with a comprehensive diagnostic accuracy of 95.9% (37). Recently, E. Klang et al. built a CNN model aimed at distinguishing benign and malignant GU from endoscopic images in the western population (38). The study retrospectively collected endoscopic images of benign and malignant GU patients undergoing endoscopy at the Chaim Sheba Medical Center from 2011 to 2019. Every included image had a corresponding biopsy result that was sampled at the same time as endoscopic examination. Endoscope images from 2011 to 2015 and from 2016 to 2017 were used for training and validation, while the retained data from 2018 to 2019 were used to test the final model. In addition, some public pictures were obtained through the Google image search engine for pretraining the model. The final model showed an AUC of 0.91 to detect malignant ulcers. For a cut-off probability of 0.5, the model had a sensitivity of 92% and a specificity of 75%.

Moreover, a DL model based on endoscopic images to diagnose gastric mucosal lesions was developed by Joon Yeul Nam et al. (39). This model was based on a CNN algorithm to achieve the purpose of lesion detection, differential diagnosis (AI-DDx model), and depth of invasion detection (AI-ID model). A total of 1,366 patients from 2 referral centers with gastric mucosal lesions were consecutively included in this study. Representative endoscopic images of benign GU, EGC or advanced gastric cancer selected by experts for each patient were used as the training and testing sets, with the histological diagnoses as the gold standard. The results identified by the models were compared with the visual diagnosis and ultrasound endoscopy results of endoscopists with different working years. The results showed that the AI-DDx model performed better than novice and intermediate endoscopists, was comparable to expert endoscopists, and reached AUCs of 0.86 in both internal and external validation. The AUCs of the AI-ID model were 0.78 in the internal validation and 0.73 in the external validation, which were significantly better than the endoscopic ultrasonography results performed by experts. In general, there are numerous related studies on the application of AI in GU complications (40–43), and detailed information can be found in **Table 1**.

CHALLENGES AND PROSPECTS

Although significant progress has been made in the application of AI in the diagnosis, management and complication prediction of PU, there are still the following areas for improvement. First, the majority of related studies have a small sample size, and only include high-quality images for AI modeling, which cannot reflect the differences in inspection equipment covering hospitals at all levels and complex clinical scenarios. Second, most studies related to AI and GU are retrospective studies, which may overestimate the real performance of AI models due to selection bias. Moreover, few studies have evaluated the auxiliary role of AI systems for endoscopists, especially juniors. Finally, most studies only consider a certain aspect of clinical information such as imaging or biomarkers, and the integration of clinical multimodal data seems essential to further improve the performance of AI systems.

Despite the fact that AI has made major breakthroughs in the field of PU, we have more expectations for the optimization of AI systems. For instance, how can AI algorithms suitable for different scenarios be developed to achieve robust, versatile and diverse multifunctional AI systems in the PU field? How can a multifunctional AI system be integrated in the future to realize the whole process management of PU lesions from risk assessment and diagnosis to treatment? Furthermore, with the gradual improvement of residents' health awareness, an increasing number of people take health check-ups. It is hoped that in the future, different endoscopic images from healthy mucosa to severe PU can be collected to study mucosal and microvascular changes before lesions occur to identify GU lesions at an early stage. Finally, and most importantly, it is urgent to carry out multicenter and large-sample clinical research on the application of AI in PU, hoping to provide a solid theoretical basis for the

TABLE 1 | Summary of applications of AI in PU's complications.

Ref.	Year	AI technology	Research Objectives	Training and Validating set	Outcomes
Karakitsos et al. (40)	1998	ANN	To discriminate benign and malignant gastric cells	2,500 cells from 23 cancer, 19 gastritis and 58 ulcer cases for training, 8,524 cells from the same cases for testing	Correct classification of >97% benign cells and >95% malignant cells, overall accuracy of >97%
Grossi et al. (41)	2008	ANN	To recognize patients at high risk of death for nonvariceal upper GI bleeding	807 patients with nonvariceal upper GI bleeding	Average sensitivity of 89.2%, average specificity of 82.9%, average accuracy of 86%, and AUC of 0.87
Rotondano et al. (42)	2011	ANN	To predict mortality in patients with nonvariceal upper GI bleeding	2,380 patients with nonvariceal upper GI bleeding	Sensitivity of 83.8%, specificity of 97.5%, accuracy of 96.8%, and AUC of 0.95
Søreide et al. (33)	2015	ANN	To predict outcomes in patients with perforated gastroduodenal ulcers	117 patients for training and 51 patients for testing	AUC of inclusive, multifactorial ANN model is 0.90
Tan et al. (30)	2018	Deep residual network	To predict PU bleeding mortality	6,367 patients diagnosed with PU bleeding	AUC of 0.94 for PU bleeding mortality prediction
Wong et al. (31)	2019	ML	To identify patients at high risk for recurrent ulcer bleeding	22 854 patients with PU for training and 1,265 patients with PU for testing	Overall accuracy of 84.3% and AUC of 0.78
Lee et al. (43)	2019	Deep neural network and transfer-learning approach	To discriminate benign ulcer and cancer	180 normal, 200 benign ulcer, and 337 cancer images for training and 20, 30, 20 images for testing	Accuracies of discriminating Normal vs cancer, Normal vs ulcer, and Cancer vs ulcer were 96.5%, 92.6% and 77.1%
Nakashima et al. (37)	2020	Advanced CNN	To discriminate gastric cancers and gastric ulcers	13,584 gastric cancer and 4,826 gastric ulcer images for training, 739 gastric cancer images and 720 gastric ulcer images for validation	Sensitivity of 93,3%, specificity of 99.0% and positive predictive value of 99.1% for gastric ulcer
Tan et al. (29)	2021	A novel end-to-end importance perception personalized deep learning method	To predict bleeding risk	6,367 patients with peptic ulcer bleeding	AUC of 0.944 at 1 year ahead of risk prediction
Klang et al. (38)	2021	CNN	To discriminate benign and malignant GU	1,299 images for training, 364 images for validation and 315 images for testing	Sensitivity of 92%, specificity of 75% and AUC of 0.91 for detecting malignant ulcers
Nam et al. (39)	2021	AI-differential diagnosis	To diagnose gastric mucosal lesions (GU, EGC, AGC)	1,009 patients for training, 112 patients for internal validation and 245 patients for external validation	AUC of 0.86 in diagnostic performance for both internal and external validation

AI, Artificial intelligence; PU, Peptic Ulcer; ANN, Artificial Neural Networks; CNN, Convolutional Neural Network; GI, Gastrointestinal; DL, Deep Learning; EGC, Early Gastric Cancer; AGC, Advanced Gastric Cancer; AUC, Area Under the Curve; Hp, Helicobacter pylori.

transformation and application of AI systems (**Supplementary Figure S1**).

CONCLUSION

This minireview elaborates on the research progress of AI in the field of PU, from PU's pathogenic factor *Helicobacter pylori (Hp)* infection, diagnosis and differential diagnosis, to its management and complications (bleeding, obstruction, perforation and canceration). Finally, the challenges and prospects of AI application in PU are prospected and expounded. It provides us with an in-depth understanding of the research status of AI in the PU field. Numerous preclinical and clinical studies have clearly demonstrated the feasibility and safety of AI, which not only ensures the diagnostic accuracy but also greatly improves diagnostic efficiency. AI unquestionably makes a significant contribution to reducing the workload of gastrointestinal endoscopists. At the same time, AI still has some limitations in the field of PU, such as an insufficient research sample size, and existing conclusions are mainly based on retrospective research. How to realize the robustness, versatility and diversity of multifunctional AI systems in PU and conduct multicenter prospective clinical research as soon as possible are the top priorities in the future.

AUTHOR CONTRIBUTIONS

P-yZ and KH performed the majority of the writing, prepared the figures and tables. R-qY and CR edited and revised the manuscript. X-hD designed the study; all authors approved the final version to be published. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Toward Exempting from Sentinel Lymph Node Biopsy in T1 Breast Cancer Patients: A Retrospective Study

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Background and Objective: Sentinel lymph node biopsy (SLNB) is used to assess the status of axillary lymph node (ALN), but it causes many adverse reactions. Considering the low rate of sentinel lymph node (SLN) metastasis in T1 breast cancer, this study aims to identify the characteristics of T1 breast cancer without SLN metastasis and to select T1 breast cancer patients who avoid SLNB through constructing a nomogram.

Methods: A total of 1,619 T1 breast cancer patients with SLNB in our hospital were enrolled in this study. Through univariate and multivariate logistic regression analysis, we analyzed the tumor anatomical and clinicopathological factors and constructed the Heilongjiang Medical University (HMU) nomogram. We selected the patients exempt from SLNB by using the nomogram.

Results: In the training cohort of 1,000 cases, the SLN metastasis rate was 23.8%. Tumor volume, swollen axillary lymph nodes, pathological types, and molecular subtypes were found to be independent predictors for SLN metastasis in multivariate regression analysis. Distance from nipple or surface and position of tumor have no effect on SLN metastasis. A regression model based on the results of the multivariate analysis was developed to predict the risk of SLN metastasis, indicating an AUC of 0.798. It showed excellent diagnostic performance (AUC = 0.773) in the validation cohort.

Conclusion: The HMU nomogram for predicting SLN metastasis incorporates four variables, including tumor volume, swollen axillary lymph nodes, pathological types, and molecular subtypes. The SLN metastasis rates of intraductal carcinoma and HER2 enriched are 2.05% and 6.67%. These patients could be included in trials investigating the SLNB exemption.

Keywords: T1 breast cancer, SLNB, exempting, axillary surgery, molecular subtypes

INTRODUCTION

Breast cancer has the highest incidence rate among female malignant tumors, accounting for 24.2% of all new cases each year (1). Breast cancer treatment drugs are constantly evolving, as is the concept of surgery. From the initial "expanded radical treatment" to "modified radical treatment," and to the current "breast-conserving surgery," all of them reflect that breast cancer surgery focuses not only on effective treatment, but also on maximizing aesthetics and minimizing trauma.

SLN is the first regional lymph node from the primary tumor metastasis and the first lymph node capable of receiving lymph fluid from a specific organ and region (2). It can be used as a treatment and prognostic factor for breast cancers (3–5). Therefore, SLNB can predict the metastasis status of ALNs with a low false-negative rate, allowing more patients to avoid upper limb pain, sensory loss, and lymphedema caused by axillary lymph node dissection (6, 7). However, approximately 65%–70% of patients have suffered from unnecessary invasive axilla surgery (8, 9). This raises the question of whether we can pinpoint who might avoid SLNB.

Several studies have found a strong association between the molecular subtypes and the axillary status in breast cancer patients (10, 11). Furthermore, whether SLNB should be performed for luminal A breast cancer is still controversial (12). At the same time, the reports verified that tumor size was positively correlated with the SLN metastasis rate (13). T1 patients with small tumors and lower SLN metastasis rates (14) are more likely to be exempt from SLNB. So we enrolled 1,619 T1 breast cancer patients in this study and identified predictors for SLN metastasis in T1 breast cancers, especially the relationship between SLN metastasis and molecular subtypes.

The goal of this retrospective study was to establish a predictive model that includes tumor volume, swollen axillary lymph nodes, pathological types, and risk subtypes for SLN metastasis in T1 breast cancers. In addition, patients with a low risk of SLN metastasis could be exempt from SLNB.

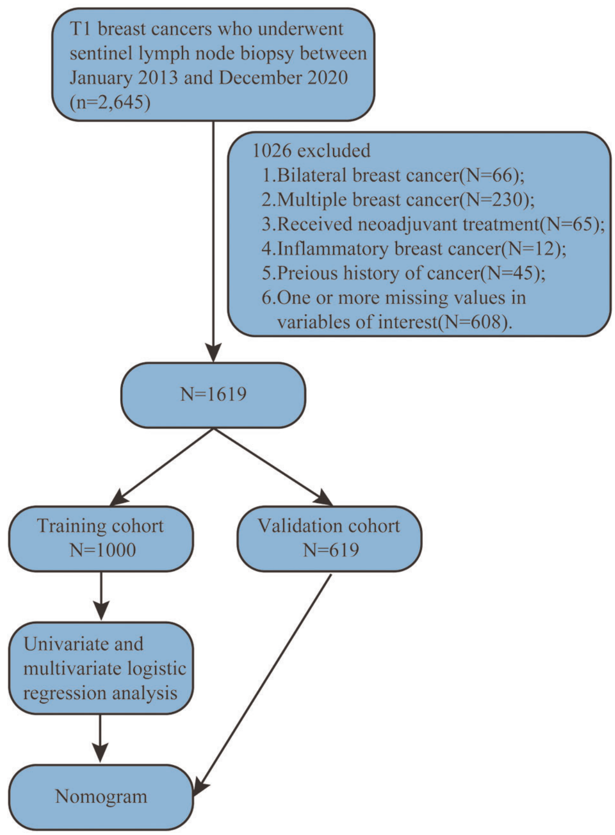

FIGURE 1 | The process for selecting patients for model development.

PATIENTS AND METHODS

Patients

We reviewed the clinicopathologic data of breast cancer patients with SLN metastasis who underwent SLNB during surgery at Harbin Medical University Cancer Hospital between January 1, 2013 and December 31, 2020. Patients with SLN metastasis were examined by SLNB during surgery. **Figure 1** depicts the selection of patients for model development.

Molecular Typing

Estrogen receptor (ER), progesterone receptor (PR) and ki67 were determined using immunohistochemistry and HER2 by immunohistochemistry or fluorescent *in situ* hybridization (FISH). Based on ER, PR, and HER2 status, patients were categorized into five molecular subtypes: luminal A[ER(+) and/or PR(+), HER2(−), ki67 ≤ 14%]; luminal B HER2(−)[ER (+) and/or PR(+), HER2(−), ki67>14%]; luminal B HER2(+) [ER(+) and/or PR(+), HER2(+)]; HER2 enriched [ER(−) and PR(−), HER2(+)] and triple negative[ER(−) and PR(−), HER2 (−)]. Based on univariate analysis results, we regrouped molecular subtypes, and defined them as risk subtypes: low-risk subtype[HER2 enriched]; median risk subtype[Luminal B HER(+) and TNBC]; high-risk subtype[Luminal A and Luminal B HER(−)].

Statistical Analysis

Univariate analysis was performed to detect predictors for SLN metastasis. Then, multivariate analysis, including all variables from the univariate analysis that were related to SLN status, was performed to test the factors' independence. Statistical significance was defined as $p < 0.05$; odds ratio (OR) and 95% confidence intervals (CI) were also calculated. Statistical tests were two-sided, and analyses were performed using SPSS v.19.0 Software (SPSS, Chicago, IL, http://www.spss.com).

RESULTS

Clinicopathological and Tumor Anatomical Factors of the Study Population

1,619 female patients with T1 breast cancer were enrolled. 1,000 patients between January 1, 2013 and April 10, 2018 were classified as a training cohort. The remaining 619 patients from April 10, 2018 to December 31, 2020 were classified as a validation cohort. The training cohort and the validation cohort were comparable in clinicopathological and tumor anatomical factors (**Table 1**). The median patient age was 55 years. The median tumor volume (length × width × width × 0.5) was 936 cm^3. The SLN metastasis rate of the training cohort was 23.8% ($n = 1{,}000$), and that of validation was 24.4% ($n = 619$).

TABLE 1 | Demographic and baseline characteristics of the study population.

Variables	Total	Training, *N* (%)	Validation, *N* (%)	*P*
No. of cases	1,619	1,000	619	
Age				
>55	774	472(47.2)	269(43.5)	0.142
≤55	905	528(52.8)	350(56.5)	
Tumor volume				
>936 cm^3	611	370(37.0)	234(37.8)	0.745
≤936 cm^3	1,068	630(63.0)	385(62.2)	
Distance from nipple				
>3 cm	714	418(41.8)	264(42.6)	0.737
≤3 cm	965	582(58.2)	355(57.4)	
Distance from surface				
>6 mm	718	409(40.8)	277(44.7)	0.128
≤6 mm	961	591(59.1)	342(55.3)	
Position of tumor				
Outer upper	710	416(41.6)	271(43.8)	0.502
Upper inner	486	296(29.6)	166(26.8)	
Lower inner	182	115(11.5)	65(10.5)	
Outer upper	301	173(17.3)	117(18.9)	
Swollen lymph nodes				
Positive	454	276(27.6)	170(27.5)	0.952
Negative	1,225	724(72.4)	449(72.5)	
ER				
Positive	1,341	774(77.4)	501(80.9)	0.091
Negative	338	226(22.6)	118(19.1)	
PR				
Positive	1,264	732(73.2)	472(76.3)	0.172
Negative	415	268(26.8)	147(23.7)	
HER2				
Positive	288	190(19.0)	98(15.8)	0.105
Negative	1,391	810(81.0)	521(84.2)	
Ki67				
>14%	752	442(44.2)	278(44.9)	0.780
≤14%	927	558(55.8)	341(55.1)	
Pathological types				
Invasive breast cancer	1,452	854(85.4)	546(88.2)	0.109
Intraductal carcinoma	227	146(14.6)	73(11.8)	

The bold values of P values means a significant difference.

The Identification of Independent Prognostic Factors for SLN Metastasis

To determine the independent predictors for SLN metastasis in the training cohort, a univariate analysis was first performed. Only tumor volume and swollen axillary lymph nodes, among tumor anatomical factors, were significantly associated with SLN metastasis (**Table 2**). Among clinicopathological factors, ER, PR, HER2, pathological types and molecular subtypes were significantly associated with SLN metastasis (**Table 3**).

TABLE 2 | Univariate analysis of tumor anatomical factors.

Variables	No. of positive SLN (%)	OR	95% CI	*P*
Age				
>55	108(22.9)	0.908	0.678–1.217	0.519
≤55	130(24.6)			
Tumor volume				
>936 cm^3	139(37.6)	3.227	2.390–4.359	**<0.001**
≤936 cm^3	99(15.7)			
Distance from nipple				
>3 cm	104(24.9)	1.107	0.825–1.486	0.497
≤3 cm	134(23.0)			
Distance from surface				
>6 mm	88(21.5)	0.806	0.597–1.088	0.159
≤6 mm	150(25.4)			
Position of tumor				
Outer upper	99(23.8)			
Upper inner	65(22.0)	0.566	0.631–1.286	0.901
Lower inner	27(23.5)	0.943	0.604–1.598	0.982
Outer upper	47(27.2)	0.389	0.798–1.789	1.194
Swollen lymph nodes				
Positive	116(42.0)	3.577	2.629–-4.869	**<0.001**
Negative	122(16.9)			

The bold values of P values means a significant difference.

TABLE 3 | Univariate analysis of clinicopathological factors.

Variables	No. of positive SLN (%)	OR	95% CI	*P*
ER				
Positive	214(27.6)	3.216	2.048–5.052	**<0.001**
Negative	24(10.6)			
PR				
Positive	205(28.0)	2.770	1.860–4.126	**<0.001**
Negative	33(12.3)			
HER2				
Positive	15(7.9)	0.226	0.130–0.391	**<0.001**
Negative	223(27.5)			
Ki67				
>14%	108(24.4)	1.065	0.795–1.426	0.675
≤14%	130(23.3)			
Pathological types				
Invasive breast cancer	235(27.5)	18.096	5.712–57.336	**<0.001**
Intraductal carcinoma	3(2.1)			
Molecular subtypes				
Luminal A	114(24.1)	4.433	2.002–9.819	**<0.001**
Luminal B(HER+)	8(12.3)	1.965	0.677–5.703	*0.214*
Luminal B(HER-)	98(39.0)	8.967	3.999–20.110	**<0.001**
TNBC	11(10.5)	1.638	0.609–4.405	*0.328*
HER2 enriched	7(6.7)			

The bold values of P values means a significant difference.

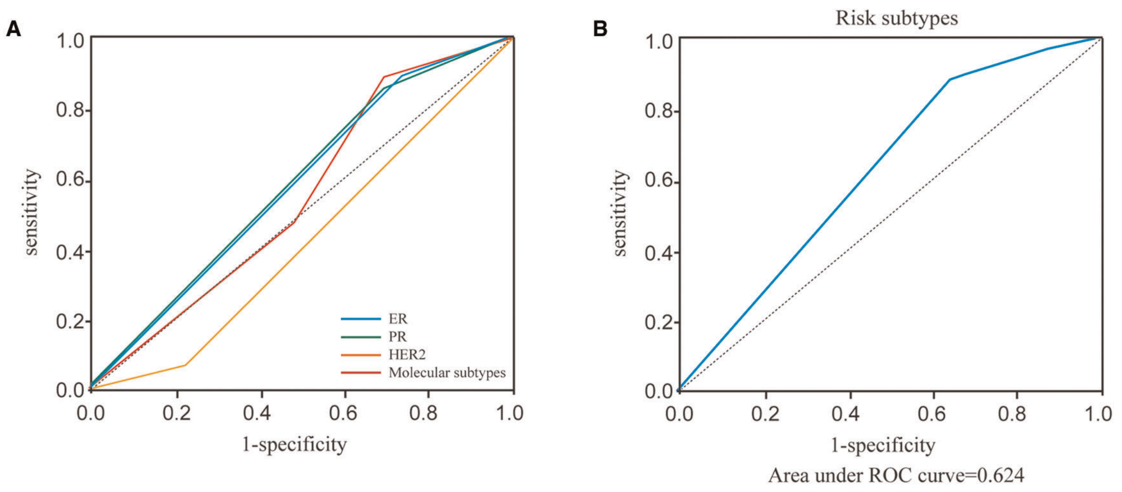

FIGURE 2 | ROC curves of ER, PR, HER2, molecular subtypes and risk subtypes. (**A**) ROC curves of ER, PR, HER2, molecular subtypes. (**B**) ROC curves of risk subtypes.

TABLE 4 | AUC curves of ER, PR, HER2, molecular subtypes and risk subtypes.

Variables	AUC	95% CI	*P*
ER	0.582	0.543–0.621	**<0.001**
PR	0.585	0.546–0.624	**<0.001**
HER2	0.417	0.378–0.455	**<0.001**
Molecular subtypes	0.562	0.524–0.600	**<0.001**
Risk subtypes	0.624	0.586–0.661	**<0.001**

The bold values of P values means a significant difference.

Therefore, breast cancer patients of ER positive, PR positive, and HER2 negative are more likely to develop SLN metastasis.

Before performing multivariate analysis, we analyzed the value of ER, PR, HER2, and molecular subtypes and compared their AUC values through Receiver-operating characteristic (ROC) analysis. The results are shown in **Figure 2A** and **Table 4**. The four variables have low AUC values. To improve their AUC, we retyped breast cancer based on the status of ER, PR, and HER2 and defined them as risk subtypes. The AUC value was 0.624 (**Figure 2B** and **Table 4**). Furthermore, the univariate analysis also showed that risk subtypes were related to SLN metastasis (**Table 5**).

Then multivariate analysis indicated that tumor volume, swollen axillary lymph nodes and pathological types were independent statistically significant predictors for SLN metastasis (**Table 6**). Furthermore, luminal A and luminal B HER2 (−), as the high-risk subtypes, were also independent statistically predictors for SLN metastasis. The SLN metastasis rates of these four variables are shown in **Figure 3**.

TABLE 5 | Univariate analysis of risk subtypes.

Variables	No. of positive SLN (%)	OR	95% CI	*P*
Risk subtypes				
Low risk				
HER2 enriched	7(6.7)			
Median risk				
Luminal B(HER+)	19(10)	1.556	0.632–3.832	*0.337*
TNBC				
High risk				
Luminal A	212(30.1)	6.020	2.750–13.179	**<0.001**
Luminal B(HER-)				

The bold values of P values means a significant difference.

TABLE 6 | Multivariate analysis of tumor anatomical location and clinicopathologic variables.

Variables	OR	95% CI	*P*
Tumor volume	5.574	3.382–8.107	**<0.001**
Swollen lymph nodes	6.423	4.365–9.453	**<0.001**
Pathological types	11.393	3.516–36.917	**<0.001**
Risk subtypes			**<0.001**
Low risk			**<0.001**
Median risk	2.231	0.823–6.048	*0.115*
High risk	11.349	4.622–27.868	**<0.001**

The bold values of P values means a significant difference.

Construction and Validation of the SLN Metastasis Nomogram

The four independent variables, including tumor volume, swollen axillary lymph nodes, pathological types, and risk subtypes, were incorporated to construct the HMU nomogram for estimating the SLN metastasis (**Figure 4A**). Each factor could be assigned a score by the HMU nomogram (**Table 7**). By summing the score of each factor together, the total score corresponded to an estimated SLN metastasis rate (**Figure 4A**).

The constructed HMU nomogram was then validated internally and externally. In the training cohort, ROC analysis showed that the AUC was 0.798 (**Figure 5A**). When fitted into the validation cohort, the AUC of the prediction model derived from the training cohort was 0.773 (**Figure 5B**). The calibration curves also revealed that the predictive model could accurately match the SLN metastasis rate (**Figure 4B**). These results demonstrated that the predictive model performs well in SLN metastasis. For example, the SLN metastasis rate in HER-type intraductal carcinoma, with tumor volume $\leq$936 cm^3 and without swollen axillary lymph nodes, is less than 0.1%. We believe that such patients do not require SLNB. If the tumor volume of HER2-invasive breast cancer is $\leq$936 cm^3, there is no swollen axillary lymph node. If the SLN metastasis rate is less than 1%, the clinician may not perform SLNB after considering the patient's wishes and clinical experience. Therefore, by calculating the patient's SLN metastasis rate according to the above four variables incorporated into the nomogram, we could provide a reference for the patient to decide whether to perform SLNB.

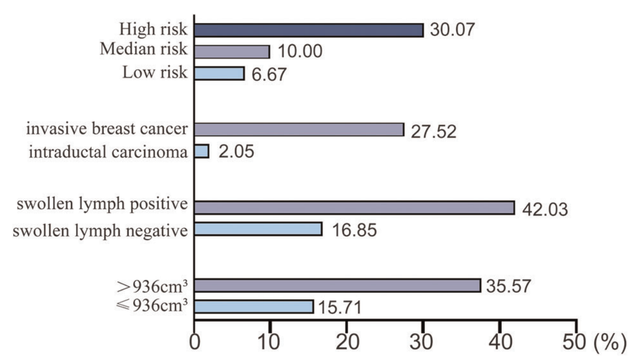

FIGURE 3 | SLN metastasis rate of four independent variables.

Patients Exempted from Sentinel Lymph Node Biopsy

According to the four variables in the HMU nomogram, we presented the SLN metastasis rate of patients with different characteristics (**Figure 6**). Patients with low metastasis rates are characterized by intraductal carcinoma (2.05%), low risk (6.67%), and median risk subtypes (10.00%). Therefore, those with HER2 enriched (group A) and intraductal carcinoma (group B) could be included in trials investigating the SLNB exemption. Patients with other characteristics would have lower metastasis rates, such as those with HER2 enriched associated tumor volume smaller than 936 cm^3 or without axillary lymphadenopathy, so they also could be included in this study.

DISCUSSION

The SLN metastasis is the gold standard for assessing ALN metastasis, but SLNB still has the following problems: positive SLN exemption, false negative rate, and complications after SLNB (6–9). Therefore, patients could avoid SLNB if some screening criteria can be defined to correctly assess the sentinel metastasis.

TABLE 7 | Detailed scores of each variable in HMU nomogram.

Variables		Nomogram scores
Tumor volume	>936 cm^3	62
	$\leq$936 cm^3	0
Swollen lymph nodes	Positive	68
	Negative	0
Pathological types	Invasive breast cancer	88
	Intraductal carcinoma	0
Risk subtypes	Low risk	0
	Median risk	50
	High risk	100

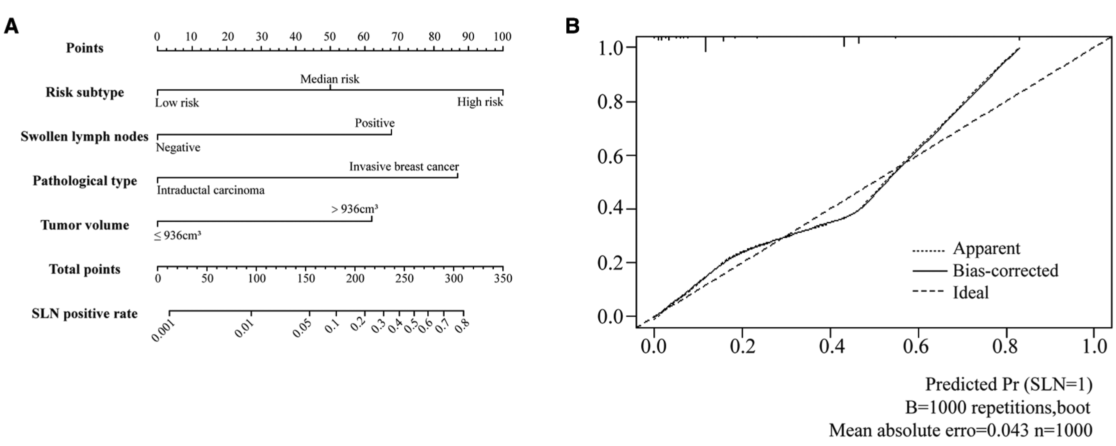

FIGURE 4 | Nomogram to predict the probability of SLN metastases in T1 breast cancer patients and calibration plot. (**A**) The nomogram of SLN metastases rate. (**B**) The calibration plot of nomogram.

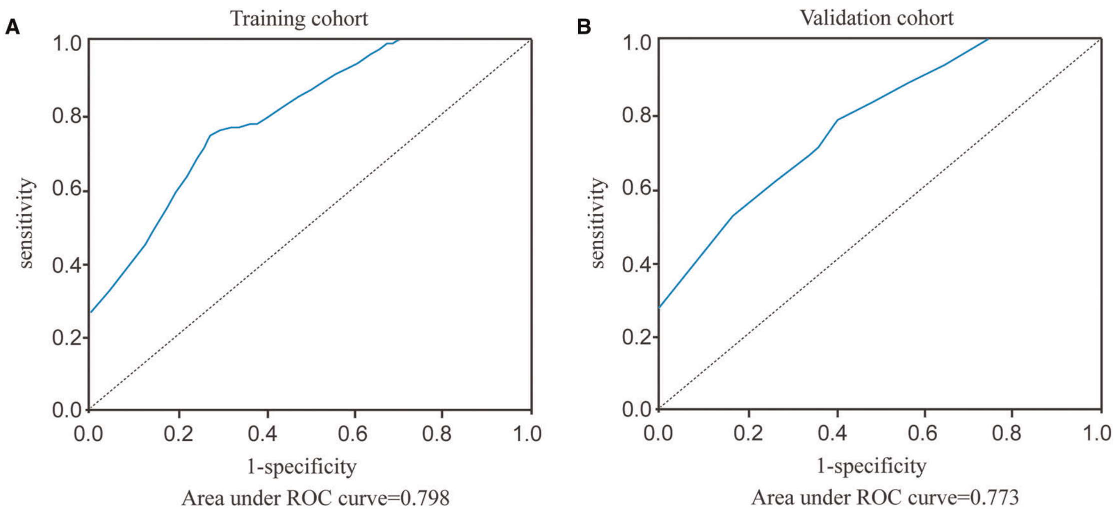

FIGURE 5 | ROC curves of our prediction model in the training cohort and validation cohort. (**A**) Area under ROC curve of training cohort. (**B**) Area under ROC curve of validation cohort.

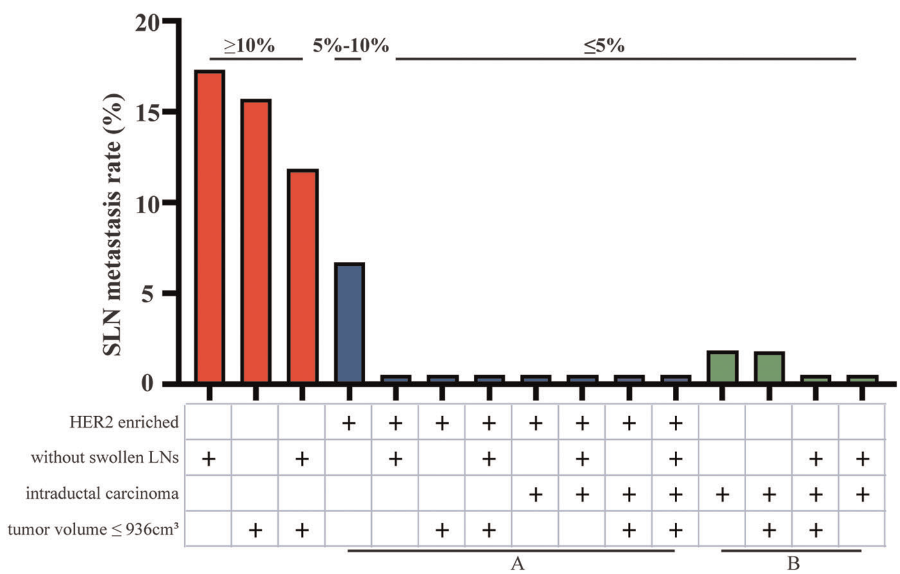

FIGURE 6 | The patients exempted from SLNB.

To fully evaluate the tumor size in this study, we adopted the concept of tumor volume, which took into account the tumor's long diameter and short diameter. When the tumor volume is less than or equal to 936 cm^3, the SLN metastasis rate is low (15.71%). This is consistent with previous studies that large tumors increase the risk of SLN metastasis (15–17). Swollen axillary lymph nodes are also highly suggestive of SLN metastasis (42.03%). However, some lymph node enlargement without SLN metastasis may be caused by congenital development of inflammation (18).

There is still controversy about whether SLNB should be performed in ductal carcinoma of breast cancer (19, 20). According to a meta-analysis, the incidence of SLN metastasis was 7.4 in patients with a preoperative diagnosis of intraductal carcinoma (21). Another study suggested that the only criterion for recommending SLNB in intraductal carcinoma should be any uncertainty about the presence of invasive lesions (22). Therefore, considering the risk of missed detection of microinvasion in some intraductal carcinomas and the high risk of intraductal carcinomas, we included intraductal carcinomas in the study. Intraductal carcinoma of the high-risk subtype has a tumor volume greater than 936 cm^3, accompanied by swollen axillary lymph nodes, and the SLN metastasis rate is as high as 30%, so SLNB should be performed. Studies have shown that the positive rate of SLNB in patients diagnosed with intraductal carcinoma by preoperative core needle biopsy is significantly higher than that in patients diagnosed with intraductal carcinoma after surgery (23, 24). If the preoperative diagnosis of intraductal carcinoma with swollen axillary lymph nodes is associated with undetected microinvasion, core needle biopsy should be performed to confirm the status of the swollen axillary lymph nodes (25–27).

Moreover, among the five molecular types of breast cancer, luminal A and luminal B HER2(−) have the highest SLN metastasis rate (30.07%). In other words, patients with ER (+)/PR(+)/HER2(−) T1 breast cancer are more likely to develop SLN metastasis. This is also consistent with previous studies, which confirm that triple-positive breast cancer is more prone to SLN metastasis (28), and that triple-negative breast cancer has a lower SLN metastasis rate (29). Our study demonstrated that ki67 has no effect on SLN metastasis of T1 breast cancer, which is consistent with Fabinshy's finding (30). However, another study found that ki67 was positively correlated with SLN metastasis (31). T1 breast cancer may be smaller, on the other hand, so ki67 is more likely to reflect the proliferation state rather than metastasis.

According to the study on an American breast cancer patient conducted by Memorial Sloan Kettering Cancer Center (MSKCC), age, tumor size, tumor type, lymphovascular invasion, tumor location, multifocality, ER and PR were all associated with SLN metastasis (32). The nomogram's AUC is 0.754. The Fudan University Shanghai Cancer Center in China, with an AUC value of 0.7649, included age, tumor size, tumor location, tumor type, and lymphovascular invasion (33). Two studies predicted the risk factors of SLN metastasis, but they ignored the impact of molecular subtypes on SLN metastasis. More importantly, our study focused on patients with low SLN metastasis rate. We thought that T1 breast cancer patients reduced the implementation of SLNB with less risk. The AUC value is 0.798 in the HMU nomogram, indicating that SLNB could be avoided more safely and effectively.

In conclusion, we developed and validated a nomogram for predicting SLN metastasis by adopting clinicopathological and tumor anatomical factors location from 1,000 T1 breast cancer patients. The remaining 619 T1 breast cancer patients were classified as validation cohort for external validation. The HMU nomogram provides comprehensive SLN metastasis information to optimize surgical procedures and benefit breast cancer patients. We focused on patients included in the SLNB exemption study, including intraductal carcinoma, HER2-enriched. Those with HER2-enriched and other low-risk factors may also be included in the study.

The potential limitations should be considered. First, more patients' information from other hospitals will be more useful for validating HMU nomograms. Second, the SLNB exemption only applies to T1 breast cancer patients, and additional and refined HMU nomograms should be further studied for various types of breast cancer patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Changhong Zhao Harbin Medical University Cancer Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SX and YZ provided direction and guidance throughout the preparation of this manuscript. GL, XM analyzed and interpreted the patient, tumor, and risk factor data as well as drafted the manuscript. JZ, XZ, YC generated the figures and made significant revisions to the manuscript. HL, LZ and XZ provided patient data and clinical information. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Modified Leak-Proof Puncture Technique for the Aspiration of Giant Ovarian Cysts by Instantly Mounting a Plastic Wrap and Gauze with Cyanoacrylates: A Retrospective Observational Study

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Objective: We developed a leak-proof puncture technique for giant ovarian cysts by instantly mounting a plastic wrap to the cysts using cyanoacrylates and aspirating cyst fluid over the wrap. Here, we modified it by inserting a gauze between the wrap and cyst to strengthen the mounting. This study aimed to clarify the feasibility of the modified procedure.

Method: A retrospective observational study was conducted in a single center. Surgical outcomes of 35 women who underwent the modified procedure from December 2013 to July 2020 were compared with those of 51 women who underwent the original procedure.

Results: Mean long-axis diameters of the cysts were 233.1 mm and 229.8 mm in the modified and original procedures, respectively. The median of surgical time, blood loss, and aspirated fluid volume were 109 min, 50 ml, and 3,050 ml, in the modified procedure, all of which were not significantly different from those of the original procedure. One case of mounting disruption and two (5.7%) cases of intraperitoneal spillage of the cyst fluid were observed in the modified procedure, whereas four (7.8%) cases of mounting disruption and five (9.8%) cases of intraperitoneal spillage occurred in the original procedure. These events were caused by aspiration difficulty of the high viscosity fluid and/or multilocular cysts. Laparotomy conversion was observed in five (14.3%) cases in the modified procedure.

Conclusion: Our modified procedure is feasible in select cases. The high viscosity of the cyst fluid and multilocular cyst may cause mounting disruption and intraperitoneal spillage of the cyst fluid.

Keywords: minimally invasive surgical procedures, ovarian cysts, cyanoacrylates, leak-proof puncture, minilaparotomy, plastic wrap

INTRODUCTION

The leak-proof puncture technique for the aspiration of cyst fluid in giant ovarian cysts is necessary for the removal of the cysts through small abdominal incisions and may prevent intraperitoneal spillage of cyst fluid during minimally invasive surgery. Several puncture techniques to aspirate the cyst contents without leakage during laparoscopic surgery have been reported (1–3). We had earlier reported a leak-proof puncture technique using cyanoacrylates and plastic wrap through mini laparotomy (4).

Our original technique consisted of instantly mounting a plastic wrap to the cyst using cyanoacrylates, followed by cyst fluid aspiration over this wrap. This technique is applicable to large and multiple cysts that exceed the umbilical height. However, the mounting between the wrap and the cyst was occasionally disrupted because of its fragility, resulting in the unexpected leakage of cyst fluid during aspiration. To reinforce the mounting between the wrap and the cyst, we modified the technique by inserting a gauze between the cyst and the wrap. Herein, we have reviewed a case series of the modified procedure and compared its surgical outcomes with those of the original procedure to clarify the feasibility and determine the appropriate recipients of the modified procedure.

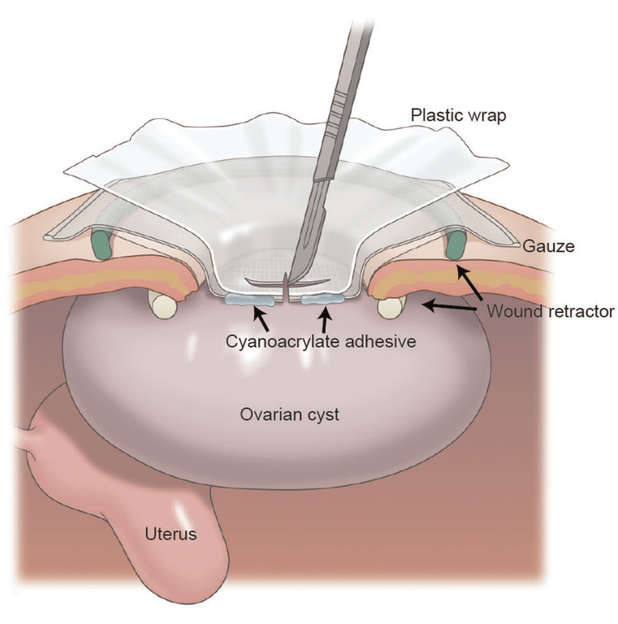

FIGURE 1 | Illustration of the modified leak-proof puncture technique for the aspiration of giant ovarian cysts. This illustration shows a cross-section of the modified leak-proof puncture technique for fluid aspiration of giant ovarian cysts. A wound retractor is attached to the abdominal small incision, and a plastic wrap and gauze are mounted to the cyst instantly using cyanoacrylate adhesive. After the mounting process, the cyst wall is cut and the cyst fluid is aspirated over the wrap.

MATERIALS AND METHODS

This is a retrospective observational study conducted in a single center. The study protocols for data analysis, including referring patient records, were approved by the Institutional Review Board at the Graduate School of Medicine, Chiba University (No. 2267). For this study, the opt-out method was applied to obtain consent for reviewing the patient records.

The study participants were women who underwent resection of giant ovarian cysts using the leak-proof puncture technique by instantly mounting a plastic wrap to the cysts using cyanoacrylates in the Chiba University Hospital. We have introduced the modified procedure in December 2013. Accordingly, we reviewed the medical records of 35 women who underwent the modified procedure in our facility from December 2013 to July 2020. To validate the modified procedure, we reviewed data of 51 women who underwent the original procedure for giant ovarian cyst fluid aspiration from January 2006 to September 2013.

The leak-proof puncture technique was applied to treat giant ovarian cysts that were determined to be benign tumors, including those which we cannot completely deny as borderline malignant tumors on preoperative imaging, mainly magnetic resonance imaging (MRI). Medical image interpretation specialists of our facility participated in a conference to determine the surgical indications relevant to the procedure.

An illustration of the modified procedure, consisting of the instant mounting of the plastic wrap and gauze to the cyst using cyanoacrylate adhesive and cyst fluid aspiration, is presented in **Figure 1**. First, we made a 3–5 cm transverse or vertical incision in the lower abdomen and attached a disposable retractor (Alexis® Wound Retractor; Applied Medical, Rancho Santa Margarita, CA, USA or other similar retractors) to visualize the cyst surface (**Figure 2A**). Then, we removed moisture from the cyst surface, placed a sterile gauze on the cyst, and applied cyanoacrylates (Aron Alpha®; Dai-ichi Sankyo, Tokyo, Japan) in a 2–4 cm diameter circle over the gauze (**Figure 2B**). Subsequently, we pressed a plastic wrap onto the gauze surface for 3 min (**Figure 2C**). The color of the adhesive changed from transparent to white following the completion of polymerization (**Figure 2D**). Subsequently, we punctured the cyst through the wrap with a sharp-pointed knife (**Figure 1**). The cyst fluid, with low viscosity, exuded from the cyst and was aspirated *via* the puncture hole (**Figure 3A**). Direct insertion of aspiration tubes into the puncture hole should be avoided to prevent the mounting from tearing. For multilocular cysts, initially, we aspirated the fluid in the largest cyst using the modified technique, punctured the adjacent cyst septum, and aspirated the cyst fluid. In cases where the adjacent cyst wall was not visible through the puncture hole, we pulled the cyst wall using forceps and extended the wall incision under direct vision. After the maximum possible aspiration of the cyst fluid, we lifted the cyst wall with the forceps (**Figure 3B**), placed it outside the body (**Figure 3C**), and performed cyst resection

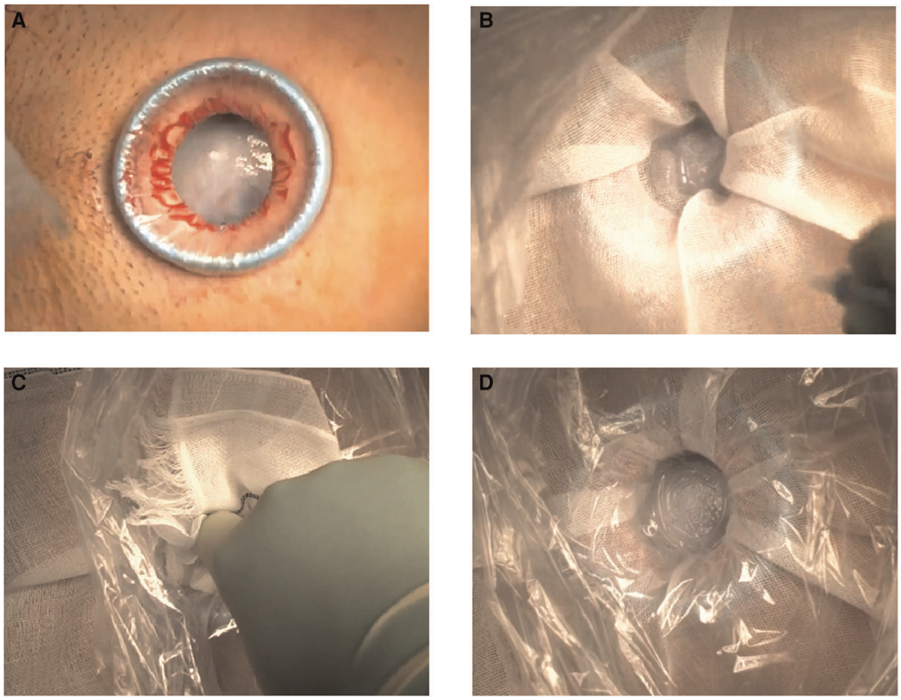

FIGURE 2 | Instant mounting of plastic wrap and gauze to the giant ovarian cyst. (**A**) Completion of the attachment of a wound retractor to the 3-cm lower abdominal transverse incision. (**B**) Condition immediately after applying cyanoacrylates on the cyst through the gauze. (**C**) Mounting the plastic wrap and gauze on the cyst. (**D**) Completion of the instant mounting to the cyst wall. The color of the adhesive has changed from transparent to white upon completion of cyanoacrylate polymerization.

(cystectomy) or oophorectomy (**Figure 3D**). We also presented a representative video (**Supplementary Material**).

We reviewed patients' age, body mass index (BMI), histories of laparotomy and/or laparoscopy as patients' characteristics and preoperative estimation of the long-axis diameter of the cysts that was measured by MRI. We also reviewed the surgical time, blood loss volume, and aspirated cyst fluid as surgical outcomes. Additionally, we analyzed the reasons for mounting disruption and/or intraperitoneal spillage of the cyst fluid. We also analyzed the reasons for conversion to laparotomy during the modified procedure. If the surgeon has little experience of the modified procedure, an experienced physician participated in the surgery as the first assistant.

JMP 14.0 (SAS Institute, Inc., Cary, NC) was used for statistical analyses. The comparison of continuous and categorical variables between women who underwent the modified procedure and those who underwent the original procedure was performed using the Student t-test and Pearson's chi-square test, respectively. Statistical significance was defined as $p < 0.05$.

RESULTS

Patient characteristics and surgical outcomes are presented in **Table 1**. Patients' age, BMI, and long-axis diameter of the cysts were not significantly different between women who underwent the modified and original procedures. The mean long-axis diameters of the cysts were 233.1 mm and 229.8 mm in the modified and original procedure, respectively. The median surgical time, blood loss volume, and aspirated cyst fluid in the modified procedure were 109 min, 50 ml, and 3,050 ml, respectively, whereas those in the original procedure were 118 min, 150 ml, and 2,800 ml, respectively. These parameters were not significantly different between the modified and original procedures except for blood loss volumea. Histopathology revealed that most of the ovarian cysts in the modified procedure were mucinous cyst adenomas.

Mounting disruption was observed in only one case in the modified procedure, whereas it was observed in four cases in the original procedure. Intraperitoneal spillage of the cyst fluid did not occur in the modified procedure because the fluid was highly viscous. Conversely, spillage was observed in all cases in the original procedure. The disruption and subsequent spillage occurred at the aspiration of multilocular cysts. Intraperitoneal spillage of the cyst fluid that was not accompanied by mounting disruption during surgery was observed in two cases in the modified procedure and two cases in the original procedure. The spillage occurred during the aspiration of multilocular cysts and/or the aspiration of the highly viscous fluid. Disruption of the cyst wall has occurred instead of the mounting disruption in these cases.

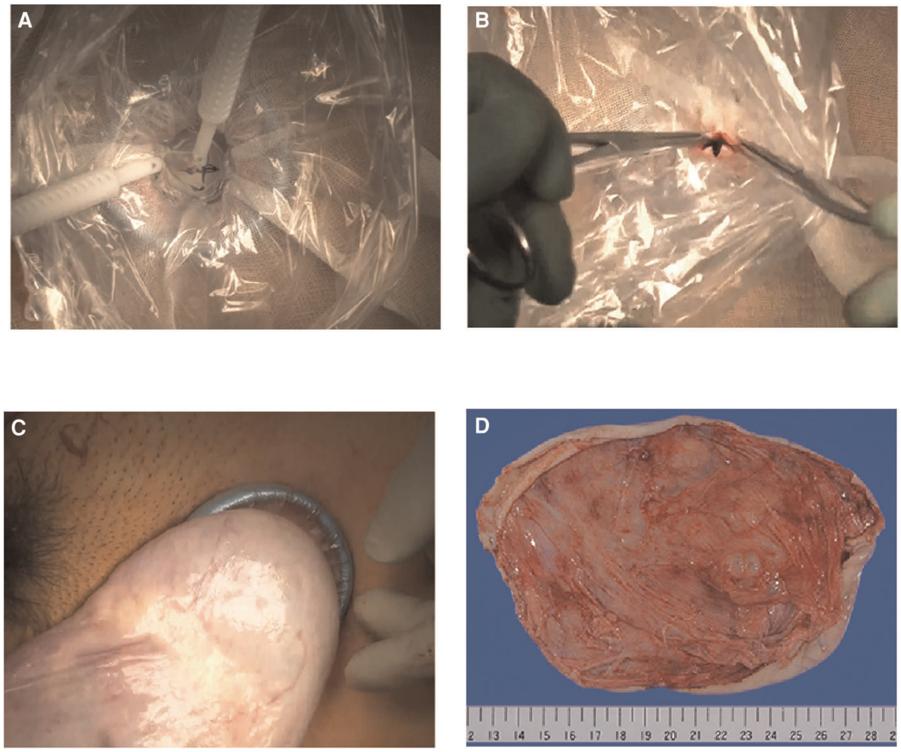

FIGURE 3 | Aspiration of the cyst fluid and cystectomy of the giant ovarian cyst. (**A**) Aspirating cyst fluid over the wrap. The cyst fluid of the serous cystadenoma flows from the puncture hole. (**B**) After cyst fluid aspiration, the mounting is pinched off with forceps to avoid intraperitoneal spillage of the cyst fluid. (**C**) The cyst is brought outside the body. (**D**) Resected giant ovarian cyst. The longitudinal diameter of the cyst is 205 mm. The pathological diagnosis was serous cystadenoma.

TABLE 1 | Patient characteristics and surgical outcomes.

	Modified procedure ($n = 35$)	Original procedure ($n = 51$)	p-value
Patient characteristics			
Age (year)[a]	50.3 ± 21.5	46.6 ± 23.0	0.4500
BMI (kg/m^2)[a]	22.6 ± 3.7	22.2 ± 4.0	0.6622
Long axis diameter of the cysts (mm)[a,c]	233.1 ± 61.9	229.8 ± 69.7	0.8246
Surgical outcomes			
Surgical time (min)[b]	109 (56–238)	118 (50–296)	0.1471
Volume of blood loss (ml)[b]	50 (5–590)	150 (10–5,335)	0.0387
Volume of aspirated cyst fluid (ml)[b]	3,050 (800–13,800)	2,800 (400–14,000)	0.6115

[a]*Data are presented as mean ± standard deviation.*
[b]*Data are presented as median (range).*
[c]*Diameter calculated by preoperative imaging evaluation.*

Conversion to laparotomy was observed in five cases in the modified procedure. Reasons for the conversion were as follows: difficulty of aspiration over the wrap because of the highly viscous cyst fluid (two cases), difficulty in picking up the entire cyst after cyst fluid aspiration due to broad and firm adhesions between the cyst and rectosigmoid colon caused by prior hysterectomy (two cases), and difficulty of mounting a plastic wrap and gauze due to the retroperitoneal location of the cyst (one case). No recurrent cases associated with intraperitoneal spillage of cyst fluid were observed.

DISCUSSION

Intraperitoneal spillage of the cyst fluid of ovarian cystic tumors should be avoided during resection, even if they are not suspected of malignancy, preoperatively. When intraperitoneal spillage of the cyst fluid occurs, peritoneal lavage is necessary. Before the introduction of the modified procedure, we had occasionally experienced intraperitoneal spillage of the cyst fluid because of the mounting disruption during the aspiration procedure. Mounting disruption may be due to the fragility of the adhesive surface. The gelatinous, highly viscous cyst fluid is challenging to aspirate over the wrap; hence, the fluid from inside the cyst is directly aspirated, leading to a strong tension over the mounting that causes its disruption. We had experienced four cases of mounting disruption out of 51 cases before the modification, and this disruption has shown an evident reduction with the modified technique (1 of 35 cases), though this difference was not significantly significant.

Although similar leak-proof puncture techniques using Dermabond and Dermabond plus (Johnson &Johnson Inc., NJ, USA) and BioGlue (CryoLife, GA, USA) for instant mounting of a plastic bag, vinyl membrane, and surgical glove to ovarian cysts have been reported (5–7), to the best of our knowledge, our modification to secure the mounting has not yet been reported. Similar to the original procedure, the modified procedure is safe, quick, and easy to perform, without requiring specialized training. In addition, it can be applied to giant ovarian cysts where the upper border is over the umbilicus. Laparoscopic surgery for the resection of huge ovarian cysts has also been reported; however, preventive methods for intraperitoneal spillage during the suction of the cyst fluid have not been mentioned in most of them. Our modification can also be applied during laparoscopic-assisted surgery.

Inadequate intraperitoneal observation throughout the small incision is a disadvantage of the modified technique at mini laparotomy, as with the original technique. Intraperitoneal adhesions between the tumor and other organs may be unidentifiable. Laparoscopy-assisted surgery could resolve this problem. Appropriate reduction of the cyst volume will enable the safe insertion of laparoscopic trocars into the abdominal wall, after pneumoperitoneum is achieved. The wound retractor, in our case series, was covered with a surgical glove and the cap closed to avoid air leakage during laparoscopy. Other authors have reported that a laparoscopic cap was put on to create and maintain pneumoperitoneum at the laparoscopy (8). The combination of laparoscopic observation and subsequent release of the adhesion may be useful in avoiding laparotomy conversion in cases of adhesion between the cyst and pelvic walls or other intraperitoneal organs.

A prior history of hysterectomy is associated with intraperitoneal adhesion between the ovarian tumor and intraperitoneal organs, including the pelvic peritoneum, gastrointestinal tract, and omentum (9). The remaining adnexa are occasionally fixed to the pelvic side wall during hysterectomy; in such cases, placing the entire ovarian cyst outside the body was observed to be difficult even after complete aspiration of the cyst contents. Therefore, careful attention must be paid to patients with prior history of hysterectomy before the application of the modified procedure.

Based on the instructions, the Aron alpha ethyl-2-cyanoacrylate used in this study, can be used below skin level and also for vessel adhesion. It has been used for soft tissue bonding in dermatologic surgeries (10) and surgical adhesion to blood vessels in vascular surgeries (11). No toxicity issues with the glue have been reported so far. Furthermore, we developed our modified procedure to reduce the risks of glue spillage inside the abdominal cavity. The gauze inserted between the plastic wrap and the cyst wall helps to trap all the glue. From this point of view, our modified procedure is much safer than the original procedure.

Cost-effectiveness including operative time in the modified procedure should be discussed. Compared with the original procedure, the modified procedure only adds a sterile gauze. It takes several seconds to insert the gauze between the plastic wrap and the cyst wall, and thus the operative time in the modified procedure may be delayed by several seconds. On the other hand, the enforcement of the bonding makes it easy to pick up the cyst outside the body. This may shorten the subsequent resection of the cyst. From this point of view, the modified procedure is also cost-effective.

This study has several limitations. First, the sample size is relatively small. Therefore, we could not detect any significance in the frequency of mounting disruption, intraperitoneal spillage of the cyst fluid, and conversion to laparotomy between the modified procedure and the original procedure. Second, we chose women who underwent the original procedure for the control. The surgeons who performed the two procedures were different, which might affect the surgical outcomes. Third, surgeons' experience in performing the procedure is a potential bias for the surgical outcomes. Finally, surgical outcomes included not only the leak-proof puncture procedures but also the subsequent cystectomy or resection of the cysts. Surgical time may extend, and blood loss volume may increase in cases of laparotomy conversion.

This procedure is important for decreasing the risk of ovarian cancer upstaging. Although we did not apply the modified procedure to apparent malignant ovarian cystic tumors in preoperative imaging diagnosis, we experienced several cases that showed malignancy in postoperative pathological diagnosis. Fortunately, intraperitoneal spillage of the cyst fluid did not occur in these cases; nevertheless, making an effort to avoid intraperitoneal spillage during the procedures was necessary.

In conclusion, we have modified our leak-proof puncture technique for fluid aspiration in giant ovarian cysts by inserting a gauze between the plastic wrap mounting and cyst. This modification reinforces the mounting and may prevent its disruption. This technique is safe, quick, and easy to perform without cyst fluid leakage. Additionally, it does not require pneumoperitoneum; therefore, it can be applied to patients in which long-term pneumoperitoneum may be avoided, for example, pregnant women. It can also be applied in laparoscopic-assisted surgery.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Board at Graduate School of Medicine, Chiba University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HI and MS contributed to conception and design of the study. HI collected and analyzed data and wrote the first draft of manuscript. MS supervised the study and reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.948073/full#supplementary-material.

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ORIGINAL RESEARCH
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Preliminary Analysis of Safety and Feasibility of a Single-Hole Laparoscopic Myomectomy via an Abdominal Scar Approach

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Purpose: This paper aims to explore the safety and feasibility of a single-hole laparoscopic myomectomy through an abdominal scar approach.

Method: The clinical data of seven patients who underwent the single-hole laparoscopic myomectomy *via* the abdominal scar approach from January to November 2021 in the Department of Gynecology, the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, were studied retrospectively. The duration of operation, the intraoperative blood loss, the decrease of postoperative hemoglobin, and the postoperative visual analogue score (0 points: no pain, 10 points: maximum pain) were recorded.

Results: All seven patients received the operation successfully, without changing to the conventional laparoscopic operation or open appendectomy. The average blood loss was 101.42 ± 7.89 ml, the average length of hospital stay was 5 ± 0.53 days, the average operation duration was 130 ± 26.86 min, and the 24-h pain score was 1.57 ± 0.53. The seven patients had no intraoperative or postoperative complications and no damage to the ureter or bladder. All patients could urinate spontaneously without urinary retention or urinary tract infection after catheter removal. No analgesic drugs were used after the operation.

Conclusion: The single-hole laparoscopic myomectomy *via* the abdominal scar approach is a more aesthetic and feasible option for eligible patients, but more cases and studies are needed for further confirmation.

Keywords: abdominal wall scar, single hole laparoscopic surgery, hysteromyoma, minimally invasive surgery, hidden scar

INTRODUCTION

Hysteromyoma is the most common gynecological benign tumor in women, especially women of childbearing age, accounting for about 20%–25% of women (1). Epidemiological statistics are far lower than the actual incidence. Although most patients have no clinical symptoms, 30% (2) of the patients still show symptoms such as increased menstruation, prolonged menstruation, anemia, frequent urination, urgent urination, and low back pain, which seriously affect the quality of life. As uterine leiomyoma is an estrogen-dependent disease, it often occurs in women of childbearing age. It is extremely rare in non-menarche women, and some fibroids may atrophy in peri-menopausal or postmenopausal women (2). For asymptomatic patients with uterine leiomyoma, regular follow-ups and treatments are often taken. For patients with symptoms, the current treatment primarily includes drug treatment, surgical treatment, and other interventional treatments. For symptomatic patients who have uterine leiomyoma but do not want to receive an operation, drugs can be used, such as progesterone, gonadotropin-releasing hormone agonist (GnRH-a), and mifepristone. The literature shows that oral progesterone can reduce symptoms or prevalence by 25% (3). GnRH-a treatment for 3 months can reduce the myoma and uterine volume by up to 50% (4), but the treatment is not well accepted because of the accompanying "quasi-menopause" symptoms. The reverse addition theory has been proposed to make up for this defect. Surgical treatment is feasible for uterine fibroids that lead to increased menstruation, anemia, frequent urination caused by bladder compression, and changes in defecation habits caused by rectal compression. For women with submucosal leiomyoma, the change in the endometrial environment affects fertility to a certain extent, increasing the rate of spontaneous abortion, and fertility can be improved after hysteroscopic treatment (3). For intramural myoma or subserous leiomyoma, transabdominal or laparoscopic surgery can be the option. Compared with laparotomy, laparoscopy has the advantages of less trauma, faster postoperative recovery, and less intraoperative bleeding (5). Since single-hole laparoscopy was first used for myomectomy (6), the operation has become increasingly mature after improvements. With people's aesthetic requirements increasing, single-hole laparoscopic myomectomy has been selected by more and more patients. Based on the successful fallopian tube recanalization by an abdominal scar approach (7), our hospital has combined the advantages of the two methods and completed the single-hole laparoscopic myomectomy through the abdominal scar approach, with achieving satisfactory results.

DATA AND METHODS

General Data

Seven patients who underwent single-hole laparoscopic myomectomy *via* the abdominal scar approach from January to November 2021 were selected from Changzhou No. 2 People's Hospital Affiliated to Nanjing Medical University. The patients were 33–46 years old, with the average age being 38.71 ± 4.89 years, and the BMI was 22.52 ± 2.62 kg/m^2 (**Table 1**). One of the patient cases was subserosal myoma, four cases were anterior intramural myoma, one case was multiple uterine myomas, and one case was broad ligament myoma. Among the seven patients, one had bilateral tubal ligation history and six had cesarean section history (two cases were a transverse scar of the cesarean section and four cases were a vertical scar of the cesarean section), including two with a vertical scar of the cesarean section combined with myomectomy history (**Table 2**).

TABLE 1 | Statistical data of the seven patients.

Characteristics	Mean ± standard deviation (*n* = 7)
Age (years)	38.71 ± 4.89
BMI (kg/m^2)	22.52 ± 2.62
Intraoperative bleeding volume (ml)	101.42 ± 7.89
Operation duration (min)	130 ± 26.86
Postoperative hospital stay (days)	5 ± 0.53
Preoperative HB (g/L)	125.42 ± 14.63
Postoperative HB (g/L)	111.86 ± 16.10
VAS	1.57 ± 0.53

BMI, body mass index; HB, hemoglobin; VAS, visual analogue score.

(1) *Inclusion criteria:* (1) Previous history of abdominal incision; (2) indication of hysteromyoma surgery (4); and (3) patient's voluntary choice of the abdominal scar approach and signing the informed consent of the operation.
(2) *Exclusion criteria:* (1) Possibility of a malignant tumor; (2) body mass index (BMI) ≥ 30 kg/m^2; and (3) patient with an underlying disease that is unsuitable for operation.

Operation Method

Preoperative Preparation

All seven patients underwent general anesthesia; fasting and water deprivation 10 h before the operation to prepare for anesthesia; skin preparation and vaginal cleaning; diet preparation 3 days before the operation to improve the intestinal environment and reduce the impact of the intestinal tract on operation; disinfection of the scar to reduce postoperative infection; and preoperative education by nurses to patients before the operation to reduce their tension.

Equipment Preparation

A complete set of digital systems for laparoscopy (such as lens, display, pneumoperitoneum system, light source system, and recorder), instrument set for conventional gynecological transabdominal surgery, and the items required for single-hole laparoscopy (such as the port and protective ring required for access, as well as the lens, operating instruments, and suture required for laparoscopy) were kept ready.

Surgical Procedures

The patient took the bladder lithotomy position (kept the head low and foot height ≥30° and the abduction of both legs <90°). After the general anesthesia was satisfactory, the patient received routine disinfection and was draped, and the assistant placed the uterine lifting device and retained the catheterization. The transabdominal scar approach was adopted. Taking the scar after a cesarean section as an example, first, an incision of 2.0 cm was made in the lower part of the scar of the original cesarean section (**Figure 1A**) layer by layer into the abdomen. Then, the incision protection ring and the single-hole

TABLE 2 | General information of patients.

Case	Age (years)	BMI (kg/m^2)	Reproductive history	Surgical history	Scar site of the abdominal wall
1	37	26.44	G5P2	History of cesarean section, history of myomectomy	Vertical scar of the abdominal wall during cesarean section
2	34	26.51	G5P3	History of cesarean section	Vertical scar of the abdominal wall during cesarean section
3	37	20.88	G5P1	History of cesarean section	Vertical scar of the abdominal wall during cesarean section
4	46	20.81	G1P1	History of cesarean section	Transverse scar of the abdominal wall during cesarean section
5	46	22.67	G3P1	History of tubal ligation	Abdominal tubal ligation scar
6	33	20.32	G3P1	History of cesarean section	Transverse scar of the abdominal wall during cesarean section
7	38	20	G2P1	History of cesarean section, history of myomectomy	Vertical scar of the abdominal wall during cesarean section

Reproductive history: G, gestation; P, production.

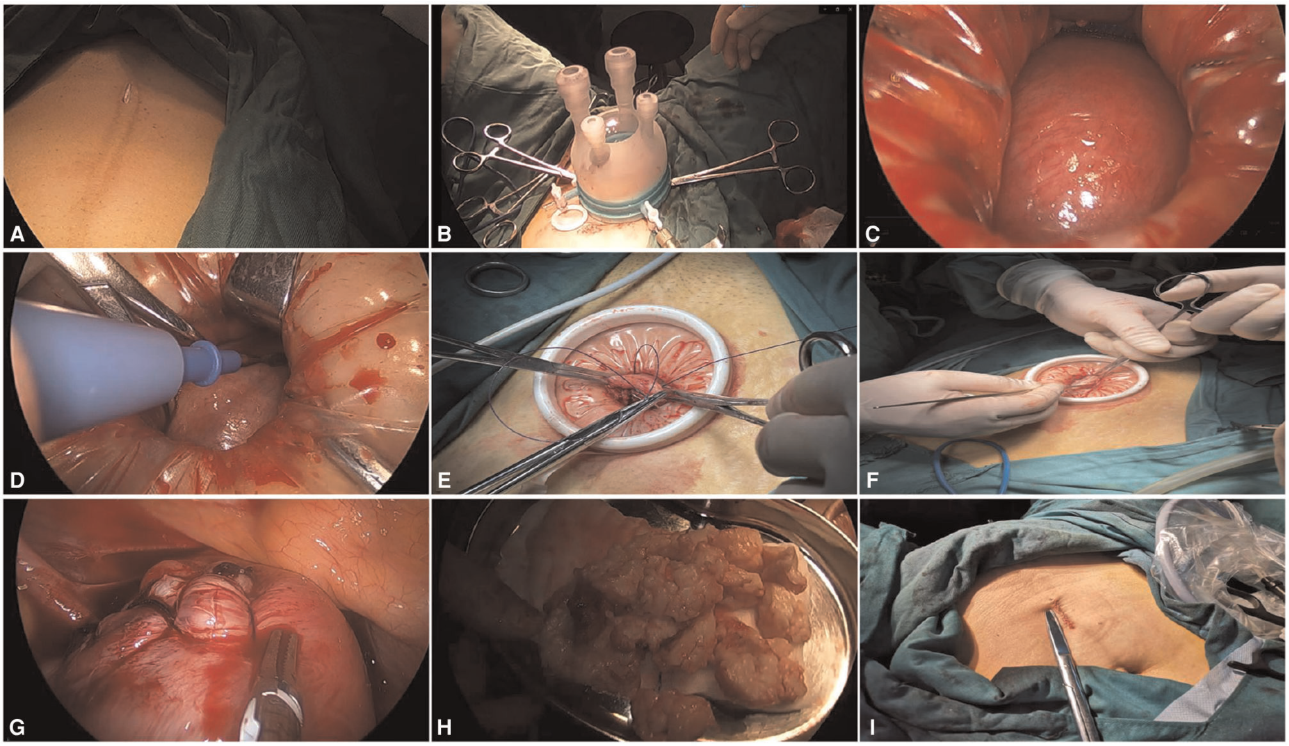

FIGURE 1 | (**A**) Incision through abdominal wall scar; (**B**) connecting the single-hole port; (**C**) using the uterine lifter to push the uterus to the incision; (**D**) dissecting the tumor with an electric knife under direct vision; (**E**) suturing the uterus under direct vision; (**F**) removing the tumor from the incision in blocks; (**G**) laparoscopic exploration and hemostasis; (**H**) stripped tumor; and (**I**) suturing abdominal incision.

laparoscopic special port was connected (**Figure 1B**), the disposable single-hole flexible sheath was fixed, the CO_2 gas was filled until the abdominal pressure reached 14 mmHg, and then the 30° laparoscopic lens and other operating instruments were placed. Single-hole laparoscopy was used to detect the abdominal adhesion and separate the adhesion with an ultrasound knife to restore the normal pelvic structure. The laparoscopic device was removed, the abdominal wall was gently lifted with a thyroid retractor, and the uterus was pushed to the abdominal wall incision by using the uterine device in conjunction (**Figure 1C**). The inject diluted vasopressin into the myometrium locally (avoiding the tumor). Under direct vision, the serous layer was cut open on the surface of the tumor with an electric knife, and the tumor was stripped bluntly and sharply with fingers or the electric knife (**Figure 1D**). The operator can extend his/her finger from the incision into the pelvic cavity and cooperate with the uterine lifter to carefully check for any other suspicious tumor tissue (for uterine leiomyoma in the posterior wall, the approach can be on the upper part of the scar and laparoscopy can be used to peel off the tumor as much as possible). Under direct vision, the myometrium and serosa of the uterine wound were sutured, the wound was closed, the dead space was avoided, and the uterine body was formed (if a certain wound surface was located in the posterior wall or it was difficult to be sutured directly, the laparoscopic device can be connected for fine suture) (**Figure 1E**). Under direct vision, the tumor was cut, removed with a scalpel or scissors, and sent for pathological examination as necessary (**Figure 1F**). The single-hole laparoscopic device was connected, the pelvis was rinsed with normal saline to avoid residue, any active bleeding of the wound was checked under the microscope (**Figure 1G**), the instrument was removed to empty the gas, and the abdominal cavity was closed layer by layer.

Postoperative Treatment

All seven patients returned to the ward smoothly without intraoperative complications. Oxytocin was given to facilitate uterine contraction and rehydration, and antibiotics were given to prevent infection as necessary. The dressing was changed after the operation.

Observation Indicators

The operation duration, intraoperative bleeding, intraoperative/postoperative complications, preoperative and postoperative hemoglobin, postoperative hospital stay, postoperative visual analogue scale (pain score scale: 0–10 represents the degree of pain from painless to intolerable pain), and grade of incision healing (Grade A refers to one-time wound healing without infection after stitch removal, Grade B refers to incision infection and healing after treatment, and Grade C refers to incision rupture or infection without healing) were used.

Postoperative Follow-Ups

Six months after the operation, follow-ups were conducted to check for any long-term complications such as incision hernia and myoma with recurrence in a short time. The follow-up results showed that the seven patients had no incision hernia and no abnormality was found in vaginal ultrasound. The symptoms of patients were significantly improved and followed up on regularly.

Statistical Analysis

SPSS Statistics was used for data statistics, and the data meeting the normal distribution conditions were expressed as mean ± standard deviation ($x \pm s$).

RESULTS

All seven patients received the operation successfully, without changing to the conventional laparoscopic operation or gynecological transabdominal surgery. The ureter or bladder was not injured during the operation, and the urine was clear after the operation. The postoperative hospital stay was 4–6 days, with an average of 5 ± 0.53 days. The average postoperative blood loss was 101.42 ± 7.89 ml, and the postoperative visual analog score was 1.57 ± 0.53. All patients had exhausted, catheter removal was performed 1–2 days after the operation, and the postoperative incision healed well, without complications such as wound infection and bleeding (**Table 3**). Abdominal drainage tubes were placed in two patients and removed on the second day. The incision sites of the seven patients were original abdominal wall scars and were not changed to traditional laparoscopy or laparotomy.

DISCUSSION

Hysteromyoma is the most common gynecological benign tumor for women of childbearing age, and its etiology is not clear, which may be related to the patient's age, not having a child or late childbearing, obesity, and other factors (4). Most patients have no clinical symptoms, and only a small number of patients have symptoms such as increased menstruation, increased vaginal secretions, and abdominal pain. For women who have fertility requirements or want to retain the uterus, hysteromyoma removal is a relatively safe and feasible method. Compared with open surgery, traditional laparoscopy or single-hole laparoscopy has a better cosmetic effect, faster postoperative recovery, and shorter hospital stay (8). However, traditional laparoscopy needs to insert 3–4 puncture devices, which increases the incidence of abdominal incision hernia to a certain extent, and the injury rate of intestinal tubes and blood vessels during puncture also increases (9). With people's aesthetic requirements increases, LESS came into being. Wheelless (10) first applied single-hole laparoscopy to gynecological tubal ligation as early as 1969. However, due to the different operation modes of single-hole laparoscopy, the operation is more difficult, which often leads to a longer operation time than traditional laparoscopy. Besides, after transumbilical single-hole laparoscopy, the umbilical hole is more difficult and the umbilical hole plastic surgery is also challenging. Many beginners have encountered the conditions of red and swollen umbilical hole tissue, seepage, necrosis, and infection after suture, resulting in the limited application of single-hole laparoscopy (11). The transabdominal scar approach can avoid umbilical hole plastic surgery and the resulting risks to a certain extent. Meanwhile, the transabdominal scar approach can reduce the formation of new abdominal scars and hide new surgical scars with the original scars to form "hidden scars" (12).

Taking the cesarean scar on the abdominal wall as an example, its location is closer to the pelvic cavity and the uterus than the single-hole laparoscopy through the umbilical approach. It has the following advantages and disadvantages: (1) The operator can cooperate using a 30° laparoscopic lens, which has a wider field of vision and more convenient operation. The surgical instruments that are double curved or of different lengths can be used to avoid the "chopstick effect" of laparoscopic surgery (13), which also helps shorten the operation duration. After stripping the tumor body in the field of vision, the operator can penetrate the finger into the pelvic cavity through the

TABLE 3 | Single-hole laparoscopic myomectomy *via* the abdominal scar approach.

Case	Number of myomas (piece)	Myoma size (cm)	Myoma location	Operation duration (min)	Intraoperative bleeding volume (ml)	Preoperative hemoglobin (g/L)	Postoperative hemoglobin (g/L)	Pathology	Grade of incision healing	Postoperative visual analogue score
1	1	6.2×4.5×5.9	Left broad ligament	125	105	139	117	Cellular leiomyoma with steatosis	A	Two
2	1	7.3×6.0×5.3	Anterior wall	120	105	127	118	Leiomyoma	A	One
3	2	Front wall 1 piece: 6.5×6.0×6.0; Rear wall 1 piece: 1.8×1.0×1.0	Front wall 1 piece and Rear wall 1 piece	110	110	118	124	Leiomyoma	A	Two
4	10	Maximum myoma: 8.1×5.1×7.9	Intramural (maximum in posterior wall)	180	90	96	79	Leiomyoma with degeneration	A	Two
5	1	7.0*6.0×5.0	Posterior wall	160	110	128	108	Leiomyoma	A	One
6	1	4.5×5.0×5.0	Anterior wall	115	90	145	133	Leiomyoma	A	One
7	2	Front wall 2 pieces: 6.0×5.0×5.0 and 4.0×4.5×4.5	Anterior wall	100	100	125	104	Leiomyoma	A	Two

incision channel and scatter the small tumor body through tactile perception, the mode that helps accurately identify the scattered small tumor body of the uterus, to peel off the myoma as much as possible and reduce the recurrence of postoperative hysteromyoma and damage to the myometrium caused by blind exploration of myoma by instruments. The authors' team has also used the "finger probe method" to complete the traditional laparoscopic myomectomy (14), which is the advantage of this method. (2) For patients with hysteromyoma on the anterior wall, they can choose to cut near the scar of the uterine fundus, combine the transabdominal operation with the pneumoperitoneum-free single-hole laparoscopic operation, cooperate with the uterine lifting device, and use the laparoscopic surgical instruments under direct vision. This method can increase the surgical field, reduce intraoperative bleeding, facilitate the suture procedure of the laparoscopic operation, and simplify the operation to a certain extent. Meanwhile, the thyroid retractor is used to gently lift the skin to avoid the damage of gram steel needle to the abdominal wall. For patients with uterine fibroids in the anterior wall, this is a more feasible scheme with a higher aesthetic value. The authors' team also completed several cases of pneumoperitoneum-free single-hole laparoscopic ovarian cyst stripping (15). For patients with posterior wall hysteromyoma, the upper abdominal scar approach can be selected, combined with laparoscopic assistance, which can address the disadvantage of small pelvic operation space through the abdominal scar approach and improve the safety of the operation. (3) The scar of the cesarean section is closer to the uterus, the operation space of laparoscopic instruments is small, and the operation is difficult. In comparison, the transumbilical approach is easier to lead to the "conflict" of surgical instruments, and the "chopstick effect" is more serious. Therefore, the operator is required to have better operation skills. Especially for patients with the transverse scar of cesarean section, because their transverse scar is close to the bladder, the operation may easily damage the bladder, and the operator is required to pay more attention to the anatomical level when entering the abdomen layer by layer. Patients should be evaluated before the operation, and other operation methods should be chosen for patients not suitable for this operation. (4) Compared with laparoscopy-assisted mini-laparotomy, the transabdominal scar approach can reduce the number of abdominal wall puncture holes. This operation is based on the abdominal wall scar; the incision is smaller, without creating a new abdominal wall scar and is more aesthetically pleasing. Meanwhile, it can fine-suture the uterus and reduce the bleeding of uterine wounds. If the position of uterine leiomyoma is difficult to suture directly, the laparoscopy can be used without adding new puncture holes. (5) For patients with a history of abdominal wall scar, the most noticeable problem is abdominal adhesion. According to research, the risk of postoperative adhesion can reach 90% regardless of the operation method adopted (16, 17), which greatly increases the difficulty of laparoscopic operation, as well as the probability of damaging pelvic and abdominal organs and the incidence of a change to transabdominal operation (18). For abdominal organ adhesion, due to the lower local heat generated by the ultrasonic scalpel and less thermal damage to the tissue, the ultrasonic scalpel is the best choice for separating adhesion (19). Because the patient has a history of surgery, the intestinal canal may adhere to the original surgical incision, which requires the operator to pay attention to the layers when entering the abdomen and be more cautious in the operation. After the incision protective ring is placed, the laparoscopic lens can be used to detect the adhesion of the abdominal wall and intestinal canal, and the patient should be changed to transabdominal operation as necessary to ensure safety.

In general, the single-hole laparoscopic myomectomy *via* abdominal scar approach is more in line with the aesthetic requirements of patients. It is a safe and feasible scheme for patients who meet the inclusion criteria of surgery. However, if it is widely used, more randomized controlled studies are needed to further validate its effectiveness and feasibility.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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Partial Nephrectomy Versus Radical Nephrectomy for Endophytic Renal Tumors: Comparison of Operative, Functional, and Oncological Outcomes by Propensity Score Matching Analysis

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Purpose: The study aimed to compare operative, functional, and oncological outcomes between partial nephrectomy (PN) and radical nephrectomy (RN) for entophytic renal tumors (ERTs) by propensity score matching (PSM) analysis.

Methods: A total of 228 patients with ERTs who underwent PN or RN between August 2014 and December 2021 were assessed. A PSM in a 1:1 ratio was conducted to balance the differences between groups. Perioperative characteristics, renal functional, and oncological outcomes were compared between groups. Univariate and multivariate logistic and Cox proportional hazard regression analyses were used to determine the predictors of functional and survival outcomes.

Results: After PSM, 136 cases were matched to the PN group (n = 68) and the RN group (n = 68). Patients who underwent RN had shorter OT, less EBL, and lower high-grade complications (all p <0.05) relative to those who underwent PN. However, better perseveration of renal function was observed in the PN group, which was reflected in 48-h postoperative AKI (44.1% vs. 70.6%, p = 0.002), 1-year postoperative 90% eGFR preservation (45.6% vs. 22.1%, p = 0.004), and new-onset CKD Stage ≥III at last follow-up (2.9% vs. 29.4%, p <0.001). RN was the independent factor of short-term (OR, 2.812; 95% CI, 1.369–5.778; p = 0.005) and long-term renal function decline (OR, 10.242; 95% CI, 2.175–48.240; p = 0.003). Furthermore, PN resulted in a better OS and similar PFS and CSS as compared to RN (p = 0.042, 0.15, and 0.21, respectively). RN (OR, 7.361; 95% CI, 1.143–47.423; p = 0.036) and pT3 stage (OR, 4.241; 95% CI, 1.079–16.664; p = 0.039) were independent predictors of overall mortality.

Conclusion: Among patients with ERTs, although the PN group showed a higher incidence of high-grade complications than RN, when technically feasible and with experienced surgeons, PN is recommended for better preservation of renal function, longer OS, and similar oncological outcomes.

Keywords: endophytic renal tumor, partial nephrectomy, radical nephrectomy, propensity score matching, oncological outcomes, function outcomes, operative outcomes

INTRODUCTION

Endophytic renal tumors (ERTs) are tumors surrounded by normal renal parenchyma and attributed to three points of the E-element in the R.E.N.A.L. Nephrometry Score (RENAL-NS) system (1–3). Most ERTs are small spherical masses in deep locations and do not protrude from the renal surface of the tumor. Partial nephrectomy (PN) is the accepted standard treatment for normal small renal masses (4), with superior long-term benefit (5, 6).

Due to its highly complex anatomy, it is difficult to remove tumors and suture incised renal parenchyma, which requires considerable expertise and higher technical skills. Furthermore, these cases are related to higher intraoperative and perioperative complication rates, including positive resection margin caused by an unclear boundary, massive bleeding due to an accidental vascular injury, urine leakage caused by an accidental pelvicalyceal system injury, and renal vascular occlusion caused by inappropriate suture (7–9). Given the above risks and challenges, in the past, most urologists preferred RN for ERMs to avoid serious complications (10, 11). Owing to technological and conceptual advances, some authors have reported the successful application of PN for ERTs (9, 10, 12–14). These results demonstrate PN as a feasible technique for such anatomically complicated renal tumors. However, given technical difficulties due to this procedure, limited evidence of oncological and functional outcomes is available. Thus, it is unknown whether PN is more appropriate for ERTs than RN.

Thus far, no report of comparison between PN and RN for the treatment of ERTs has been published. We aimed to compare the operative, functional, and oncological outcomes for ERTs by PN or RN treatment by propensity score-matching (PSM) analysis; these findings may guide the treatment of ERTs.

MATERIALS AND METHODS

Patient Cohort

Patients with ERTs who underwent PN or RN between 1 August 2014 and 31 December 2021 at the First Affiliated Hospital of Nanchang University were assessed retrospectively. Of the 2,438 patients with a primary diagnosis of renal tumor or carcinoma, 228 patients with ERTs were identified and included in this study based on the following inclusion criteria: (1) imaging assessment of the location of the tumor was preserved in our radiographic database; (2) ERTs that were surrounded by normal renal parenchyma and attributed to three points for the E-element in the RENAL-NS system (3); (3) those who accepted surgical treatment by PN or RN, and (4) those without multiple lesions included endophytic masses (n >2), including multiple renal angiomyolipomas with endophytic lesion. The flowchart for the enrollment of patients with ERTs is shown in **Figure 1**. Patients who simultaneously met the above inclusion criteria (n = 228) were divided into the PN (n = 131) and RN (n = 97) groups according to the surgical method.

All operations were conducted by highly experienced urologists using laparoscopic or robot-assisted laparoscopic techniques; no open surgery was performed. After adequate exposure to the kidney and renal artery, intraoperative ultrasound was performed to locate the renal tumor during PN. The proximal renal artery away from the tumor was then clamped with bull's-head forceps to separate the tumor from the normal renal tissue with a pair of cold scissors, and two layers of suturing were performed to close the renal injury. Afterward, the bulldog forceps were removed for hemostatic evaluation, and the warm ischemia time was recorded. Apart from intraoperative ultrasound to locate tumors during PN, other detailed surgical procedures of PN and RN through laparoscopic or robot-assisted laparoscopic techniques for ERTs were the same as those for exophytic tumors described previously (14–16).

Research Materials

The demographic characteristics, including age, gender, body mass index (BMI), diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD) Stage ≥III, abdominal surgery history, age-adjusted Charlson's comorbidity index (ACCI), Eastern Cooperative Oncology Group Performance Status (ECOG PS), American Society of Anesthesiologists (ASA), preoperative serum creatinine (Scr), estimated glomerular filtration rates (eGFR), preoperative hemoglobin, and surgical technique were extracted from the prospectively managed clinical database. The Cockcroft–Gault (C–G) formula was used to calculate eGFR, and all values were standardized by body surface area of patients.

The oncology characteristics, including tumor size, location, laterality, clinical T stage (cTn), and RENAL-NS, were assessed by reviewing the computed tomography (CT) or magnetic resonance imaging (MRI) from our radiographic database. All the imaging information was blindly assessed and collected by urologists SX and Mj, and disputed cases were evaluated by a more senior urologist, LC.

Collected perioperative outcomes included operating time (OT), warm ischemia time (WIT), estimated blood loss (EBL), perioperative transfusion rate, surgery conversion rate, restoration time of bowel functions, drainage tube removal time, postoperative

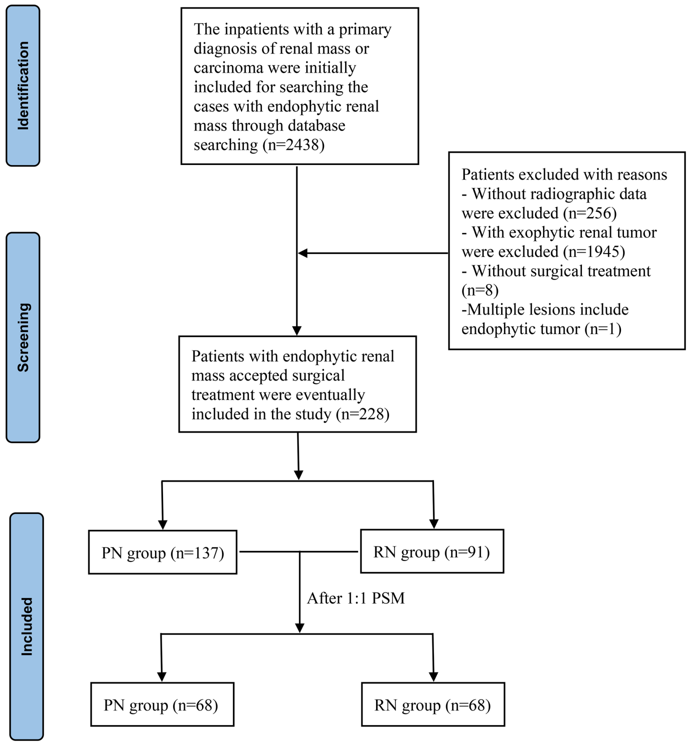

FIGURE 1 | Flow chart for inclusion of patients. PN, partial nephrectomy; RN, radical nephrectomy.

hospitalization time, postoperative complications, 48-h postoperative Scr, 48-h postoperative eGFR, 48-h postoperative eGFR descent, and 48-h postoperative acute kidney injury (AKI). Postoperative complications were determined by the Clavien–Dindo classification (17). AKI was defined as either a >50% increase in the postoperative serum creatinine relative to preoperative Scr or an absolute increase of >0.3 mg/dl according to the Acute Kidney Injury Network (AKIN) criteria (18).

All tumor specimens were reviewed for diagnosis by a single urological pathologist. The pathologic characteristics consisted of histological subtype, TNM stage, Fuhrman nuclear grade (I/II grade were classified into low grade and III/IV into high), parasitic (or tentacular) invasion, and distant extension according to the eighth edition of the American Joint Committee on Cancer (AJCC) cancer staging manual.

According to the standardized institutional postoperative protocol, the regular follow-up was conducted every 3 months after surgery for 6 months, every 6 months for the next 3 years, and annually after that. The essential oncology follow-up consisted of CT or MRI scans for the chest and entire abdomen. The changes in eGFR calculated using Scr followed up at postoperative 3-, 6-, and 12 months and 3- and 5 years reflected the renal function outcomes. Survival outcomes included cancer-specific survival (CSS), progression-free survival (PFS), and overall survival (OS), defined as the interval from the date of surgery to death related to the renal tumor; the first tumor recurrence, or metastasis, and death due to any cause, respectively.

Statistical Analysis

To eliminate differences between groups in preoperative demographic and tumor characteristics, PSM analysis was performed using variables of age, gender, BMI, DM, HTN, CKD, abdominal surgery history, ACCI, ECOG PG, ASA, preoperative Scr, preoperative eGFR, preoperative hemoglobin, tumor laterality, tumor size, clinical T stage, RENAL-NS, and surgical technique. The propensity score was evaluated by non-parsimonious multivariate logistic regression. Finally, 68 patients in the PN group were successfully matched with a nearest neighbor matching algorithm to the same number of patients in the RN group at a 1:1 ratio. The preoperative covariate differences between the two groups before and after PSM were compared.

All categorical variables compared using the Pearson χ^2 test were presented in the form of numbers and percentages. As for continuous variables, the normally distributed variables using the Student's t-test are presented as mean and standard deviation, and the non-normally distributed variables using the Wilcoxon rank sum test are presented as median and interquartile range. A Kaplan–Meier survival analysis was used to compare OS, PFS, and CSS outcomes between groups. Univariate and multivariate logistics and Cox proportional hazard regression were used to determine the predictors of functional and survival outcomes. The univariate results were used to determine the candidate variables for the final multivariate model. All statistical analyses were performed using SPSS 24.0 software (SPSS, Chicago, IL, USA) and R software (version 4.1.0). The p <0.5 level was considered statistically significant.

RESULTS

During the study period, 228 patients with ERTs were included in the final analysis based on the inclusion and exclusion criteria. A total of 131 and 97 patients underwent PN and RN, respectively. According to the demographic and clinical characteristics shown in **Table 1**, statistically, significant differences are found for some variables before PSM. The patients in the RN group showed higher mean age (51.4 vs. 47.5 years, p = 0.037), lower mean BMI (22.9 vs. 23.7, p = 0.039), bigger tumor size (4.0 vs. 2.8 cm, p <0.001), higher overall RENAL-NS (10.1 vs. 8.8, p <0.001), higher R score (1.5 vs. 1.2, p <0.001), higher N score (3.0 vs. 2.5, p <0.001), and higher L score (2.6 vs. 2.2, p <0.001) relative to the PN group. Furthermore, the RN group had a higher ratio of ECOG PS score of ≥2 (13.4% vs. 5.3, p = 0.033), clinical T stage ≥cT1b (49.5% vs. 15.3%, p <0.001), hilar location (43.3% vs. 15.3%, p <0.001), and a lower ratio of robot-assisted laparoscopic technique (18.6% vs. 37.4%, p = 0.002) compared to the PN group. No statistical difference was found in other variables between groups was observed. After performing 1:1 PSM, all statistically significant covariates achieved a good balance among the matched groups (with 68 patients in both PN and RN groups). The median follow-up duration in the PN and RN groups before the PSM was 41.2 and 45.3 months, respectively; after the PSM, the corresponding values were 44.8 and 45.2 months, respectively.

Operative, pathological, and renal functional outcomes for PN and RN groups after PSM are shown in **Table 2**. Patients in the PN group showed longer OT (194.4 vs. 171.3 mins, p = 0.014) and more EBL (198.5 vs. 140.7 ml, p = 0.038) than those in the RN group, whereas no statistical difference in required blood transfusion (2.9% vs. 5.9%, p = 0.680) was observed. Postoperative recovery indices, which included restoration time of bowel functions, drainage tube removal time, and postoperative hospitalization time, were similar between the groups. Two cases of surgical conversion (to RN) for intraoperative massive and repeated bleeding in the PN group, and no conversion in the RN group, or to open method were recorded. The mean warm ischemia time in the PN group was 27.6 min. No positive resection margins were observed in either group. Patients in the PN group had a similar ratio of overall and low-grade (Clavien–Dindo grades I–II) complications (p = 0.060 and p = 0.341, respectively) but showed a higher ratio of high-grade (Clavien–Dindo grades III–IV) complications (10.3% vs. 1.5%, p = 0.029) relative to the RN group. High-grade complications included ICU management (n = 1), urine leak

TABLE 1 | Preoperative basic characteristics of patients before and after propensity score matching.

Variables	Before propensity score matching			After propensity score matching		
	PN (n = 131)	RN (n = 97)	*p*-value	PN (n = 68)	RN (n = 68)	*p*-value
Age, years, mean (SD)	47.5 (12.7)	51.4 (15.3)	**0.037**	46.8 (13.7)	49.7 (14.8)	0.230
Gender (male), n (%)	75 (57.3%)	56 (57.7%)	0.942	35 (51.5%)	38 (55.9%)	0.606
BMI, mean (SD)	23.7 (2.8)	22.9 (2.9)	**0.039**	23.4 (2.8)	23.1 (2.9)	0.479
Diabetes mellitus, n (%)	12 (9.2%)	7 (7.2%)	0.529	7 (10.3%)	4 (5.9%)	0.345
Hypertension, n (%)	21 (16.0%)	17 (17.5%)	0.887	10 (14.7%)	9 (13.2%)	0.805
CKD Stage ≥III, n (%)	13 (9.9%)	12 (12.4%)	0.559	6 (8.8%)	7 (10.3%)	0.771
Abdominal surgery history, n (%)	23 (17.6%)	14 (14.4%)	0.527	10 (14.7%)	10 (14.7%)	NA
ACCI score, mean (SD)	4.1 (1.7)	4.3 (1.9)	0.265	4.0 (1.8)	4.2 (1.8)	0.534
ECOG PS score ≥2, n (%)	7 (5.3%)	13 (13.4%)	**0.033**	4 (5.8%)	6 (8.8%)	0.511
ASA score ≥2, n (%)	73 (55.7%)	53 (53.6%)	0.870	41 (60.3%)	37 (54.4%)	0.488
Scr, mg/dl, mean (SD)	0.88 (0.33)	0.86 (0.47)	0.726	0.83 (0.25)	0.82 (0.31)	0.791
eGFR, ml/min/1.73 m^2, mean (SD)	91.5 (26.4)	89.0 (26.7)	0.480	94.8 (26.9)	92.7 (26.8)	0.644
Hemoglobin, g/dl, mean (SD)	132.8 (15.6)	129.8 (16.4)	0.221	130.7 (16.6)	130.0 (14.8)	0.802
Laterality (left), n (%)	72 (55.0%)	48 (49.5%)	0.413	37 (54.4%)	36 (52.9%)	0.863
Tumor size, cm, mean (SD)	2.8 (1.0)	4.0 (1.5)	**<0.001**	3.3 (1.0)	3.6 (1.3)	0.077
Clinical T stage ≥cT1b, n (%)	20 (15.3%)	48 (49.5%)	**<0.001**	20 (29.2%)	28 (41.2%)	0.151
RENAL-NS, mean (SD)	8.8 (1.5)	10.1 (1.2)	**<0.001**	9.4 (1.3)	9.8 (1.2)	0.065
R score, mean (SD)	1.2 (0.4)	1.5 (0.6)	**<0.001**	1.3 (0.5)	1.4 (0.5)	0.149
N score, mean (SD)	2.5 (0.8)	3.0 (0.3)	**<0.001**	2.8 (0.6)	2.9 (0.4)	0.067
L score, mean (SD)	2.2 (0.9)	2.6 (0.7)	**<0.001**	2.4 (0.9)	2.5 (0.8)	0.309
Hilar location, n (%)	20 (15.3%)	42 (43.3%)	**<0.001**	17 (25.0%)	24 (35.3%)	0.191
Surgical Technique			**0.002**			0.252
Open	0	0		0	0	
Laparoscopic, n (%)	82 (62.6%)	79 (81.4%)		46 (67.6%)	52 (76.5%)	
Robot, n (%)	49 (37.4%)	18 (18.6%)		22 (32.4%)	16 (23.5%)	

RN, radical nephrectomy; PN, partial nephrectomy; SD, standard deviation; BMI, body mass index; CKD, chronic kidney disease, CKD Stage ≥III defined as eGFR<60 ml/min; Sc, serum creatinine; eGFR, estimated glomerular filtration rate; ACCI, age-adjusted Charlson's comorbidity index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ASA, American Society of Anesthesiologists; RENAL-NS, R.E.N.A.L. Nephrometry Score.
The bold numbers mean statistically difference.

TABLE 2 | Perioperative and oncological outcomes for PN and RN after propensity score matching.

Variables	PN (n = 68)	RN (n = 68)	*p*-value
OT, min, mean (SD)	194.4 (48.8)	171.3 (58.6)	**0.014**
WIT, min, median (IQR)	27.5 (26.3-29.0)	–	–
EBL, mL, median (IQR)	200 (100-200)	100 (100-150)	**<0.001**
Transfusion, n (%)	2 (2.9%)	4 (5.9%)	0.680
Surgery conversion, n (%)			
To RN	2 (2.9%)	–	–
Positive resection margin, n (%)	0	0	–
Restoration time of bowel functions, days, median (IQR)	2 (2-3)	2 (2-3)	0.305
Drainage tube removal time, days, median (IQR)	3 (3-5.75)	3 (3-4)	0.804
Postoperative hospitalization time, days, median (IQR)	7 (5-9)	6 (5-8)	0.061
Postoperative complications, n (%)	19 (27.9%)	10 (14.7%)	0.060
Clavien–Dindo grades I–II, n (%)	12 (17.6%)	9 (13.2%)	0.341
Clavien–Dindo grades III–IV, n (%)	7 (10.3%)	1 (1.5%)	**0.029**
ICU management	1 (1.5%)	0	–
Urine leak	3 (4.4%)	0	–
Hemorrhage treated by embolization	1 (1.5%)	0	–
Acute renal failure	1 (1.5%)	1 (1.5%)	–
Second operation	1 (1.5%)	0	–
Histologic subtype			0.062
Benign, n (%)	15 (22.1%)	7 (10.3%)	
Malignant, n (%)	53 (77.9%)	61 (89.7%)	
ccRCC, n (%)	46 (86.8%)	47 (77.1%)	–
pRCC, n (%)	2 (3.8%)	6 (9.8%)	–
chRCC, n (%)	1 (1.9%)	3 (4.9%)	–
Others, n (%)	4 (7.5%)	5 (8.2%)	–
Pathologic stage			0.115
pT1, n (%)	50 (94.3%)	52 (85.2%)	
pT3, n (%)	3 (5.7%)	9 (14.8%)	
Fuhrman grade			0.247
Low grade (I/II), n (%)	44 (91.7%)	42 (84.0%)	
High grade (III/IV), n (%)	4 (5.8%)	8 (16.0%)	
Lymph node metastasis, n (%)	0	2 (2.9%)	–

RN, radical nephrectomy; PN, partial nephrectomy; OT, operating time; WIT, warm ischemia time; EBL, estimated blood loss; SD, standard deviation; ICU, intensive care unit; ccRCC, clear cell renal cell carcinoma; pRCC, papillary renal cell carcinoma; chRCC, chromophobe renal cell carcinoma; eGFR, estimated glomerular filtration rate.
The bold numbers mean statistically difference.

(n = 3), hemorrhage treated by embolization (n = 1), acute renal failure (n = 1), and the second operation for suspected residual tumor (n = 1) in the PN group, and acute renal failure (n = 1) in the RN group.

Among pathologic characteristics, no statistically significant differences in histological subtype, pathological stage, or Fuhrman grade were observed between the two groups (all p >0.05).

Among postoperative renal functional outcomes (**Table 3**), the PN group showed a significant association with higher 48-h postoperative eGFR (70.5 vs. 57.4 ml/min/1.73m^2, p <0.001) than the RN group. Compared with preoperative eGFR, 48-h postoperative eGFR decreased in the PN and RN groups by 24.3 and 35.3 ml/min/1.73m^2, respectively (p = 0.002). Univariate and multivariate logistic analyses showed that RN

TABLE 3 | Preoperative functional outcomes for PN and RN after propensity score matching.

Variables	PN (n = 68)	RN (n = 68)	*p*-value
Preoperative Scr, mg/dl, mean (SD)	0.83 (0.25)	0.82 (0.31)	0.791
Preoperative eGFR, ml/min/1.73 m^2, mean (SD)	94.8 (26.9)	92.7 (26.8)	0.644
48-h postoperative Scr, mg/dl, mean (SD)	1.13 (0.42)	1.24 (0.47)	0.157
48-h postoperative eGFR, ml/min/1.73 m^2, mean (SD)	70.5 (22.8)	57.4 (17.5)	**<0.001**
48-h postoperative eGFR descend, ml/min/1.73 m^2, mean (SD)	23.9 (16.6)	35.3 (23.8)	**0.001**
48-h postoperative AKI, n (%)	30 (44.1%)	48 (70.6%)	**0.002**
1-year postoperative Scr, mg/dl, mean (SD)	0.98 (0.40)	1.19 (0.59)	**0.021**
1-year postoperative eGFR, ml/min/1.73 m^2, mean (SD)	84.4 (30.1)	66.7 (21.6)	**<0.001**
1-year postoperative 90% eGFR preservation, n (%)	31 (45.6%)	15 (22.1%)	**0.004**
Last follow-up Scr, mg/dl, mean (SD)	0.99 (0.43)	1.22 (0.74)	**0.028**
Last follow-up eGFR, ml/min/1.73 m^2, mean (SD)	82.1 (24.9)	66.1 (19.4)	**<0.001**
New-onset CKD Stage ≥III at last follow-up, n (%)	2 (2.9%)	20 (29.4%)	**<0.001**

RN, radical nephrectomy; PN, partial nephrectomy; SD, standard deviation; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; CKD, chronic kidney disease.
The bold numbers mean statistically difference.

(OR, 2.812; 95% CI, 1.369–5.778; p = 0.005) was an independent risk factor for 48-h postoperative AKI (**Table 4**). Throughout the follow-up period, the renal function in the PN group was significantly better than that in the RN group (all p <0.001) (**Figure 2**). One-year postoperative 90% eGFR preservation occurred in 45.6% of patients in the PN group and 22.1% in the RN group (p = 0.004). Furthermore, the patients in the PN group had a lower rate of new-onset CKD Stage ≥III at the last follow-up relative to the RN group (2.9% vs. 29.4%, p <0.001). The results of univariate and multivariate logistic analyses suggested that hilar location (OR, 3.726; 95% CI, 1.283–10.823; p = 0.016) and RN (OR, 10.242; 95% CI, 2.175–48.240; p = 0.003) were independent risk factors for new-onset CKD Stage ≥III at the last follow-up (**Table 5**).

TABLE 4 | Univariate and multivariate Logistic analysis of independent risk factors for 48-h postoperative AKI.

Variables	Univariate Analysis		Multivariate Analysis	
	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age	1.01 (0.99–1.04)	0.260		
Gender				
Female (Re.) vs. male	0.90 (0.46–1.78)	0.763		
BMI	1.11 (0.98–1.26)	0.109		
Diabetes mellitus	0.59 (0.17–2.05)	0.409		
Hypertension	1.03 (0.38–2.74)	0.959		
Abdominal surgery history	0.71 (0.27–1.83)	0.473		
ACCI score	0.98 (0.81–1.19)	0.844		
ECOG PS score ≥2	0.73 (0.20–2.64)	0.626		
ASA score ≥2	0.81(0.41–1.61)	0.543		
Preoperative eGFR	1.01 (1.00–1.02)	0.201		
Preoperative hemoglobin	0.99 (0.96–1.01)	0.185		
Laterality				
Left (Re.) vs. Right	1.81 (0.91–3.62)	0.092		
Tumor size	0.98 (0.73–1.30)	0.865		
RENAL-NS	1.03 (0.80–1.34)	0.807		
R score	1.24 (0.60–2.57)	0.554		
N score	1.13 (0.58–2.17)	0.725		
L score	0.95 (0.63–1.42)	0.793		
Hilar location	0.81 (0.39–1.69)	0.567		
Technique				
Laparoscopic (Re.) vs. Robot	0.97 (0.45–2.07)	0.937		
Operating method				
PN (Re.) vs. RN	3.04 (1.50–6.17)	**0.002**	2.81 (1.37–5.78)	**0.005**
Operating time	1.00 (0.99–1.00)	0.154		
Estimated blood loss	1.00 (0.99–1.00)	0.199		
Transfusion	1.51 (0.27–8.56)	0.639		
Postoperative hospitalization time	0.85 (0.74–0.98)	**0.024**	0.87 (0.76–1.00)	0.055
Postoperative complications	1.96 (0.79–4.86)	0.144		
Histologic subtype				
Benign (Re.) vs. Malignant	1.77 (0.71–4.45)	0.221		
Pathologic stage				
pT1 (Re.) vs. pT3	0.88 (0.26–3.05)	0.844		
Fuhrman grade				
I/II (Re.) vs. III–IV	0.90 (0.26–3.06)	0.864		

BMI, body mass index; ACCI, age-adjusted Charlson's comorbidity index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ASA, American Society of Anesthesiologists; eGFR, estimated glomerular filtration rate; Re, reference; RENAL-NS, RENAL-Nephrometry Score; RN, radical nephrectomy; PN, partial nephrectomy.
The bold numbers mean statistically difference.

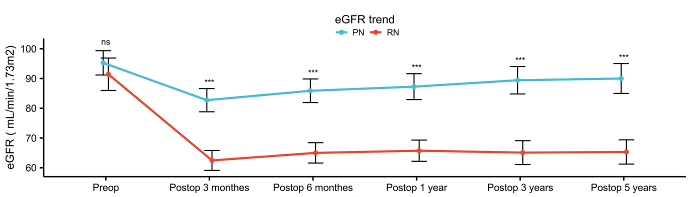

FIGURE 2 | Postoperative eGFR trend of patients in PN group and RN group after propensity score matching. eGFR, estimated glomerular filtration rate; PN, partial nephrectomy; RN, radical nephrectomy. "***" means p<0.001; "ns" means not statistically significant.

TABLE 5 | Univariate and multivariate Logistic analysis of independent risk factors for new onset CKD stage ≥ II at last follow-up.

Variables	Univariate Analysis		Multivariate Analysis	
	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age	1.04 (1.00–1.08)	**0.030**	1.04 (1.00–1.08)	0.060
Gender				
Female (Re.) vs. male	0.68 (0.27–1.69)	0.675		
BMI	0.88 (0.79–1.03)	0.110		
Diabetes mellitus	0.50 (0.06–4.08)	0.495		
Hypertension	1.47 (0.44–4.93)	0.536		
Abdominal surgery history	1.36 (0.41–4.54)	0.616		
ACCI score	1.14 (0.89–1.45)	0.305		
ECOG PS score ≥2	1.23 (0.67–2.27)	0.511		
ASA score ≥2	1.09 (0.43–2.75)	0.857		
Preoperative eGFR	0.99 (0.97–1.01)	0.361		
Preoperative hemoglobin	0.99 (0.97–1.02)	0.697		
Laterality				
Left (Re.) vs. Right	2.32 (0.90–5.97)	0.081		
Tumor size	0.99 (0.67–1.46)	0.961		
RENAL-NS	0.95 (0.67–1.34)	0.775		
R score	1.14 (0.44–2.96)	0.783		
N score	0.89 (0.39–2.06)	0.785		
L score	0.90 (0.53–1.53)	0.701		
Hilar location	3.52 (1.38–9.00)	**0.009**	3.73 (1.28–10.82)	**0.016**
Technique				
Laparoscopic (Re.) vs Robot	1.04 (0.37–2.90)	0.939		
Operating method				
PN (Re.) vs RN	13.8 (3.07–61.65)	**0.001**	10.24 (2.18–48.24)	**0.003**
Postoperative complications	1.35 (0.36–4.99)	0.655		
48-h postoperative AKI	2.95 (1.02–8.55)	**0.046**	1.79 (0.54–5.87)	0.339
Histologic subtype				
Benign (Re.) vs Malignant	1.27 (0.34–4.77)	0.724		
Pathologic stage				
pT1 (Re.) vs pT3	2.09 (0.51–8.60)	0.306		
Fuhrman grade				
I/II (Re.) vs III–IV	1.74 (0.42–7.24)	0.447		

BMI, body mass index; ACCI, age-adjusted Charlson's comorbidity index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ASA, American Society of Anesthesiologists; eGFR, estimated glomerular filtration rate; RENAL-NS, RENAL-Nephrometry Score; RN: radical nephrectomy; PN, partial nephrectomy.
The bold numbers mean statistically difference.

During the follow-up in the matched cohort, 8 and 16 patients developed local recurrence/distant metastasis in the PN and RN groups, respectively. The overall mortality was 4 patients in the PN group and 15 in the RN group. Cancer-related mortality occurred in 2 patients in the PN group and 8 in the RN group. Kaplan–Meier analyses suggested statistically significant differences in CSS, PFS, and OS in favor of PN (p = 0.006, 0.036, and 0.034, respectively) (**Figure 3**). Within the matched cohort, the patients in the PN group showed a longer OS compared with those in the RN group (p = 0.042). However, no statistically significant differences were observed in CSS and FPS between the two groups (p = 0.15 and 0.21, respectively). Univariate and multivariate Cox regression analyses showed that RN (OR, 7.36; 95% CI, 1.14–47.42; p = 0.036) and pathological T3 (pT3) stages were the predictors of overall mortality (OR, 4.241; 95% CI, 1.079–16.664; p = 0.039) (**Table 6**).

DISCUSSION

When technically feasible, the management of renal tumors has shifted from RN to PN to reduce the risk of CKD and cardiovascular diseases (6, 7). With the spread of this concept and improvements in surgical technology, the application of PN for renal tumors has been extended to more challenging cases, including ERTs (1). Although several authors have reported their successful experiences and beneficial results (19–21), the evidence in support of PN as a standard is weak. Due to the highly complex branching anatomical structure, it is challenging to remove deep endophytic tumors and suture incised renal parenchyma and hilar structures without increasing perioperative complications; this requires considerable anatomical knowledge and technical skill (2, 9). Park et al. showed that postoperative renal function and contralateral renal volume measured by 3D reconstructive technology according to the endophytic degree of tumors are similar between the OPN and ORN groups. Therefore, they recommended RN as a priority surgical option for ERTs (11). Superior surgical decisions regarding ERTs are of substantial importance; this debate is ongoing. The optimal management of ERTs should balance the potential benefits of intervention with competing risks of mortality in the best interests of these patients. Considering the various risks and benefits of different operating methods, we present here the first report on the perioperative, functional, and oncological outcomes of PN and RN for ERTs.

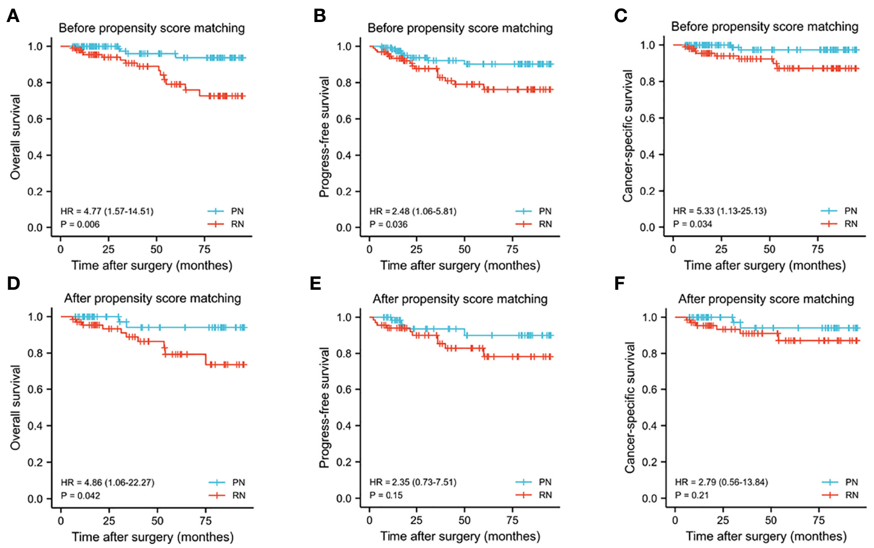

FIGURE 3 | Kaplan–Meier curves for overall survival **(A, D)**, progress-free survival **(B, E)**, cancer-specific survival **(C, F)** between the PN and RN groups before and after propensity score matching. PN, partial nephrectomy; RN, radical nephrectomy.

In this retrospective study, compared with patients who underwent PN, those who underwent RN were more likely to be the elderly with a poor general condition or larger tumor size, and highly complex tumors with high RENAL-NS. Such biases can be identified in other comparative studies between different surgical methods (partial and radical nephrectomy) (22–24). To eliminate selection bias and the influence of confounding factors, PSM analysis was conducted, as shown in **Table 1**. In the matched cohort, patients in the PN group showed a longer OT and more EBL relative to those in the RN group. A systematic review and meta-analysis by Yang et al. comprising 13 retrospective cohort studies with 13,269 patients showed that lower EBL was associated with PN and not RN for T1 renal tumor (25). Li et al. reported a similar result in another meta-analysis (26). Unlike PN, considering the omission in removing tumor and renorrhaphy during RN, the advantages of OT and EBL can be explained. Nevertheless, these advantages do not seem to be conducive to decreasing the length of postoperative hospital stays, which may be related to the similar transfusion rate, conversion rate, recovery time for postoperative bowel function, the duration of drainage, and incidence of overall complications between the two groups.

The occurrence of complications tended to be associated with the anatomical complexity of renal tumors and the basic characteristics of patients (27, 28). No statistically significant differences were observed in the incidence of overall complications between the two groups. However, after categorizing complications by Clavien–Dindo classification, in the intergroup comparison, the PN group was considerably higher than the RN group (10.3% vs. 1.5%, $p = 0.029$). Like in other retrospective studies on PN for the treatment of ERTs (29, 30), high-grade complications included urinary leakage, a requirement for ICU admission, excessive hemorrhage requiring embolization, acute renal failure, and a second operation for persistent drop in blood pressure and hemoglobin. In a meta-analysis involving 30,018 patients with RCC, Yang reported that PN is associated with an increased risk of postoperative hemorrhagic complications and urinary fistula as compared to RN (31). As a complex renal tumor, the risk of complications is higher for ERTs than for general renal tumors. The following surgical difficulties are the reasons for a higher incidence of high-grade complications in the PN group: first, ERTs are generally small in size, deep in location, and have invisible boundaries; thus, it takes a long time to locate and remove the tumor. Furthermore, the resection margin can be positive because of the indistinct tumor expansion during its removal (8), which has a major impact on the prognosis. Second, ERTs are prone to be close to the collecting system and renal sinus, wherein they are highly close to or even infiltrate into the secondary and tertiary renal arteries and veins. It is challenging to remove ERTs with a high risk of accidental vascular or pelvicalyceal system injury, which can lead to accidental rupture, massive bleeding, and urine leakage (7). Finally, even if the kidney tumor is successfully removed, the wound surface is so deep that sewing it up is challenging (9). Because the base of the wound is close to the collecting system or branch blood vessels, inappropriate suture may cause renal vascular occlusion or urine leak from the collecting system. Therefore, we recommend surgeons with rich experience and high technical skills perform PN for ERTs when a tumor-localizing device is available.

Removal of anatomically complicated tumors is inevitably associated with decreased preservation of normal parenchymal nephrons and prolonged WIT, both of which lead to increased renal impairment (32, 33). Despite these adverse factors, our findings showed that patients who underwent PN had less postoperative eGFR reduction (24.3 vs. 35.3 ml/min/1.73 m^2, $p = 0.002$) and a lower incidence of 48-h postoperative AKI

TABLE 6 | Univariate and multivariate Cox analysis of independent risk factors for overall mortality.

Variables	Univariate Analysis		Multivariate Analysis	
	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	-value
Age	1.11 (1.05–1.17)	**<0.001**	1.07 (0.95–1.20)	0.285
Gender				
Female (Re.) vs. male	1.89 (0.51–7.00)	0. 343		
BMI	1.04 (0.84–1.30)	0.725		
Diabetes mellitus	6.09 (1.63–22.70)	**0.007**	7.19 (0.98–36.45)	0.052
Hypertension	2.98 (0.79–11.30)	0.108		
Preoperative CKD	1.44 (0.19–11.29)	0.727		
Abdominal surgery history	2.36 (0.64–8.79)	0.200		
ACCI score	1.81 (1.36–2.41)	**<0.001**	1.34 (0.54–3.33)	0.533
ECOG PS ≥2	3.77 (2.41–6.93)	**<0.001**	0.40 (0.06–2.56)	0.332
ASA score ≥2	3.05 (0.82–11.32)	0.096		
Preoperative eGFR	0.98 (0.96–1.00)	0.086		
Preoperative hemoglobin	0.97 (0.94–1.00)	0.089		
Laterality				
Left (Re.) vs. Right	0.89 (0.28–2.81)	0.846		
Tumor size	1.29 (0.81–2.06)	0.279		
Clinical T stage ≥cT1b	3.42 (1.03–11.37)	**0.045**	1.42 (0.33–6.18)	0.642
RENAL-NS	1.79 (0.93–3.46)	0.084		
R score	2.75 (0.87–8.68)	0.084		
N score	5.77 (0.03–973.0)	0.503		
L score	1.70 (0.66–4.42)	0.275		
Hilar location	0.62 (0.17–2.29)	0.454		
Technique				
Laparoscopic (Re.) vs. Robot	0.77 (0.23–2.55)	0.665		
Operating method				
PN (Re.) vs. RN	7.36 (1.14–22.99)	**0.038**	7.36 (1.14–47.42)	**0.036**
Postoperative complications	1.02 (0.21–4.99)	0.981		
48-h postoperative AKI	2.72 (0.73–10.06)	0.135		
New onset CKD stage ≥III	1.37 (0.37–5.08)	0.637		
Histologic subtype				
Benign (Re.) vs. Malignant	2.65 (0.34–20.57)	0.351		
Pathologic stage				
pT1 (Re.) vs. pT3	4.24 (1.08–16.66)	**<0.001**	4.24 (1.30–33.21)	**0.039**
Fuhrman grade				
I/II (Re.) vs. III–IV	2.94 (0.58–14.78)	0.191		

BMI, body mass index; ACCI, age-adjusted Charlson's comorbidity index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ASA, American Society of Anesthesiologists; eGFR, estimated glomerular filtration rate; RENAL-NS, RENAL-Nephrometry Score; RN, radical nephrectomy; PN, partial nephrectomy.
The bold numbers mean statistically difference.

(44.1% vs. 70.6%, $p = 0.002$) relative to those who underwent RN. These results were similar to those of a recent study that investigated the impact factors of perioperative AKI (34). Multivariate analysis showed that the significant predictor of 48-h postoperative AKI was the surgical method, whereby the risk in the RN group was 2.812 times greater than the PN group ($p = 0.005$). In other comparative studies between PN and RN groups, significant differences in perioperative decreased renal function were observed not only for small tumors but also for anatomically complicated tumors (22, 35). The quality and quantity of preserved parenchyma are the main contributors to postoperative long-term renal function (36). The EORTC randomized trial 30904 compared the impact of NSS compared to RN on kidney function in patients with small (≤5 cm) renal tumors. The findings demonstrated that the incidence of at least moderate renal dysfunction was reduced substantially among patients who underwent NSS relative to RN (37). Our results showed similar functional outcomes. PN was more favorable for long-term renal function in patients with ERTs than RN, which was reflected in higher 48-h postoperative eGFR and a higher rate of 1-year postoperative 90% eGFR preservation. At the last follow-up, 20 of 22 cases showed new-onset CKD stage ≥III, wherein the kidney was removed completely. The significant predictors of new-onset CKD stage ≥III were hilar location and RN. It is well known that RN is the main cause of CKD stage ≥III after surgery. Additionally, by calculating the product of eGFR and relative change in renal function before and after surgery for patients with hilar renal tumors, Hinata et al. (38) reported a decrease in the 180-day postoperative renal function; resected weight was the independent predictor of the decrease in the function after PN. This was more likely correlated with preserved normal renal parenchyma and longer WIT due to the location of renal hilar tumors close to the main renal vessels (32, 33, 38).

The survival outcomes before PSM showed that the patients who underwent RN had worse OS relative to those who underwent PN. The loss of functional nephrons is related to a high likelihood of downstream metabolic disorders, including osteoporosis, anemia, and cardiovascular accidents (39, 40). Weight et al. (41) have shown that RN is associated with a 25% increased risk of cardiac death and a 17% increased risk of death due to any cause, ultimately leading to reduced OS (42). Additionally, age, BMI, and ACCI are influencing factors for OS (43–45). After eliminating these influencing factors by PSM, the RN group showed a worse OS status. Multivariate analysis confirmed that RN and pT3 stages were the predictors of overall mortality. The present results showed that non-metastatic pT3 RCC after laparoscopic management incurred metastatic progression of 26% and the three-year mortality rate was 33% (46). A study by Leibovich et al. (47) has shown that the risk ratio for death is 1.87 times higher in patients with peripheral perinephric or renal sinus fat invasion compared with those without fat invasion (p <0.001). Liu et al. (48) compared the survival benefit between PN and RN for renal tumors ≤7 cm with stage pT3a from the SEER database and found that PN yielded better OS for the ≤4 cm group than RN. Furthermore, the Cochrane meta-analysis by Chung et al. (49) compared the oncological outcomes between PN and RN among patients who were upstaged from cT1 renal tumor to pT3a renal cell carcinoma. Relative to RN, patients who underwent PN had better or at least similar oncological outcomes, with a significant improvement in OS, particularly. Therefore, if PN is feasible, RN should be avoided for better survival outcomes among patients with ERTs that can improve in stage.

Interestingly, significant differences between CCS and PFS disappeared after the selection bias and confounding factors of oncological characteristics, including tumor size and RENAL-NS, were balanced by PSM. The results of Palacios et al. (50) indicated that unfavorable oncological outcomes (i.e., CSS and RPS) for localized RCC were mostly associated with aggressive tumor characteristics, not renal function. Zhang et al. (51) reported that tumor size is significantly correlated with nuclear grade and pathological stage, and larger tumors are prone to higher grades and stages. Here, Fuhrman Grade III occurred in 6.9% of renal tumors, which were 2.1 to 4.0 cm in diameter, and 22.3% of tumors between 4.1 and 7 cm in diameter. A study comprising 886 cases of SRM confirmed that increased tumor anatomical complexity quantified by RENAL-NS was independently related to malignancy and high nuclear grade (52). Chen et al. (53) indicated that R- and N-scores were associated with higher postoperative pathological grades. In our study, before PSM, tumors in the RN groups showed larger size (4.1 vs. 2.8 cm, p <0.001), higher overall RENAL-NS (10.1 vs. 8.8, p <0.001), with higher R score (1.5 vs. 1.2, p <0.001), and higher N score (3.0 vs. 2.5, p <0.001) relative to the PN group. Thus, all the indicators favorable to tumor progression were skewed toward the RN group. When these significantly different indicators were balanced, the results of similar CSS and PFS in the matched cohort could be easily interpreted.

However, this study is not devoid of limitations. This study was retrospective and based on a single center database. Although PSM analysis was performed to account for the preoperative basic and oncological characteristics, the underlying selection biases or confounding factors may be uncontrollable to a certain extent. Anatomical features and oncological characteristics were assessed by two-dimensional cross-sectional imaging. Therefore, because of the experience and subjective factors of the observers, there might have been judgment biases in this study. Preoperative and postoperative renal functions were not estimated using radioisotope renography, the ideal tool but impractical for every patient. Thus, eGFR was calculated using the internationally recognized Cockgroft–Gault equation, and the results for all patients were standardized by body surface area to improve their reliability. Finally, considering the operating challenges, experienced urologists at a tertiary referral institution performed the procedures, and thus, these results cannot be generalized and should be interpreted with caution.

Despite these limitations, to our knowledge, this retrospective study is the first to evaluate the safety and efficacy of PN and RN for treating ERTs. Additionally, the results of this study are based on PSM analysis to balance influencing factors, which improved the reliability of these findings to a greater extent.

CONCLUSION

In conclusion, in the matched cohort of patients with ERTs, RN resulted in more favorable surgical outcomes, but these advantages did not translate into faster postoperative recovery. Additionally, RN was an independent risk factor for short-term and long-term renal function decline. The incidence of overall complications was comparable to that of RN, but PN was more prone to high-grade complications due to the complex anatomical structure of these tumors. Even so, patients who underwent PN showed better preservation of renal function, longer OS, and similar oncological outcomes compared to those who underwent RN. Therefore, we suggest that PN be preferentially considered for ERTs when technically feasible and the surgeon is experienced.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Board and the ethical committee of the First Affiliated Hospital of Nanchang University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SX and MJ collected the data. SX and BF conceived the manuscript. SX wrote the manuscript. SX and YJ made tables and figures together. WD and BH provides guidance in statistical analysis. RC and ZY provides guidance on the making of figures. LC, XL and XW provided input into the revision of the manuscript. XW sent the manuscript to a native English speaker to correct spelling and grammatical errors. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Fertility-sparing treatment for endometrial cancer and atypical endometrial hyperplasia in patients with Lynch Syndrome: Molecular diagnosis after immunohistochemistry of MMR proteins

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Introduction: Lynch Syndrome (LS) represents the hereditary condition that is most frequently associated with endometrial cancer (EC). The aim of this study is to assess the presence of Lynch Syndrome (LS) in young women with mismatch repair (MMR)-deficient atypical endometrial hyperplasia (AEH) and non-myoinvasive FIGO G1 endometrioid EC and its possible impact on the outcome of conservative treatment.

Methods: Six MMR-deficient cases identified from a previous cohort of 69 conservatively treated patients were selected to be screened for germline mutations in MMR genes. In each patient, the outcomes of conservative treatment for AEH and EEC, including response, relapse, progression, and pregnancy, were assessed.

Results: Five out of 6 patients underwent genetic test for LS. Three out of these 5 patients showed a positive genetic test. Patient 1 showed the c.942 + 2 T>A heterozygous variant of *MSH2* mutation; after 12 months of complete response, she had relapse and progression of disease. Patient 4 showed the c.2459-1G>C variant of *MSH2* mutation; after complete response, she failed to achieve pregnancy; she had relapse after 24 months and underwent hysterectomy. Patient 6 showed the c.803 + 1 heterozygous variant of *PMS2* mutation; she had relapse of disease after 18 months from the first complete response and then underwent hysterectomy.

Conclusions: In this series, 3 out of 6 women with MMR-deficiency had LS. None of the patients achieved pregnancy, and those who responded to treatment had subsequent relapse of disease. Patients undergoing fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer should perform MMR immunohistochemical analysis in order to screen LS.

KEYWORDS

endometrial cancer, Lynch Syndrome, fertility-sparing treatment, immunohistochemistry, mismatch repair, genetic testing

Introduction

Endometrial cancer (EC) is the fifth cause of cancer in women and the most common gynecological cancer in developed countries (1–3). Nearly 90% of cases of EC occur in women >50 years of age, with a mean age at diagnosis of 63 years, while 4% occurs in young women under 40 years old (4). Ninety-five percent of EC are sporadic, while 5% are hereditary. The hereditary condition that is most frequently associated with EC is Lynch Syndrome (LS), an autosomal dominant disorder characterized by a germline pathogenic variant of one of the Mismatch Repair (MMR) genes (MLH1, PMS2, MSH2, MSH6) (5), resulting in microsatellite instability (MSI). MSI is a condition in which there is an altered number of repeats of short DNA sequences, called microsatellites, between tumor and normal tissue. MSI might represent the consequence of phenotypic evidence of MMR deficiency (6, 7). MSI analysis and MMR protein immunohistochemistry (IHC) have an important role in diagnosis: two studies reported high concordance between MSI and IHC analysis both in colorectal cancer (CRC) and EC, with discordance in the rare MMR-proficient/MSI-high cases (<1%) in EC patients, probably due to POLE-EDM variants (6, 7), while Ryan et al. reported how IHC outperforms MSI for tumor triage and is a reliable method for identifying both germline and somatic MMR mutations in women with EC (8). Women with LS have an increased risk to develop EC (up to 61% that is 39 times higher than the general population) (9–12) as well as other cancers, including colorectal (up to 57%), ovary (up to 40%), kidney, small bowel and biliary tract cancers (LScarisk.org). The prevalence of LS among ECs ranges from 0.5 to 4.6% (13), although it is probably underestimated. EC could represent a sentinel event of LS, since it is often the first cancer to occur, in over 50% of cases (14, 15). The median age at diagnosis of EC for women with LS is generally lower than in sporadic cases (49 vs. 60 years, respectively) (15). EC is associated with MMR abnormalities and LS has worse prognostic factors and outcomes (10). According to Lu et al., patients with EC and LS tend to have a lower BMI (16), except for patients with MSH6 mutation who seem to have a clinical profile more similar to those with sporadic cancers. However, data on the clinicopathological characteristics of LS-related EC are missing, as the studies are mostly conflicting. In these patients, the tumor is more often in the uterine isthmus and mostly presents as a well-differentiated endometrioid adenocarcinoma (5). However, other studies showed a higher percentage of non-endometrioid histotypes, a higher FIGO stage at presentation, a higher number of G3 tumors, a deeper myometrial invasion, and a higher mitotic index in the LS-related EC (17). The 4 genes responsible for LS have different penetrance and expressivity. The risk of endometrial cancer (EC) is higher especially among carriers of *MSH2* (49%), *MSH6* (41%) and *MLH1* (37%) mutations. Cancer is also common in elderly women with PMS2 mutations (13%) (18, 19). The screening for LS is often based on clinical criteria, such as the Amsterdam criteria and the Bethesda criteria although the latter are of less importance nowadays, which consider age (<50 years), family history of colorectal cancer, positive personal history for cancer of the LS spectrum. The clinical suspect must be confirmed by molecular analysis, which allows the characterization of the patient's genotype. However, the clinical criteria do not always allow to effectively identify the pathogenic variants for LS (20–23). The benefit for universal screening in CRC and EC is well known: Kunnackal John et al. showed how LS screening in EC yielded significantly higher somatic mutations compared to CRC [pooled percentage 16.94 vs. 5.23%, 95% CI 4.93–5.47%—Mann Whitney test, $p < 0.0001$], suggesting the possibility for IHC and somatic mutation testing before germline testing in EC due to higher prevalence of somatic mutations as well as germline testing in these patients and in other major Lynch-associated tumors (24). The early identification of patients with LS is necessary to allow a close follow-up and personalized/conservative therapy, for the patient him/herself and his/her affected relatives.The objective of our study was to assess the presence of LS in young women undergoing conservative management for atypical endometrial hyperplasia (AEH) and non-myoinvasive FIGO IA endometrioid endometrial cancer (EEC), evaluating its possible impact on the response rate, relapse rate, progression rate, and pregnancy rate.

Materials and methods

The MMR-deficient patients were identified from a previous retrospective cohort of 69 patients submitted to fertility-sparing treatment for FIGO IA G1 EC and AEH, between January 2004 and December 2018. The study was carried out at the "Fondazione Policlinico Universitario A. Gemelli—IRCCS" of Rome and at the University "Federico II" of Naples. All medical records of patients with AEH and EEC belonging to the two centers were retrospectively analyzed.

Therapy outcome and follow-up

All patients underwent hysteroscopic resection of the pathology followed by progestin therapy: patients 1 and 6 with Megestrol Acetate (Megace) 160 mg daily given orally: patients 2, 3, 4, and 5 with Levonorgestrel releasing Intra Uterine Device (IUD) (Mirena). Oncological outcomes at histologic examinations were defined as complete response (CR), stable disease (SD), progression (P) and relapse (R). CR was defined as the complete disappearance of AEH or EEC; SD as persistence of AEH or EEC; P as progression of AEH to EEC or worsening of the histological grade of EEC. R was defined as the presence of EEC or AEH after CR had been previously achieved. In agreement with international guidelines (25, 26), the presence of at least two consecutive CR was defined as "regression of disease", while the lack of two consecutive CR was labeled "resistance". The reproductive outcome was assessed as the achievement of a successful pregnancy. For every patient, we collected pathology reports of hysteroscopic biopsies at 3, 6, 12 and up to 27 months after treatment, as well as data on pregnancies (spontaneous delivery, cesarean section, miscarriages).

Screening and sequencing procedure

Cases were labeled as "MMR-deficient" based on immunohistochemical screening for MLH1, MSH2, MSH6, and PMS2 proteins (25). In patients with lack of MLH1 expression, MLH1 promoter methylation was analyzed by MS-MLPA (Mrc Holland) in order to exclude somatic hypermethylation. In patients with MMR-d tumors, screening for germline mutations in MMR genes was conducted by Next Generation Sequencing on Ion Torrent PGM with a homemade 4-genes panel (*MSH2, MSH6, MLH1, PMS2*). Sequencing data of the targeted genes were analyzed with Torrent Suite (Life Technologies). Additional Sanger sequencing was performed for regions containing putative variants. Exon deletions and duplications were assessed by MPLA (Mrc Holland). Alterations were classified based on guidelines established by Insight (2018-06_InSiGHT_VIC_v2.4) into the following categories: (5) pathogenic variant (PV); (4) variant, likely pathogenic; (3) variant, unknown significance; (2) variant, likely benign; (1) benign.

Ethical statement

The study received approval from the Institutional Review Board of the Catholic University of the Sacred Heart of Rome and the University of Naples Federico II (Prot. No. 0048361/20). All included patients signed informed written consent for the use of their biospecimens for research purposes and all data were anonymized in order to avoid the identification of the subjects. The whole study was performed following the Declaration of Helsinki.

Results

From the case history of our previous study, including 69 patients [47 (68.1%) with AEH and 22 (31.9%) with EEC] (25), six (8.7%) (3 with AEH and 3 with EEC) were enrolled in our study based on a deficient pattern of expression of the MMR proteins. The patient's characteristics are resumed in Table 1. Of the 6 MMR-deficient patients, one had MSH2/MSH6 deficiency (EEC), 3 had MSH6 deficiency (1 EEC and 2 AEH) and 2 had PMS2 deficiency (1 EEC and 1 AEH) (Table 2). Five out of 6 patients received the diagnosis of EEC/AEH before 40 years old, with mean age at diagnosis of 36 ($\pm$ 4.28 SD) years old (range 31–43). The mean BMI was 24.9 ($\pm$ 7.26 SD) with only one patient with BMI higher than 30 kg/m^2 (39.3 kg/m^2) (Table 1). None of the patients reported tumor risk factors for EC (diabetes, hypertension, PCOS); 2 (33.3%) had a positive family history for neoplasms of the LS spectrum (patient 1 for CRC, patient 4 for EC). The dosage of CA125 was negative ($<$ 35 UI/mL) in all patients.

Results of genetic tests

The genetic testing was carried out on 5 of the 6 MMR-d patients because one patient refused. In patient 1 with MSH2 deficiency on tissue sample, the c.942 + 2 T>A heterozygous variant has been identified by Next Generation Sequencing (NGS). This sequence change affects a donor splice site in intron 5 of the *MSH2* gene. It is expected to disrupt RNA splicing and likely to cause the skipping of exon 5, resulting in an abnormal protein, p.(Val265_Gln314del), or a transcript that is subject to nonsense-mediated mRNA decay. This variant has been classified as Likely Pathogenic (class 4 IARC) (27) according to the Insight criteria (Table 2). In patient 2, who showed MSH6 deficiency on tissue sample, genetic testing did not reveal any mutation. Patient 3, with PMS2 deficiency on

TABLE 1 Patients' characteristics.

Patients	Age at diagnosis (years)	BMI (kg/m^2)	Tumor risk factors	Previous pregnancy	Symtomps	Family history for endometrial cancer	Family history for other SL-related cancers
1	33	19.5	No	No	None	No	Yes (Colorectal)
2	43	21.36	No	No	Metrorrhagia	No	No
3	31	39.3	No	No	Metrorrhagia	No	No
4	38	22.4	No	No	None	Yes	Yes (Colorectal)
5	37	24.61	No	No	Metrorrhagia	No	No
6	34	22	No	Yes*	Metrorrhagia	No	No

BMI, body mass index; *2 previous vaginal delivery.

tissue sample, refused consent for the genetic test. In patient 4, exhibiting MSH6 deficiency on tissue sample, the c.2459-1G>C heterozygous variant has been identified by NGS. This sequence change affects an acceptor splice site in intron 14 of the *MSH2* gene. It is expected to disrupt RNA splicing and likely to cause skipping of exon 15, resulting in an absent or disrupted protein product leading to the formation of a premature stop codon after 3 amino acids p.(Gly820Alafs*3). This variant has been classified as Likely Pathogenic (class 4 IARC) (27) according to the Insight criteria (Table 2). In patient 5 with MSH6 deficiency on tissue sample, the genetic test did not reveal any mutation. In patient 6, who showed PMS2 deficiency on tissue sample, the c.803 + 1 heterozygous variant of the coding sequence of the PMS2 gene has been identified. This sequence change affects a donor splice site in intron 7 of the *PMS2* gene. It is expected to disrupt RNA splicing and likely to cause the skipping of exon 7 leading to the formation of a premature stop codon after 30 amino acids p(Leu236HisfsTer30). This variant has been classified as Likely Pathogenic (class 4 IARC) (27) according to the Insight criteria (Table 2).

Oncological and reproductive outcomes

In patient 1 SD with AEH on the first follow-up and CR at 12 months was observed. After further 12 months (at 24 months follow-up), she had R with P to EEC. Despite adequate counseling where the need for radical surgery was explained, she chose to maintain medical therapy with a close follow-up every 3 months, given her strong desire for offspring. After further 18 months (at 42 months follow-up), she had a new R to EEC and she finally decided to undergo hysterectomy. Patient 2 decided to undergo hysterectomy after stable disease SD at 3, 6 and 12 months of follow-up. Patient 3 showed CR at 12 months; however, CR was not confirmed in the subsequent follow-up biopsy (at 15 months follow-up), and the patient chose to undergo hysterectomy. Patient 4 had CR at 3, 6 and 12 months. After unsuccessful attempts to get pregnant, she showed R after 24 months from the initial CR (at 27 months follow-up). Thus, she decided to undergo hysterectomy. Patients 5 had CR on 4 consecutive biopsies. After unsuccessful attempts, she had R after 39 months of initial CR (42 months follow-up) and underwent hysterectomy. Patient 6 had CR after 3 months but developed R 18 months later (at 21 months of treatment) with SD on the subsequent biopsy, and underwent hysterectomy (Table 2). In all patients that underwent hysterectomy, the pathology report of the surgical specimen confirmed the hysteroscopic diagnosis. No patients showed a recurrence with a median follow-up of 20 months.All patients tried to get pregnant spontaneously and during all follow-up period, without resorting to any medical therapy.MMR-deficient (dMMR) cases, defined by lack of MMR protein expression detected by IHC analysis of tumor tissue, showed resistance to treatment more commonly than MMR-proficient (pMMR) cases [2 (33.3%) vs. 10 (15.9%)], with a RR of 2.1 (95%CI: 0.6–7.5) but with no statistical significance (p = 0.2508). Recurrence of AEH/EEC after a complete regression occurred significantly more commonly in dMMR cases than pMMR cases [6 (100%) vs 17 (26.4%)], with a RR of 3.8 (95%CI: 2.4–5.9, $p < 0.0001$). In predicting recurrence of disease after a complete regression, a deficient immunohistochemical expression of MMR showed sensitivity = 22.2%, specificity = 100%, and AUC = 0.61 (95%CI: 0.44–0.76) (21).

Discussion

In this study, we considered 6 MMR-deficient cases of conservatively treated AEH and EEC from a cohort of 69 patients (25). The conservative managemet included hysteroscopic resection followed by local or systemic drug theraphy: 36 (52.2%) women underwent LNG-IUD insertion, and 33 (47.8%) MA administration. Overall, 17.4% of women showed resistance to treatment, while 31.6% of women who responded showed a subsequent recurrence. Out of 5 patients who underwent genetic test, 3 (60%) were carriers of a germline variant of MMR genes: 2 patients showed a pathogenic mutation of *MSH2* and 1 patient of *PMS2*. All patients with confirmed

TABLE 2 Diagnosis, MMR-deficiency at immunochemistry, genetic test result with variant identified in patients 1, 4, and 6 and located in a recognized site of splicing (±1 o ±2), and outcomes of the 6 patients (EEC, Stage IA G1 endometrioid endometrial cancer; AEH, atypical endometrial cancer; PR, partial response; CR, complete response; SD, stable disease; R, relapse; P, progression; §THL + SOB; *for patient's choice; **drop-out; [a]LNG-IUD from the 6th month).

Patients	Diagnosis	MMR-d	Mutated gene	Nucleotide or amino acid substitution@	IARC Classification	Medical therapy	3 months follow-up	6 months follow-up	12 months follow-up	15 months follow-up	18 months follow-up	21 months follow-up	24 months follow-up	27 months follow-up	42 months follow-up	Pregnancy	Radical surgery§
1	Stage IA G1 EEC	MSH6/ MSH2	*MSH2*	c.942+2T>A p.(Val265_ Gln314del)	Class 4 (likely pathogenetic)	Megace®	SD (AEH)	SD[a]	CR	CR	CR	CR	R; P	/	R	No	Yes
2	Stage IA G1 EEC	MSH6	/	/	/	Mirena®	SD	SD	SD	/	/	/	/	/	/	No	Yes
3	Stage IA G1 EEC	PMS2	/**	/	/	Mirena®	SD	SD	CR	R	/	/	/	/	/	No	Yes
4	AEH	MSH6	*MSH2*	c.2459-1G>C p.(Gly820A lafs*3)	Class 4 (likely pathogenetic)	Mirena®	CR	CR	CR	/	/	/	/	R	/	No	Yes*
5	AEH	MSH6	/	/	/	Mirena®	CR	CR	CR	/	/	/	/	/	R	No	Yes
6	AEH	PMS2	*PMS2*	c.803+1G>T p.(Leu236His fsTer30)	Class 4 (likely pathogenetic)	Megace®	CR	CR[a]	CR	CR	CR	R	SD	/	/	No	Yes

@The methods analysis included: Next Generation Sequencing on Ion Torrent PGM for the screening of germline mutations in MMR genes, Torrent Suite (Life Technologies) for the sequencing of the targeted genes, Sanger sequencing for the sequencing of regions containing putative variants, and MPLA (Mrc Holland) for the assessment of exon deletions and duplications.

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LS responded to conservative treatment; however, all failed to achieve pregnancy and had relapse of disease. The rate of LS endometrial cancer patients in this series (4.3%) was almost superimposable to that reported in the literature (11). Among MMR-deficient cases, recurrence occurred after 24 and 39 months in the LNG-IUD group, and after 12 and 18 months in the MA group. In predicting recurrence of disease after a complete regression, a deficient immunohistochemical expression of MMR showed sensitivity = 50%, specificity = 100%, and area under the curve (AUC) = 0.75 (95%CI: 0.00–1.00) in the LNG-IUD subgroup, and sensitivity = 14.3%, specificity = 100%, and AUC = 0.57 (95%CI: 0.35–0.79) in the MA subgroup (25). The lifetime risk of developing cancer is significantly higher in patients with MSH2, and MLH1 mutations compared to PMS2 and MSH6 mutations. Patients with MLH1, MSH2, and MSH6 mutations have a rapidly rising risk of gynecological cancers from 40 years of age (18). In these patients, the incidence of EC is 51% among carriers of MSH2 mutation, 49% among carriers of MSH6 mutation, 34% among carriers of MLH1 mutation. In our study, 2 patients (MSH2 mutation confirmed) had a family history for colorectal cancer and both colorectal cancer and EC, respectively. In 2016, Rubio et al. reported how all patients with pathogenic mutations in any of the MMR genes had a family history (first-degree relatives) compatible with LS, but more than half (61.79%) of patients with no pathogenic mutation had a positive family history. These differences are explained by a selection bias related to one of the inclusion criteria concerned the family history of cancer of the LS spectrum (20). In 2019, a review and meta-analysis estimated that only 56% of cases of LS are diagnosed based on traditional clinical-anamnestic indicators, while 43% of cases would be lost and undiagnosed if we exclusively used these criteria. This provides further support to the current data present in literature, suggesting the need for a universal screening approach to all new cases of EC arising in young women, in order to maximize the detection of LS patients (28). In our study, we used IHC analysis as a screening method, but many studies also propose the analysis of microsatellites. In 2016, Rubio et al. used both methods, demonstrating high sensitivity and specificity in selecting patients with LS mutations (20). In particular, a study by Leenen et al. (29) on 183 women showed a 100% agreement between the two techniques and Walsh et al. (30) reported similar results (97.5%). It is estimated that the specificity of the MSI analysis for LS is around 90.2% and that the sensitivity is 91% for MLH1/MSH2 and 77% for MSH6/PMS2. The specificity and sensitivity of the IHC analysis, on the other hand, are respectively 88.8 and 83% (31). A universal screening approach would certainly have considerable economic implications; for this reason, it is essential to aspiring to cost optimization. The analysis of MSI has limitations, represented by the inability to discriminate the type of protein of the MMR deficient and also many MMR-d tumors for MSH6 are low instability (MSI-L), therefore, this technique cannot be very sensitive in detecting many low-penetrance MSH6 germline mutations. The IHC analysis has lower costs. Thus, the best screening approach, in terms of cost-effectiveness, would therefore be to start with an IHC investigation of the expression of MMR proteins in order to limit further costs and to refer patients with IHC MMR-d phenotype to genetic testing at a later time or, in case of strong clinical suspicion, despite the expression of MMR proteins being intact (19). Furthermore, in the event that the IHC shows a deficit of expression of MLH1 or PMS2, it is advisable to first perform the analysis of methylation of the MLH1 promoter, which in most cases allows excluding sporadic forms of EC from MSI, although this methylation is rarely the consequence of a germline mutation of the promoter. Since a germline mutation of the MLH1 promoter is configured as a rare event, in the absence of a personal or family history strongly suggestive of a hereditary process, for which a genetic analysis would be carried out on the promoter, the methylation of the promoter is considered a fairly reliable indicator of sporadic cancer (19). Considering that IHC is a highly sensitive technique for identifying mutations in MMR genes in CRC, it could be expected that an IHC-based screening approach could prevent a significant number of LS patients remain undiagnosed (19). Our sample was analyzed for the IHC expression of MMR proteins using two different criteria in the two centers. Patients from Fondazione Policlinico A. Gemelli—IRCCS of Rome were analyzed for all four proteins of the MMR (MSH2, MSH6, PMS2, MLH1); those of the University of Naples center were analyzed exclusively for two proteins, MSH6 and PMS2. The latter approach agrees with two studies (32, 33), according to which an initial screening limited to two proteins can significantly reduce costs without affecting efficacy—as MSH6 and PMS2 are mandatory partners, respectively, of MSH2 and MLH1—whereby the lack of expression of these proteins reflects a deficit of their partners. The evaluation of the clinical and anamnestic data of our patients with pathogenic variants has also revealed a tendentially lower BMI, compared to women with sporadic forms of EC, and negativity for the normal risk factors typical of sporadic forms of EC, in accordance with data in literature. It is important to identify LS patients among new EC because these patients have an increased risk to develop other types of cancers of the LS spectrum, synchronous or metachronous, allowing such patients to benefit from close surveillance (through colonoscopy and transvaginal ultrasound) and possible preventive interventions (34). Furthermore, MMR status is starting to acquire prognostic value, as studies are beginning to demonstrate differences in characteristics and outcomes between MMR-proficient and MMR-deficient EC (35). In presence of young women with Stage IA G1 EEC or AEH, strongly persuaded to preserve their fertility and candidates for conservative treatment (36–38), identifying MMR-deficient patients and, possibly, patients with LS could also be essential in guiding adequate counseling: indeed, our data show how these patients tend to have a worse outcome than MMR-proficient patients (39, 40). In detail, all patients with confirmed LS responded to conservative treatment in our series. However, none achieved pregnancy, and all had relapse of disease. This underlines the unfavorable impact of LS on the outcomes of AEH and EEC. As a consequence, the search for tailored treatment strategies for women affected by LS could provide a good strategy to maximize clinical benefit. Further studies are necessary to assess whether a successful pregnancy may be achieved by lengthening the relapse-free period. The comprehension of predictive genetic testing for LS by patients is fundamental to avoid refusals, as happened in our case with patient 3, also involving families considering that they often play an important role in the decision compared to health professionals; also, the deconstruction of current misconceptions related to potential abuses of genetic information, the emphasis of clinical utility of genetic assessment, and the use of genetics to the specific context of cancer care is crucial for patients' inclusion with newly diagnosed cancer of LS spectrum in clinical cancer genetics services (41). Genetic analysis in women treated conservatively for AEH/EEC under 45 years old can help to find LS families that would not have been identified using existing criteria and to provide them adequate counseling regarding screening of other cancers of the LS spectrum. The screening procedure could begin, as for colorectal cancer, with the IHC analysis, although it has limitations as abovementioned. The mutations found in our sample, although small, are different from those described more frequently for every single gene and therefore there is the need to intensify genetic studies to identify a greater number of pathogenic variants that would allow us to diagnose not only spectrum tumors of LS but also other types of cancer. The need for biomolecular and genetic prognostic factors that can facilitate decision making is nowadays essential (42, 43). On the whole, prospective and larger population studies are needed to evaluate the applicability and usefulness of a "screening test" for LS in young women diagnosed with AEH and EEC which could be based on IHC analysis and then select among these, patients eligible to carry out the genetic test.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Catholic University of the Sacred Heart of Rome and the University of Naples Federico II (Prot. No. 0048361/20). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

UC and LDC contributed to conception of the study, interpretation of data, statistical analysis, and drafting the article. AR, AT, and EL contributed to acquisition and interpretation of data and drafting the article. EL contributed to acquisition and interpretation of data. VM, GB, and AD contributed to drafting the article. GS and FF contributed to review the article critically for important intellectual content and final approval of the version to be published.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Laparoscopic retroperitoneal resection of the duodenal gastrointestinal stromal tumors in neurofibromatosis type 1; Case Report and literature review

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Background: Neurofibromatosis type 1, also known as NF1, is a disorder that is passed down in an autosomal dominant manner. It manifests in a wide variety of tumors and affects several organ systems. It is expected that those carrying the NF1 gene will develop a rare mesenchymal tumor known as a gastrointestinal stromal tumor (GIST) more than general population.

Case report: This research discusses a 42-year-old female patient with NF1 who was identified with a duodenal GIST but clinically and radiographically misinterpreted as having a retroperitoneal neurofibroma. She had minimally invasive retroperitoneal laparoscopic surgery to remove the tumor and primary anastomosis of the affected duodenal wall. A spindle cell GIST was entirely excised during surgery, as indicated by the pathologist. As a consequence of dialogue at a multidisciplinary team meeting, the patient was discharged from the hospital on the fourth postoperative day and is presently undergoing regular clinical follow-up.

Conclusion: Anatomically problematic sites, such as the duodenal GIST in NF1 patients, can be treated safely with the laparoscopic retroperitoneal approach even when retroperitoneal neoplasia arises from the intrabdominal structure and protrudes into the retroperitoneal region.

KEYWORDS
neurofibromatosis, gastrointestinal stromal tumors, retroperitoneal tumor, retroperitoneal approach, laparoscopic resection

Introduction

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen's disease, is an inherited autosomal dominant syndrome that impacts many body organ systems and manifests clinically in various ways (1). NF1 is the most prevalent of the three neurofibromatoses, with a birth incidence of 1 in 2000, which is characterized by neurofibromas (peripheral nerve tumors) that cause skin abnormalities and bone deformation (2). In contrast, schwannomatosis (SWN) and NF2 are rare, with a birth incidence of 1 in 27,956 and 1 in 68,956, respectively (3). While typical cutaneous characteristics defined NF1 from other variants, hearing loss with vestibular dysfunction and severe pain distinguished NF2 and SWN, respectively (1, 4–6).

Neurofibroma, a kind of nerve sheath tumor that may grow close to the spinal cord, peripheral nerves, or cranial nerves, is characteristic of NF1. In addition to the pigmentary abnormalities that are usually present, it is possible to see dysplasia of the skeleton, low-grade gliomas, and involvement of many organ systems. Additionally, Eric Legius et al. provide the updated neurofibromatosis type 1 criteria in 2021 (7) (**Table 1**). The NF1 disorder progresses gradually during an individual's lifetime; however, the particular symptoms, the pace of advancement, and the severity of consequences significantly differ from person to person. Currently, there is no definitive treatment, and most clinical care is limited to monitoring and treating symptoms, most often through surgery. NF1 is caused by the NF1 gene, which codes for neurofibromin. This gene was found in 1990, and its function and significance in tumor formation and other NF1 symptoms have since been extensively studied. As a consequence of more excellent knowledge of NF1 clinical features, several targeted medications have emerged and are currently being explored in preclinical models and phase II clinical studies. This is an exciting time for NF1 patients, as new medicines on the horizon promise to improve their quality of life (QOL) (8).

TABLE 1 Revised diagnostic criteria for neurofibromatosis type 1 (NF1).

A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present:
• Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals. • Freckling in the axillary or inguinal region. • Two or more neurofibromas of any type or one plexiform neurofibroma. • Optic pathway glioma. • Two or more iris Lisch nodules identified by slit-lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging. • A distinctive osseous lesion such as sphenoid dysplasia, b anterolateral bowing of the tibia, or pseudarthrosis of a long bone. • A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells.
B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present

a. If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1 but exceptionally the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.
b. Sphenoid wing dysplasia is not a separate criterion in the case of an ipsilateral orbital plexiform neurofibroma.

However, the best treatment for neurofibroma and schwannoma is still the complete removal of the mass and capsule without causing injury to the attached organs. Recent advancements in minimally invasive surgery have led to the publishing of several different laparoscopic methods for treating retroperitoneal schwannomas. Unlike the reported cases of coincident GIST in NF1 patients that were managed regularly through a transperitoneal approach, either open or laparoscopically (9, 10). In our case, we did minimal invasive retroperitoneal laparoscopic surgery for duodenal GIST, which went as smoothly as usual for partial and total nephrectomy.

Case report

A 42-year-old female patient with neurofibromatosis was hospitalized at the department of general surgery with 10 days of right upper abdomen pain but no other symptoms such as diarrhea, vomiting, or bleeding. In addition, the patient said that she has had several nodules on her body for as long as she can remember and that both her mother and daughter have neurofibromatosis. However, during her abdominal MRI examination, a mass on the left side was found, which was described as a retroperitoneal tumor; she was then transferred to the department of urology. At the initial examination, significant café au lait spots and freckling were found over the patient's body, but the mass filling the left abdominal quadrant was inaccessible (**Figure 1**). Her blood pressure was 125/76 mmHg, and her heart rate was 74 beats per minute. Biochemistry and hematological tests revealed mild anemia (Hb: 97 g/L and Htc: 31.3 L/L); however, other parameters (liver function, renal function, electrolytes, coagulation function, blood cortisol, ACTH, blood aldosterone, renin, CRP, gastrin, insulin, and glucagon) were normal. No lesion or abnormality was discovered during the thorax CT scan evaluation. Abdominal magnetic resonance imaging (MRI) revealed an uneven tumor underneath the pancreatic body that occupies the left retroperitoneal region. The mass had about 3.8 cm × 5.7 cm × 2.8 cm in size, which has an unclear boundary with some surrounding intestinal tubes. The uncinate process in the pancreas is moved to the right. While the focus T1W image illustrates a low signal mass, the T2-weighted image indicates a high-signal tumor; and the diffusion-weighted displays an obvious high-signal tumor; additionally, enhanced MRI scans of the arterial, venous, and excretion phases clearly show uneven and noticeable enhancement (**Figure 2**). There were no gastrointestinal problems in our case. as well as the tumor's location based on imaging results led to the establishment of a primary diagnosis of retroperitoneal neurofibroma.

After three days of pre-operative preparation, the patient was taken to the operating room. Minimally invasive surgery

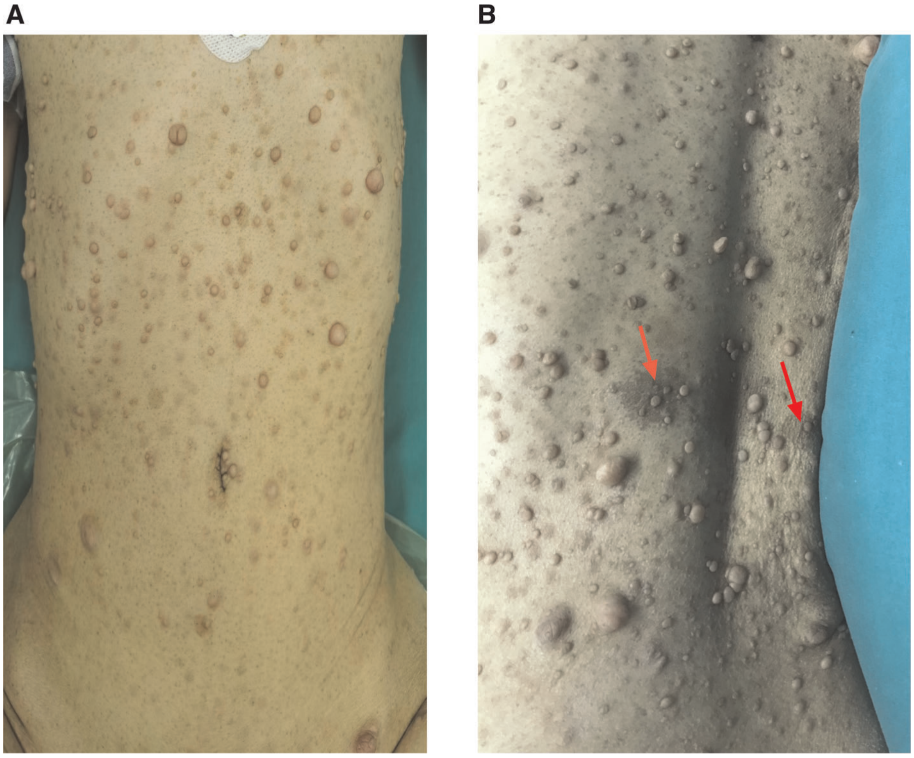

FIGURE 1
Individuals who have neurofibromatosis type 1 NF1 may exhibit a variety of cutaneous characteristics, including (A), the growth of nerve sheath tumors (neurofibromas)is a prominent hallmark of NF1. Neurofibromas can develop as isolated nodules or as cutaneous neurofibromas (B). pigmentary feature of NF1 patient (café-au-lait macules) on the back of the patient as (arrow).

was performed using a three-port retroperitoneal approach (**Figure 3**). A 2-centimeter incision is made on the posterior axillary line, beneath the 12th rib, anterior to the sacrospinal muscle. The muscle layer and lumbodorsal fascia were divided bluntly with a long hemostatic forcep. By insertion of the index finger into the retroperitoneal space (posterior pararenal space) and dissecting the fatty tissue from top to bottom and back to front, while simultaneously pushing the peritoneum anteriorly. Following that, the space is enlarged using a balloon expander. Subsequent trocar insertions will be directed from the retroperitoneal area using the index finger. Trocar 1 is entered *via* the first skin incision and sutured to secure the trocar, then a 10 mm camera trocar (Trocar 2) is placed two fingers breadths superior to the iliac crest on the midaxillary line; finally, trocar 3 is introduced on the anterior axillary line at the subcostal margin. On the dominant hand side of the surgeon, a 12 mm trocar is usually used, and a 5 mm trocar by a non-dominant one. CO2 insufflation *via* camera trocar with a pressure range from 10 to 14 mmHg to creates pneumoperitoneum. while the surgeon performs an operation on the patient's abdominal wall using trocar 1 and 3, the assistant stands on the backside holding camera using trocar 2. Firstly, retroperitoneal adipose tissue is mobilized from the infra-phrenic superiorly to the iliac fossa inferiorly and from the peritoneal reflection internally to the psoas major externally. after exposing the lateral conical fascia, it is longitudinally incised posterior to the retroperitoneal fold. After that, the dissection is conducted posteriorly between the posterior renal fascia and the psoas major, outside fascia. Due to the fact that the renal fascia is connected with quadratus lumborum fascia, these two fascias are always dissected together to expose the deeper psoas muscle fibers. superiorly, the plane of dissection extends to the diaphragm, while inferiorly it extends to the iliac fossa. Then, between the fusion fascia (the fascia posterior to the mesocolon) and the anterior renal fascia on the inferomedial pole of the kidney, precise anterior dissection is performed, accessing the first avascular plane (anterior pararenal space). At this point mass was seen and tumor boundaries dissection progress and we discovered a mass attached anteriorly to the duodenojejunal flexure. A portion of the duodenum was resected to remove the tumor mass, and primary anastomosis was accomplished through the retroperitoneal without manipulation of other abdominal organs.

A postoperative drain was placed through a small hole in the left posterior peritoneum, and a tumor mass of 6.5 cm ×

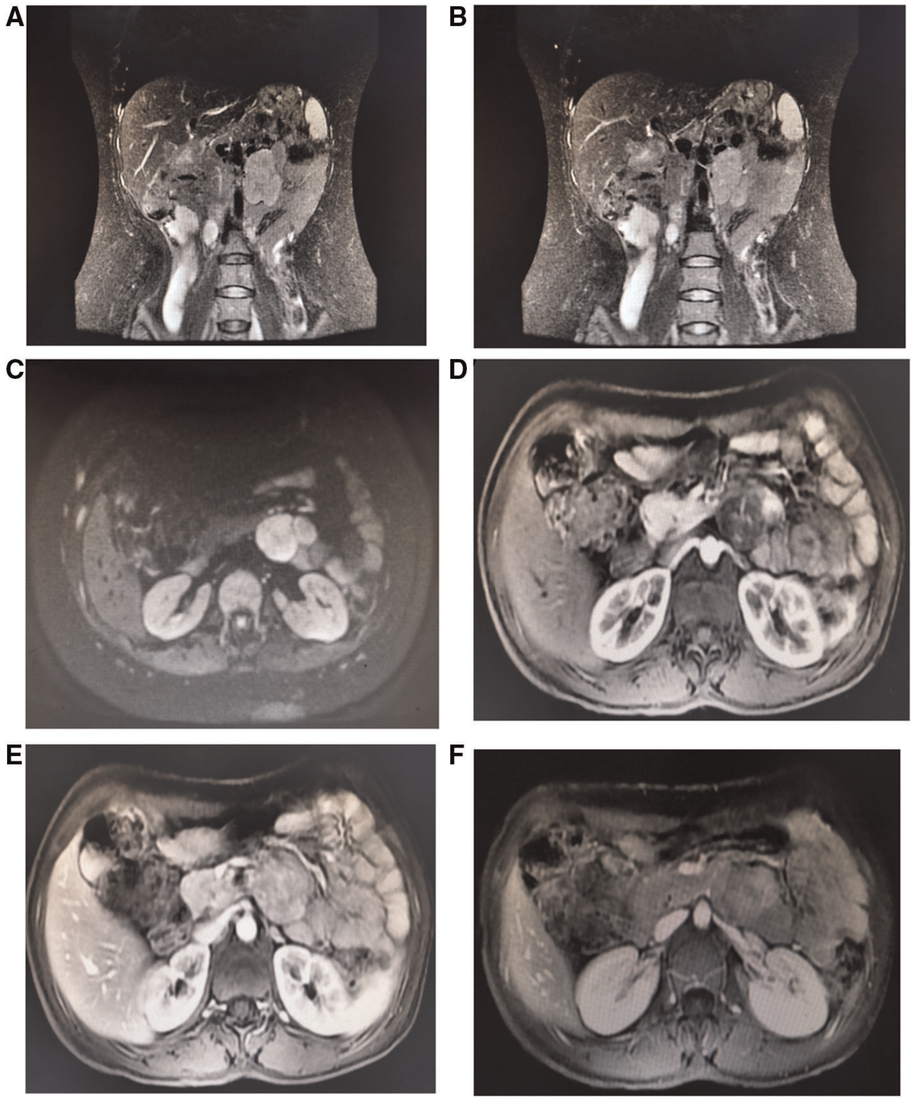

FIGURE 2
Abdominal MRI shows an irregular retroperitoneal mass under the pancreatic body and the pancreatic uncinate process is pushed forward to the right. The mass had about 3.8 cm × 5.7 cm × 2.8 cm in size, which has unclear boundary with some surrounding intestinal loops (A,B). Coronal T2-weighted image depicts high signal tumor; (C) Transverse Diffusion-weighted image shows obvious high signal tumor; (D–F) enhancement MRI scan on arterial, venous and excretion stages show uneven and obvious enhancement.

5 cm × 3 cm in size was extracted. Following surgery, the patient spent one day in a critical care unit before being discharged to the wards. Finally, the drain was also put through the retroperitoneum to avoid peritonitis and reduce the risk of death, which is another advantage. On surgical day 9, the patient began an oral diet, and she was released from the hospital on day 14. Histopathologic investigations revealed that the resected mass was a composite of that CD117(+), CD34(+), desmin(−), DOG-1 (+), Ki-67(+5%), S-100(−), SDH-B(+), and SMA(−), all of which are consistent with GIST tumor (**Figure 4**).

Discussion

Neurofibromatosis type 1 is an uncommon neurogenetic condition characterized by pigmentary abnormalities, learning and social difficulties, and a susceptibility for benign and malignant tumor growth due to NF1 gene germline mutations (11). In comparison to other neoplasms, patients with NF1 had considerably lower disease-specific survival (DSS) rates if they developed undifferentiated pleomorphic sarcoma (UPS), high- grade glioma (HGG), malignant peripheral nerve tumor (MPNST), ovarian cancer, or melanoma. Individuals with

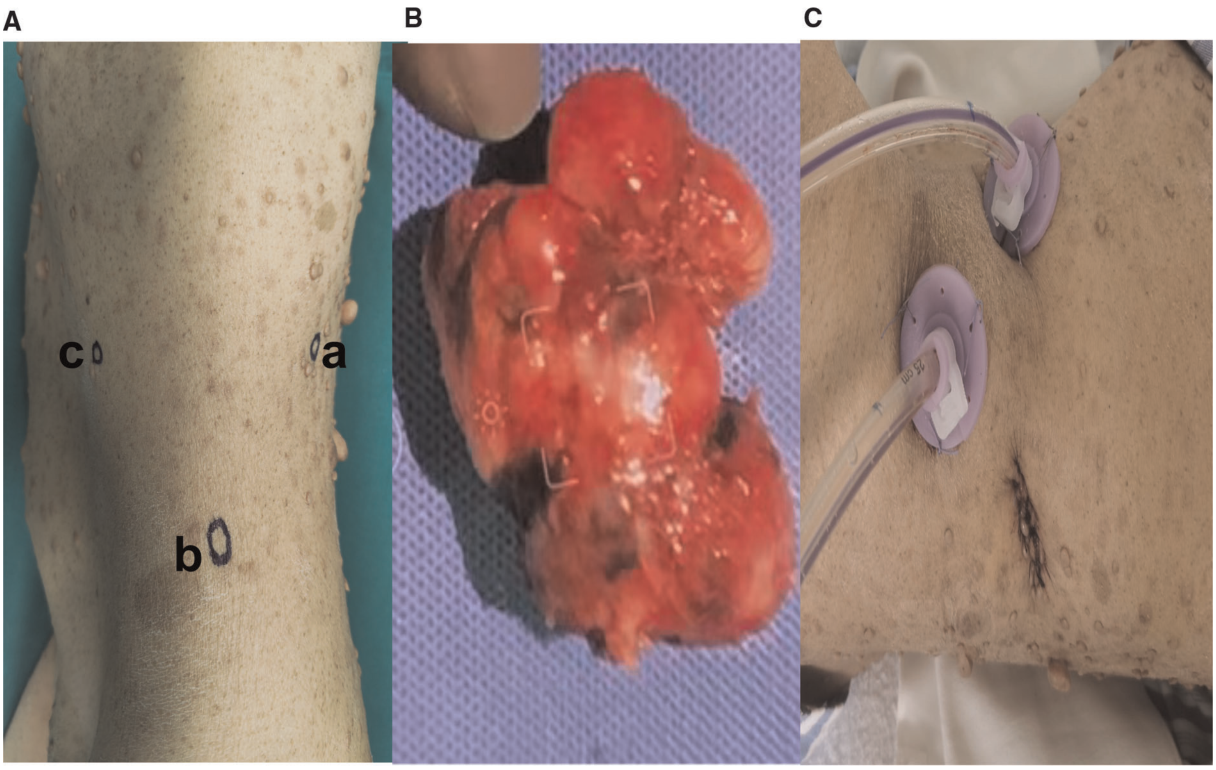

FIGURE 3
(A) Trocars configuration for left retroperitoneal laparoscopic approach; [trocar a] is inserted *via* 2 cm skin incision made below the 12th rib, anterior to the Sacro-spinal muscle, on the posterior axillary line and the skin incision is sutured to fix the trocar, [trocar b] A 10 mm camera trocar is inserted two fingers breadths above the iliac crest on midaxillary line; [trocar c] is inserted at the subcostal margin on anterior axillary line (B). Extracted tumor mass specimen (C). Postoperative drain in retroperitoneal space.

NF1 have a significantly increased risk of developing a variety of neoplasms other than neurofibromas. Several of these are known to be associated with NF1, whereas others were previously unrelated to NF1. These neoplasms had significant associations with patient outcomes (5, 12). Life expectancy is 10 to 15 years less than in the general population, a decrease associated with malignant neoplasms (13).

Patients who have NF1 are born with mutations in just one allele of the gene that controls the tumor suppressor gene (Neurofibromin). The NF1 gene was cloned in the year 1990, and subsequent cell biology research has shown that neurofibromin, the product of the NF1 gene, mainly roles as a GTPase-activating protein (GAP) that hinders the RAS/MAPK pathway by increasing the hydrolysis of RAS-linked GTP. Recent developments in cell biology and animal models have led to the discovery of MEK antagonists as prospective treatment agents for plexiform neurofibromas (7, 14). A range of regionally and temporally distinct malignancies and other clinical manifestations is formed throughout development as a result of the loss of heterozygozygosity (LOH) of the other NF1 gene. These tumors and other clinical features are formed dependent on the cell type that is impacted. Over the past few years, a substantial amount of work has been put into tracing the origins of cancerous cells. This revelation has an important impact on both our understanding of underlying biology and our capacity to administer treatment that is specifically focused. In order to create an accurate model of how disease begins and progresses, it is necessary to discover where a tumor cell came from. In addition to this, it makes it possible to identify the molecular components that, in a step-by-step approach, accelerate the course of human cancer. Once we have a solid understanding of these stages, we will be able to locate important targets within tumor cells. In the context of NF1, it will be tremendously important to understand the subsequent steps that lead from Nf1 LOH to the creation of neurofibromas. Currently, there is virtually little treatment available for neurofibroma in NF1 patients other than surgical excision. This disparity between our current understanding of neurofibroma biology and clinical results could be explained by the lack of a reliable preclinical model that accurately depicts the cause of NF1 disease (14).

Thus far, the only therapeutic choices for cutaneous NFs have been surgical removal, various laser treatments, and electrosurgical excision (15). Selumetinib was authorized by

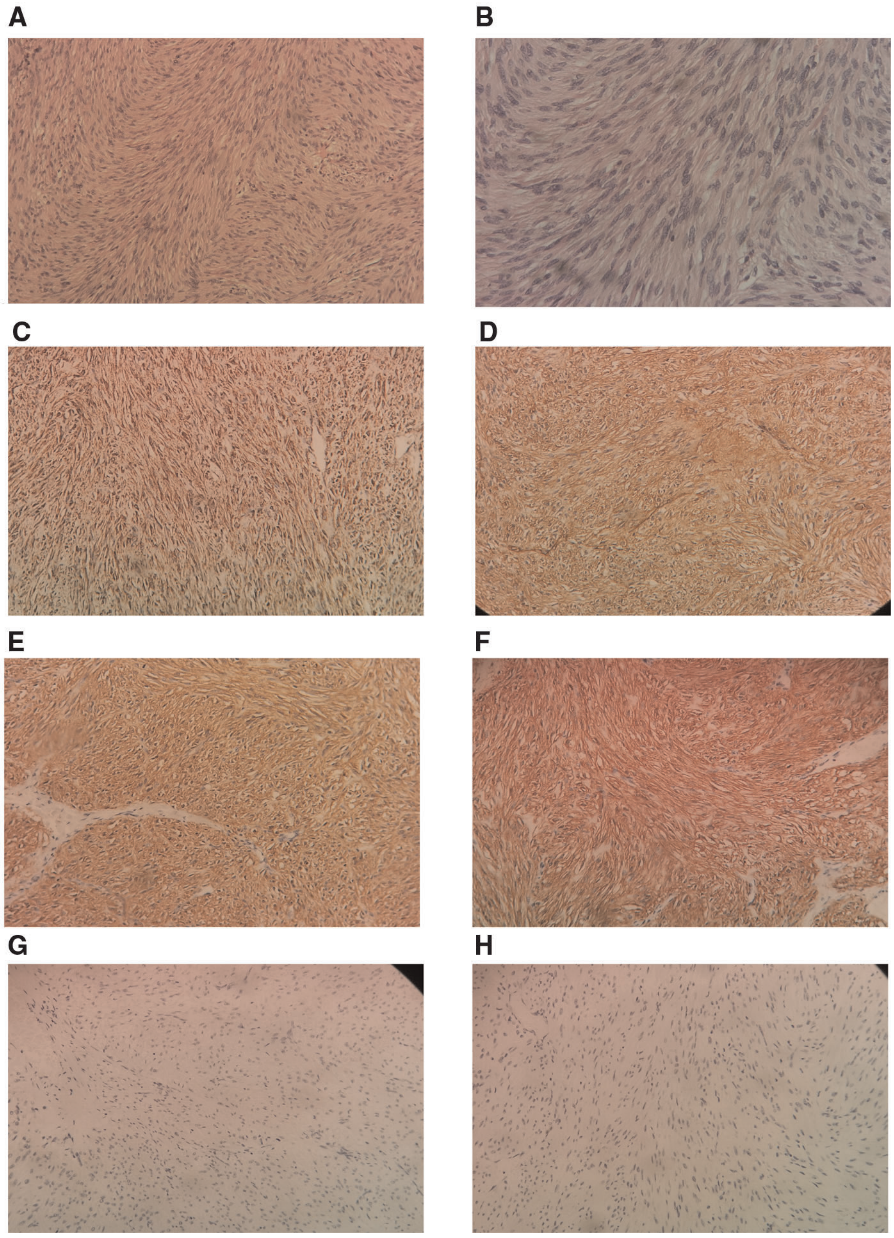

FIGURE 4
Histological sample. (A) Low power H & E Showing spindle shaped tumor cells arranged in fascicles and bundles. for tumor (B). Higher power view showing the spindle appearance of tumor cells. IHC positivity for SDH-B (D). IHC positivity for CD 34 (E). IHC positivity for DOG1 (F). IHC positivity for CD117 (G). IHC negativity for desmin (H). IHC negativity for S-100. H & E, hematoxylin and eosin stain; IHC, immunohistochemistry of tumor cells (200×).

the US Food and Drug Administration in April 2020 for the treatment of children with NF1-related symptomatic plexiform neurofibroma (16). Nearly all NF1 patients develop neoplasms neurofibromas,and in epidemiological studies, such as those conducted in Finland, show an absolute lifetime risk of malignancy of around 55%–60%, which is 5%–15% higher than the general population, 40% risk and an absolute excess of 15%–20%, as well as a life expectancy that is 10–15 years shorter than the general population (2, 5, 12, 17–19). Neurofibromas and plexiform neurofibromas are two common neurogenic tumors found outside the central nervous system (20). Plexiform neurofibromas are histologically benign tumors of the peripheral nerve sheath that affect up to 50% of people with neurofibromatosis type 1 and can cause significant consequences (16, 21). Neurofibromas in persons with NF1 can occur anywhere in the body, and at least 40%

of affected adults have neurofibromas internally, though most are not noticeable on physical examination (22).

Primary retroperitoneal tumors are an infrequent, heterogeneous category of tumors originating outside the major organs in the retroperitoneal space (23). CT and MRI findings in conjunction with the patient's medical history can narrow down the possible diagnoses and even portray a retroperitoneal mass accurately. The histopathological results of neurofibromas must be consistent with their imaging characteristics (24). Neurofibromas on a CT scan have a uniform density and round shape with obvious, smooth edges. The CT density is reported at 20–25 HU on plain pictures, mildly and homogenously enhancing after contrast material administration, with a CT density of 30–35 HU on contrast-enhanced images. At MR imaging, neurofibromas may have a target-like in appearance with distinct behavior in the central region than in the periphery. In T1-weighted images, the central portion of the tumor is slightly hyperintense compared to the peripheral part, whereas in T2-weighted images, the periphery of the mass appears hyperintense. The central part is of intermediate signal intensity on T2-weighted images and enhances after gadolinium injection (23). Furthermore, NF1 may be associated with retroperitoneal tumors, the most malignant of which is MPNST, which has a significant progression rate and the potential for metastasis. Retroperitoneal tumors are uncommon and may be discovered inadvertently during imaging examinations. A pathology diagnosis should be considered, and the patient should be closely monitored, as malignant retroperitoneal tumors, such as MPNST, are possible (25, 26).

NF1 has been associated with several conditions, such as MEN2 syndrome, hereditary breast tumor, and GIST (27–30). Numerous GIST coexisting with NF1 have been documented, although the precise risk of developing GIST in NF1 patients remains unknown. In one postmortem research of over 27,000 cases, 3/12 (25%) of patients with NF1 had numerous GISTs, but clinical investigations show that GISTs are seen in 5%–25% of NF1 individuals (31). A GIST was observed in one-third of NF1 patients in an autopsy series, and a published review article noted that more than half of GISTs in NF1 were discovered accidentally, compared to just one in five individuals without NF1 (31–33). GIST is a rare mesenchymal tumor that almost always develops in the abdomen, specifically in the stomach or the small intestine. Symptoms may include abdominal discomfort, nausea, vomiting, bowel habits changes, or gastrointestinal tract bleeding (33). Many studies have been done on GISTs' morphological and immunophenotypic characteristics; the majority of CD117 and CD34-positive cells are robustly and diffusely stained, whereas desmin and S-100 protein are usually negative (31, 32). Surgical resection is a possibility for patients with GIST who have localized lesions, and neoadjuvant therapy with tyrosine kinase inhibitors is an option for those with advanced disease (33–36). Alterations in the KIT gene or particular platelet-derived growth factor receptor alpha (PDGFRA) gene aberrations in the cancerous cells indicate a positive response to this medication. On the other hand, cancers that lack KIT or PDGFRA mutations ("wild-type" GISTs) are often unresponsive to such therapy. Imatinib is not very effective for treating advanced GIST individuals who also have NF1 since the NF1 mutation seems to be the primary driver of the disease. As a result, the consensus is to avoid providing adjuvant imatinib to patients with NF1-related GIST unless an imatinib-sensitive mutation (e.g., KIT exon 11) is also present, which has rarely been described (33, 35, 37). While immunotherapies are approved in multiple cancer types, their role in the treatment paradigm of GIST is still unclear (38, 39). A review of studies of GIST in NF1 across databases for the last 10 years is identified in **Table 2** (10, 40–48).

Despite advances, surgical excision remains the standard of care for non-metastatic GIST (24, 40, 41). The majority of GIST cases in neurofibromatosis type 1 have been described using an open technique, primarily exploratory laparotomy. The development of minimally invasive surgery has impacted the number of procedures performed. Surgery using the laparoscopic approach is rapidly becoming the standard of care for numerous operations due to the generalized benefits of lower pain, shorter hospital stays, and speedier return to regular life activity. The use of minimally invasive surgery in oncologic procedures is a point of dispute. A significant amount of research has been conducted on a number of different cancers to demonstrate that a laparoscopic technique can be safe and result in a safe oncologic margin. Additionally, research has been conducted to determine whether or not a laparoscopic method is as effective as open surgery and results in comparable oncologic outcomes. There has been limited consensus on the use of minimally invasive methods in the excision of GISTs since GISTs are a newly identified entity and a rare neoplasm. This lack of agreement is mostly due to the fact that GISTs are uncommon. The surgical therapy of GIST has undergone a significant shift ever since Lukaszczyk and Preletz reported the first laparoscopic removal of a stomach GIST identified unintentionally during a cholecystectomy (9, 49). Previous researchers have looked into laparoscopy as a potential treatment for GIST removal. The biological properties of these tumors make laparoscopic resection a preferable treatment option for removing them, despite the fact that there is not yet a widespread agreement about the significance of minimally invasive techniques in their removal. Local excision rather than formal organ resection has been the preferred treatment strategy for GISTs as a result of the rarity of submucosal and lymphatic invasion. This has made laparoscopic resection an enticing alternative to traditional surgery, which is more intrusive. Large resection margins have always been recommended, despite the fact that there has

TABLE 2 List of reported cases of gastrointestinal stromal tumor in NF1.

Authors (ref.)	Year	Country	Sex/ age (years)	GIST location	Presenting symptoms	Size	Associated condition	Management
Mishra A et al. (40)	2021	Nepal	Male, 57	Jejunum	Vomiting, melena	10.1 cm × 7.33 cm × 6.2 cm		Exploratory laparotomy
Arif AA et al. (41)	2021	Canada	Female, 67	Small-bowel	Abdominal pain and pneumoperitoneum	1 cm	Pancreatic Gastrinoma, Pheochromocytoma, and Hürthle Cell Neoplasm	Open surgery
Naoki Makita et al. (42)	2021	Japan	Female, 45	Duodenum	Fecal occult blood	4 cm	Neuroendocrine tumor	Open Pancreaticoduodenectomy
Tim N Beck et al. (43)	2020	USA	Male, 61	Distal jejunum	Hypertension, esophagitis and intermittent gastrointestinal bleeding	7 cm		Exploratory laparotomy
Park EK et al. (44)	2019	Korea	Female, 37	Proximal jejunum	Postprandial epigastric pain	1.5 cm and 1.6 cm		Pylorous- preserving pancreatoduodenectomy followed by adjuvant chemotherapy, consisting of etoposide and cisplatin
Park EK et al. (44)	2019	Korea	Male, 55	Duodenal 2nd portio	Incidentally	3 cm × 3 cm		Pancreatoduodenectomy
Park EK et al. (44)	2019	Korea	Female, 80	Retroduodenal mass	General weakness and weight loss	1.5 cm and 1.7 cm		Transduodenal ampullectomy and separate tumorectomy
Karolina Poredska et al. (45)	2019		Male, 58	Multiple GIST at proximal duodenum and jejunum	Hypertension, dyspepsia	(5–7 mm)	Right Pheochromocytoma	Surgery(a pancreaticoduodenectomy) Approach not mentioned
Dongfeng Pan et al. (46)	2016	China	Male, 56	Small intestine	Hypertension, abdominal pain	(1.3 cm × 1.3 cm × 1 cm)	Left Pheochromocytoma	Surgery excision
Hakozaki Y et al. (10)	2017	japan	Female, 70	Duodenum	positive fecal occult blood	6 mm nodule	Rectal carcinom	Laparoscopic anterior resection
Myrella Vlenterie et al. (47)	2013	Netherlands	Female, 59	Stomach and small intestine	extreme fatigue	3 cm and 0.8 cm in diameter	Left adrenal gland	Open surgical removal
Myrella Vlenterie et al. (47)	2013	Netherlands	Male, 55	Jejunum	Hypertension and tachycardia	4 mm	Bilateral adrenal gland	Open abdominal exploration and tumor resection
Beyza Ozcinar et al. (48)	2013	Turkey	Male, 48	Small intestine	Hypertension And melena	(1.5–3.5 cm)	Right adrenal gland	Transabdominal approach with tumor resection
Present study	2022	China	Female, 42	Duodenum		6.5 cm × 5 cm × 3 cm		Laparoscopic retroperitoneal resection

been no relationship established between them and enhanced survival or recurrence. As a direct consequence of this, extensive margins and the dissection of lymph nodes are not required. It is generally agreed upon that achieving a negative gross surgical margin is essential for lowering the risk of GISTs returning locally and spreading to other organs. It was advised that laparoscopy be reserved for GISTs that are smaller than 2 centimeters in size. This recommendation was made due to concerns regarding tumor rupture and seeding of the peritoneum and the capacity to construct an appropriate oncologic margin. In spite of these challenges, surgeons continued to resect GISTs laparoscopically with success, prompting the NCCN to alter the criteria contained in their 2010 Task Force Report to include GISTs measuring up to 5 centimeters as candidates for laparoscopic resection (49). GIST resection surgery is governed by the ideas of retaining an intact capsule to avoid tumor spillage and establishing a negative margin to secure thorough excision of localized illness. These principles help ensure that all diseased tissue is removed from the body during the procedure.

A retroperitoneal tumor can be in close contact with structures such as the duodenum, renal vein, and IVC, which often require meticulous dissection to avoid Damage, like in our case in which the final diagnosis was GIST of the duodenum that originated from its stroma. Second, with recent advances in the field of minimally invasive surgery, several laparoscopic approaches to retroperitoneal schwannomas have been reported (50–52). Laparoscopic surgery, which has become a useful and feasible option for this procedure, is associated with minimal invasiveness and early postoperative recovery (50). We have been done the duodenal stromal tumor retroperitoneal laparoscopy and avoided open surgery or entering the abdomen. Retroperitoneal laparoscopic surgery for duodenal tumors is rare, but our surgery went smooth, and the patient recovered quickly because we did not enter through the abdominal cavity and had little manipulation of other intestines.

Conclusion

A histological diagnosis should be deemed required since it is possible to misdiagnose a retroperitoneal neurofibroma as another kind of tumor, such as a GIST that is linked with individuals who have NF1. When dealing with retroperitoneal structures, the laparoscopic retroperitoneal method is one that is not only almost risk-free but also offers a number of benefits. Anatomically challenging locations, such as the duodenal GIST in NF1 individuals, can be managed effectively by using the minimally invasive laparoscopic retroperitoneal approach even when retroperitoneal neoplasia arises from the intrabdominal structures. For the purpose of demonstrating the optimum safety and efficacy of this method, more large cohort studies need to be carried out.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The research involving human volunteers did not need an ethical assessment and approval in compliance with local and institutional regulations. The participant gave informed permission in writing to engage in this research. The individual's written informed permission was acquired prior to the publishing of any potentially identifying photos or information contained within this publication.

Author contributions

AA writing and manuscript preparation; ZX, DY, AA edited the article and performed the operation, perioperative management of the patient and figure preparation; MS, MA, AA responsible for literature review; AA, ZX, DY responsible for manuscript review. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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O-arm-guided percutaneous microwave ablation and cementoplasty for the treatment of pelvic acetabulum bone metastasis

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Objective: This study aims to evaluate the indications, safety, and efficacy of microwave ablation combined with cementoplasty under O-arm navigation for the treatment of painful pelvic bone metastasis.
Methods: We retrospectively collected data from 25 patients with acetabulum bone metastasis who underwent microwave ablation combined with cementoplasty. All patients underwent percutaneous microwave ablation combined with cementoplasty under O-arm navigation. The postoperative follow-up included evaluations of pain, quality of life, function, the incidence of bone cement leakage, and the presence of perioperative complications. Pain and quality of life were evaluated using the visual analog scale (VAS) and the QLQ-BM22 quality of life questionnaire for patients with bone metastases, respectively. The functional scores were calculated using the MSTS93 scoring system of the Bone and Soft Tissue Oncology Society.
Results: There were 10 males and 15 females with an average age of 52.5 ± 6.5 years, all 25 patients received percutaneous procedures, and no technical failure occurred. Major complications, including pulmonary embolism, vascular or nervous injury, hip joint cement leakage, and infection, were not observed in the current study. Pain regression was achieved in 24 of 25 patients. The mean VAS scores significantly decreased to 3.4 ± 1.0, 2.5 ± 1.2, and 1.2 ± 0.6 points at 1 week, 1 month, and 3 months after the procedure, respectively, compared with 7.0 points before the procedure ($P < .05$). The mean QLQ-BM22 score significantly decreased to 36.2 ± 4.9, 30 ± 5.6, and 25.4 ± 2.3 points at 1 week, 1 month, and 3 months after the procedure, respectively, compared with 55.8 points before the procedure ($P < .05$). The preoperative Musculoskeletal tumour society (MSTS) functional score of 25 patients was 18.5 ± 5.3 points, and MSTS score was 20.0 ± 3.0, 21.4 ± 4.9, and 22.8 ± 2.3 at 1 week, 1 month, and 3 months after the procedure, respectively ($P < .05$). The average bone cement injection volume was 8.8 ± 4.6 ml.
Conclusion: The use of O-arm-guided percutaneous microwave ablation combined with cementoplasty for the treatment of pelvic metastases could quickly and significantly alleviate local pain, prevent pathological fracture, and improve the quality of life of patients with reduced complications.

KEYWORDS
pelvic bone metastasis, O-arm, microwave ablation, cementoplasty

Introduction

The pelvis is one of the common sites of bone metastasis, which occurs in 20%–80% of advanced cancer patients (1, 2). The lung, breast, and prostate are the most common organs affected (3). Bone metastasis could result in skeletal-related events (SREs), including pain, pathological fracture, hypercalcemia, and nerve and visceral compression (4), which seriously affect the quality of life (QoL) of cancer patients, while more than 50% of patients received inadequate pain control treatment (5). With the development and advancement of various new anticancer drugs, next-generation sequencing, targeting, and immunotherapy, the treatment mode of patients with bone metastasis has gradually shifted to a chronic disease management mode. Long-term systemic follow-up and the continuous adjustment of drugs according to the patient's condition can confer long-term survival benefits, which is particularly important for improving tumor-bearing survival and QoL (6).

For pelvic bone metastases, surgical resection leads to the stripping of pelvic soft tissue and muscle attachment and addressing bone defects, causing more intraoperative bleeding, prolonging the healing time, and increasing the risk of wound complications, which in turn result in a longer recovery period for patients who often have a limited life expectancy (7). In some cases, in which medium-sized pelvic metastases, poor control after radiotherapy, local pain, and pathological fracture occur, surgical intervention can yield new problems, such as excessive bleeding, poor physical tolerance, the interruption of systemic treatment and radiotherapy, and adverse effects that result in the poor control of systemic tumors. Therefore, less invasive procedures, including percutaneous microwave ablation, radiofrequency ablation, cryoablation, and high-energy ultrasound with or without bone cement injection, have become salient options (8). While microwave ablation technology has been used for the treatment of bone tumors for more than 30 years and could be employed as an independent percutaneous minimally invasive treatment for benign bone tumors like Osteoid osteoma (9) and bone metastases (10). It has also been used as an intraoperative adjuvant treatment for the emergent control of intraoperative life-threatening tumor hemorrhage (11). In addition, tumor ablation can help to improve the safety margins during tumor resection (12). Yu et al. (13) took the lead in organizing and issuing the clinical guidelines for microwave ablation of bone tumors in limbs, which provided a good theoretical reference for microwave ablation of bone tumors and made the application of microwave ablation in bone tumors in limbs more standardized and professional. Percutaneous cementoplasty for the acetabulum was introduced by researchers (14–16). In addition, in the previous literature, pain control effects have been consistently reported (17–20), with common complications such as cement leakage and cement embolism. However, there has been no consensus and guidelines regarding how to reduce complications in the palliative treatment of pelvic bone metastasis, especially in regards to cementoplasty and microwave ablation, with few relevant clinical reports available.

Our team has focused on minimally invasive treatment of bone metastases for decades (21). The purpose of the current study was to evaluate cases of O-arm-guided microwave ablation combined with cementoplasty for the treatment of acetabular bone metastasis performed at our center in recent years to summarize the relevant indications, surgical methods, safety, and postoperative efficacy, with the aim of popularizing these technologies and sharing our clinical experience.

Materials and methods

The indications were as follows: advanced cancer patients, (1) who had refractory pain caused by pelvic bone metastasis, did not respond to conservative treatment, (2) advanced cancer patients with an osteolytic lesion (in predominance) in the weight-bearing area around acetabulum suitable for the pain, (3) patients with limited life expectancy (less than 3–5 years). There was no absolute contraindication of the procedure; however, the relative contraindications were as follows: (1) patients in poor condition who had an expected survival period of less than 3 months; (2) bone destruction of the internal iliac plate with soft tissue mass contaminating important organs, nerves and blood vessels.

A total of 25 cases of pelvic bone metastasis treated in our center from June 2018 to June 2020 were retrospectively analyzed. The average age of the patients was 52.5 ± 6.5 years, including 10 males and 15 females. There were six cases of primary lung cancer, four cases of breast cancer, two cases of colon cancer, three cases of renal cell carcinoma, three cases of liver cancer, two cases of gastric cancer, one case of thyroid cancer, two cases of prostate cancer, one case of myeloma, and one case of cervical cancer (**Table 1**). All patients received PET-CT, local x-ray, enhanced CT, and enhanced MRI before operation. The pathology of all patients was determined by postoperative pathology. According to the location of the focus, there were 14 cases of periacetabulum (P), five cases of Pubic ischium + periacetabulum (PI + P), and six cases of area illium + periacetabulum (I + P). There were 15 cases of simple osteolytic bone destruction and 10 cases of mixed bone destruction. There were 10 cases of oligiometastasis and 15 cases of multiple metastases. All patients included in this series were evaluated by a multidisciplinary team from a quaternary care hospital, including specialists in oncology and radiation oncology, orthopedic surgery, and musculoskeletal interventional radiology. The majority of our patients were in palliative care after the failure of other treatments. All had received radiation

TABLE 1 Clinical characteristic of 25 patients.

Primary tumor	Number	Pelvic Enecking region	Pathology
Lung cancer	6	II (4), II + III (2)	Adenocarcinoma (2), neuroendocrine type (1), squamous cell carcinoma (2), adenosquamous cell carcinoma (1)
Prostate cancer	2	II (2)	Prostate adenocarcinoma 2
Breast cancer	4	II (2), II + III (2)	Intraductal carcinoma (2), invasive carcinoma (2)
Renal cancer	3	II (3)	Clear cell renal cell carcinoma (3)
Liver carcinoma	3	I + II (3)	Hepatocellular carcinoma 2, cholangiocarcinoma (1)
Gastric cancer	2	I + II (2)	Adenocarcinoma 1, squamous cell carcinoma (1)
Thyroid carcinoma	1	II (1)	Myeloid carcinoma (1)
Myeloma	1	II (1)	Myeloma (1)
Colorectal cancer	2	II + III (2)	Adenocarcinoma 1, undifferentiated carcinoma (1)
Cervical carcinoma	1	II (1)	Squamous cell carcinoma (1)

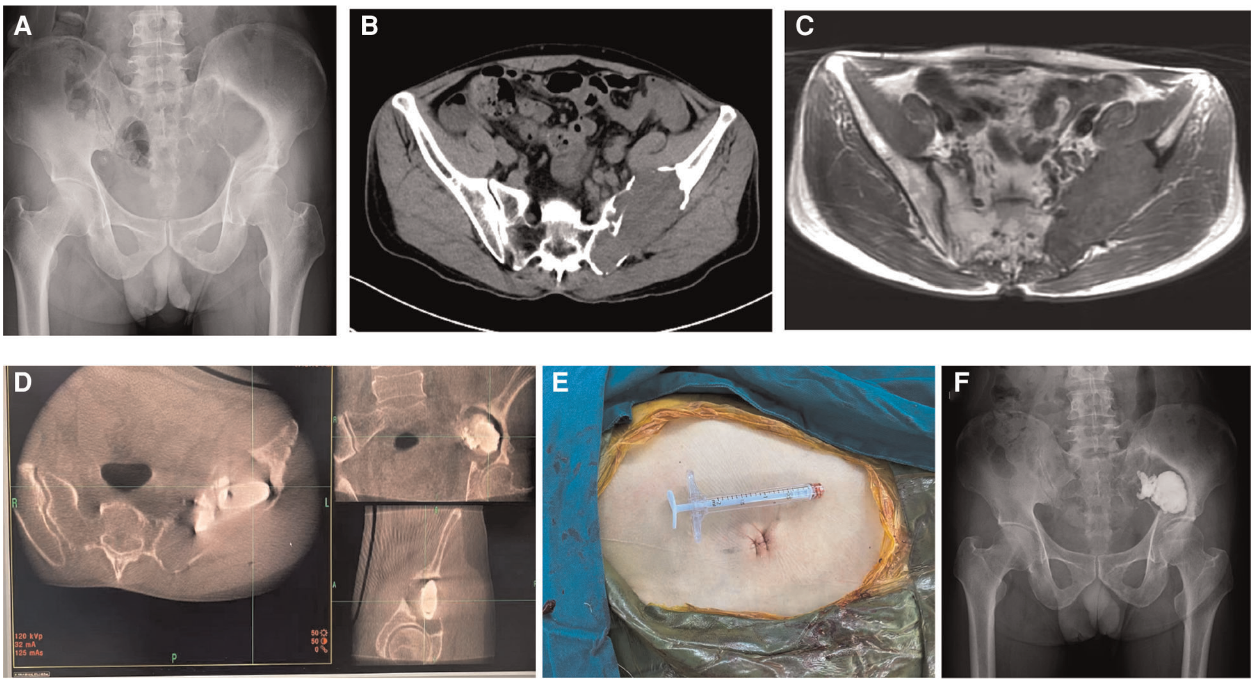

FIGURE 1
55-year-old man with metastatic renal cell carcinoma and a painful pelvic metastasis. (A) Preoperative pelvic x-ray. (B,C) Preoperative pelvic CT and MRI scans. (D) Intraoperative O-arm 3D image during puncture and cementoplasty. (E) Skin incision. (F) Postoperative pelvic x-ray 6 months after the procedure.

therapy before the cementoplasty procedure and presented with persisting pain. This study was approved by the institutional ethics committee.

All patients underwent routine preoperative skin and bowel clearing preparation. General anesthesia with endotracheal intubation was applied in the supine position on a carbon spine bed (Allen, Hill Rock Company, MA, USA). For I + P bone metastasis, a lateral iliac plate approach approximately 2 cm above the acetabular roof is usually employed for puncture to avoid femoral nerve and vessel injury. Trocar needle positioning was then confirmed under O-arm navigation using a 3D mode scan. After the tumor tissue biopsy, the microwave needle (Nanjing Viking Jiuzhou) was inserted, and the radiographic reconfirmed. The microwave frequency was set to 2.45 kmHz. The insertion depth and position of the microwave needle were set according to the preoperative CT scan. After ablation

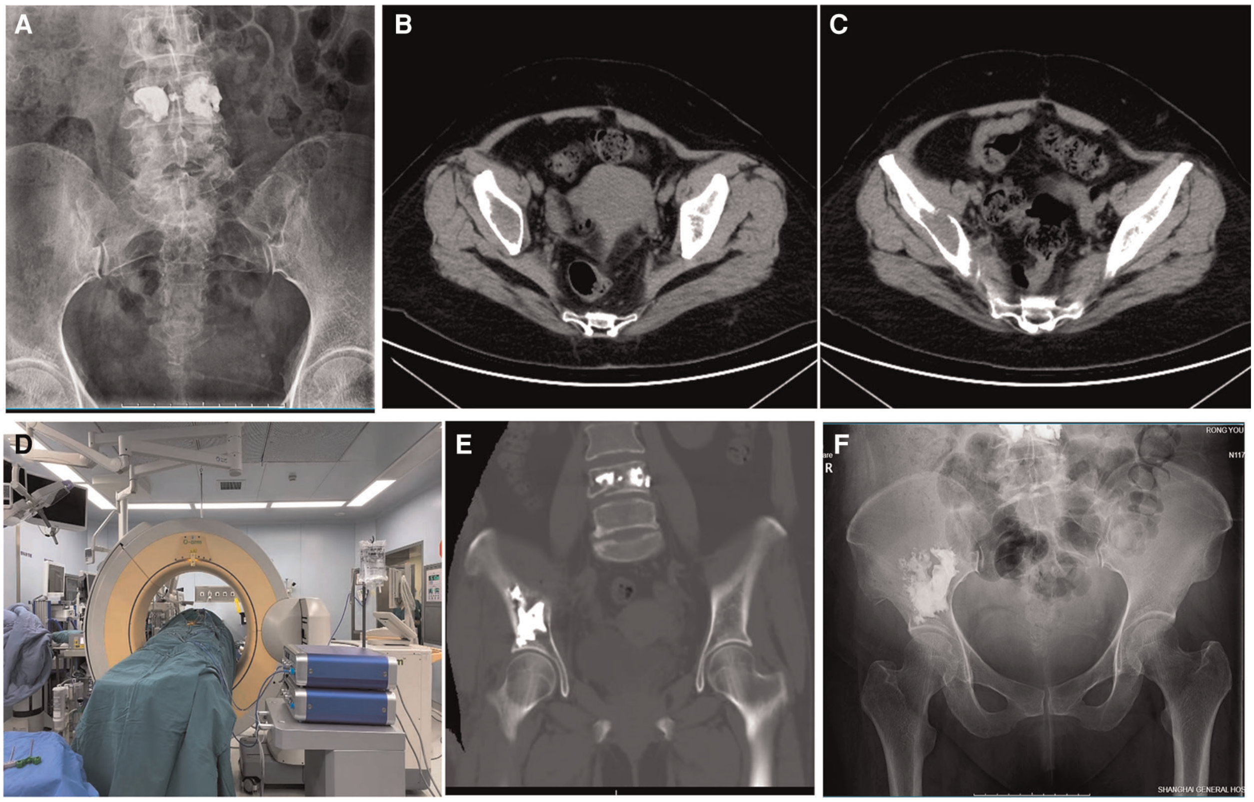

FIGURE 2
59-year-old man with metastatic liver carcinoma and a painful pelvic metastasis. (A) Preoperative pelvic x-ray. (B,C) Preoperative pelvic CT scan. (D) Intraoperative O-arm 3D image during puncture and cementoplasty. (E) Postoperative pelvic CT scan. (F) Postoperative pelvic x-ray 6 months after the procedure.

applicator positioning through the trocar, the ablation procedure was conducted according to the protocol supplied by the equipment manufacturer. Single intraosseous lesions are routinely ablated with 60 W for 5–10 min; if the tumor diameter is larger than 5 cm, the position of the microwave needle can be adjusted for repeated ablation. For mixed lesion bone lesion, repeated ablations with multiple needles are recommended, usually, the bone cement injection should be very careful because of the high pressure intraosseous and high risk of cement leakage. During the ablation process, the ablation applicator is used with ice-cold saline-saturated gauze at the puncture site to protect the surrounding soft tissue. After microwave thermal ablation, the biopsy was confirmed to check the thermal ablation efficacy. Pelvic cementoplasty is used for pain management and bone reinforcement in certain cases of pelvic bone fractures and metastasis. Polymethyl methacrylate (PMMA) was then mixed and injected under O-arm real-time imaging control through the trocar, and the injection was suspended when satisfactory filling was obtained or leakage was detected (Figures 1 and 2).

According to the size of the bone metastasis, the patients were given antibiotics and methylprednisolone therapy intravenously 1–2 times after the operation, and pain relief and 24-h continuous hydration and alkalization treatment were also employed to protect renal damage after the absorption of ablation-induced necrosis. All patients were followed up before the operation, as well as 1 week, 1 month, and 3 months after the operation. The VAS pain score, QLQ-BM22 quality of life score (22), MSTS93 function score, and imaging evaluation were performed.

Statistical analysis

The clinical parameter is expressed as the mean ± SD. Statistical analysis was carried out by GraphPad Prism software. The VAS and functional outcomes comparison was performed using the Tukey's multiple comparisons test. $P < .05$ indicated that the difference was statistically significant.

Results

All 25 patients received percutaneous procedures with no technical failure or major complications. All procedures were completed by experienced doctors in our team. The average operation duration was 45 ± 18 min, the ablation power was 60 W, the average microwave ablation time was 8 min, and the average bone cement filling volume was 8.8 ± 4.6 ml. Pain regression was achieved in 24 of 25 patients and one patient experienced recurrent pain caused by pelvic bone metastasis and received a repeat procedure. Posttreatment radiographs did not reveal osteolysis in the area of cementation, bone cement dislocation, or loosening within the acetabular bone. Pathological fracture within the strengthened acetabulum was not found. No one was reverted to secondary open reconstruction surgery.

Surgical-related complications

Major complications, including pulmonary embolism, vascular or nervous injury, hip joint cement leakage, and infection, were not observed in the current study. One patient with acetabular roof ablation encountered ablation needle fracture due to direction adjustment during the ablation process and received open surgery for foreign bodies removal. One patient had local wound problems one month after I + P ablation and underwent debridement. Six of 25 patients experienced transient hip pain during anesthesia-induced anabiosis (lasting 2 h) and received 100 mg of methylprednisolone, which is considered to elicit a thermal effect on the nerves behind the acetabulum, to relieve pain soon after treatment. There were no other complaints or discomfort after the operation.

TABLE 2 Pain, function and QoL score.

Parameter/ Time	Preoperative	1 week (post)	1 month (post)	3 months (post)
VAS score	7.0 ± 1.8	3.4 ± 1.0	2.5 ± 1.2	1.2 ± 0.6
MSTS score	18.5 ± 5.3	20.0 ± 3.0	21.4 ± 4.9	22.8 ± 2.3
EORTC QLQ-BM22	55.8 ± 9.5	36.2 ± 4.9	30 ± 5.6	25.4 ± 2.3

VAS, visual analog scale.

Postoperative pain and functional outcome

The mean VAS scores significantly decreased to 3.4 ± 1.0, 2.5 ± 1.2, and 1.2 ± 0.6 points at 1 week, 1 month, and 3 months after the procedure, respectively, compared with 7.0 ± 1.8 points before the procedure ($P < .05$ for all pairs). While the mean QLQ-BM22 scores significantly decreased to 36.2 ± 4.9, 30 ± 5.6, and 25.4 ± 2.3 points at 1 week, 1 month, and 3 months after the procedure, respectively, compared with 55.8 ± 9.5 points before the procedure, the quality of life of patients was significantly improved, and the difference was statistically significant ($P < .05$ for all pairs). The preoperative MSTS score of 25 patients was 18.5 ± 5.3 points, and MSTS score was 20.0 ± 3.0, 21.4 ± 4.9, and 22.8 ± 2.3 at 1 week, 1 month, and 3 months after the procedure, respectively ($P < .05$ for all pairs) (**Table 2**, **Figure 3**).

Discussion

It is difficult to monitor the adjacent critical structures of the pelvis during minimally invasive procedures of pelvic bone metastasis due to its complex anatomy, which requires a high level of experience and professional equipment. Medtronic's O-arm system is a new generation of intraoperative imaging platforms that are perfectly compatible with real-time three-dimensional (3D) images for surgery (23). To our knowledge, this is the first study using a strategy of O-arm-guided percutaneous microwave ablation and pelvic cementoplasty to treat painful pelvic bone metastasis, the results are in line with those described in the literatures. Through preoperative and intraoperative imaging

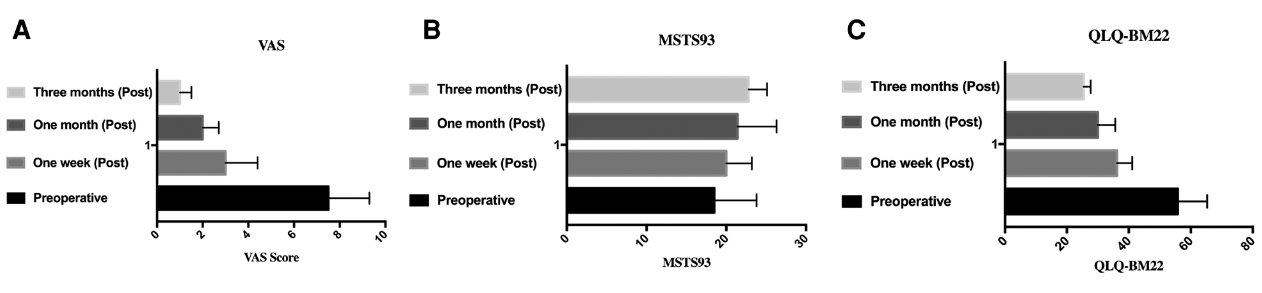

FIGURE 3
VAS, MSTS93, and QLQ-BM22 scores before and after operation. (A) VAS score in preoperative, 1 week, 1 month, and 3 months postoperative. (B) MSTS93 in preoperative, 1 week, 1 month, and 3 months postoperative. (C) QLQ-BM22 score in preoperative, 1 week, 1 month, and 3 months postoperative. VAS, visual analog scale.

measurements, we can implement accurate microwave ablation and cementoplasty to achieve satisfactory bone reinforcement, pain alleviation, greatly improved safety, and postoperative functional efficacy with the O-arm system. Kim et al. (8) found that local complications and extraosseous bone cement leakage were often observed (36%, 72/201 of pelvises). Among them, 21 showed intraarticular leakage into the hip joint, and 51 showed leakage into areas other than the hip joint. Moser et al. (19) reported that cement leakage was absent for 24 lesions (54.5%), articular leakage was absent for 6 lesions (13.6%), muscular or venous leakage was absent for 13 lesions (29.5%), and foraminal leakage was absent for one sacral lesion (2.3%). Compared with the procedures of previous studies carried out with CT device or mobile C-arm unit or in an angiography suite, the current study used O-arm-guided technology to monitor percutaneous ablation and cement bone reinforcement, and there were no major perioperative complications in this group. Only one patient had intraoperative leakage of the ablation needle. Six of 25 patients experienced transient hip pain, which was relieved soon after returning to the ward. And the procedure could be more efficient with its compatible navigation system, like the Medtronic stealthStation S8 system, the real-time image will not only greatly decrease the radiation exposure for patients and surgeons, but also help to reduce puncture-related risks. The combination procedure significantly reduced the operation time and local tumor contamination (compared with unpublished data), promoted rapid postoperative recovery, significantly relieved pain, and allowed most patients to receive systemic treatment of tumors in a short time with fewer complications compared with previous studies. The results of the current study suggested that O-arm-guided percutaneous microwave ablation and cementoplasty can effectively enhance the stability of the iliac and acetabulum in patients with pelvic bone metastases with little risk of complication.

Microwaves can be used to ablate tumors by agitating polar water molecules in the tumor tissue. The friction of water molecules produces heat of approximately 100–120 °C, thus inducing cellular death *via* coagulation necrosis. Compared with radiofrequency ablation, it has the advantage of rapid temperature rise, high temperature in the tumor, short time, little influence by carbonized blood flow, and no influence by impedance, so it has made great progress in its clinical application. Several studies have reported microwave ablation in bone tumor treatment, but there are only a few studies on the setting of ablation time and temperature parameters of microwave ablation in bone tumors (24, 25).

In this study, we adopted different ablation and bone cement strengthening strategies for pelvic metastatic lesions with different sizes and bone destruction forms: (1) For lesions with complete internal iliac plates, the lesions can be ablated repeatedly for 5 min, and bone cement strengthening can be performed after biopsy. (2) For patients with partial defects of the internal iliac plate, it is recommended to directly form bone cement after ablation for 3–5 min to reduce the risk of internal cement leakage and pelvic organ injury. (3) For patients with large lesions involving both internal and external plates, percutaneous ablation is not recommended. Local open surgery under the control of an abdominal aortic balloon or embolization is recommended. Furthermore, we usually do not endorse inserting two or more needles for ablation or cement filling, partly because of the low cost-effect ratio of microwave ablation in bone metastasis treatment, the other reason is multiple uses of ablation needles increase the risk of cement leakage and other complications.

The limitation of this study, however, is the retrospective design and the small cohort of patients may represent a limit to the statistical analysis, which is due to the specific location and scarcity nature included in our study, which also caused the lack of control cohort is current study, which could be solved by designing prospective comparative clinical trials for the combinations of those procedures. One of our limitations, however, is the compatibility between the biopsy kit and the microwave ablation trocar; there is currently no commercially available kit that is compatible for bone biopsy, microwave, and bone cement strengthening; we had to change the trocar to finish the procedure, which definitely added to the risk of bone destruction and cement leakage, but also increased the risk of re-puncture positioning. And we are now working on another project to develop a more compatible bone biopsy kit in order to overcome those limitations and push forward the palliative treatment.

In summary, we confirmed the safety and efficacy of the combination of percutaneous microwave ablation and cementoplasty under O-arm navigation in terms of pain relief and recovery of their QoL. Moreover, this strategy has a low risk of complications compared with radiofrequency ablation or cryoablation with or without an intraoperative CT scan.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

DZ contributed to the study design and manuscript; HM contributed to the tables and figures; MXS contributed to the data analysis; CW, ZC, JS, and WS contributed to the study design and revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Can a reresection be avoided after initial *en bloc* resection for high-risk nonmuscle invasive bladder cancer? A systematic review and meta-analysis

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Background: This study aims to evaluate the effectiveness of *en bloc* resection for patients with nonmuscle invasive bladder cancer (NMIBC) and explore whether a reresection can be avoided after initial *en bloc* resection.
Material and methods: We conducted research in PubMed, EMBASE, Cochrane Library, and Web of Science up to October 12, 2021, to identify studies on the second resection after initial *en bloc* resection of bladder tumor (ERBT). R software and the double arcsine method were used for data conversion and combined calculation of the incidence rate.
Results: A total of 8 studies involving 414 participants were included. The rate of detrusor muscle in the ERBT specimens was 100% (95%CI: 100%–100%), the rate of tumor residual in reresection specimens was 3.2% (95%CI: 1.4%–5.5%), and the rate of tumor upstaging was 0.3% (95%CI: 0%–1.5%). Two articles compared the prognostic data of the reresection and non-reresection groups after the initial ERBT. We found no significant difference in the 1-year recurrence-free survival (RFS) rate (OR = 1.44, 95%CI: 0.67–3.09, $P = 0.35$) between the two groups nor in the rate of tumor recurrence (OR = 0.72, 95%CI: 0.44–1.18, $P = 0.2$) or progression (OR = 0.98, 95%CI: 0.33–2.89, $P = 0.97$) at the final follow-up.
Conclusions: ERBT can almost completely remove the detrusor muscle of the tumor bed with a very low postoperative tumor residue and upstaging rate. For high-risk NMIBC patients, an attempt to appropriately reduce the use of reresection after ERBT seems to be possible.

KEYWORDS

high-risk, nonmuscle-invasive bladder cancer, *en bloc* resection, reresection, systematic review and meta-analysis

Introduction

At present, transurethral resection of the bladder tumor (TURBT) combined with postoperative intravesical instillation is the gold standard for the treatment of nonmuscle invasive bladder cancer (NMIBC) (1). However, due to piecemeal resection, traditional TURBT has a high tumor residual rate, making it difficult to provide accurate pathological staging (2, 3). For accurate staging and detection of tumor residue, reresection is recommended for patients with high-risk NMIBC, although it significantly increases the complication risk and financial stress (1, 4).

Different from traditional TURBT, as a new strategy, transurethral *en bloc* resection of bladder tumor (ERBT) can theoretically wholly remove the bladder tumor and even achieve a 100% detrusor muscle (DM) presence rate. Several recent studies also confirmed that detrusor muscle was present in above 95% of ERBT specimens (5–9). Some previous studies showed that the presence rate of DM was closely related to recurrence and could be a surrogate marker of resection quality (10–12). Although the latest study by Mastroianni et al. showed that the absence of DM has no impact on tumor recurrence, the high DM presence rate and tumor tissue integrity could provide a significant advantage in tumor staging (13, 14). Xu et al. performed reresection on high-risk NMIBC patients who underwent initial ERBT. The results showed that the residual tumor rate and tumor progression rate were only 5.9% and 3.9%, respectively. Moreover, they found that reresection did not seem to improve the prognosis of these patients (5). Given the advantages of ERBT, is it possible to reduce the need for a reresection in high-risk NMIBC patients after initial ERBT?

To answer this question, we conducted a meta-analysis to evaluate the efficacy of ERBT in treating NMIBC by integrating DM presence rate in primary ERBT specimens and tumor residual and upstaging rate in reresection specimens. In addition, we also compared the prognostic indicators of the reresection and non-reresection groups to assess whether patients would benefit from reresection. We believe that if the efficacy of ERBT is satisfactory and the patient cannot derive sufficient benefit from reresection, an attempt can be made to avoid reresection appropriately.

Methods

Search strategy

We conducted research in PubMed, EMBASE, Cochrane Library, and Web of Science up to October 12, 2021, to identify studies on reresection after initial ERBT. The search terms used include: (“bladder neoplasm” OR “bladder cancer” OR “bladder tumor” OR “carcinoma of bladder”) and (“en bloc” OR “en-bloc” OR “en-bloc”) and (“second” OR “repeat” OR “reresection” OR “restaging” OR “reTUR”). We also scanned references of key articles and searched the grey literature to ensure we did not miss any relevant articles. We reported the study according to the preferred reporting items of the systematic review and meta-analysis (PRISMA) (15).

Inclusion and exclusion criteria

Inclusion criteria are as follows: (P) patients diagnosed with primary high-grade Ta (TaHG) or T1 NMIBC who have received initial ERBT; (I) reresection performed within 12 weeks after initial ERBT; (C) no reresection after initial ERBT; (O) outcome indicators should include at least one of the following: detrusor muscle presence rate in primary ERBT specimens, tumor residual rate in reresection specimens, tumor upstaging rate in reresection specimens, comparison of prognostic data between reresection and non-reresection groups; and (S) observational study (prospective or retrospective).

Exclusion criteria are as follows: (a) case reports, comments, conference abstracts, and republished literature; (b) no interest outcome; and (c) data incomplete or invalid.

Selection process and data abstraction

The authors first read the titles and abstracts to conduct a preliminary literature screening. Documents that meet the inclusion and exclusion criteria will be directly included in the full-text evaluation. During the full-text evaluation phase, disputes were settled by two authors through consultation. If no agreement can be reached, a third author was consulted.

Two authors independently extracted data using a predesigned data extraction table. Baseline data included the following: first author and publication year, country, study type, ERBT method, reresection cases, and reresection time. Clinicopathological data included the following: the stage and grade of the primary tumor, primary tumor size, number of primary tumors, location of the residual tumor, follow-up, and prognosis. Data required for meta-analysis included the following: detrusor muscle presence rate in primary ERBT specimens, tumor residual rate in reresection specimens, tumor upstaging rate in reresection specimens, and comparison of prognostic data between reresection and non-reresection groups.

Literature quality and risk of bias assessment

We assessed the quality of literature using a Methodological index for nonrandomized studies (MINORS). The first eight items of MINORS were specially used for quality assessment of noncomparative studies, with 16 points. A score greater than or equal to 12 points was considered moderate to high literature quality (16).

Statistical analysis

All statistical analyses in this study were performed using R software and Cochrane Review Manager 5.3 (China). The significance level was $P < 0.05$. In a meta-analysis of prevalence, if the event incidence was greater than 0.8 or less than 0.2, the double arcsine method will be used (17). Inconsistencies (I^2) statistics were used to assess heterogeneity. $I^2 > 50\%$ indicates that the heterogeneity is very significant, and the random-effect model should be adopted. $I^2 < 50\%$ indicates that the heterogeneity is acceptable, and the fixed-effect model should be adopted. If heterogeneity was significant, sensitivity analysis and subgroup analysis will be used to explore the source of heterogeneity. Egger's test was used to evaluate publication bias quantitatively. $P > 0.05$ indicated no significant publication bias.

Results

Basic characteristics and quality assessment

A PRISMA flow diagram visually illustrated the screening process (**Figure 1**). At last, eight studies (5–9, 18–20), including 414 participants, were included by carefully screening 252 articles. Among them, five (7, 8, 18–20) were prospective and three (5, 6, 9) were retrospective. In addition, five studies (5, 6, 18–20) were laser-based ERBT, two (7, 8) were based on electrotomy, and one (9) was based on laser or electrotomy (**Table 1**). The clinicopathological features of patients with reresection are presented in **Table 2**. The MINORS scale showed that all included studies had scores greater than or equal to 12 points, and the quality of the literature was satisfactory (**Table 3**).

Meta-analysis results

Detrusor muscle presence rate in primary ERBT specimens

Overall, the DM presence rate was reported by eight studies (5–9, 18–20). In the process of tumor resection, Yang et al. distinguished the clinical stage of bladder tumor in real-time and did not resect the detrusor muscle of the Ta tumor, so the actual DM presence rate was 97.1% (34/35) (7). Since the present rate of DM in ERBT specimens in the included studies was as high as 97.1%–100%, we adopted the double arcsine method for data conversion and, at the same time, corrected the data with the present rate of DM of 100%. Due to no pronounced heterogeneity observed ($I^2 = 0\%$), the meta-analysis results using the fixed effects model showed that the pooled DM presence rate in the ERBT specimens and its 95% confidence interval was 100% (95%CI: 100%–100%) (**Figure 2**).

Tumor residual rate in reresection specimens

Tumor residual rate was reported by eight studies (5–9, 18–20). Since the tumor residual rates in the included studies were all lower than 10%, we used the double arcsine method for data conversion, and at the same time, we corrected the data with a tumor residual rate of 0. Due to no pronounced heterogeneity observed ($I^2 = 6\%$), the meta-analysis results using the fixed effects model showed that the pooled tumor residual rate in reresection specimens and its 95% confidence interval was 3.2% (95%CI: 1.4%–5.5%) (**Figure 3**).

Tumor upstaging rate in reresection specimens

The tumor upstaging rate was reported by eight studies (5–9, 18–20). After data conversion and correction using the double arcsine method, the meta-analysis results using the fixed effects model showed that the pooled tumor upstaging rate in reresection specimens and its 95% confidence interval was 0.3% (95%CI: 0%–1.5%) (**Figure 4**).

Comparison of prognostic data between reresection and non-reresection groups

Two studies (5, 6) compared the prognostic data of the reresection and non-reresection groups after the initial ERBT (**Table 4**). We found no significant difference in the 1-year recurrence-free survival (RFS) rate (OR = 1.44, 95%CI: 0.67–3.09, $P = 0.35$, $I^2 = 0\%$) (**Figure 5**) between the two groups nor in the rate of tumor recurrence (OR = 0.72, 95%CI: 0.44–1.18, $P = 0.2$, $I^2 = 0\%$) (**Figure 6**) or progression (OR = 0.98, 95%CI: 0.33–2.89, $P = 0.97$, $I^2 = 0\%$) (**Figure 7**) at final follow-up.

Publication bias

We used Egger's test to evaluate publication bias quantitatively, and the results showed that no obvious publication bias was found in all outcome index groups. We showed Egger plots and P values for the primary outcome indicators in **Figure 8**.

Discussion

To our knowledge, this study is the first meta-analysis to explore whether a reresection can be avoided for high-risk NMIBC patients after initial ERBT. For high-risk NMIBC patients who underwent traditional TURBT, the primary purposes of reresection are to improve the present rate of DM, clarify tumor stage, reduce tumor residue, and improve the prognosis of patients (21, 22). However, our study showed that the present rate of DM in primary ERBT specimens

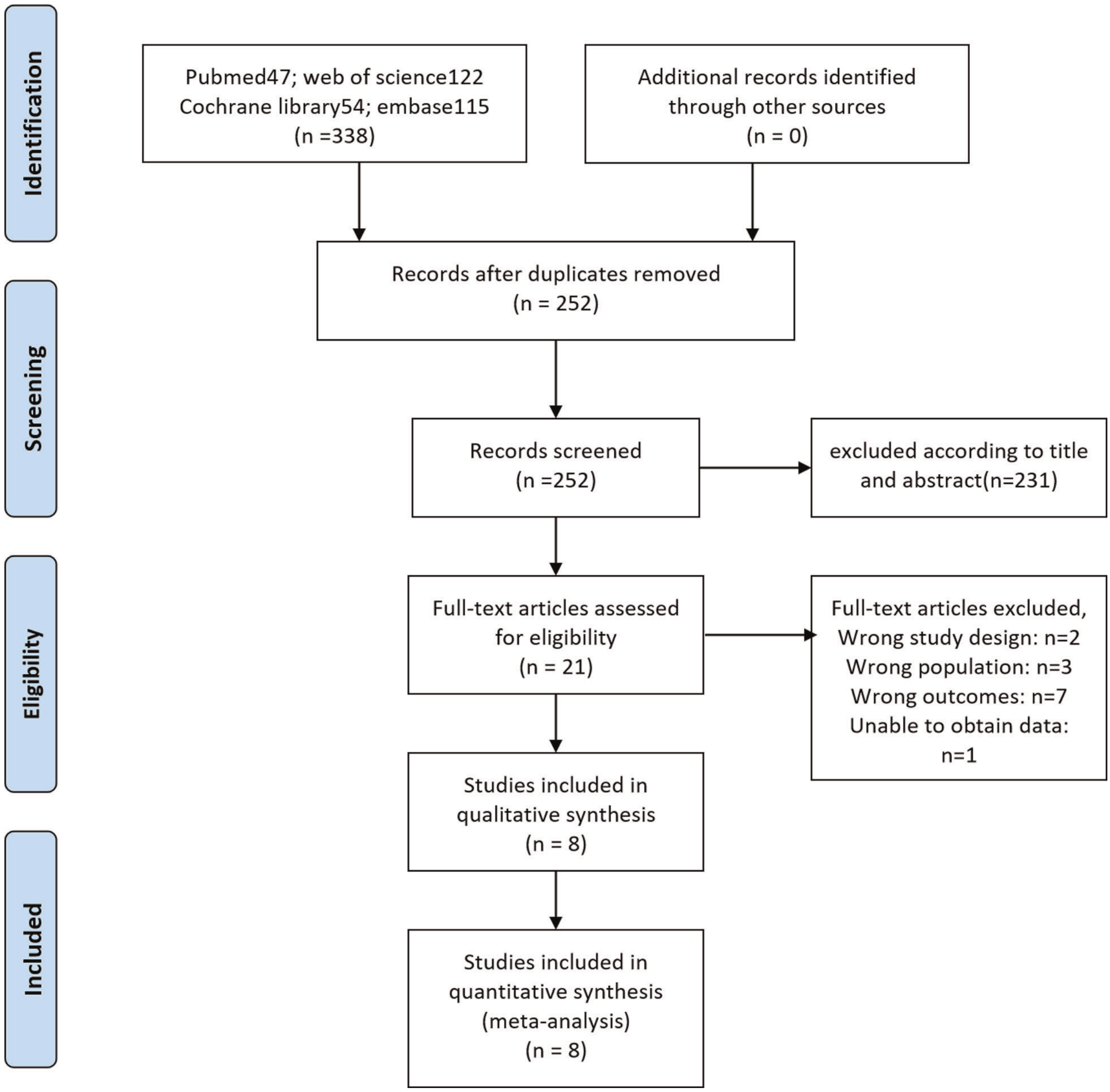

FIGURE 1
Literature search and selection.

could reach 100%. On this basis, the tumor upstaging rate and tumor residual rate in reresection specimens were extremely low. A recent meta-analysis involving 29 studies also showed that ERBT had a significantly higher DM presence rate in primary ERBT specimens and a significantly lower tumor residual rate in reresection specimens than traditional TURBT. It is consistent with our study (23). In addition, our study also found that reresection did not seem to improve the prognosis of high-risk NMIBC patients with initial ERBT. It can be seen that the advantages of ERBT over traditional TURBT seem to have satisfied the original intention of carrying out reresection. Reresection after initial ERBT in high-risk NMIBC patients does not appear to be critical and essential. Considering the trauma and economic pressure brought by reresection, for patients with poor physical conditions who are difficult to tolerate reresection, it seems that an attempt can be made to avoid reresection appropriately.

When there is no DM in the initial specimen, reresection can provide detrusor muscle of the tumor bed, thus improving the accuracy of tumor staging (24). Gordon's study

TABLE 1 Literature basic information and literature quality evaluation results.

Study	Country	Study type	ERBT method	Reresection cases	Reresection time	Outcomes	Quality scores
Wolters 2011	Germany	PS	Thulium laser	5	6 weeks	ABC	12/16
Muto 2014	Italy	PS	Thulium laser	49	30–90 days	ABC	13/16
Migliari 2015	Italy	PS	Thulium laser	53	90 days	ABC	14/16
Hurle 2020	Italy	RS	Thulium laser/Electrotomy	78	40 days	ABC	13/16
Soria 2020	Italy	PS	Electrotomy	42	2–6 weeks	ABC	14/16
Yang 2020	China	PS	Electrotomy	28	2–6 weeks	ABC	14/16
Zhou 2020	China	RS	Thulium laser	108	2–6 weeks	ABCD	14/16
Xu 2021	China	RS	RevoLix 2-μm laser	51	2–6 weeks	ABCD	13/16

PS, prospective study; RS, retrospective study; A, detrusor muscle presence rate in ERBT specimens; B, tumor residual rate in reresection specimens; C, tumor upstaging rate in reresection specimens; D, comparison of prognostic data between reresection and non-reresection groups.

TABLE 2 Clinicopathological features of patients with reresection.

Study	Initial resection results			Reresection results	Follow-up and prognosis
	T state and grade	Tumor diameter (cm)	Single lesion	Location of the residual tumor	
Wolters 2011	TaG1:1 (20%); TaG2:1 (20%); T1G3:3 (60%)	<3 (100%)	4 (100%)	0	NA
Muto 2014	TaLG:31 (63.3%); T1HG:18 (36.7%)	2.36 ± 1.47	Mixed	In situ:1	16 mon (RFS = 41/48, 85.4%; PFS = 100%); 18mon (RFS = Ta:90%, T1:76%)
Migliari 2015	TaLG:30 (56.6%); T1HG:23 (43.4%)	2.5 (0.5–4.5)	53 (100%)	0	20mon (RFS = 46/58, 79.3%; PFS = 100%) 18mon (RFS = Ta:90%; T1:76%)
Hurle 2020	Ta:17 (21.8%); T1:57 (73.1%); Tis:4 (5.1%); G3:72 (92.3%)	1.9 (1–3.5)	Mixed	In situ:1; Ectopic:4	30.8mon (RFS = 67/78, 85.9%; PFS = 77/78, 98.7%) 3mon (RFS = 75/78, 96.2%)
Soria 2020	Ta:27 (64.3%); T1:8 (19.0%); Tis:7 (16.7%)	2 (1–3)	21 (50%)	In situ:1; Ectopic:1	NA
Yang 2020	HG or T1	2 (1–3)	Mixed	In situ:2	NA
Zhou 2020	Ta:60 (55.6%); T1:48 (44.4%); LG:25 (23.2%); HG:83 (76.8%)	2.74 ± 0.13	56 (51.9%)	NA	41.5mon (RFS = 85/108, 78.7%; PFS = 104/108, 96.3%) 12mon (RFS = 92.6%; PFS = 98.1%); 36mon (RFS = 84.3%; PFS = 96.3%)
Xu 2021	Ta:16 (31.4%); T1:35 (68.6%) LG:13 (25.5%); HG:38 (74.5%)	<3 cm (42.9%) ≥3 cm (46.7%)	22 (46.8%)	NA	27mon (RFS = 41/51, 80.4%; PFS = 49/51, 96.1) 12mon (RFS = 94.1%)

LG, low grade; HG, high grade; RFS, recurrence-free survival; PFS, progression-free survival; NA, not available.

showed that the present rate of DM in traditional TURBT specimens was 71.2%, which increased to 87.8% after reresection (25). Han et al.'s study showed that the tumor upstaging rate was 16.1% after referring to the reresection specimens (26). A recent systematic review also showed that tumor upstaging occurred in 0%–32% (T1 to ≥T2) of cases (24). In a single-center retrospective study by Zhou et al., DM was present in all 251 ERBT participants' specimens, and the tumor upstaging rate was only 1.9% (2/108) after reresection of 108 high-risk NMIBC patients (6). Subsequently, Xu et al. also obtained similar results in the study of 115 patients, with the DM presence rate in primary ERBT specimens and the tumor upstaging rate in reresection specimens of 100% and 3.9%, respectively (5). Our study, which integrated all available data, showed that DM was present in 100% of ERBT specimens and the tumor upstaging rate was 0.3% after referring to the reresection specimens. Regarding tumor staging, ERBT has a high presence rate of DM and excellent staging accuracy. Therefore, reresection does not seem to be indispensable in terms of tumor staging.

Cumberbatch et al. conducted a systematic review of studies on reresection after traditional TURT. For Ta tumors, the rate of residual tumors found at reresection ranged from 17% to 67%, and for T1, it ranged from 20% to

TABLE 3 MINORS assessment of included studies.

Study	MINORS criteria								
	Clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aims of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow-up less than 5%	Prospective calculation of the study size	Total
Wolters 2011	2	1	2	2	1	2	2	0	12
Muto 2014	2	2	2	2	1	2	2	0	13
Migliari 2015	2	2	2	2	2	2	2	0	14
Hurle 2020	2	2	2	2	1	2	2	0	13
Soria 2020	2	2	0	2	2	2	2	2	14
Yang 2020	2	2	2	2	2	2	2	0	14
Zhou 2020	2	2	2	2	2	2	2	0	14
Xu 2021	2	2	1	2	2	2	2	0	13

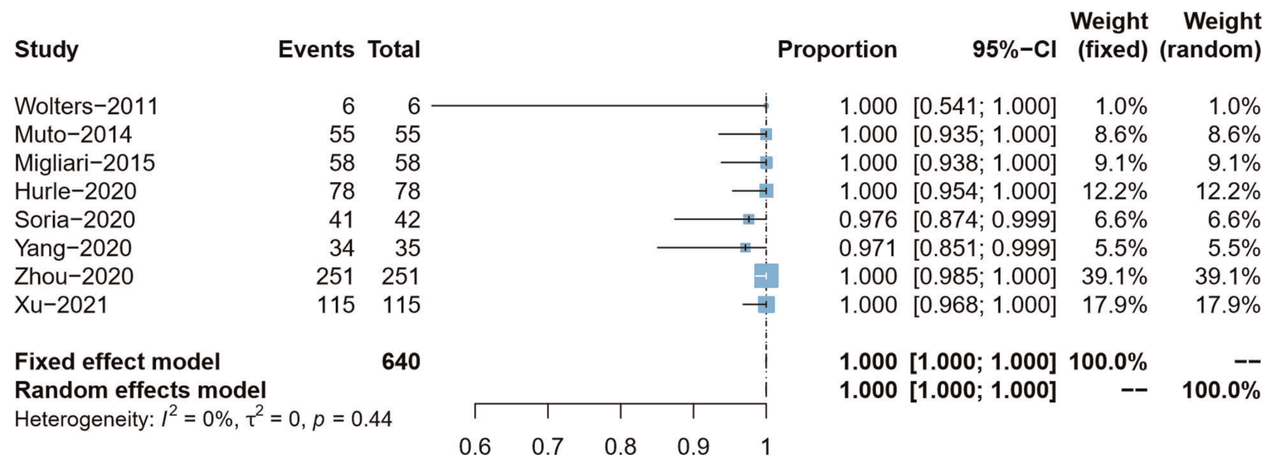

FIGURE 2
Forest plot – detrusor muscle presence rate.

71% (24). Subsequently, the study of Akitake et al. also showed that among 143 high-risk NMIBC patients with traditional TURBT, 66 tumor residues (46.2%) were found after reresection (27). Unlike the high tumor residual rate of traditional TURBT, our study showed that patients with initial ERBT found an extremely low tumor residual rate (3.2%) at reresection. In addition, Zhou et al. and Xu et al. performed cystoscopy on patients in the non-reresection group three months after ERBT. They found that the tumor residual rate was similar to that in the reresection group (5, 6). They believe that although the cystoscopy timing differed between groups, the results may have been biased. Nevertheless, in part, it might reflect that reresection after the initial ERBT did not seem to reveal more tumor residuals than non-reresection. In summary, the tumor residual rate of ERBT is low, and reresection may not find more residual tumors. It provides a basis for avoiding reresection.

In a prospective study, patients with T1 NMIBC at initial diagnosis were randomly divided into reresection and non-reresection groups. The first- and third-year recurrence-free survival rates were 82% and 65% in the reresection group and 57% and 37% in the non-reresection group, respectively. It indicates that the reresection can significantly improve the recurrence-free survival rates of patients (28). However, the study of Calo et al. showed that if the initial resection was complete, reresection did not improve RFS and progression-free survival (PFS) in patients with high-grade T1 NMIBC (29). The study of Gontero et al. also pointed out that if the detrusor muscle was not present in the initial TURBT

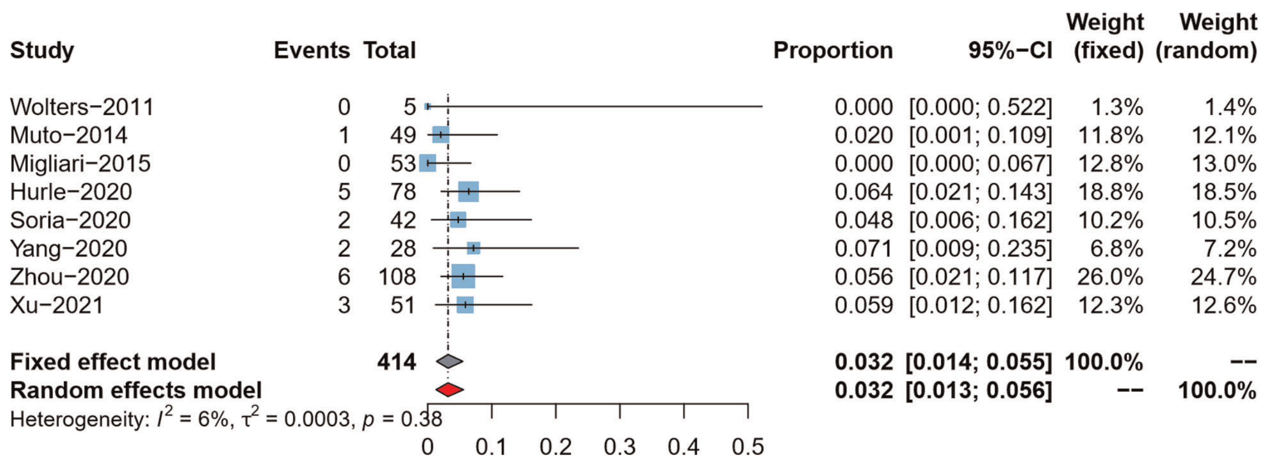

FIGURE 3
Forest plot – tumor residual rate.

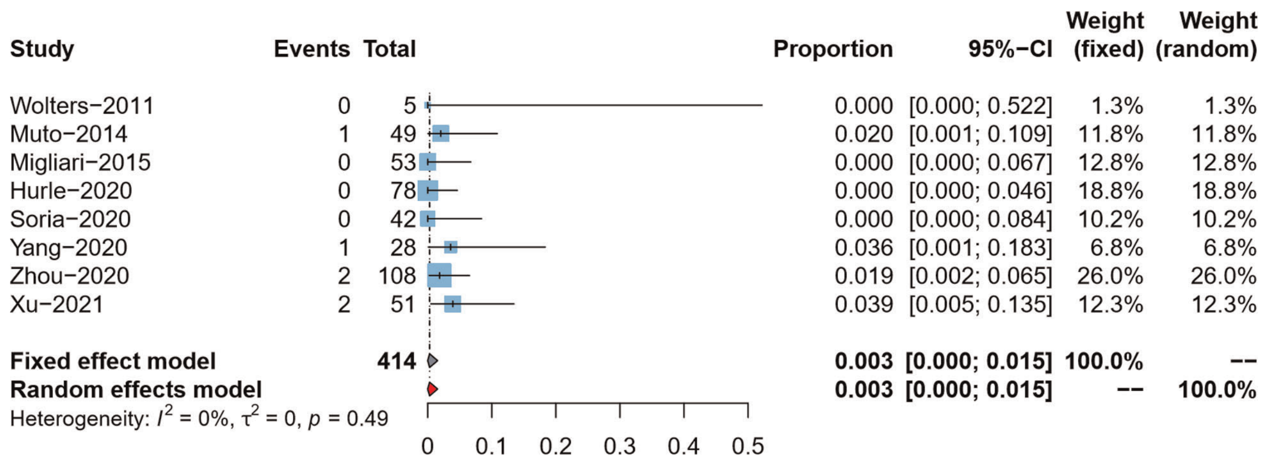

FIGURE 4
Forest plot – tumor upstaging rate.

TABLE 4 Prognosis of patients with high-risk NMIBC after initial ERBT (reresection vs. non-reresection).

Study	Groups	Initial resection result		follow-up (months)	1-year recurrence-free rate	*P*	Tumor recurrence	*P*	Tumor progression	*P*
		T stage	Grade							
Xu 2021	Reresection ($n = 51$)	Ta:16 (31.4%) T1:35 (68.6%)	LG:13 (25.5%) HG:38 (74.5%)	27 (5–60)	48/51 (94.1%)	0.269	10/51 (19.6%)	>0.05	2/51 (3.9%)	0.430
	Non-reresection ($n = 64$)	Ta:15 (23.4%) T1:49 (76.6%)	LG:13 (25.5%) HG:38 (74.5%)		58/64 (90.6%)		18/64 (28.1%)		1/64 (1.6%)	
Zhou 2020	Reresection ($n = 108$)	Ta:60 (55.6%) T1:48 (44.4%)	LG:25 (23.2%) HG:83 (76.8%)	40 (3–72)	100/108 (92.6%)	>0.05	23/108 (21.3%)	>0.05	4/108 (3.8%)	>0.05
	Non-reresection ($n = 143$)	Ta:87 (60.8%) T1:56 (39.2%)	LG:49 (34.3%) HG:94 (65.7%)		129/143 (90.2%)		37/143 (27.3%)		7/143 (4.0%)	

LG, low grade; HG, high grade.

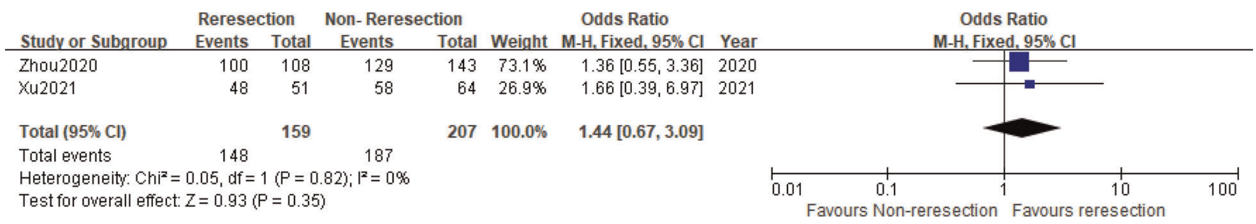

FIGURE 5
Forest plot – comparison of the 1-year recurrence-free survival rate between reresection and non-reresection groups.

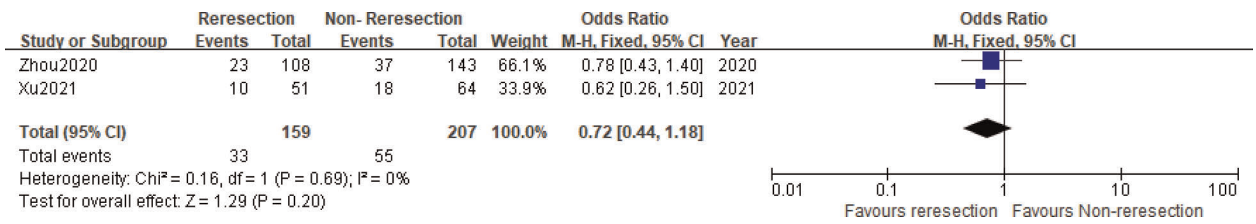

FIGURE 6
Forest plot – comparison of the tumor recurrence rate between reresection and non-reresection groups.

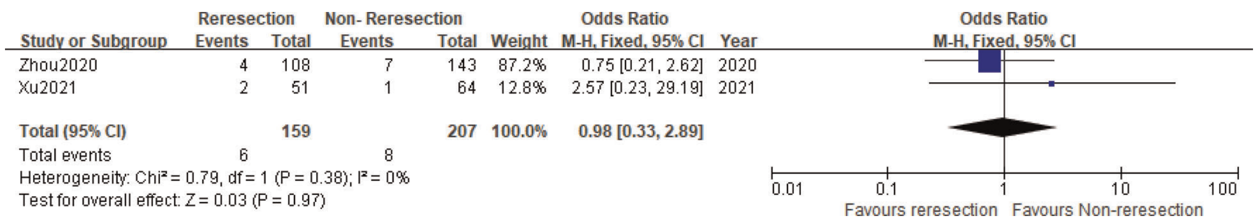

FIGURE 7
Forest plot – comparison of the tumor progression rate between reresection and non-reresection groups.

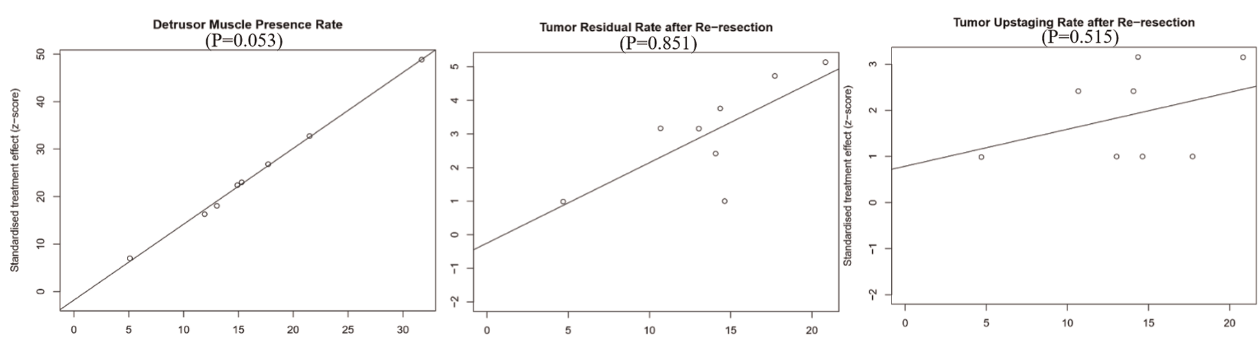

FIGURE 8
Publication bias – Egger's graph.

specimen, the RFS and PFS of T1HG patients could be improved by reresection. If the detrusor muscle was present, the patient's prognosis could not be improved by reresection (30). We believe that the mechanism of reresection to improve prognosis lies in removing the DM in the tumor bed and removing the residual tumor as much as possible. In contrast, in ERBT patients who have almost achieved R0 resection, the effect of reresection to improve prognosis will no longer be indispensable. Our results confirm this hypothesis. We found no significant difference in the 1-year RFS rate between the reresection and non-reresection group, nor in the tumor recurrence rate or progression at final follow-up. Due to a lack of data, we included only two studies, which, despite possible bias, have demonstrated to some extent that high-risk NMIBC patients with initial ERBT do not seem to obtain significant improvement in prognosis from reresection.

Limitations

Admittedly, there are still flaws in our research. First, this study is a meta-analysis of the rate and lacks a control group, which cannot directly reflect the difference between ERBT and traditional TURBT. Second, only two studies compared the prognosis of the reresection and non-reresection groups, which is theoretically not suitable for meta-analysis. Third, due to the lack of primary data, we could not detail how many CIS, BCG nonresponse, multifocal, and 3 cm HG bladder tumors were reported in selected studies. Again, because of insufficient data, our study was not limited to T1 cases or included in subgroup analyses. Fourth, we did not consider the possibility of acquiring diabetes in sections far from the deepest part of the tumor, which may have skewed the results. Finally, despite the meta-analysis, the total sample size is still insufficient, and more large-sample randomized controlled studies are needed in the future to verify our results further.

Conclusion

ERBT can almost completely remove the detrusor muscle of the tumor bed with very low postoperative tumor residue and upstaging rate. Reresection after initial ERBT in high-risk NMIBC patients does not appear to be critical and essential. For patients with poor physical conditions who are difficult to tolerate reresection, it seems that an attempt can be made to appropriately avoid reresection.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author/s.

Author contributions

Conception and design: HY. Administrative support: HY. Provision of study materials or patients: JX, ZX. Collection and assembly of data: JX, ZX. Data analysis and interpretation: JX, ZX. Manuscript writing: All authors. Final approval of manuscript: All authors. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Time is crucial in malignant tumor cases: Speeding up the process of patient-specific implant creation

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Purpose: Patient-specific implants are commonly used to reconstruct lower jaw defects following surgical treatment for head and neck squamous cell carcinoma. The planning process of surgery is time-consuming and can delay the "time to surgery," which should be as short as possible. Therefore, this study aimed to evaluate the planning process to speed up and identify any sources of problems.

Patients and methods: In this retrospective study, we enrolled patients who underwent continuous resection of the mandible in combination with reconstruction with a patient-specific implant between 2016 and 2021. The predictor variables were in-house training of the engineers and implant complexity (complex [with additional features] vs. less complex [resembling standard reconstruction plates]). The outcome variables were the duration of communication, message length, and the need for synchronous communication or modifications to the original design. Descriptive and univariate statistics were computed, and statistical significance was set at $P < 0.05$.

Results: The data from 83 patients were included in this study. The mean duration of communication was 14.05 ± 13.58 days. The implant complexity and training status of the engineer had no statistically significant influence on the primary outcome variables. As for the secondary outcome variables, the implant complexity significantly influenced the chance that the planned operation had to be postponed (15/16 [93.75%] were complex cases, $P = 0.001$). The most frequent cause of problems in the planning process was an insufficient dataset, which was not dependent on the type of imaging.

Conclusions: The overall duration of the patient-specific implant creation process is too long to meet oncological requirements. Therefore, standardization of the planning process to accelerate implant creation is of utmost importance. In addition, a common standard imaging format (independent of the type of imaging) for oncological cases could eliminate all delays caused by insufficient datasets in the future.

KEYWORDS

head and neck squamous cell carcinoma, patient-specific implant, time-to-treatment, mandible, workflow, computer-aided design, artificial intelligence

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide, with an increasing incidence per year. It accounts for approximately 3% of new cancer diagnoses in the United States and almost 900,000 new cases annually worldwide, resulting in approximately 450,000 deaths worldwide in 2018. HNSCC, the most common head and neck cancer accounts for more than 90% of all cases, often arises from the epithelium of the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx (1–4).

Treatment for HNSCC usually involves a diagnostic and staging phase followed by treatment *via* a selection or combination of surgery, radiotherapy, or chemotherapy (4). An important prognostic factor is the time between the initial diagnosis and the start of treatment (time-to-treatment initiation) (5). An increase in time-to-treatment initiation seems to be associated with worsening mortality, even if this relationship may be multifaceted, with sociodemographic issues, management of comorbid conditions, and complexity of treatment modalities contributing to increased time-to-treatment initiation and decreased overall survival (6–8).

Time to surgery (TTS) is a crucial factor in the surgical treatment of HNSCC. A study by Rygalski et al. in 2020 showed a 29% increase in mortality for certain tumor locations when oropharyngeal surgery was delayed by more than 30 days relative to surgery performed within 30 days. Additionally, the patients who had a TTS longer than 67 days were independently predicted to experience worse overall survival than those with a TTS of 67 days or less. Rygalski et al. concluded that reasonable efforts should be made to expedite primary surgery for HNSCC, especially in the oropharynx and oral cavity subsites (9).

This commonly known relationship between time, tumor progression, and tumor survival has led to a recommendation for HNSCC treatment by Lauritzen et al. in collaboration with the Danish Head and Neck Cancer Group: 21 calendar days for diagnosis; 7 or 11 days for the planning of surgery or radiotherapy, respectively, and therefore, a total of 28 or 32 calendar days from suspicion of cancer to initiation of surgery or radiotherapy (10).

The planning of surgery, which should be performed within 7 days, includes aspects of patient-specific tumor therapy or patient-specific reconstruction of tumor therapy-induced hard and soft tissue defects. HNSCC of the alveolar crest or mouth floor, for example, can lead to partial resection of the mandible. State of the art therapy of mandibular defects nowadays includes the use of patient-specific implants to reconstruct the mandible, with or without bone grafts (11, 12). Patient-specific implants are usually planned through interactions between medical engineers and surgeons. This interaction is time-consuming and can be interrupted by systematic or communication errors, causing this complex process to extend the postulated 7 days between diagnosis and the start of surgical therapy (13). Another potential disadvantage of the patient-specific reconstruction technique is the difficulty in adapting to situations in which the intraoperative surgical plan changes (e.g., positive margins on frozen section examination). Therefore, the time between surgical planning and surgery should also be minimized to avoid amplification of the tumor margins (14).

The technical aspects of producing patient-specific implants *via* selective laser melting and transport algorithms are relatively fixed and therefore cannot be accelerated significantly. To facilitate the production of patient-specific implants in less than one week, the focus must be turned to the planning process. To our knowledge, this is the first study on the influence of patient-specific implants on the preparation time of surgical tumor therapy.

Therefore, this study focused on the communication between engineers and surgeons and its immanent problems to improve the workflow in the planning process of patient-specific mandibular implants in a time-efficient manner. The investigators hypothesized that the level of training of engineers and complexity of planning would influence the duration of the overall process. The specific aims of this study were as follows: 1)

Abbreviations: 3D, three-dimensional; CBCT, cone-beam computed tomography; CT, computed tomography; HNSCC, head and neck squamous cell carcinoma; IPS, Individual Patient Solutions; TTS, time to surgery.

to evaluate communication during the planning of patient-specific mandibular implants, 2) to identify possible measures of acceleration, and 3) to determine the effect of in-house training of engineers on planning speed.

Materials and methods

This single-center, retrospective study included patients who were treated with a patient-specific mandibular implant (Individual Patient Solutions [IPS] Implants, KLS Martin Group, Tuttlingen, Germany) for continuous defects of the mandible from 2016 to 2021 at Hannover Medical School, Germany. The exclusion criteria were non-continuous defects and reconstructions requiring multiple implants, as communication in such cases was assumed to be more difficult and time-consuming regardless of the engineer's training or implant complexity. Other exclusion criteria were missing data or a lack of consent for data usage. Mandibular reconstruction with patient-specific implants was planned using the IPS Gate platform (KLS Martin Group). The IPS Gate platform is a browser-based communication tool that uses a chat function and graphic interface for asynchronous planning of patient cases.

Some medical engineers using this platform were trained within the Department of Oral and Maxillofacial Surgery at Hannover Medical School, and therefore, attended surgery and gained insight into the surgeon's needs. These medical engineers are categorized as "trained." Other engineers were trained at the company without further exposure with the medical side of patient-specific implants. These medical engineers were categorized as "trained" or "untrained."

Cases were also grouped as per the level of planning complexity. Patient-specific implants resembling conventional mandibular reconstruction plates were considered simple (Figure 1), whereas implants with a Y-shaped fixation at the mandibular ramus, implants reconstructing the chin area, and implants with additional retention hooks were considered complex (Figure 2).

Variables

Training status (whether additional training was completed in the hospital or not) and implant complexity were regarded as predictor variables. The total duration of communication (time in days from the first to last message) was quantitatively recorded as the primary outcome variable. The secondary outcome variables were the need to postpone the planned operation, problems in the planning process, length of the messages (number of words per message), need for additional synchronous communication (yes/no), and need for changes to the original design (yes/no). As general patient information (age, sex) is irrelevant to engineers, these third category variables were not assessed in this study.

Data collection

The chat logs saved on the IPS Gate platform were retrospectively evaluated. These include the total duration of communication, message length, and response time. The complexity of the implant was assessed based on standard triangle language files created during planning. Finally, the causes of communication problems were identified through qualitative evaluation.

Data analysis

For group comparisons, the Mann–Whitney rank sum test was chosen because of the failure of the normality test (Shapiro-Wilk test). The chi-square test was used to compare categorical data. Statistical significance was set at $P < 0.05$, based on a 95% confidence interval. Statistical analyses were performed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) and SigmaPlot 13.0 (Systat Software, Palo Alto, CA, USA).

Ethics approval statement

This study was approved by the Institutional Ethics Committee of the investigators' institution (reference number 9403_BO_K_2020) and was conducted in accordance with the Declaration of Helsinki. The participants provided written informed consent to participate in this study.

Results

A total of 83 patients were included in this study. The mean duration of communication was 14.05 ± 13.58 days. On average, 355.65 ± 251.61 words were written, with the engineers writing significantly more per message than the surgeons (200.23 ± 172.00 words vs. 155.42 ± 100.13 words; P = .001). The mean total duration of communication was not significantly shorter for simple patient-specific implants than for complex patient-specific implants (17.25 ± 15.77 days vs 12.97 ± 12.73 days; P = .337; Figure 3). For all cases, there was no statistically significant difference in the mean total duration of communication depending on the engineer's training status (untrained 14.56 ± 14.51 days vs. trained 12.92. ± 11.21 days; P = .606; Figure 3). In 28 cases (33.73%), additional synchronous communication (web meetings or telephone calls) was required for clarification. There were no statistically significant differences

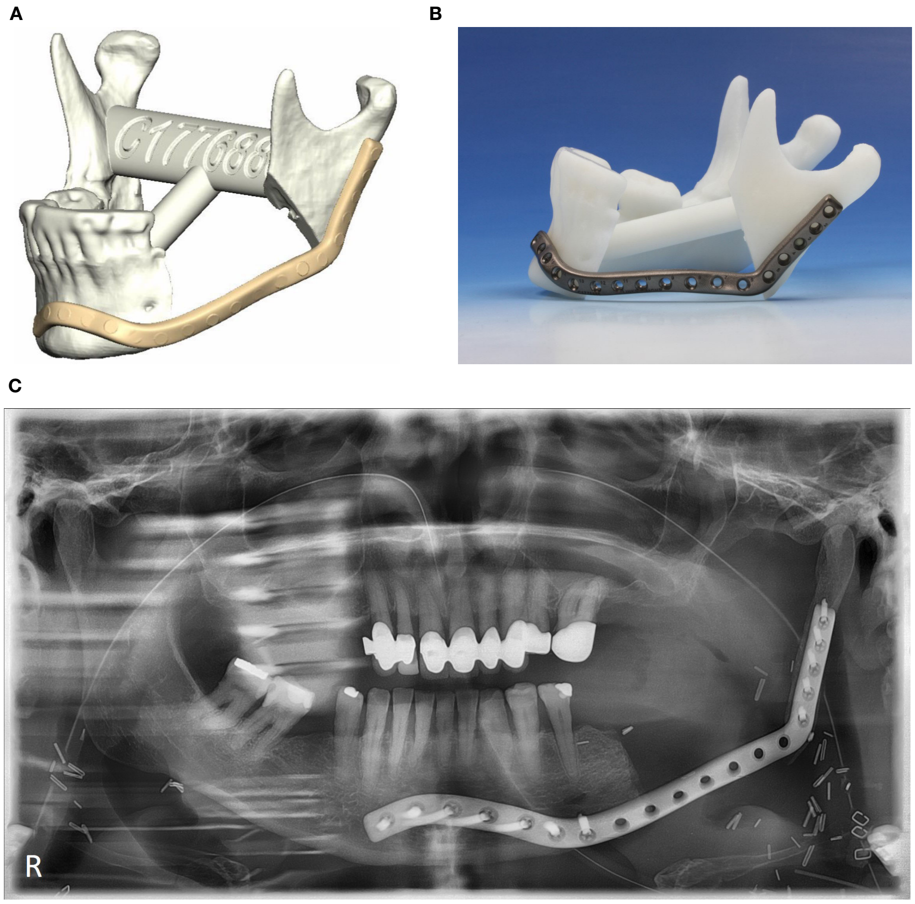

FIGURE 1
Non-complex patient-specific implants. **(A)** Digital planning, **(B)** patient-specific implant on plastic model, **(C)** postoperative orthopantomogram.

in the need for additional synchronal communication depending on the engineers' training status or the level of planning complexity (P = .0.700, P = .685; Table 1). However, a difference became evident when the need to postpone the planned operation was considered. In 16 of 83 cases (19.23%), the initial planned deadline for the operation could not be met. Of the 16 patients, 15 (93.75%) had complex patient-specific implants. Therefore, surgery for patients with a complex patient-specific implant had a significantly higher chance of being postponed than for those with simple patient-specific implants (P = 0.001; Table 1). However, the chance of postponing the operation was not significantly influenced by the training status of the engineer (P = 0.227; Table 1). The most frequent cause of communication problems was insufficient three-dimensional (3D) datasets (computed tomography [CT] or cone-beam CT [CBCT]). Specifically, either the slices were too thick or the relevant areas were not visible; such scans were unsuitable for implant planning (10.84%, n = 9). Cases planned based on CBCT were surprisingly less represented in this group than cases planned based on CT (two vs. six). Other causes were difficulty in making an appointment for synchronous communication (7.23%, n = 6) and changes in the engineer or surgeon involved (3.661%, n = 3). In almost three-quarters of the cases (72.29%, n = 60), the clinician requested changes to the initial plan. These requests were not significantly influenced by the complexity or training level of the planner (P = 0.16, P = 0.52, respectively; Table 1).

Discussion

In this study, we investigated engineer-surgeon communication while planning patient-specific implants in malignant tumor cases and its impacts on the TTS.

Surprisingly, the duration of communication was not significantly influenced by predictor variables (additional training and implant complexity). Therefore, it can be concluded that the overall time to create patient-specific implants in HNSCC cases involving the mandible is not dependent on the design of the implant or training status of the

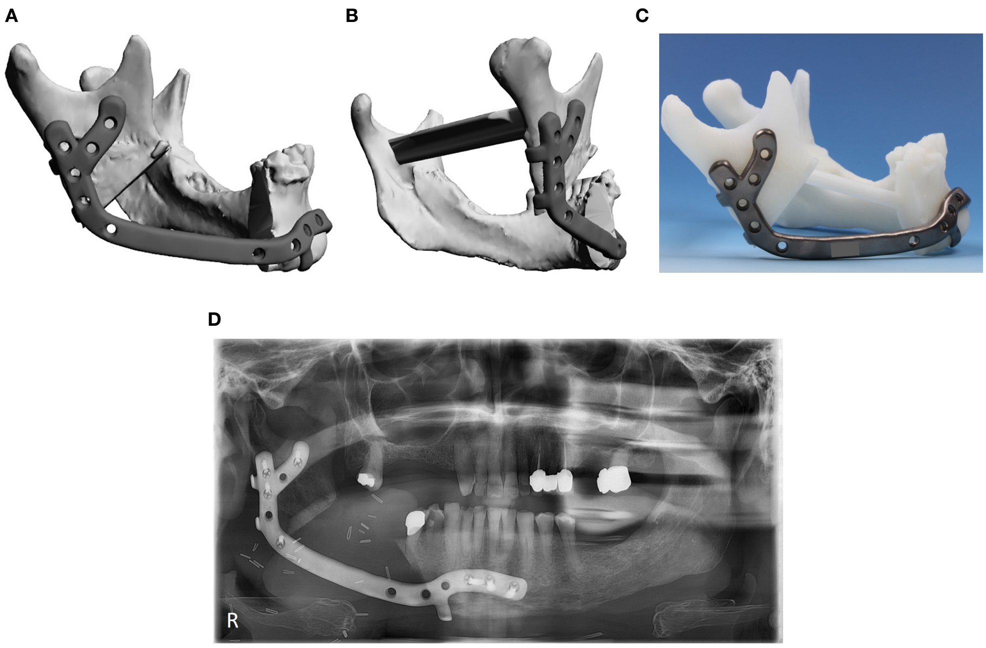

FIGURE 2
Complex patient-specific implant. **(A)** digital planning lateral view, **(B)** digital planning posterior-lateral view, **(C)** patient-specific implant on plastic model, **(D)** postoperative orthopantomogram.

involved engineer. Nevertheless, the average total planning time (approximately 14 days) was much longer than expected and far too long compared to the desired 7 days of surgical planning time. A closer look at the cases showed that a delay in the operation was necessary; in other words, the TTS was increased, and it became obvious that the complexity of the implant is not only an influence but also plays a crucial role. Of the 16 delayed cases, 15 involved complex patient-specific implants. Therefore, the risk for

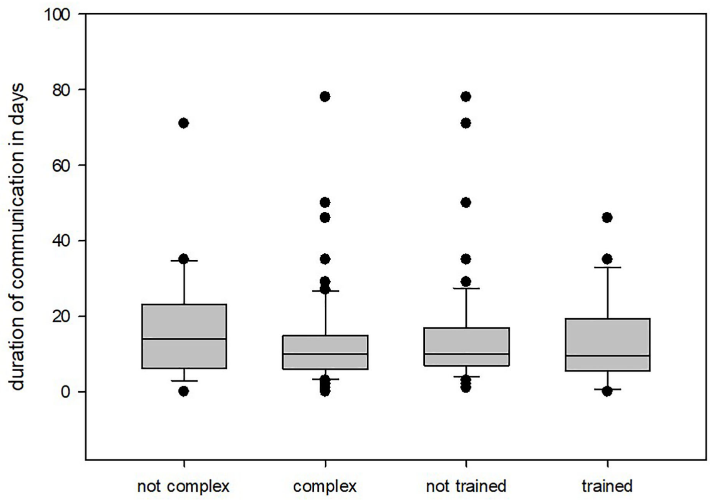

FIGURE 3
Duration of communication depending on engineer training or implant complexity.

TABLE 1 Outcomes depending on implant complexity and engineer training status.

Implant design	Synchronous planning	Asynchronous planning	Design change	No design change	Postponed operation	Operation on time
Complex	22	14	48	15	15	48
Not complex	6	41	12	8	1	19
P	0.700*		0.524*		**0.001***	
Engineer training status	Synchronous planning	Asynchronous planning	Design change	No design change	Postponed operation	Operation on time
Trained	8	18	20	6	3	23
Untrained	20	37	40	17	13	44
P	0.685*		0.524*		0.227*	

*chi-square test.

increased TTS was significantly linked to the complexity of the patient-specific implant (P = .001).

In another study performed by our group involving patient-specific orbital implants, we observed that in-house engineer training saved time during the planning process (13). Even if the present study does not support this claim, one conclusion can be drawn from both studies: implant complexity influences the planning process and TTS. Since the TTS is crucial for surgical treatment of malignancies, it is of utmost importance to avoid any unnecessary delay.

One possibility for speeding up the process of patient-specific implant creation without losing its benefits is the standardization of individualization. In other words, standardize all possible factors while maintaining patient-specific features. For example, keep the fixation areas to the bony defect margins patient-specific and follow standards concerning implant thickness and screw diameters. This standardization should include not only the implant itself, but also the planning process.

Yang et al. developed a surgeon-driven standard design process to optimize the planning process and concluded that the development of a surgeon-friendly software, preferably with an artificial intelligence algorithm, as well as the optimization of biomechanical properties and post-processing of 3D-printed surgical plates is necessary to standardize this fast-developing technology (15).

Other possibilities for optimizing the workflow in patient-specific treatment of malignancies would include the implementation of standards concerning imaging and 3D-data processing or deep learning algorithms (16). These standards or improvements should focus on our opinion on better software solutions using artificial intelligence and on the quality of 3D-imaging. The quality of 3D-imaging's simple imaging parameters, such as the distance between two sectional views, seems to be more important than the type of imaging, such as CT or CBCT. This assumption is supported by the fact that, in our patient cohort, more image quality problems occurred in cases planned based on CT than on CBCT. To date, some companies still refuse to plant patient-specific implants based on CBCT scans without any scientific reasons.

Another possibility for speeding up the planning process is to simplify patient-specific implants. However, this would negate the benefits of these implants, such as the reconstruction accuracy (12, 17–20), and therefore, should not be considered.

This study had some limitations, mainly the retrospective nature of the evaluation. In addition, there could be confounding factors (e.g., holiday time) that influenced the communication duration, which we were unable to address. Furthermore, the sample size was small; therefore, a multicenter study may provide a more profound analysis of the influence of patient-specific implant creation on the TTS.

In conclusion, the process of patient-specific implant creation should be accelerated *via* standardization of the implant design and planning process. This can be achieved by using or developing modern software solutions for the planning process by addressing computer-aided design and communication pathways. In addition, the 3D-imaging quality plays an important role in the planning process and should, therefore, be predefined in coordination between surgeon and engineer to meet diagnostic and patient-specific treatment needs. If it is not possible to produce the patient-specific implant in a timely manner, it is often possible to change from a patient-specific treatment to a standard surgical procedure without a customized implant. Since TTS is a crucial factor in surgical tumor therapy that influences mortality, efforts should be made to keep it as low as possible.

Data availability statement

The datasets presented in this article are not readily available because the raw data includes patient information and cannot be shared. Requests to access the datasets should be directed to SS, spalthoff.simon@mh-hannover.de.

Author contributions

SS: Conceptualization, Methodology, Statistics, Writing – Original Draft. NN-R: Investigation, Methodology, Statistics, Writing – Original Draft. BR: Conceptualization, Methodology, Writing – Original Draft. PJ: Methodology, Writing – Review & Editing. FL: Writing – Review & Editing. N-CG and PK: Conceptualization, Project Administration, Writing – Review & Editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effect of fetoscopic laser surgery on the placental characteristics and birth-weight discordance of twins with twin-to-twin transfusion syndrome

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Objective: This study explored the effect of fetoscopic laser surgery on the placental structure and birth-weight discordance of twin-to-twin transfusion syndrome (TTTS).

Methods: A retrospective cohort study was conducted in TTTS patients who were admitted to the Peking University Third Hospital between April 2014 and April 2020. The patients were divided into two groups: laser group and control group. Placentas with twin survival were injected, and pregnancy outcomes and placental characteristics of the two groups were compared. The correlation between the birth-weight discordance and placental characteristics in each group was analyzed.

Results: The gestational age at first diagnosis in the laser group was significantly smaller than that in the control group (21.6 ± 2.8 weeks vs. 27.7 ± 3.0 weeks, $p < 0.001$). The proportion of patients with TTTS stage-I in the laser group was significantly lower than the control group (9.4 vs. 64.0%, $p < 0.001$). The gestational age at delivery in the laser group was significantly larger than that in the control group (33.6 ± 2.1 weeks vs. 31.4 ± 2.5 weeks, $p = 0.001$). In the laser group, the birth-weight discordance ratio was positively correlated with the placental territory discordance ratio (Spearman coefficient = 0.556; $p = 0.001$).

Conclusion: The birth-weight discordance is positively correlated with placental territory discordance in TTTS patients after FLS.

KEYWORDS

twin-to-twin transfusion syndrome, birth-weight, placental territory, anastomoses, fetoscopic laser surgery

Background

Twin-to-twin transfusion syndrome (TTTS), as a specific complication of monochorionic twins, accounts for 10–15% of monochorionic twin pregnancies (1, 2). Previous studies have demonstrated that the placental characteristics, in addition to placental anastomoses, placental share, and umbilical cord insertion sites affect the treatment and prognosis of TTTS. Although the mechanism involved in the initiation of blood transfusion between two fetuses remains elusive, and it is currently considered that the superficial artery-vein (AV) anastomoses of the monochorionic placenta serve as the anatomical basis of TTTS (3). Therefore, the first-line treatment for TTTS is fetoscopic laser surgery (FLS) that causes superficial placental anastomoses to coagulate, thus blocking the blood flow and exchange of blood between the two fetuses. Previous studies have confirmed that FLS can significantly reduce the incidences of intrauterine fetal death and neonatal mortality of TTTS and improve the pregnancy outcome (4). However, no related studies have been published on the birth-weight discordance of two neonates in TTTS patients after FLS; therefore, the influencing factors remain to be ascertained. As a complex twin pregnancy resulting from the special placenta of monochorionic twins, its pathogenesis, diagnosis, treatment, and prognosis, with due consideration to the structure of the placenta, need to be discussed (3, 5–7). This study attempted to compare the placental characteristics of TTTS with conservative treatment and FLS treatment as well as to explore the correlation between the placental characteristics and the birth-weight discordance of two neonates in TTTS patients after FLS treatment.

Methods

This study was based on a retrospective analysis of the TTTS patients admitted to Peking University Third Hospital between April 2014 and April 2020. The patients who chose to terminate the pregnancy out of the fear of the negative neonatal outcome, those who delivered the baby/ies at the local hospital, those who had one or two fetuses intrauterine death, and those with placenta breakage after the delivery failed to perfusion were excluded from the study. The remaining patients with two live neonates were divided into the control and laser treatment groups. The control group included patients in whom the operation could not be performed because of the factors such as the gestational age, patients who underwent conservative treatment at the TTTS Stage I, or those patients received reduction in the amniotic fluid. The laser-treatment group included patients who received FLS treatment. The approval of the ethics committee of the hospital was sought for procuring the placenta of the patients after delivery with their informed consent, on which perfusion was performed later. To investigate the correlation between the birth-weight discordance and placental characteristics in each group, the placentas of TTTS patients who delivered live twins were examined.

TTTS diagnostic criteria: Ultrasound examination of women with monochorionic twin pregnancies based on the polyhydramnios-oligohydramnios sequence (8), which means that, before 20 weeks, the maximum vertical pocket (MVP) of the recipient fetus was $\geq$ 8 cm, while the MVP of the donor fetus was $\leq$ 2 cm. After 20 weeks, the MVP of the recipient fetus was $\geq$ 10 cm, while the MVP of the donor fetus was $\leq$ 2 cm. According to the Quintero staging criteria (8), TTTS was divided into five stages, as follows: stage I: the bladder of the donor fetus is visible; stage II: the bladder of the donor fetus is no longer visible; stage III: the presence of any fetus showing abnormal blood flow; stage IV: the recipient fetus showing edema; and stage V: any or all fetuses are dead.

After seeking approval of the ethics committee and the medical record department, we employed the medical record system to collect the clinical data included the age of the patients, complications associated with their pregnancy, the gestational age when TTTS was diagnosed, therapeutic regime, the gestational age of the fetus at the time of delivery, and the birth weight of the two neonates. Birth weight discordance ratio = (weight of heavier neonate − weight of lighter neonate)/weight of heavier neonate.

The placenta of the patients with monochorionic twins after delivery were examined in the hospital to verify the diagnosis. According to the protocol published by our center and past studies (9–11), all intact monochorionic placentas were perfused with the pigment to examine the placental anastomoses, placental portions, and insertion of the umbilical cord (**Figure 1A**). Briefly, after delivery, the amniotic membranes were removed, and each umbilical cord was cut 5 cm from its placental insertion site. The placental vessels were gently squeezed to eliminate the blood clots. The umbilical vein and one of the umbilical arteries were then cannulated and clamped with an intravenous catheter. The placental vessels were injected with saline until all the branches were visible. The last step was performed using four 20-mL syringes, each filled with a distinctively colored dye (i.e., white, green, yellow, and red) to visualize the umbilical cord arteries and veins of the two fetuses. Images of the injected placentas were placed vertically under a grid harboring a scale were captured with a high-resolution digital camera.

We measured and recorded the features indicating superficial placenta that included the type, number, diameter of anastomoses, the placental share between the two fetuses, and the distance between the umbilical cord insertion points. The diameter of artery–artery (AA) and vein–vein (VV)

Abbreviations: FLS, fetoscopic laser surgery; TTTS, twin-to-twin transfusion syndrome; AA, artery-to-artery; AV, artery-to-vein; VV, vein-to-vein.

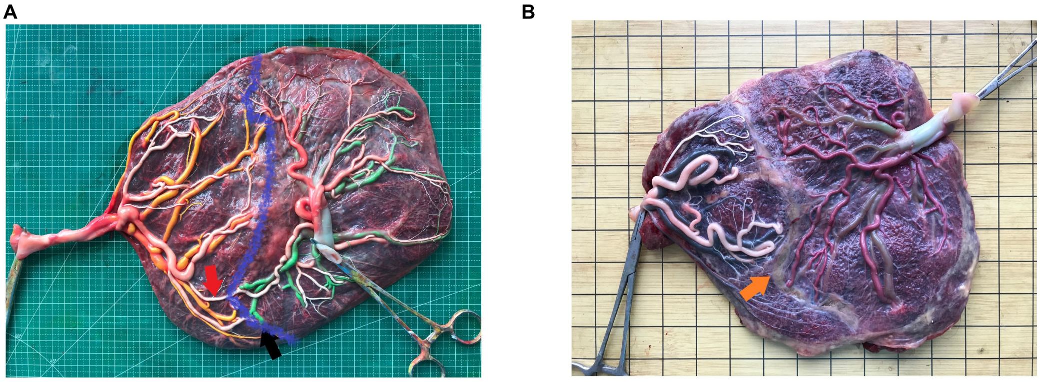

FIGURE 1
An image of the placenta after dye injection **(A)** placenta without laser surgery, red arrow, artery-artery anastomosis, black arrow, artery-vein anastomosis, blue curve, placental separate line; **(B)** placental with laser surgery, orange arrow, laser coagulation line.

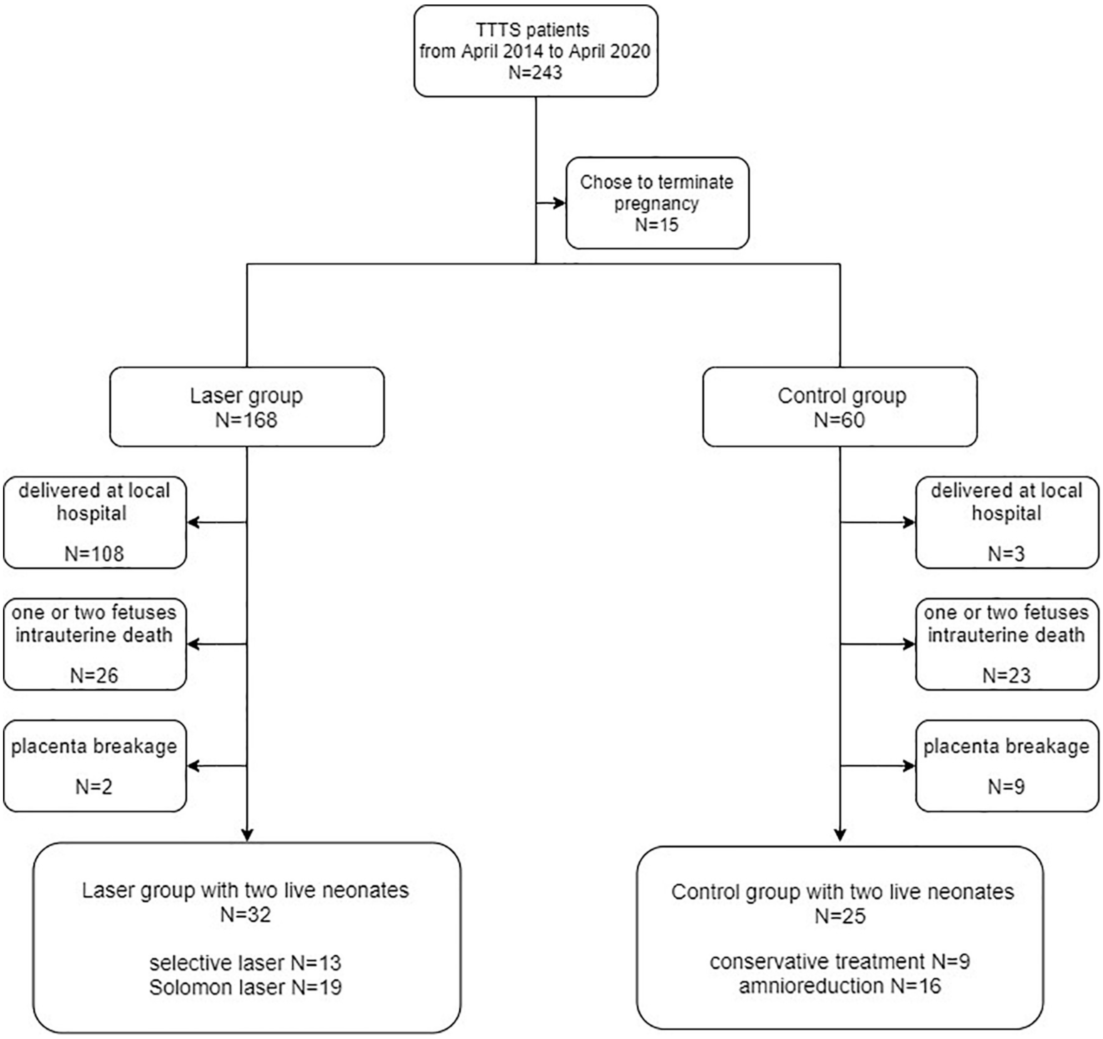

FIGURE 2
Flowcharts depicting the patient inclusion criteria.

anastomoses was measured in the narrowest part. Deep arteriovenous (AV) anastomoses were defined as sites where an unpaired artery from one twin had penetrated the chorionic plate within < 1.0 mm of an unpaired vein from the other twin and the diameter of AV anastomoses was measured on the arterial side (10). The anastomoses of the placenta after the FLS operation were residual anastomoses (**Figure 1B**). The attachment sites of the umbilical cord included marginal attachment, velamentous attachment, and central attachment. To avoid the influence of individual differences on the size of the placenta, the umbilical cord insertion ratio was determined, that is, the distance between two umbilical cord insertion points/maximum placental diameter. The umbilical cord insertion distance was defined as the distance between the centers of two umbilical cord insertion sites (9–11). The maximum placental diameter was the largest range of placental parenchyma edges (10).The placental territory of the two fetuses was determined on the basis of the sites of anastomoses and was measured using the ImageJ 1.51j8 software for windows (National Institute of Health, USA). The placental territory discordance ratio = (large placental territory − small placental territory)/large placental territory.

The SPSS 24.0 software was used to analyze the data. The data were expressed as mean ± standard deviation or median (maximum, minimum). The data was analyzed to determine whether it was normally distributed. If the data was found to be normally distributed, an independent sample *t*-test and Pearson's correlational analysis were performed, and the mean ± standard deviation was used as the statistical measure to express the data. In case the data did not show normal distribution, Mann–Whitney test, a non-parametric test, and Spearman correlational analysis were performed, and the median and range were used for expressing the data. Categorical data were compared using Chi-square test or Fisher's exact test, as deemed appropriate. $P < 0.05$ was considered to be statistically significant.

TABLE 1 The clinical features of TTTS patients between the two study groups.

Category	Laser treatment (*n* = 32)	Control (*n* = 25)	*P*-value
Age [Year, *M* (*min–max*)]	27 (24–38)	29 (23–40)	0.382
Application of assisted reproductive technology [Case (%)]	4 (12.5)	1 (4.0)	0.372
Hypertensive disorders in pregnancy [Case (%)]	2 (6.3)	1 (4.0)	1.000
Gestational diabetes [Case (%)]	4 (12.5)	2 (8.0)	0.686
The gestational age at the first diagnosis of TTTS (±*s*)	21.6 ± 2.8	27.7 ± 3.0	< 0.001
Quintero stage [Case (%)]			
Stage I	3 (9.4)	16 (64.0)	< 0.001
Stage II	12 (37.5)	2 (8.0)	0.052
Stage III	10 (31.3)	1 (4.0)	0.064
Stage IV	7 (21.9)	6 (24.0)	1.000
Gestational age of delivery	33.6 ± 2.1	31.4 ± 2.5	0.001
The birth weight of the recipient fetus (g)	2076 ± 438	1792 ± 599	0.044
Neonatal asphyxia [Case (%)]	5 (15.6)	6 (24.0)	0.508
The birth weight of the donor fetus (g)	1645 ± 477	1334 ± 393	0.011
Neonatal asphyxia [Case (%)]	4 (12.5)	9 (36.0)	0.056
Birth weight discordance ratio	0.23 (0.01, 0.61)	0.24 (0.01, 0.57)	0.426

M (*min–max*) represent the median (minimum–maximum).

Results

A total of 243 TTTS patients were admitted to the Obstetrics Department of Peking University Third Hospital from April 2014 to April 2020, among whom 15 patients opted to terminate their pregnancies. Moreover, 168 patients were treated with laser and 60 underwent a conservative treatment, therapeutic amniocentesis. The patients who delivered the baby/ies at other hospitals, those who had one or two fetuses intrauterine death, and those with placenta breakage after the delivery failed to perfusion were excluded from the study. Retrospective analysis of the data of 57 TTTS patients, including 32 patients in the laser group and 25 patients in the control group, was performed. **Figure 2** illustrates the details regarding the patients included in the study and the criteria for inclusion.

Comparison of the clinical data of the two groups of TTTS patients has been illustrated in **Table 1**. The gestational age at the preliminary diagnosis of TTTS in the laser treatment group was significantly lower than that in the control group. The difference between the two groups with respect to the Quintero stages was statistically significant. The comparison of the two groups revealed that the proportion of stage I in the laser treatment group was significantly lower than that in the control group ($P < 0.001$) and that there was no significant difference between the two groups with regard to the respective stages: Stage II, III, and IV ($P = 0.052/0.064/1.000$, respectively). The gestational age at the time of delivery, the birth weight of the recipient fetus, and the birth weight of the donor fetus in the laser treatment group were significantly higher than those in the control group.

The placental characteristics of the patients in the two groups have been illustrated in **Table 2**. The correlations between birth weight discordance ratio and the total diameter of AA anastomoses in the superficial placenta, the total diameter of AV anastomoses, the total diameter of VV anastomoses, placental territory discordance ratio, and umbilical cord insertion ratio in each group were analyzed respectively in **Table 3**. The results demonstrated that the birth weight discordance ratio was positively correlated with the placental territory discordance ratio in the laser treatment group (Spearman coefficient = 0.556). There was no positive linear correlation between the birth-weight discordance ratio and the indicators of placental structure in the control group.

TABLE 2 The placental characteristics of TTTS patients between the two study groups.

Category	Laser treatment (n = 32)	Control (n = 25)	P-value
AA anastomoses*			
The prevalence rate [Case (%)]	7 (21.9)	8 (32.0)	0.546
The total number [Count, M (min–max)]	1 (1,1)	1 (1,1)	1.000
The total diameter [mm, M (min–max)]	3.6 (0.7,5.1)	2.0 (0.5,5.3)	0.094
AV anastomoses*			
The prevalence rate [Case (%)]	9 (28.1)	24 (96.0)	< 0.001
The total number [Count, M (min–max)]	4 (1,9)	5 (1,13)	0.207
The total diameter [mm, M (min–max)]	2.1 (1.1,7.4)	5.5 (1.3,15.3)	0.018
VV anastomoses*			
The prevalence rate [Case (%)]	9 (28.1)	6 (24.0)	0.771
The total number [Count, M (min–max)]	1 (1, 1)	1 (1,2)	0.607
The total diameter [mm, M (min–max)]	3.0 (0.7,6.4)	1.6 (1.0,6.5)	0.955
The total number of all types of anastomoses*	0 (0,11)	6 (2,14)	< 0.001
The total diameter of all types of anastomoses*	0 (0,16.8)	6.1 (1.7,18.6)	< 0.001
Placental territory discordance ratio [M (min–max)]	0.39 (0.02,0.67)	0.25 (0.02,0.75)	0.236
Velamentous umbilical insertion [Case (%)]	6 (18.8)	3 (12.0)	0.717
Umbilical cord insertion ratio	0.61 ± 0.20	0.66 ± 0.17	0.377
Birth weight discordant ratio/placental territory ratio	1.55 (0.17,17.29)	1.26 (0.03,15.17)	0.074

M (*min–max*) represent the median (minimum–maximum), *Residual vascular anastomosis for laser-treatment group.

Discussion

The pathogenesis of TTTS is closely associated with the placental structure (7). Previous studies have confirmed that the shared placenta, vascular anastomoses, and umbilical cord attachment are essential factors that affect the incidence of complex complications and prognosis in monochorionic twins (5, 12–15). Therefore, complex twins are considered a placental disease. First, the study explored the effect of fetoscopic laser surgery on the placental characteristics and birth-weight discordance of twins with twin-to-twin transfusion syndrome.

The findings of the present study revealed that, when compared to the control group, a significant positive correlation was recorded between birth weight discordance ratio and placental territory discordance ratio in the laser treatment group (Spearman coefficient = 0.556). Lewi et al. conducted a study of 100 cases of monochorionic twin placentas without TTTS and reported that the birth weight discordance ratio was positively correlated with the placental territory discordance ratio (16). Considering that the TTTS patients were excluded from the study conducted by Lewi et al. the factors influencing the birth weight discordance in the two live births by TTTS patients, especially in those who received FLS, remained elusive. Birth weight discordance was found to be positively correlated with placental territory discordance in TTTS patients who received FLS. The findings of the present study were consistent with that of the study conducted by Lewi et al. Moreover, our study focused on TTTS patients and thus compensated for the limitations of the research conducted by Lewi et al. On the basis of these findings, it was speculated that when placental anastomoses were coagulated with successful FLS, placental sharing between the two fetuses impacted their growth. Therefore, neonatal birth weight discordance was positively correlated with placental territory discordance. The placental territory of the donor fetus is always smaller than that of the recipient fetus (17), as anastomoses from the recipient fetus to the donor fetus might compensate for the blood supply of the smaller placental territory to a certain extent in TTTS patients. Coagulation of anastomoses after fetoscopic surgery aggravates the degree of ischemia and hypoxia in the fetus with a smaller placental territory (16).

Previous studies have reported an incidence of selective intrauterine growth restriction (sIUGR) in patients with TTTS of 40–78% (18), and the incidence of intrauterine death of the fetus with growth restriction was higher in patients after FLS (18, 19). A recent study conducted in our center found that the

TABLE 3 Correlation between birth-weight discordance ratio and the placental structure characteristics in the two study groups.

			The total diameter of AA anastomoses [mm, *M* (min–max)]	The total diameter of AV anastomoses [mm, *M* (min–max)]	The total diameter of VV anastomoses [mm, *M* (min–max)]	Placental territory discordance ratio	Distance ratio of umbilical cordattachment points
Birth weight discordance ratio	Laser treatment group 0.23 (0.01,0.61)	Figures	3.6 (0.7,5.1)	2.1 (1.1,7.4)	3.0 (0.7,6.4)	0.39 (0.02,0.67)	0.62 (0.15,1.00)
		Spearman coefficient	−0.468	0.248	−0.067	0.556	−0.250
		P-value	0.289	0.171	0.865	0.001	0.167
	Control group 0.24 (0.01,0.57)	Figures	2.0 (0.5,5.3)	5.5 (1.3,15.3)	1.6 (1.0,6.5)	0.25 (0.02,0.75)	0.65 (0.38,1.00)
		Spearman coefficient	0.551	−0.085	0.314	0.329	0.099
		P-value	0.157	0.686	0.544	0.108	0.638

M (*min–max*) represent the median (minimum–maximum).

occurrence of thick placental AA anastomoses in TTTS with sIUGR was significantly higher than in those with only TTTS (20). The thick AA anastomoses could partially supplement the blood supply to the growth-restricted fetus. It was thus speculated that the coagulation of these thick AA anastomoses by FLS aggravates the degree of ischemia and hypoxia in fetuses suffering from restricted growth, which led to intrauterine death of the fetuses. However, the fetoscopic surgery creates a distinct separation of the two fetal vascular territories on the surface of the placenta (4). FLS can significantly improve the pregnancy and neonatal outcome of TTTS, which is consistent with our results and the finding of relevant past studies. Placental characteristics affect the prognosis of TTTS. The lower prevalence of AA anastomoses could potentially lead to these conflicting outcomes (21). TTTS is caused by unbalanced vascular anastomoses within the placenta. AV anastomosis is believed to act as the foundation of TTTS. AA anastomosis is believed to act as a protective factor against TTTS occurrence (21, 22). There was at least one AV anastomosis on almost all TTTS placentas, whereas past studies have revealed a low prevalence of AA anastomoses in the TTTS placentas (3). The incidence of AV anastomoses was 95.8%, while that of AA anastomoses was 33.3% (11). Therefore, it was suggested that further study should be undertaken to explore whether the thick AA anastomoses of TTTS patients with sIUGR should be preserved during FLS.

For the indication and timing of FLS in TTTS patients, most studies suggested that 16–26 weeks were suitable for FLS of TTTS patients in Stages II–IV (2). Our study indicated that the proportion of patients in Stage I in the laser treatment group was significantly lower than that in the control group and that the gestational age of the fetus in the laser treatment group at the time when the disease was first diagnosed was lower than that in the control group. This finding was consistent with the findings of the studies conducted earlier. Numerous studies have confirmed that FLS can significantly improve the pregnancy outcome of TTTS patients (4). The results of the present study also found that the gestational age at the time of delivery, the birth weight of the recipient fetus, and the birth weight of the donor fetus in the laser treatment group were significantly higher than those in the control group, which is consistent with the finding of the studies conducted earlier (4).

The study also posed some limitations. First, most of the patients returned to the local hospital for delivery after undergoing FLS in our hospital. Second, the sample size of this study was relatively small and hence the probability of statistical bias could not be ignored. Third, because of a significant time span, two different methods of FLS, namely selective laser coagulation and Solomon operation were performed during this period in our hospital. As the effects of the two methods could not be compared, considering the small sample size, the possibility of statistical deviation could not be ignored.

Conclusion

In summary, the findings of the present study indicated that birth weight discordance between two live births was positively correlated with the placental territory discordance in TTTS patients after FLS.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Peking University Third Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XW and LL conceived the study concept and wrote the manuscript. LL and PY collected the data and contributed to data analysis. YZ contributed to data consultation and study guidance. YW contributed to manuscript revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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