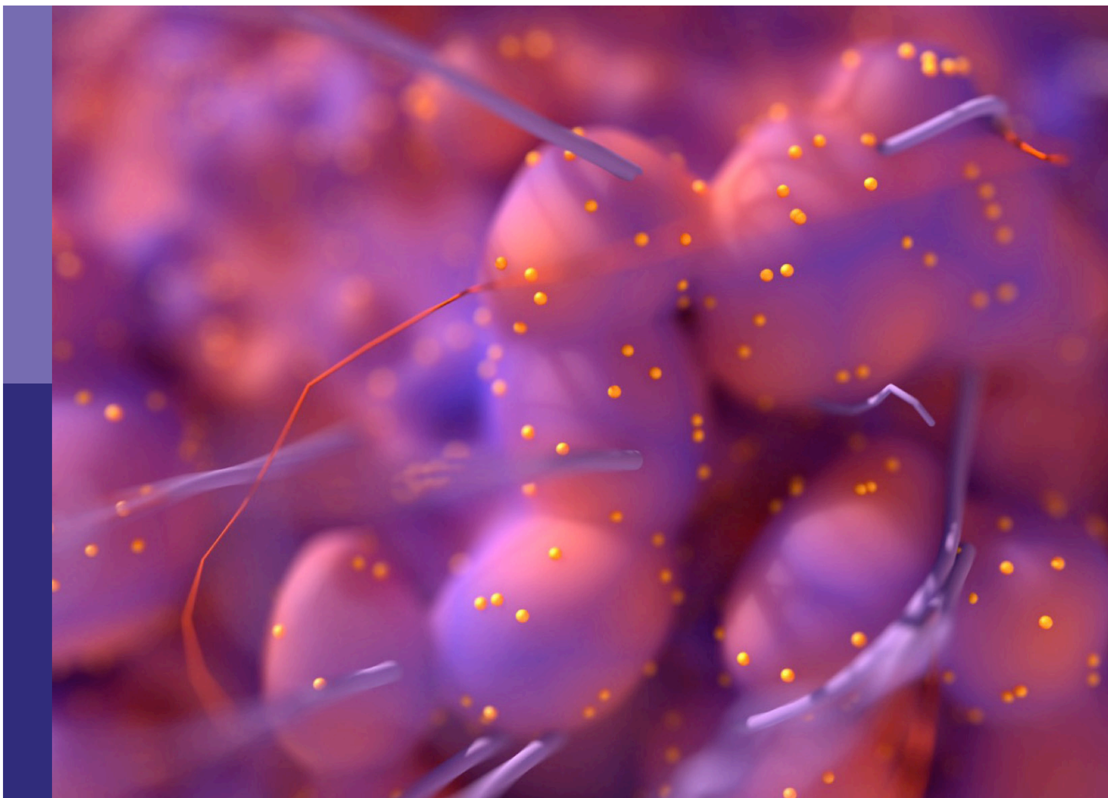
frontiers | Research Topics

Interdisciplinary surgical strategies for complex tumor defects in modern oncology

Edited by
Raymund E. Horch, Andreas Arkudas, Marco Rainer Kesting, Stefan Fichtner-Feigl and Stephan Kersting

Published in
Frontiers in Oncology



ISSN 1664-8714
ISBN 978-2-83251-751-2
DOI 10.3389/978-2-83251-751-2

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Interdisciplinary surgical strategies for complex tumor defects in modern oncology

Topic editors

Raymund E. Horch — University Hospital Erlangen, Germany
Andreas Arkudas — University Hospital Erlangen, Germany
Marco Rainer Kesting — University Hospital Erlangen, Germany
Stefan Fichtner-Feigl — Klinik für Allgemeine und Viszerale Chirurgie, Freiburger Universitätsklinikum, Germany
Stephan Kersting — University Hospital Erlangen, Germany

Citation

Horch, R. E., Arkudas, A., Kesting, M. R., Fichtner-Feigl, S., Kersting, S., eds. (2023). *Interdisciplinary surgical strategies for complex tumor defects in modern oncology*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83251-751-2

Table of contents

frontiers | Frontiers in Oncology

TYPE Editorial
PUBLISHED 10 February 2023
DOI 10.3389/fonc.2023.1146719

Check for updates

OPEN ACCESS

EDITED AND REVIEWED BY
Aali Jan Sheen,
Manchester Royal Infirmary,
United Kingdom

*CORRESPONDENCE
R. E. Horch
Raymund.Horch@uk-erlangen.de

SPECIALTY SECTION
This article was submitted to
Surgical Oncology,
a section of the journal
Frontiers in Oncology

RECEIVED 17 January 2023
ACCEPTED 25 January 2023
PUBLISHED 10 February 2023

CITATION
Horch RE, Kesting MR, Kersting S,
Fichtner-Feigl S and Arkudas A (2023)
Editorial: Interdisciplinary surgical
strategies for complex tumor defects
in modern oncology.
Front. Oncol. 13:1146719.
doi: 10.3389/fonc.2023.1146719

Editorial: Interdisciplinary surgical strategies for complex tumor defects in modern oncology

R. E. Horch[1]*, M. R. Kesting[2], S. Kersting[3], S. Fichtner-Feigl[4] and A. Arkudas[1]

[1]Department of Plastic and Hand Surgery, University Hospital Erlangen, Erlangen, Germany, [2]Department of Oral and Maxillofacial Surgery, University Hospital Erlangen, Erlangen, Germany, [3]Universitätsmedizin Greifswald, Greifswald, Germany, [4]Department of General and Visceral Surgery, University of Freiburg Medical Center, Freiburg, Germany

KEYWORDS

cancer surgery, interdisciplinary surgical approaches, surgical tumor reconstruction, outcome, quality of life

Editorial on the Research Topic
Interdisciplinary surgical strategies for complex tumor defects in modern oncology

Interdisciplinarity is a key element for modern cancer treatment. This is not only true for the interaction between various medical disciplines, but also a necessity due to the everlasting subspecialization within the field of surgery itself. Increasing surgical capabilities and technical advances within all specialized surgical disciplines have dramatically changed the face of modern surgical approaches to cure patients with malignant diseases (1).

While basically until the middle of the last century the sole removal of malignant tumors in any part of the human body was a challenge that had to be mastered by general surgeons on their own, it is now common sense and practice that specialized surgeons join the effort and come together to remove even advanced tumors and allow for safe simultaneous reconstructions (2–4). The various approaches depend on the extent of the tumor, infestation of vital structures, invovlement of neighbouring anatomic structures, presence of metastases, tissue conditions after neoadjuvant therapies etc.

Based on these newer concepts today even tumors which had hitherto been deemed to be unresectable or inoperable, may now be successfully operated upon. At the same time the collaboration of the resectional oncologic surgeon with reconstructive surgeons not only allows more radical tumor surgery but also can aid to reduce surgical complications (5) and enhances the remaining quality of life (QOL) for such patients (6, Peng et al.). Also, even when a tumor cannot be completely cured, interdisciplinary surgery can offer improve the quality of life in palliative situations (7). Pictures of decaying and unpleasant smelling tissue due to ruptured progressing tumors that hinder social contacts and lead to isolation hopefully belong to the past. This is another prospect of interdisciplinarity that yet has to be exploited whenever indicated.

Not only has the practice of surgery changed and undergone a significant evolution over the past 4 decades [e.g., introduction of new procedures and technological advancements (8, 9)], but newer specialties and subspecialties within surgery and surgical oncology have been created based on narrower anatomic regions and the application of increasingly advanced and specific technologies (10) (Zhang et al.; Gallina et al.). By their very nature, these growing surgical specialties and subspecialties tend to be consolidated in academic centers and larger urban regions where most teaching and training occurs (Lu et al.).

While on the one hand technical advances such as the evolution of minimally invasive surgery has been an important milestone in the field of surgical oncology or which has almost totally globally replaced open gastrectomy in treating gastric cancer, the individual knowledge of technically advanced instruments and tools, including high defintion imaging techniques is continuousy contributing to push the limits of possible resections and reconstructions forward over the course of the 20th and 21st century, based largely on the focus on specific organ systems or anatomic regions or specific surgical techniques (Cianci et al.). By integrating various surgical disciplines into tumor surgery more radical tumor resections can therefore be more safely performed and interdisciplinary reconstructions optimize the outcome of the individual patient`s treatment along with increased quality of life despite radical and oncologically sufficent cancer surgery.

The special issue comprises relevant hot topics and variants of interdisciplinary surgical oncology. Chen et al. describe their approach towards primary spinal Ewing sarcoma (ES)/peripheral primitive neuroectodermal tumors (pPNETs). This entities are extremely rare, and the current understanding of these tumors is poor. The authors aim to illustrate the clinical characteristics of primary spinal ES/pPNETs and to discuss prognostic factors by survival analysis. They show that otal en bloc resection can significantly improve PFS for primary spinal ES/pPNETs and adjuvant radiotherapy was a favorable factor for PFS in their patients. Total en bloc resection and adjuvant radiotherapy considerably improve overall survival (OS) for patients with primary spinal ES/pPNETs.

Thiele et al. compare the pros and cons of various perineal reconsturctive techniques following the resection of anorectal malignancies, which may result in extensive perineal/pelvic defects that require an interdisciplinary surgical approach involving reconstructive surgery. Their experience with either a myocutaneous gracilis flap (MGF) or a gluteal fold flap (GFF) compares the outcome regarding clinical key parameters. They conclude that MG-flaps and GF-flaps prove to be reliable and robust techniques for perineal/pelvic reconstruction. They suggest a decision-making based on distribution of adipose tissue for dead space obliteration, intraoperative patient positioning, and perforator vessel quality/distribution.

As a typical example of interdisciplinary oncologic surgery in this context the use of a transpelvic vertical rectus abdominis flap (VRAM) for relapsing or far advanced rectal and anal cancers in female patients with previous irradiation prior to the surgical resection has been described in detail by Horch et al. This interdisciplinary approach can minimize the downside of abdomino-perineal resection or exenteration especially in women when parts of the vagina need to be resected. Derived from their experince with over 300 patients receiving pelvic and perineal reconstruction with a transpelvic vertical rectus abdominis myocutaneous (tpVRAM) flap they found that the tpVRAM flap is reliably perfused and helps to reduce long term wound healing desasters in the irradiated perineal/vaginal/gluteal region (Figure 1).

Steiner et al. analyzed the interdisciplinary treatment of breast cancer which is based on the histological tumor type, the TNM classification, and the patient’s wishes. They demonstrate that following tumor resection and (neo-) adjuvant therapy strategies, breast reconstruction represents the final step in the individual interdisciplinary treatment plan. Their analysis comprises data from autologous microsurgical breast reconstruction with the deep inferior epigastric artery perforator (DIEP) or the muscle-sparing transverse rectus abdominis myocutaneous (ms-TRAM) flap. I a retrospective study focusing on the safety of autologous breast reconstruction upon mastectomy using abdominal free flaps in an academic university hospital they show a high success rate with comparatively few complications. Using preoperative computer tomography angiography, intraoperative fluorescence angiography, titanized hernia meshes for rectus sheath reconstruction, and venous coupler systems, autologous breast reconstruction with DIEP or ms-TRAM free flaps is a safe and standardized procedure in high-volume microsurgery centers.

Tan et al. studied the effectiveness and safety of the enhanced recovery after surgery (ERAS) protocol vs. traditional perioperative care programs for breast reconstruction. Ten studies were included in their meta-analysis. Their results suggest that ERAS protocols can decrease LOS and morphine equivalent dosing; therefore, they discuss that further larger, and better-quality studies that report on bleeding amount and patient satisfaction are needed to validate their findings.

Weitz et al. studied reconstructions of complex scalp after ablative resection or by post-traumatic tissue loss, that can make a

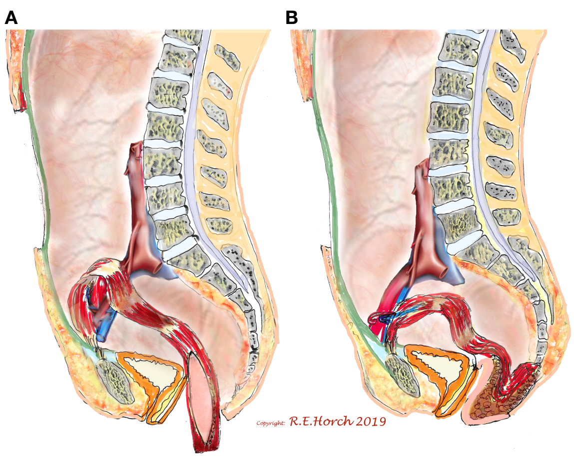


FIGURE 1
Schematic drawing of principle of vaginal wall reconstruction with pedicled transpelvic VRAM flap. **(A)** VRAM flap mobilized and routed through pelvis into resectional defect. **(B)** VRAM flap sutured to remaining anterior vaginal wall and constructing new posterior vaginal wall Horch et al.

simultaneous interdisciplinary two-team approach complicated, which is considered a major disadvantage regarding safety and operation time. Finally their data leed to the assumption that parascapular flap seem to be a good alternative for reconstruction of complex tumor defects of the scalp besides the latissimus dorsi flap. Stable long-term results and little donor site morbidity are enabled with good aesthetic outcomes and shorter operation time in an interdisciplinary two-team approach.

Cao et al. assessed the impact of enhanced recovery after surgery (ERAS) protocols in pancreaticoduodenectomy. They found no significant increase in mortality, readmission, reoperation, or delayed gastric emptying. Therefore they come to the conclusion that their analysis revealed that using ERAS protocols in pancreatic resections may help decrease the incidence of pancreatic fistula and infections. Furthermore, ERAS also reduces length of stay and cost of care. This study provides evidence for the benefit of ERAS protocols. Weber et al. describe that craniofacial osteosarcomas (COS) and extracranial osteosarcomas (EOS) show distinct clinical differences. They conclude that the reduced Gli1 expression in COS could be interpreted as reduced activation of the Hedgehog (Hh) signaling pathway. The increased M1 polarization and reduced Hh activation in COS could explain the low incidence of metastases in these osteosarcomas.

Zheng et al. aimed to compare survival outcome after receiving radiofrequency ablation (RFA) and surgical resection (SR) for solitary hepatocellular carcinoma (HCC) with size large as 5 cm. They found that by applying several effective sensitivity analyses, OS and CSS were similar between the patients with tumors smaller than 3 cm receiving RFA and SR. But SR may be a superior treatment option with better long-term outcome than RFA in patients with tumor measuring 3.1-5 cm.

Liang et al. performed a retrospective study to identify the prognostic significance of time to local recurrence (TLR) with regard to overall survival (OS) and survival after local recurrence (SAR) in patients with soft tissue sarcoma (STS) of the extremity and abdominothoracic wall. From their results they conclude that in patients with STS of the extremity and abdominothoracic wall, ELR after R0 resection indicated a worse prognosis than those with LLR, and TLR can be considered an independent prognostic factor for OS and SAR. Furthermore, local recurrence was significantly influenced by the depth and the histopathological grading of the primary tumor, and reoperation after local recurrence could improve survival, which means salvage surgery may still be the preferred treatment when there are surgical indications after recurrence.

Conclusion

The contributions to this special issue highlight recent advances and approaches to the art of interdisciplinary oncological surgical and show how the challenges go along with functional organ or tissue preservation or restoration/reconstruction to maintain the highest possible QOL without reducing the aim of oncologic radicality.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Acknowledgments

The Editors want to thank all contributors for their scientific input that made up this exciting Research Topic.

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.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. van Ramshorst TME, Giani A, Mazzola M, Dokmak S, Ftériche FS, Esposito A, et al. Benchmarking of robotic and laparoscopic spleen-preserving distal pancreatectomy by using two different methods. *Br J Surg* (2022) 110(1):76–83. doi: 10.1093/bjs/znac352

2. Frank K, Ströbel A, Ludolph I, Hauck T, May MS, Beier JP, et al. Improving the safety of DIEP flap transplantation: Detailed perforator anatomy study using preoperative CTA. *J Pers Med* (2022) 12(5):701. doi: 10.3390/jpm12050701

3. Geierlehner A, Horch RE, Ludolph I, Arkudas A. Intraoperative blood flow analysis of DIEP vs. ms-TRAM flap breast reconstruction combining transit-time flowmetry and microvascular indocyanine green angiography. *J Pers Med* (2022) 12(3):482. doi: 10.3390/jpm12030482

4. Horch RE, Ludolph I, Arkudas A, Cai A. Personalized reconstruction of genital defects in complicated wounds with vertical rectus abdominis myocutaneous flaps including urethral neo-orifice. *J Pers Med* (2021) 11(11):1076. doi: 10.3390/jpm11111076

5. Ludolph I, Arkudas A, Müller-Seubert W, Cai A, Horch RE. *[Complications and their management following axillary, inguinal and iliac lymph node dissection]*. (Heidelb: Chirurgie). (2022) 94(2):130–7. doi: 10.1007/s00104-022-01736-2

6. Götzl R, Sterzinger S, Arkudas A, Boos AM, Semrau S, Vassos N, et al. The role of plastic reconstructive surgery in surgical therapy of soft tissue sarcomas. *Cancers (Basel)* (2020) 12(12):3534. doi: 10.3390/cancers12123534

7. Horch RE, Ludolph I, Arkudas A. [Reconstruction of oncological defects of the perianal region]. *Chirurg* (2021) 92(12):1159–70. doi: 10.1007/s00104-021-01394-w

8. Rosen SA, Rupji M, Liu Y, Paul Olson TJ. Robotic proctectomy: Beyond the initial learning curve. *Am Surg* (2022) 31348221146931. doi: 10.1177/00031348221146931

9. Di Benedetto F, Magistri P, Di Sandro S, Sposito C, Oberkofler C, Brandon E, et al. Safety and efficacy of robotic vs open liver resection for hepatocellular carcinoma. *JAMA Surg* (2022) 158(1):46–54. doi: 10.1001/jamasurg.2022.5697

10. Morise Z. Current status of minimally invasive liver surgery for cancers. *World J Gastroenterol* (2022) 28(43):6090–8. doi: 10.3748/wjg.v28.i43.6090

frontiers in Oncology

ORIGINAL RESEARCH
published: 25 June 2019
doi: 10.3389/fonc.2019.00555

Treatment Outcomes and Prognostic Factors of Patients With Primary Spinal Ewing Sarcoma/Peripheral Primitive Neuroectodermal Tumors

*Jun Chen[1], Mengxue Li[2], Yifeng Zheng[1], Lei Zheng[3], Fanfan Fan[1] and Yu Wang[1]**

[1] Department of Neurosurgery, Tongji Medical College, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China, [2] Department of Ultrasonics, The 991th Hospital of the Joint Logistics Support Unit of the Chinese People's Liberation Army, Xiangyang, China, [3] Department of Orthopedics, Tongji Medical College, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China

OPEN ACCESS

Edited by:
Aali Jan Sheen, Manchester Royal Infirmary, United Kingdom

Reviewed by:
Kun Zhang, Xavier University of Louisiana, United States
Alex Nicolas Gordon-Weeks, University of Oxford, United Kingdom

***Correspondence:**
Yu Wang
330722474@qq.com

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: 22 February 2019
Accepted: 06 June 2019
Published: 25 June 2019

Citation:
Chen J, Li M, Zheng Y, Zheng L, Fan F and Wang Y (2019) Treatment Outcomes and Prognostic Factors of Patients With Primary Spinal Ewing Sarcoma/Peripheral Primitive Neuroectodermal Tumors. Front. Oncol. 9:555. doi: 10.3389/fonc.2019.00555

Purpose: Primary spinal Ewing sarcoma (ES)/peripheral primitive neuroectodermal tumors (pPNETs) are extremely rare, and the current understanding of these tumors is poor. The authors aimed to illustrate the clinical characteristics of primary spinal ES/pPNETs and to discuss prognostic factors by survival analysis.

Methods: A total of 40 patients who were pathologically diagnosed with primary spinal ES/pPNETs between 2000 and 2018 were enrolled in this study. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan–Meier method to identify potential prognostic factors. Factors of $p \leq 0.1$ in the Log-rank tests were subjected to multivariate analysis by Cox regression analysis.

Results: The mean follow-up period was 23.8 (range, 2–93) months, and 24 (60.0%) patients had local recurrence and 11 (27.5%) patients had distant metastasis. The 1-, 2-, and 5-year PFS rates were 57.7, 30.4, and 9.5%, respectively. The 1-, 2-, and 5-year OS rates were 74.8, 50.7, and 12.2%, respectively. The univariate analysis suggested that resection mode, postoperative Frankel score, adjuvant chemotherapy and adjuvant radiotherapy were potential prognostic factors for OS and PFS. However, after these factors were subjected to multivariate analyses, only adjuvant radiotherapy and resection mode remained as independent prognostic factors.

Conclusions: Total en bloc resection can significantly improve PFS for primary spinal ES/pPNETs and adjuvant radiotherapy was a favorable factor for PFS. Total en bloc resection and adjuvant radiotherapy considerably improve OS for patients with primary spinal ES/pPNETs.

Keywords: Ewing sarcoma, primitive neuroectodermal tumors, survival, prognostic factor, spinal

INTRODUCTION

Primary spinal Ewing sarcoma (ES)/peripheral primitive neuroectodermal tumors (pPNETs) are regarded as undifferentiated malignant small round cell tumors, which mostly occur in long bones, flat bones, ribs, and soft tissue. ES/pPNETs account for 6–8% of primary malignant bone tumors, and rarely affect intraspinal/vertebral deep mesenchymal/meningeal tissue (1–3). Due to a lack of clinic symptoms and specific biomarkers at the early stages of primary spinal ES/pPNETs, most patients are not diagnosed until advanced stages, which concomitantly worsens outcomes. Furthermore, because the tumor has an aggressive clinical course—with a high tendency for both local recurrence and distant metastasis—a timely and accurate preoperative diagnosis of primary spinal ES/pPNETs could provide useful information for surgical planning. Therefore, comprehensive studies on the clinical characteristics of primary spinal ES/pPNETs are warranted.

The rarity of the disease makes its purported surgical management and prognostic factors controversial. In addition, most related information about this disease comes from individual case reports or small case-series reports, which lack robust statistical outcomes. To illustrate the surgical management and prognostic factors of primary spinal ES/pPNETs, we retrospectively reviewed all of the cases surgically treated and pathologically confirmed as primary spinal ES/pPNETs at our institution between 2000 and 2018. Clinical, radiological, and pathological factors associated with longer progression-free survival (PFS) and overall survival (OS) were also analyzed.

MATERIALS AND METHODS

A total of 40 patients were surgically treated in Tongji Hospital (Tongji Medical College, Huazhong University of Science and Technology) between February 2000 and November 2018. All cases were analyzed by two experienced independent neuropathologist and were diagnosed according to the World Health Organization (WHO) classification of tumors. Clinical and spinal MRI follow-up data for patients with spinal ES/pPNETs were mainly obtained through outpatient review, supplemented by a telephone interview. Regular assessments were performed at 3, 6, and 12 months after initial surgery, every 6 months for the next 2 years, and then annually for life. The clinical data and surgical records for patients of primary spinal ES/pPNETs were retrospectively reviewed. Preoperative and postoperative neurologic statuses were classified according to the Frankel score (4). In the present study, all of the cases were divided into the following two subtypes: vertebral type and spinal canal type. The vertebral type was defined as any case in which the maximum diameter of the lesion was located in the vertebral body or accessory. The spinal canal type was defined as any case in which the maximum diameter of the lesion was located in the spinal canal.

Adjuvant treatment consisting of chemotherapy and/or radiotherapy was performed based on the patient's postoperative Karnofsky performance status (KPS) scores, age, preference, and tolerance. Patients with postoperative KPS scores $\geq$ 70 were recommended to undergo chemotherapy. Radiotherapy was performed in patients whose age was more than 3 years and who were unwilling to receive chemotherapy. In patients treated with chemotherapy, radiotherapy was performed based on the patient's age, preference, and tolerance. The vincristine, ifosfamide, doxorubicin, etoposide (VIDE) or vincristine, doxorubicin, cyclophosphamide (VAC) protocol was suggested for chemotherapy. We performed radiotherapy on the tumor resection site and the radiation dose ranged from 40 to 55 Gy.

The objective of this study was to illustrate the clinical, radiological, and pathological features of primary spinal ES/pPNETs and to discuss prognostic factors by survival analysis. PFS was defined as the time from the initial surgery to the time of the first event (i.e., tumor progression or death). The diagnosis of progression—including tumor recurrence, distant metastasis, and regrowth—was made on the basis of clinical presentations and imaging manifestations (e.g., enhanced magnetic resonance imaging or computed tomography scans). OS was defined as the time from the initial surgery to the date of death from any cause. The length of follow-up was recorded as the period from the date of the initial operation to death, or until November 2018 for surviving patients.

Statistical Analysis

The univariate and multivariate analyses of various clinical, radiological, and pathological factors were performed to identify possible variables which could predict PFS and OS. The patient factors included age, gender, disease duration, preoperative Frankel score, and postoperative Frankel score. Tumor factors included subtype, involved segments, Ki67 index, bone destruction, and distant metastasis. The treatment factors were resection mode, postoperative radiotherapy, postoperative chemotherapy, and intraoperative blood loss. PFS and OS were evaluated by the Kaplan-Meier method to identify possible prognostic factors. Differences between survival curves were compared by using a log-rank test. Factors with $p \leq 0.1$ in the log-rank tests were subjected to multivariate analysis by Cox regression analysis. We regarded $p < 0.05$ as statistically significant. Data were analyzed using SPSS version 20.0 package software (IBM Corp., Armonk, New York, USA).

RESULTS

Patient Descriptions

The basic information of 40 patients is described in **Tables 1**, **2**. The present study consisted of 24 (60%) males and 16 (40%) females with an average age of 21.9 (range, 1–45) years. The mean duration of the initial symptoms was 42 days (range 3–180 days). In our series, 28 (70%) patients presented with varied degrees of limb weakness, 20 (50%) patients presented with pain, and eight (20%) patients presented with incontinence.

Radiological data are summarized in **Table 1**. Based on MRI scans, the lesions were hypointense ($n = 35$, 87.5%) or isointense ($n = 5$, 12.5%) on the T1-weighted images (**Figures 1–3**), and isointense ($n = 8$, 20.0%) (**Figures 1**, **2**) or hyperintense ($n = 32$,

TABLE 1 | Radiological characteristics of 40 patients with primary spinal ES/pPNETs.

Characteristic	No. of cases (%)
Location	
Cervical only	5 (12.5)
Thoracic only	19 (47.5)
Lumbar only	6 (15.0)
Sacrum only	2 (5.0)
Cervical and thoracic	1 (2.5)
Thoracic and lumbar	4 (10.0)
Lumbar and sacrum	3 (7.5)
Number of involved segments	
Single	7 (17.5)
Multiple	33 (82.5)
Subtype	
Spinal canal type	32 (80.0)
Vertebral type	8 (20.0)
Border of tumor	
Well defined	25 (62.5)
Poorly defined	15 (37.5)
T1 And T2 Signals	
Hypointense T1 and isointense T2	8 (20.0)
Hypointense T1 and hyperintense T2	27 (67.5)
Isointense T1 and hyperintense T2	5 (12.5)
Enhancement	
Homogeneous	5 (12.5)
Heterogeneous	35 (87.5)
Bone destruction	
Yes	17 (42.5)
No	23 (57.5)

80.0%) on the T2-weighted images. Thirty-five (87.5%) lesions showed significant heterogeneous enhancement (**Figures 1–3**) and five (12.5%) lesions showed significant homogeneous enhancement on MRI scans. The lesions involved the cervical spine in six (15.0%) cases, thoracic spine in 24 (60.0%) cases, lumber spine in 13 (32.5%) cases, and sacrum in five (12.5%) cases, respectively. Among these cases, one case showed involvement of both the cervical and thoracic spines, three cases showed involvement of both the sacral and lumbar spines, and four cases showed involvement of both the thoracic and lumbar spines. In addition, tumor lesions involved a single segment in seven (17.5%) cases, and multiple segments in 33 (82.5%) cases. Seventeen patients were radiographed for intraspinal tumors and vertebral bone destruction (**Figures 1**, **2**). Regarding the subtypes, the spinal canal type (**Figure 1**) was detected in 32 (80.0%) cases and vertebral type (**Figure 2**) was detected in eight (20.0%) cases.

All of the patients underwent at least one surgery. Partial resection, subtotal resection, total piecemeal resection, and total en bloc resection were performed in four (10.0%) cases, 17 (42.5%) cases, 13 (32.5%) cases, and six (15.0%) cases, respectively. Postoperative radiotherapy was performed in 25 cases, with a median dose of 45 Gy (range, 40–55 Gy). Postoperative chemotherapy was performed in 28 cases.

The mean follow-up period was 23.8 (range, 2–93) months. At the last follow-up, local recurrence occurred in 24 (60%) cases, and seven patients underwent a second operation and one patient underwent a third operation. Distant metastasis occurred in 11 (27.5%) cases. The distant metastatic sites was the lung in six cases, rib in one case, sternum in one case, mediastinum in one case, and spinal cord in two cases (**Figure 3**).

Pathology

Light microscopy revealed that the tumor nodule was mainly composed of small, round, undifferentiated cells with hyperchromatic nuclei and reduced cytoplasmic volume (**Figure 4**). Immunohistochemical studies showed that 40 cases were positive for CD99 (**Figure 4**). Vimentin was positive in 25 (62.5%) cases. Strong immunoreactivity for Friend Leukemia Virus Integration 1 (FLI-1) was detected in 27 (67.5%) patients (**Figure 4**). The average Ki-67 labeling index was 30% (range, 3–80%). Furthermore, a fluorescent *in situ* hybridization (FISH) study was performed in two cases, and EWS/FLI1 translocation was found to be present (**Figure 4**). However, a corresponding FISH study was not performed in the other 38 cases.

Univariate and Multivariate Analysis of Prognostic Factors for Progression-Free Survival

The median PFS was 14 months. The 1-, 2-, and 5-year PFS rates were 57.7, 30.4, and 9.5%, respectively. The univariate analysis of prognostic factors affecting PFS is presented in **Table 2**. In the present study, we applied the four following surgical treatment: partial resection, subtotal resection, total piecemeal resection, and total en bloc resection. The PFS rate was statistically significant difference among the four kinds of resection modes ($p < 0.001$). The PFS rate was significantly higher in patients with adjuvant radiotherapy than that of patients without adjuvant radiotherapy ($p < 0.001$). Patients who underwent chemotherapy had a significantly higher PFS rate than those of patients treated without chemotherapy ($p = 0.016$). In addition, the PFS rate was significantly lower in patients with postoperative Frankel score (A–C) than that of those with postoperative Frankel score (D–E) ($p = 0.019$). There were no significant differences among the other factors (i.e., age, gender, disease duration, preoperative Frankel score, subtype, involved segments, Ki-67 index, intraoperative blood loss, and bone destruction).

Possible prognostic factors, extracted by the univariate analysis, were subjected to the multivariate analysis (**Table 3**). Multivariate analysis showed that resection mode ($p < 0.001$) and adjuvant radiotherapy ($p < 0.001$) were independent prognostic indicators. The Kaplan-Meier curve of PFS for resection mode and adjuvant radiotherapy are shown in **Figure 5**. Multivariate analysis revealed that postoperative Frankel score and adjuvant chemotherapy were not independent prognostic factors for PFS. Detailed results are presented in **Table 3**.

TABLE 2 | Patient characteristics and univariate analysis of prognostic factors affecting progression-free survival and overall survival.

Factors	Number	Progression-free survival		Overall survival	
		Median time (month)	*p* value	Median time (month)	*p* value
Age					
<20/≥20 (year)	18/22	13 vs. 14	0.411	25 vs. 23	0.206
Gender					
Male/female	24/16	13 vs. 15	0.839	25 vs. 23	0.940
Disease duration					
<2/≥2 (month)	25/15	14 vs. 15	0.318	25 vs. 21	0.171
Preoperative frankel score					
A–C/D–E	26/14	13 vs. 15	0.487	23 vs. 27	0.436
Subtype					
Spinal canal type/vertebral type	32/8	15 vs. 8	0.329	25 vs. 18	0.481
Number of involved segments					
<3/≥3	12/28	13 vs. 15	0.572	25 vs. 25	0.931
Resection mode					
Total en bloc/total piecemeal/STR/PR	6/13/17/4	48 vs. 20 vs. 8 vs. 3	<0.001	55 vs. 28 vs. 18 vs. 7	<0.001
KI-67 index					
≤30/>30%	24/16	18 vs. 11	0.160	25 vs. 18	0.235
Adjuvant radiotherapy					
Yes/no	25/15	18 vs. 7	0.001	26 vs. 10	0.001
Adjuvant chemotherapy					
Yes/no	28/12	15 vs. 9	0.016	25 vs. 18	0.029
Postoperative frankel score					
A–C/D–E	13/27	11 vs. 15	0.019	18 vs. 25	0.013
Intraoperative blood loss					
<1,500/≥1,500 (mL)	19/21	15 vs. 14	0.972	25 vs. 23	0.991
Bone destruction					
Yes/no	17/23	9 vs. 15	0.386	18 vs. 26	0.285
Distant metastasis					
Yes/no	11/29	–	–	10 vs. 25	0.036

STR, subtotal resection; PR, partial resection.

Univariate and Multivariate Analysis of Prognostic Factors for Overall Survival

The results of the univariate analysis of the possible prognostic factors affecting OS are presented in **Table 2**. The median OS was 25 months. The 1-, 2-, and 5-year OS rates were 74.8, 50.7, and 12.2%, respectively. Univariate analysis shown that a significant difference was observed in patients with resection mode ($p < 0.001$), adjuvant radiotherapy ($p = 0.001$), postoperative Frankel score (A–C/D–E) ($P = 0.013$), adjuvant chemotherapy ($p = 0.029$), and distant metastasis ($p = 0.036$). These prognosis related factors extracted by univariate analysis were submitted to Cox regression analysis (**Table 3**). Resection mode ($p = <0.001$) and adjuvant radiotherapy ($p < 0.001$) were remained highly significant independent prognostic factors for OS. Details of the above five prognostic factors by multivariate analysis are presented in **Table 3**. Additionally, the Kaplan-Meier curves of OS for resection mode and adjuvant radiotherapy are shown in **Figure 5**.

Complications

Erectile dysfunction occurred in one patient. Leakage of cerebrospinal fluid occurred in four patients and was cured within 1 week by lumbar cistern drainage. Three patients were stricken with pneumonia but recovered after being treated with antibiotics for approximately 1 week. No thrombosis, subcutaneous emphysema, secondary spinal malformation, or internal fixation failure were observed after surgery or during the long-term follow-up.

DISCUSSION

Primary spinal ES/pPNET is an extremely rare family of malignancies that has an aggressive clinical course with high recurrent potential and poor prognosis (5–8). The special anatomical structure of the spine poses a huge challenge for surgical management of ES/pPNET and increases the postoperative recurrence rate. While preventing recurrence, increasing PFS and OS after initial operation is a significant effort

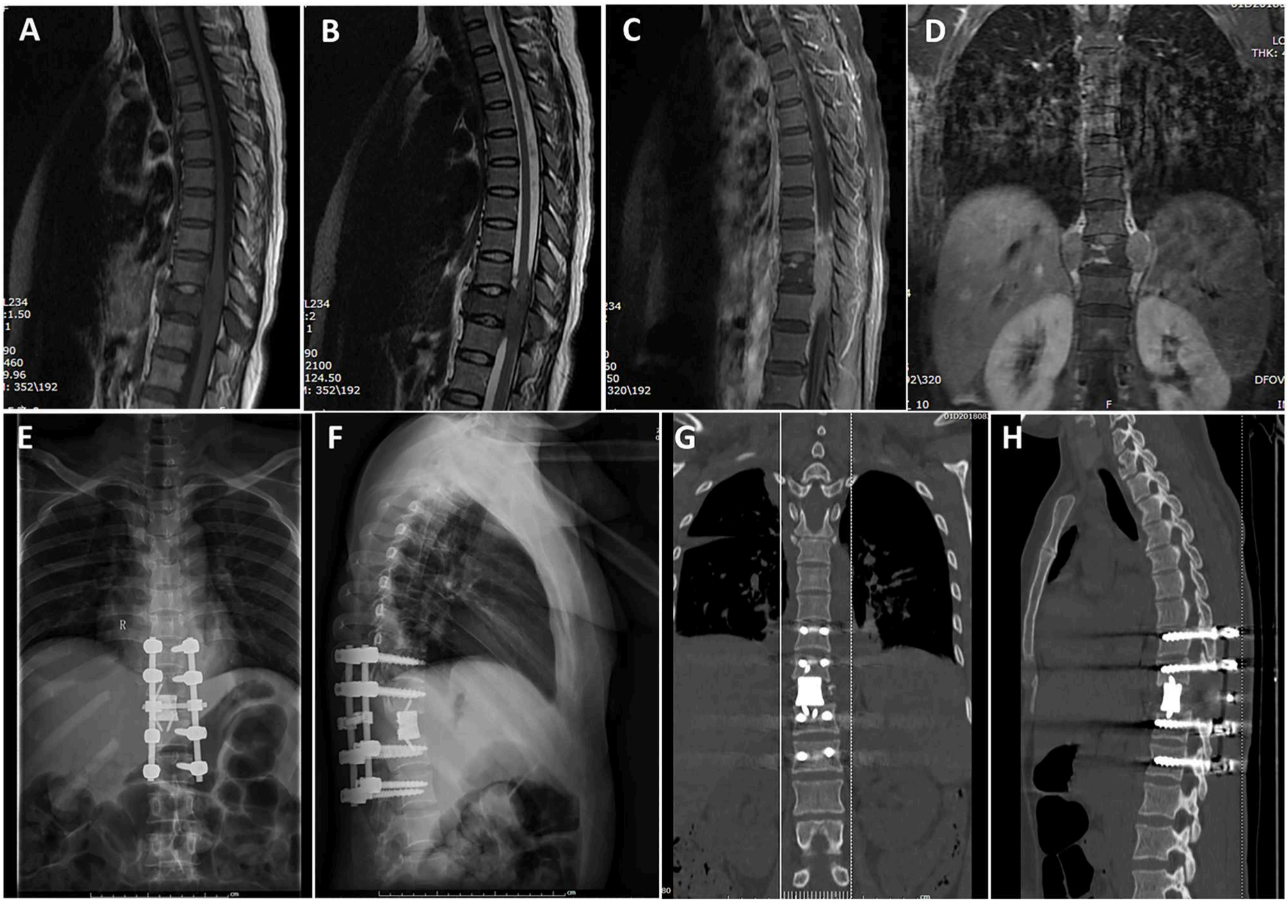


FIGURE 1 | A case labeled as spinal canal type because the maximal diameter of the tumor was located in the spinal canal. Preoperative T1-weighted **(A)** and T2-weighted **(B)** images revealed a tumor at the T10–12 level. Contrast-enhanced sagittal **(C)** and coronary **(D)** images revealed that the tumor showed heterogeneous enhancement. Postoperative X-ray showed sound reconstruction by a 3D printed microporous titanium vertebral body and posterior screw-rod system. Anterior-posterior view **(E)**. Lateral view **(F)**. Postoperative computed tomographic scan of the thoracic spine 1 year after surgery showing excellent spinal fusion and the absence of tumor recurrence. Coronal section image **(G)**. Sagittal section image **(H)**.

that should be pursued and achieved. Due to the low incidence of primary spinal ES/pPNET, the clinical features and prognostic factors remain unclear. In this study, we performed survival analysis to explore independent prognostic factors related to PFS and OS in patients with primary spinal ES/pPNET. The results indicate that total en bloc resection and adjuvant radiotherapy were independent prognostic factors that can significantly improve PFS and OS for patients with primary spinal ES/pPNET.

In the present study, the average age was 21.9 years, which is slightly greater than that in previous reports (5). Similar to other studies (6, 9), our cohort showed clear male predominance in incidence (male:female ratio = 1.5:1). Limb weakness (70%) and pain (50%), as well as incontinence (20%), were the most common initial symptoms, which is largely consistent with previous reports (5, 9). The mean duration of symptoms before the first operation was 42 days, which is longer than that of previous reports (5, 10). The lesions were generally located in the thoracic spine (60.0%), which is consistent with previous reports (11). However, univariate analysis showed that age, gender, and disease duration were not influential factors for prognosis of patients (all $p > 0.05$).

The ES/pPNET tumor nodule is mainly composed of small, round, undifferentiated cells (5). Accurate diagnoses rely on immunohistochemistry and molecular genetic analysis. Some studies showed that membranous expression of CD99 was detected in 97% of cases, and the most sensitive and specific detection method for the diagnosis of primary spinal ES/pPNET was the combination of CD99 and FLI-1 immunohistochemistry (2, 12, 13). In the present study, positive expression of CD99 was found in 40 (100%) cases, consistent with the diagnosis of ES/pPNET. As has been known, the gold standard for diagnosing ES/pPNETs is the identification of the tumor type-specific fusion genes EWSR1/FLI-1 (2, 14–17). However, FISH studies have only been performed in a small portion of the reported cases in the English literature (9). In our series, a FISH study was performed in two cases, and EWS/FLI-1 translocation was found to be present. In addition, our study showed that the average Ki-67 labeling index was 30% with a range of 3–80%. An association

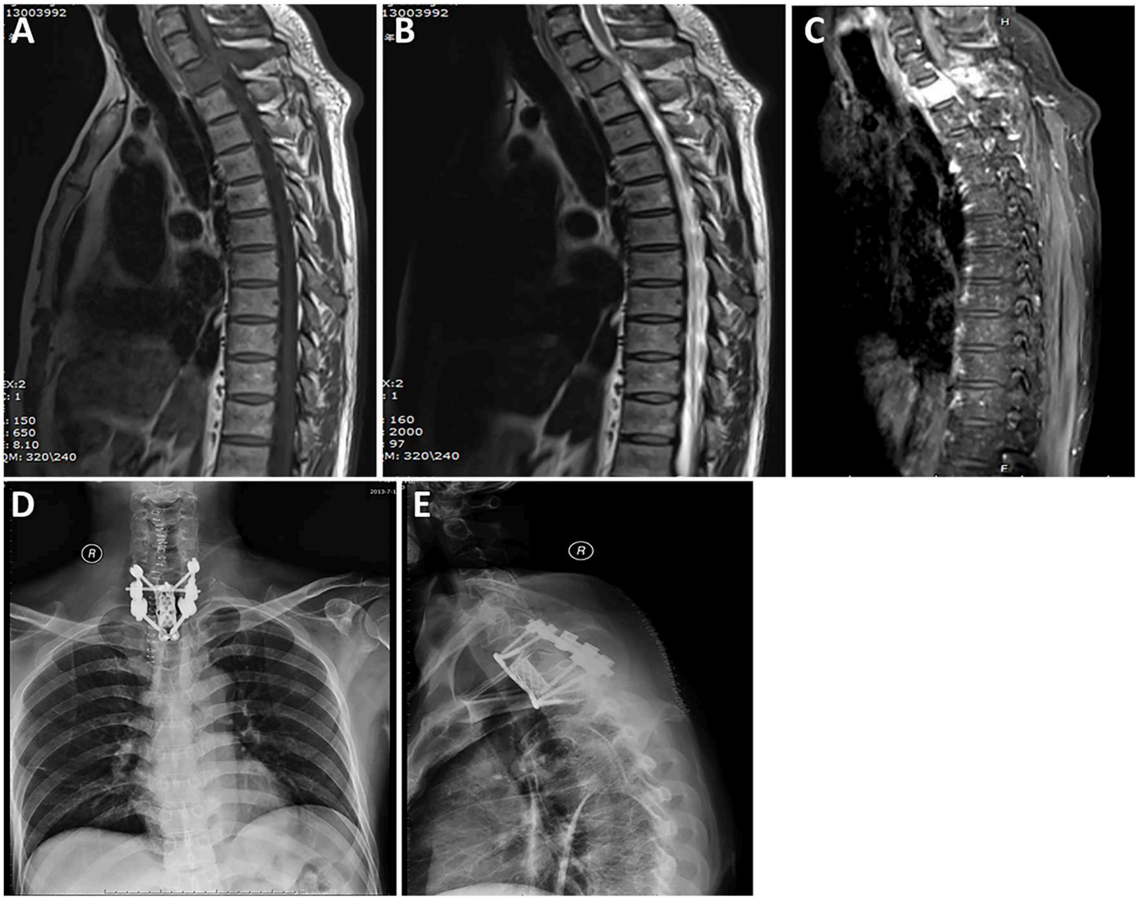


FIGURE 2 | A case labeled as vertebral type because the maximal diameter of the tumor was located in the vertebral body and accessory. Preoperative T1-weighted **(A)** and T2-weighted **(B)** images revealed a tumor at the T1 level. Contrast-enhanced sagittal **(C)** image revealed that the tumor showed significant homogeneous enhancement. Postoperative radiograph of the thoracic spine after surgery showing that the reconstructed thoracic spine was well-maintained. Anterior-posterior view **(D)**. Lateral view **(E)**.

between ki-67 index and PFS or OS was not reported in related studies; however, our statistical analysis determined that ki-67 index was not a potential prognostic factor for PFS and OS (all $p > 0.05$).

Surgical treatment is the first-line treatment for primary spinal ES/pPNET, in terms of preserving functionality, removing lesions, relieving symptoms, controlling local recurrence, and promising prolonged survival (16). Since ES/pPNETs have the character of local infiltration, the local recurrence rate will be high if initial surgery is inadequate. Previous studies have demonstrated that gross total resection can result in better prognosis than subtotal resection (5, 10). In our study cohort, resection mode included partial resection, subtotal resection, total piecemeal resection, and total en bloc resection. Our results shown that patients who underwent total en bloc resection had markedly higher PFS rates and OS rates than those treated by total piecemeal resection, subtotal resection, and partial resection. However, en bloc resection of spinal ES/pPNET with wide margins may be difficult because of residual tumor cells on such vital structures as the dura, spinal cord, major blood vessels, or other critical nerves. Allowing for constraints for achieving total en bloc resection to fulfill wide margins, adjuvant radiotherapy, and/or chemotherapy is a critically important consideration in these patients.

Aside from case reports, there is no retrospective analysis focused on surgical management and prognostic factors for patients with ES/pPNET in the spine (vertebral type). The surgical treatments applicable to the vertebral lesion include the simplest subtotal resection, total piecemeal spondylectomy, and the most complex total en bloc spondylectomy (TES) (18–21). In these series of subtypes, surgical resection and reconstruction of the spine were difficult and TES was challenging. The potential role of radiotherapy and/or chemotherapy is still debatable, and no robust direct evidence of impact in survival has been discovered (16). In the present subtype series, total resection, especially TES, combined with radiotherapy with an intensity 40–55 Gy can significantly improve the PFS and OS rates.

Our statistical analysis indicated that total resection, especially total en bloc resection, led to a better prognosis than without total resection ($p < 0.001$). However, some tumors may still relapse

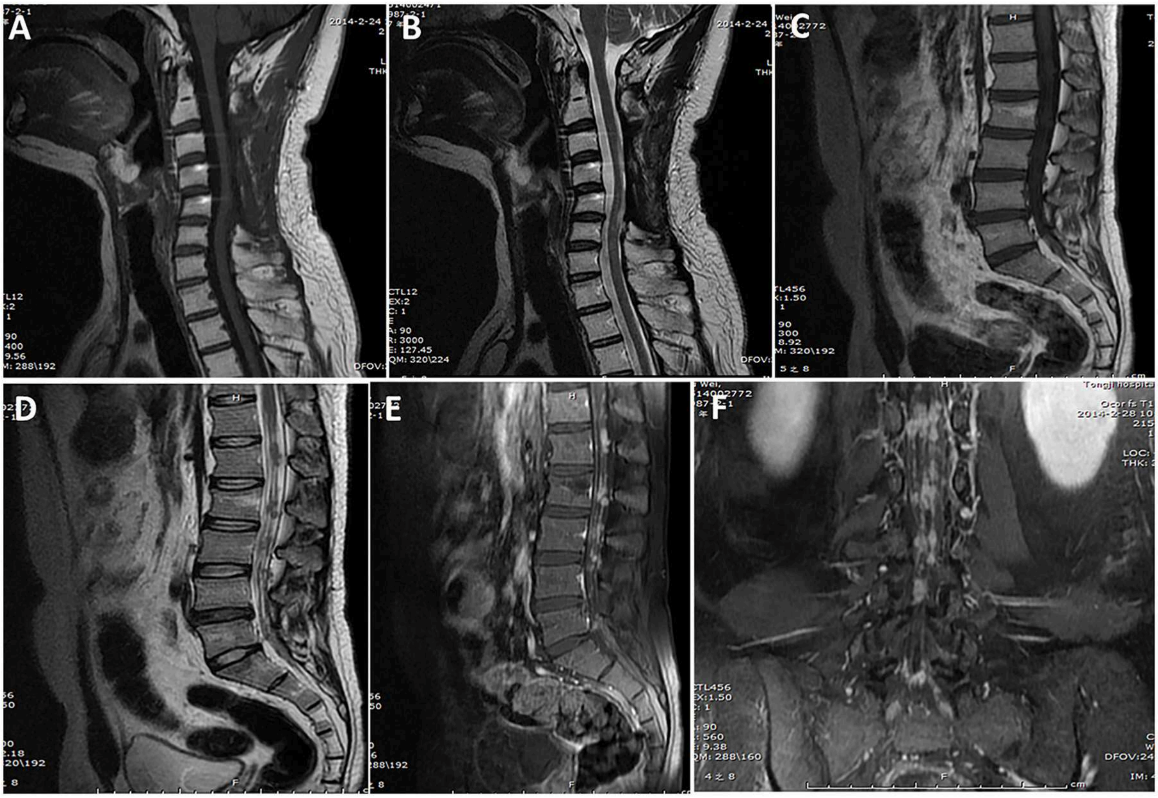


FIGURE 3 | A case of primary intradural ES/pPNET at the C3–C5 level. Images obtained 14 months after the first surgery **(A,B)** showed no tumor local recurrence at the C3–5 level (lack of preoperative MRI examination findings), but they did show multiple metastases in the spinal canal through the cerebrospinal fluid **(C–F)**.

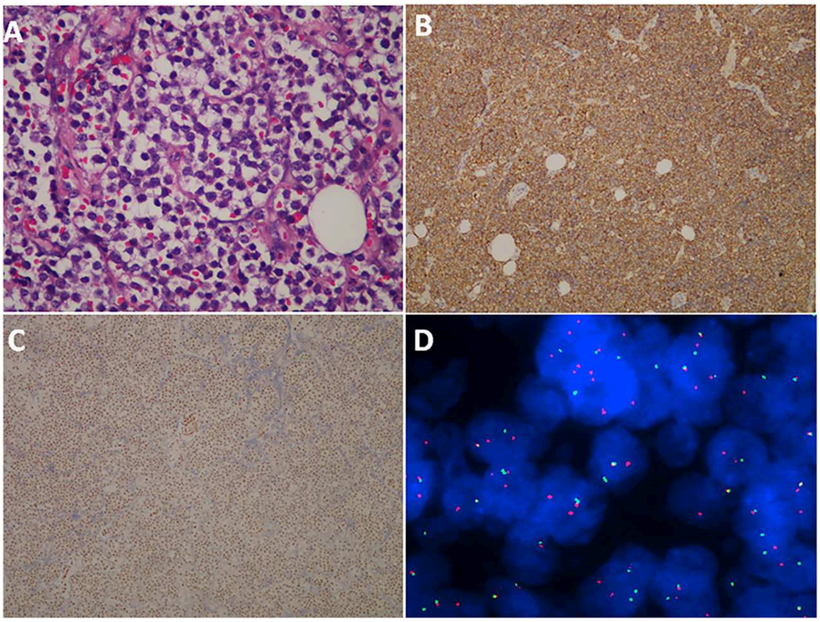


FIGURE 4 | Histopathological, immunohistochemical, and cytogenetic examination of ES/pPNET. Light microscopy showed a highly cellular ES/pPNET tumor consisting of undifferentiated, small, round cells with frequent mitoses **(A)** (hematoxylin–eosin × 400). Immunohistochemical staining showed positivity for CD99 (×100) **(B)**. Microphotograph showing immunohistochemical staining of FLI-1 **(C)**. The representative FISH result using EWSR1 (22q12) dual color break apart rearrangement probe (Vysis). Tumor cells of the ES/pPNET displayed one fusion (yellow signal), and the simultaneous split pattern of one orange and one green signal, being indicative of a rearrangement of one copy of the EWSR1 gene **(D)**.

TABLE 3 | Multivariate analysis of prognostic factors for progression-free survival and overall survival.

Factors	PFS			OS		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Resection mode	1.083	1.255–10.495	<0.001	0.813	1.243–6.115	<0.001
Adjuvant radiotherapy	0.500	1.583–4.217	0.004	0.454	2.082–5.064	<0.001
Adjuvant chemotherapy	–	–	0.189	–	–	0.813
Postoperative Frankel score	–	–	0.303	–	–	0.762
Distant metastasis	–	–	–	–	–	0.491

CI indicates confidence interval; HR, hazard ratio.

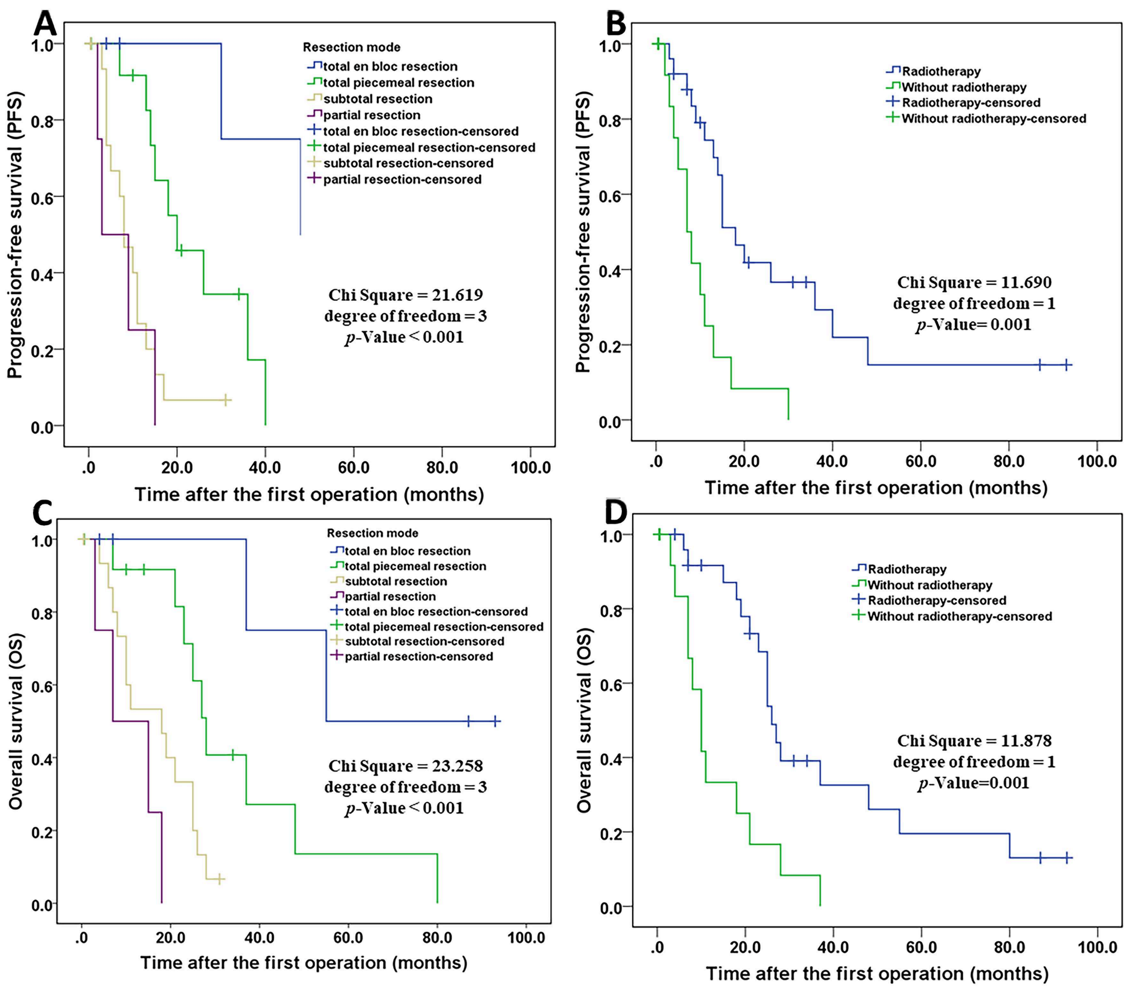


FIGURE 5 | Kaplan–Meier curves of progression-free survival and overall survival. Kaplan–Meier curves of progression-free survival for resection mode **(A)**. Kaplan–Meier curves of progression-free survival for patients treated with radiotherapy and without radiotherapy **(B)**. Kaplan–Meier curves of overall survival for resection mode **(C)**. Kaplan–Meier curves of overall survival for patients treated with radiotherapy and without radiotherapy **(D)**.

and/or progress to metastasis after total piecemeal resection. In our present study, two patients who underwent total piecemeal resection did not show local recurrence, but did show multiple metastases in the spinal canal after 1 year. The reason may be that piecemeal resection is related to a possibility of cancer cell contamination in the field of surgery. Therefore, total resection, especially total en bloc resection when possible, should be strived for in patients with primary spinal ES/pPNETs to avoid tumor cells contaminating the surgical field and increase PFS and OS.

To our knowledge, our present study is a relatively larger series to date on spinal ES/pPNETs, with the longest follow-up until now; additionally, it is the first such study to focus on prognostic factors for PFS and OS. Nevertheless, there are some limitations. First, this is a retrospective design and, thus, potential biases exist. Second, we only focused on surgical cases, and neglected cases from patients who did not undergo surgery. Third, some patients had a relatively short follow-up, which makes OS appear higher than it may be in actuality.

CONCLUSIONS

Primary spinal ES/pPNETs is a challenging and rare clinical entity given its high local recurrence rate and distant metastasis. Resection mode and adjuvant radiotherapy are independent prognostic factors for primary spinal ES/pPNETs. Total en bloc resection can significantly improve PFS for primary spinal ES/pPNETs and adjuvant radiotherapy is a favorable factor for PFS. Total en bloc resection and adjuvant radiotherapy considerably improve OS for patients with primary spinal ES/pPNETs.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the supplementary files.

ETHICS STATEMENT

Because this study was a retrospective study and did not involve any experimental interventions, according to the rules of the ethics committee of Tongji Hospital, it did not require special ethics approval.

AUTHOR CONTRIBUTIONS

YW and JC: study design. JC, ML, YZ, LZ, and FF: data collections. JC and ML: data analysis. JC: writing. All authors reviewed the manuscript.

FUNDING

This study was funded by the National Natural Science Foundation of China (grant number 81571242).

REFERENCES

1. Sato S, Mitsuyama T, Ishii A, Kawakami M, Kawamata T. Multiple primary cranial Ewing's sarcoma in adulthood: case report. *Neurosurgery*. (2009) 64:E384–6; discussion: E6. doi: 10.1227/01.NEU.0000337128.67045.70
2. Ke C, Duan Q, Yang H, Zhu F, Yan M, Xu SP, et al. Meningeal Ewing sarcoma/peripheral PNET: clinicopathological, immunohistochemical and FISH study of four cases. *Neuropathology*. (2017) 37:35–44. doi: 10.1111/neup.12325
3. Chen J, Jiang Q, Zhang Y, Yu Y, Zheng Y, Chen J, et al. Clinical features and long-term outcome of primary intracranial Ewing sarcoma/peripheral primitive neuroectodermal tumors: 14 cases from a single institution. *World Neurosurg*. (2018) 122:e1606–e1614. doi: 10.1016/j.wneu.2018.11.151
4. Frankel HL, Hancock DO, Hyslop G, Melzak J, Michaelis LS, Ungar GH, et al. The value of postural reduction in the initial management of closed injuries of the spine with paraplegia and tetraplegia. I. *Paraplegia*. (1969) 7:179–92. doi: 10.1038/sc.1969.30
5. Tong XZ, Deng XF, Yang T, Yang CL, Wu L, Wu J, et al. Clinical presentation and long-term outcome of primary spinal peripheral primitive neuroectodermal tumors. *J Neuro Oncol*. (2015) 124:455–63. doi: 10.1007/s11060-015-1859-1
6. Ellis JA, Rothrock RJ, Moise G, McCormick PC, Tanji K, Canoll P, et al. Primitive neuroectodermal tumors of the spine: a comprehensive review with illustrative clinical cases. *Neurosurg Focus*. (2011) 30:E1. doi: 10.3171/2010.10.FOCUS10217
7. Kampman WA, Kros JM, De Jong TH, Lequin MH. Primitive neuroectodermal tumours (PNETs) located in the spinal canal; the relevance of classification as central or peripheral PNET: case report of a primary spinal PNET occurrence with a critical literature review. *J Neurooncol*. (2006) 77:65–72. doi: 10.1007/s11060-005-9006-z
8. Deme S, Ang LC, Skaf G, Rowed DW. Primary intramedullary primitive neuroectodermal tumor of the spinal cord: case report and review of the literature. *Neurosurgery*. (1997) 41:1417–20. doi: 10.1097/00006123-199712000-00040
9. Saeedinia S, Nouri M, Alimohammadi M, Moradi H, Amirjamshidi A. Primary spinal extradural Ewing's sarcoma (primitive neuroectodermal tumor): report of a case and meta-analysis of the reported cases in the literature. *Surg Neurol Int*. (2012) 3:55. doi: 10.4103/2152-7806.96154
10. Qi W, Deng X, Liu T, Hou Y, Yang C, Wu L, et al. Comparison of primary spinal central and peripheral primitive neuroectodermal tumors in clinical and imaging characteristics and long-term outcome. *World Neurosurg*. (2016) 88:359–69. doi: 10.1016/j.wneu.2015.12.033
11. Tsutsumi S, Yasumoto Y, Manabe A, Ogino I, Arai H, Ito M. Magnetic resonance imaging appearance of primary spinal extradural Ewing's sarcoma: case report and literature review. *Clin Neuroradiol*. (2013) 23:81–5. doi: 10.1007/s00062-013-0222-1
12. Muller K, Diez B, Muggeri A, Pietsch T, Friedrich C, Rutkowski S, et al. What's in a name? Intracranial peripheral primitive neuroectodermal tumors and CNS primitive neuroectodermal tumors are not the same. *Strahlenther Onkol*. (2013) 189:372–9. doi: 10.1007/s00066-013-0315-4
13. Folpe AL, Goldblum JR, Rubin BP, Shehata BM, Liu W, Dei Tos AP, et al. Morphologic and immunophenotypic diversity in Ewing family tumors: a study of 66 genetically confirmed cases. *Am J Surg Pathol*. (2005) 29:1025–33. doi: 10.1097/01.pas.0000167056.13614.62
14. Bailly RA, Bosselut R, Zucman J, Cormier F, Delattre O, Roussel M, et al. DNA-binding and transcriptional activation properties of the EWS-FLI-1 fusion protein resulting from the t(11;22) translocation in Ewing sarcoma. *Mol Cell Biol*. (1994) 14:3230–41. doi: 10.1128/MCB.14.5.3230
15. Delattre O, Zucman J, Melot T, Garau XS, Zucker JM, Lenoir GM, et al. The Ewing family of tumors–a subgroup of small-round-cell tumors defined by specific chimeric transcripts. *N Engl J Med*. (1994) 331:294–9. doi: 10.1056/NEJM199408043310503
16. Hrabalek L, Kalita O, Svebisova H, Ehrmann JJr, Hajduch M, Trojanec R, et al. Dumbbell-shaped peripheral primitive neuroectodermal tumor of the spine–case report and review of the literature. *J Neurooncol*. (2009) 92:211–7. doi: 10.1007/s11060-008-9744-9
17. Vural C, Uluoglu O, Akyurek N, Oguz A, Karadeniz C. The evaluation of CD99 immunoreactivity and EWS/FLI1 translocation by fluorescence *in situ* hybridization in central PNETs and Ewing's sarcoma family of tumors. *Pathol Oncol Res*. (2011) 17:619–25. doi: 10.1007/s12253-010-9358-3
18. Boriani S, Weinstein JN, Biagini R. Primary bone tumors of the spine. Terminology and surgical staging. *Spine*. (1997) 22:1036–44. doi: 10.1097/00007632-199705010-00020

19. Tomita K, Kawahara N, Murakami H, Demura S. Total en bloc spondylectomy for spinal tumors: improvement of the technique and its associated basic background. *J Orthop Sci*. (2006) 11:3–12. doi: 10.1007/s00776-005-0964-y
20. Jia Q, Yin H, Yang J, Wu Z, Yan W, Zhou W, et al. Treatment and outcome of metastatic paraganglioma of the spine. *Eur Spine J*. (2018) 27:859–67. doi: 10.1007/s00586-017-5140-5
21. Kato S, Murakami H, Demura S, Yoshioka K, Kawahara N, Tomita K, et al. More than 10-year follow-up after total en bloc spondylectomy for spinal tumors. *Ann Surg Oncol*. (2014) 21:1330–6. doi: 10.1245/s10434-013-3333-7

Conflict of Interest Statement: 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.

frontiers in Oncology

SYSTEMATIC REVIEW
published: 30 July 2019
doi: 10.3389/fonc.2019.00687

Impact of Enhanced Recovery After Surgery on Postoperative Recovery for Pancreaticoduodenectomy: Pooled Analysis of Observational Study

Yang Cao[1†], *Hui-Yun Gu*[2†], *Zhen-Dong Huang*[1†], *Ya-Peng Wu*[3], *Qiong Zhang*[3], *Jie Luo*[1], *Chao Zhang*[1*] *and Yan Fu*[3*]

[1] Center for Evidence-Based Medicine and Clinical Research, Taihe Hospital, Hubei University of Medicine, Shiyan, China, [2] Department of Surgery, Zhongnan Hospital of Wuhan University, Wuhan University, Wuhan, China, [3] Department of Surgery, Taihe Hospital, Hubei University of Medicine, Shiyan, China

OPEN ACCESS

Edited by:
Aali Jan Sheen,
Department of General Surgery,
Manchester Royal Infirmary,
United Kingdom

Reviewed by:
Paul Willemsen,
Ziekenhuisnetwerk Antwerpen
Middelheim, Belgium
Michael Anthony Silva,
Oxford University Hospitals NHS Trust,
United Kingdom

***Correspondence:**
Yan Fu
fuyan_taihe0601@163.com
Chao Zhang
zhangchao0803@126.com

†These authors share first authorship

Specialty section:
This article was submitted to
Surgical Oncology,
a section of the journal
Frontiers in Oncology

Received: 01 April 2019
Accepted: 12 July 2019
Published: 30 July 2019

Citation:
Cao Y, Gu H-Y, Huang Z-D, Wu Y-P, Zhang Q, Luo J, Zhang C and Fu Y (2019) Impact of Enhanced Recovery After Surgery on Postoperative Recovery for Pancreaticoduodenectomy: Pooled Analysis of Observational Study. Front. Oncol. 9:687. doi: 10.3389/fonc.2019.00687

Purpose: To assess the impact of enhanced recovery after surgery (ERAS) protocols in pancreaticoduodenectomy.

Methods: Four databases were searched for studies describing ERAS program in patients undergoing pancreatic surgery published up to May 01, 2018. Primary outcomes were mortality, readmission, reoperation and postoperative complications. Secondary outcomes were the length of stay and cost.

Results: A total of 19 studies met inclusion and exclusion criteria and included 3,387 patients. Meta-analysis showed a decrease in pancreatic fistula (OR = 0.79, 95% CI: 0.67 to 0.95; $I^2 = 0\%$), infection (OR = 0.63, 95% CI: 0.50 to 0.78; $I^2 = 0\%$), especially incision infection (OR = 0.62, 95% CI: 0.42 to 0.91; $I^2 = 0\%$), and pulmonary infection (OR = 0.28, 95% CI: 0.12 to 0.66; $I^2 = 0\%$). Length-of-stay (MD: −3.89 days, 95% CI: −4.98 to −2.81; $I^2 = 78\%$) and cost were also significantly reduced. There was no significant increase in mortality, readmission, reoperation, or delayed gastric emptying.

Conclusion: This analysis revealed that using ERAS protocols in pancreatic resections may help decrease the incidence of pancreatic fistula and infections. Furthermore, ERAS also reduces length of stay and cost of care. This study provides evidence for the benefit of ERAS protocols.

Keywords: pancreaticoduodenectomy, enhanced recovery after surgery, mortality, postoperative complications, delayed gastric emptying

INTRODUCTION

The concept of enhanced recovery after surgery (ERAS) (1–3) was firstly applied in colorectal surgery and is increasingly applied to other surgical fields, such as gastric (4) and orthopedic (5) surgeries. In 2013, guidelines for perioperative care for pancreaticoduodenectomy (PD) were published by the European Society for Clinical Nutrition and Metabolism and the International Association for Surgical Metabolism and Nutrition; these guidelines contain 27 care items and change to three aspects; preoperation, intraoperation, and postoperation (6). The purpose of these changes was to reduce patients' stress responses and time-to-recovery by close cooperation between surgeons, anesthesiologists, intensive care workers and nurses (7).

At present, pancreaticoduodenectomy is one of the major treatments for malignancies such as pancreatic cancer, periampullary cancer and endocrine neoplasm (8). PD is a technically complex and subtle operation, which has been performed with increasing frequency and decreased mortality rates (9) using ERAS protocols over the past few years. However, morbidity rates have remained high (30–60%) (10). Four meta-analyses confirmed that ERAS can reduce length-of-stay (LOS) and hospital costs; one meta-analysis published in 2013 (11) indicated that the incidence of delayed gastric emptying (DGE) and pancreatic fistula (PF) did not differ significantly between groups, whereas the other three, published in 2015 (12), 2016 (13), and 2018 (14) found that the incidence of DGE was lower in the ERAS groups. In a study from 2015, additional outcome measures were used, and postoperative complication rate and mortality, were reduced in the ERAS groups. Another article published in 2018 (14) mentioned that ERAS has a lower incidence of the mild complications, and abdominal infection. Therefore, ERAS programs in patients undergoing PD have not been completely analyzed, and the use of various outcome measures in different studies increases the difficulty of comparison.

To solve this problem, we need to clarify the real impact of ERAS protocols in this study. The purpose of this meta-analysis was to evaluate the influence of ERAS programs for patients undergoing PD and to provide information for establishing reliable predictions for clinical treatment outcomes.

METHODS

Selection of Studies

Our search used the guidelines of Preferred Reporting Items for Meta-analysis (15). We obtained a list of eligible studies from the following databases: Ovid MEDLINE, OVID EMBase, the Cochrane Library, and ISIWeb of Science, published in English up to May 01, 2018. The search strategy is shown in **Supplemental Method 1**.

Inclusion and Exclusion Criteria

Studies were included in the meta-analysis if the following criteria were met: studies that involved patients undergoing PD, pylorus-preserving pancreatoduodenectomy (PPPD), pancreaticojejunostomy, proximal pancreatic resection, or distal pancreatectomy, approached either with open or minimally invasive surgery; studies that included both an ERAS group and a conventional group, treated by ERAS protocols and conventional care, respectively; studies that reported outcomes such as mortality (in-hospital death, irrespective of duration of stay, or death occurring within 30 days of discharge), reoperation and hospital readmission, various types of fistula such as pancreatic fistula (16) [PF, according to the International Study Group on Pancreatic Fistula (ISGPF), defined as any measurable amount of drainage fluid, with amylase three times the normal level, on or after postoperative day 3], anastomosis leakage, biliary fistula, chylous fistula, intestinal fistula, different types of infections, DGE (17) (need for nasogastric decompression or vomiting occurring), length of hospital stay (LOS) including the postoperative LOS and total LOS and/or costs. Primary outcome measures were mortality, reoperation, readmission, and postoperative complications; complications mainly cover fistula, infection, and DGE. Other outcomes were seen as secondary outcome. The type of study design was observational study.

Studies meeting any of the following selection criteria were excluded: (1) the language is not English, (2) repetitive studies, (3) unobtainable source literature or original data cannot be obtained from the literature, (4) emergency operations, and (5) total pancreatectomy.

Data Extraction and Quality Assessment

Relative data were extracted by two independent authors (Cao and Huang) with a unified standard. Differences or contradictions between the authors were resolved by discussion or consultation of a third investigator (Gu). The extracted variables include country of author; publication year; study design; the age and gender of patients; follow-up time; operation; LOS; mortality; readmission and complications, including fistula, infection, and DGE. Hospital costs were also extracted from the articles, if possible. Methodological quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS) (18, 19) with eight items. A study can be rewarded a maximum of nine stars, with a maximum of two stars for Comparability and one star for each numbered item within the Selection and Exposure categories. More than six stars indicate a study of high quality.

Assessment of Bias

Identified studies were roughly divided into 2 types, either cohort studies or case-control studies, and were assessed using the NOS with the accompanying coding manual for bias. Two authors (Cao and Huang) were independently responsible for assessment of bias.

Statistical Analysis

Meta-analysis was conducted by using the R Programming Language. Dichotomous variables mainly used odds ratio (OR) for mortality, reoperation, readmission, various fistula, infection, and DGE and 95% confidence intervals (CI) obtained by standard technique (20). Mean difference (MD) and standard deviation were calculated for continuous variables. The results were presented graphically using forest plots. Heterogeneity (21) of the included results was detected by I^2. If $I^2 \geq 40\%$, we chose the random effect model, else we selected the fixed effect model. The I^2 statistics represents the amount of variability in the meta-analysis attributed to study heterogeneity. All analyses were conducted with a significance level of 0.05 (22). To determine the source of heterogeneity, results of fistula, infection, DGE, and LOS were analyzed by subgroup; fistula and infection were classified according to type, DGE was divided according to severity, and LOS was divided into preoperative and total time, which can determine the source of heterogeneity.

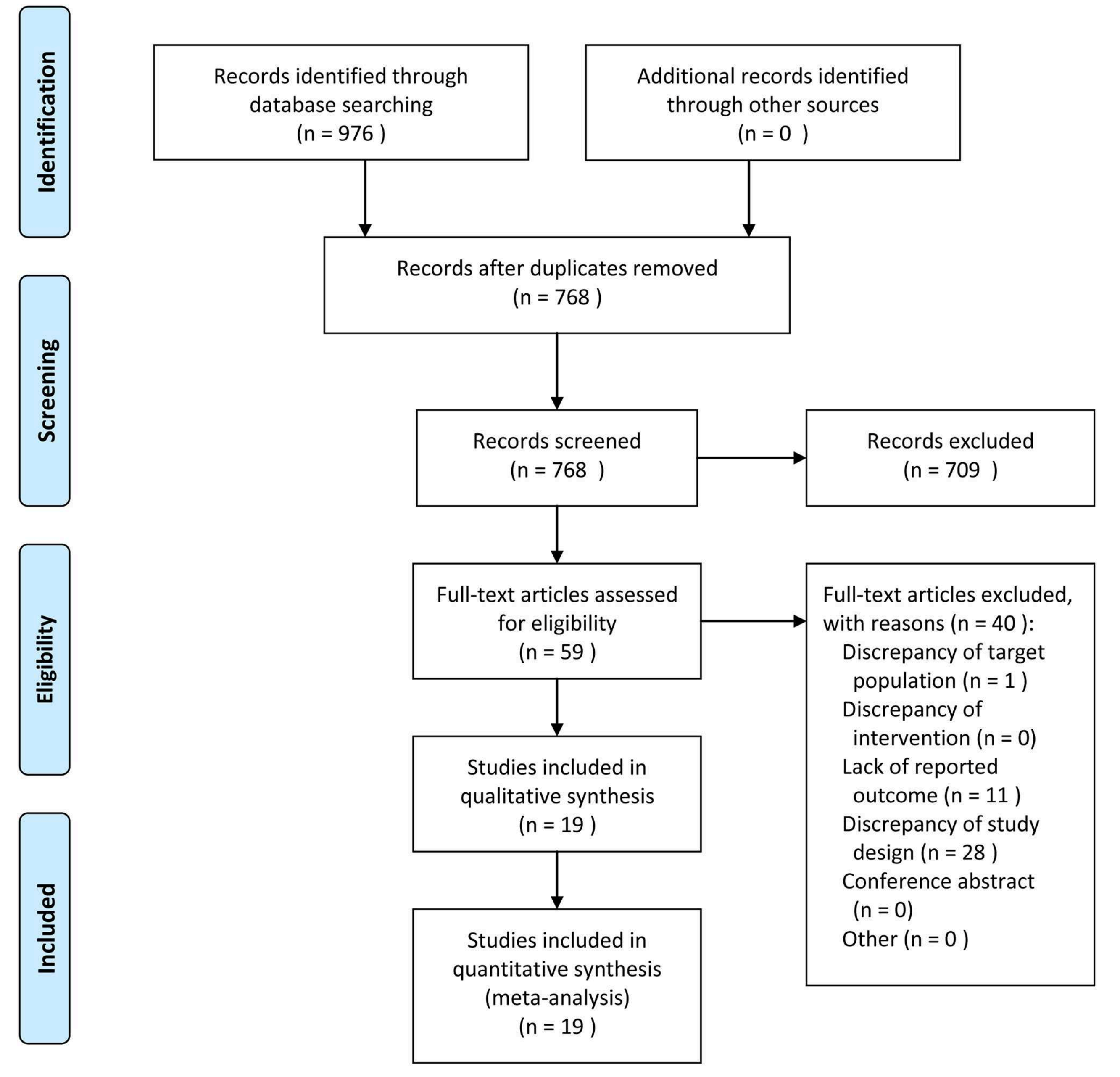


FIGURE 1 | Meta-Analyses (PRISMA) flow diagram depicting the process of identification and inclusion of selected studies.

RESULTS

Literature Identification

The flow of study identification and inclusion is shown in **Figure 1**. The initial search resulted in 976 abstracts. After removing 208 duplicate studies, 768 potentially relevant studies were selected on the basis of the abstract. Then, 709 studies were further excluded on the basis of the abstract, and the full texts of the remaining 59 articles were assessed for eligibility. An additional 40 articles (**Supplemental Table 1**) were excluded. Finally, 19 articles were included in this study.

Study Characteristics

The characteristics of the 19 included articles, which comprised 7 cohort studies (8, 23–28) and 12 case-control studies (7, 29–39), are shown in **Table 1**, which totally contains 3387 patients. Thirteen studies (8, 23, 26, 28–34, 37–39) included patients undergoing PD, one study (35) included patients undergoing distal pancreatectomy (DP), one study (25) included patients undergoing proximal pancreatic resection, one study (36) included patients undergoing laparoscopic pancreatoduodenectomy (LDP), and three studies (7, 24, 27) included patients undergoing two forms of pancreatectomy.

TABLE 1 | Study characteristics.

References	Study design	Group	Age (years)	Male/female	Operations	Follow-up time (months)	Sample size	Country
Balzano et al. (23)	Cohort study	ERAS	64.3 ± 13.75	155/97	PD	36	252	England
		CPC	62.9 ± 14.5	148/104	PD	48	252	
French et al. (25)	Cohort study	ERAS	53.8 ± 11.6	NA	PPR	18	9	England
		CPC	66.2 ± 10.3	NA	PPR	18	49	
Abu Hilal et al. (29)	Case-control	ERAS	68.5 ± 5.58	10/10	PD	15	20	England
		CPC	68.92 ± 11.97	10/14	PD	15	24	
Nikfarjam et al. (33)	Case-control	ERAS	65.5 ± 9	13/7	PD	88	20	Australia
		CPC	55 ± 16.5	12/9	PD	88	21	
Braga et al. (31)	Case-control	ERAS	69 ± 2.17	66/49	PD	26	115	Italy
		CPC	69 ± 2.17	66/49	PD	33	115	
Coolsen et al. (7)	Case-control	ERAS	67 ± 11	44/42	PD/PPPD	24	86	Netherlands
		CPC	62 ± 13	58/39	PD/PPPD	120	97	
Kobayashi et al. (32)	Case-control	ERAS	67.5 ± 10.7	61/39	PD	36	100	Japan
		CPC	65.4 ± 10.8	62/28	PD	48	90	
Pillai et al. (8)	Cohort study	ERAS	44.2 ± 15.9	9/11	PD	8	20	India
		CPC	47.6 ± 12.0	10/10	PD	NA	20	
Williamsson et al. (38)	Case-control	ERAS	69 ± 16.25	31/19	PD	NA	50	Sweden
		CPC	67 ± 14	26/24	PD	36	50	
Richardson et al. (36)	Case-control	ERAS	63.41 ± 12.68	9/13	LDP	19	22	England
		CPC	56.81 ± 22.22	20/24	LDP	48	44	
Shao et al. (27)	Cohort study	ERAS	56.96 ± 11.50	194/131	PD/PPPD	24	325	China
		CPC	57.05 ± 12.30	184/126	PD/PPPD	24	310	
Zouros et al. (39)	Case-control	ERAS	65.9 ± 10.5	46/29	PD	48	75	Greece
		CPC	63.9 ± 11.6	34/16	PD	48	50	
Shah et al. (37)	Case-control	ERAS	61.9 ± 9.1	84/58	PD	50	142	India
		CPC	59.1 ± 10.4	30/16	PD	28	46	
Partelli et al. (34)	Case-control	ERAS	77.75 ± 1.75	14/8	PD	NA	22	Italy
		CPC	78 ± 1.75	33/33	PD	NA	66	
Bai et al. (30)	Case-control	ERAS	58 ± 13	69/55	PD	15	124	China
		CPC	57 ± 12	37/26	PD	9	63	
Dai et al. (24)	Cohort study	ERAS	58.5 ± 12.75	34/34	PD/PPPD	28	68	China
		CPC	58.2 ± 11.5	51/47	PD/PPPD	28	98	
van der Kolk et al. (28)	Cohort study	ERAS	64.59 ± 12.04	56/39	PD	24	95	Netherlands
		CPC	65.29 ± 10.67	35/13	PD	36	52	
Pecorelli et al. (35)	Case-control	ERAS	62.4 ± 13.4	49/51	DP	48	100	Italy
		CPC	60.4 ± 13.8	44/56	DP	48	100	
Kagedan et al. (26)	Cohort study	ERAS	65 ± 13.51	74/47	PD	12	121	Canada
		CPC	65.85 ± 12.10	31/43	PD	18	74	

ERAS, Enhanced Recovery after Surgery; CPC, conventional perioperative care; PD, Pancreaticoduodenectomy; PPR, proximal pancreatic resection; PPPD, pylorus-preserving pancreatoduodenectomy; DP, Distal pancreatoduodenectomy. Values of Age are mean ± SD.

ERAS Characteristics

Characteristics of these studies are shown in **Table 2**. The most common ERAS interventions in the studies were preoperative counseling, antimicrobial prophylaxis and skin preparation, epidural analgesia, postoperative artificial nutrition, and early and scheduled mobilization. That was followed by anti-thrombotic prophylaxis, postoperative nausea and vomiting (PONV) and avoiding hypothermia. However, none of the studies reported on perioperative biliary drainage, preoperative smoking, wound catheters or transversus abdominis plane block, alcohol consumption, or somatostatin analogs.

Quality Assessment of Included Studies

Cohort and case-control studies were both evaluated for bias based on the New-castle-Ottawa Scale (**Supplemental Tables 2, 3**). Among cohort studies, six studies received more than six stars,

TABLE 2 | ERAS characteristics.

References	Group	Enhanced recovery after surgery/Conventional perioperative care interventions																									
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Balzano et al. (23)	ERAS	√								√	√	√	√		√					√						√	√
	CPC									√	√	√	√		√												
French et al. (25)	ERAS																										
	CPC																										
Abu Hilal et al. (29)	ERAS				√						√				√		√			√						√	√
	CPC				√						√	√			√		√			√							
Nikfarjam et al. (33)	ERAS	√			√			√		√	√		√		√			√	√	√					√	√	√
	CPC							√		√	√															√	√
Braga et al. (31)	ERAS	√			√	√	√	√	√	√	√	√			√		√		√	√						√	√
	CPC	√			√	√		√		√	√	√					√		√	√						√	√
Coolsen et al. (7)	ERAS	√			√				√										√								
	CPC																										
Kobayashi et al. (32)	ERAS	√			√		√	√			√	√			√				√							√	√
	CPC							√			√	√			√												
Pillai et al. (8)	ERAS	√									√	√	√		√			√	√							√	√
	CPC										√		√					√								√	
Williamsson et al. (38)	ERAS	√			√					√	√		√		√					√	√				√	√	√
	CPC	√						√			√		√		√												
Richardson et al. (36)	ERAS							√											√		√		√			√	√
	CPC				√																					√	
Shao et al. (27)	ERAS											√														√	
	CPC											√															
Zouros et al. (39)	ERAS	√					√	√	√	√	√	√	√				√			√			√		√	√	√
	CPC																										
Shah et al. (37)	ERAS	√								√	√		√										√			√	√
	CPC																										
Partelli et al. (34)	ERAS	√					√		√	√	√	√					√	√		√		√				√	√
	CPC								√	√	√		√				√	√									√
Bai et al. (30)	ERAS	√					√			√	√		√		√								√				
	CPC	√									√		√		√												
Dai et al. (24)	ERAS	√					√				√	√					√			√			√			√	√
	CPC	√									√	√					√						√				
van der Kolk et al. (28)	ERAS	√			√					√	√	√					√	√		√							√
	CPC	√			√					√	√	√					√	√									√
Pecorelli et al. (35)	ERAS	√					√		√	√	√	√			√		√	√		√			√			√	√
	CPC	√								√	√	√					√	√									√
Kagedan et al. (26)	ERAS	√			√							√						√	√	√						√	√
	CPC																										

ERAS, Enhanced Recovery after Surgery; CPC, conventional perioperative care; Items of Enhanced Recovery After Surgery/Fast-Track Surgery Interventions: 1 = Preoperative counseling, 2 =Perioperative biliary drainage, 3 = Preoperative smoking and alcohol consumption, 4 = Preoperative nutrition, 5 = Perioperative oral immunonutrition (IN), 6 = Oral bowel preparation, 7 = Preoperative fasting and preoperative treatment with carbohydrates, 8 = Preanaesthetic medication, 9 = Anti-thrombotic prophylaxis, 10 = Antimicrobial prophylaxis and skin preparation, 11 = Epidural analgesia, 12 = Intravenous analgesia Some evidence, 13 = Wound catheters and transversus abdominis plane block, 14 = Postoperative nausea and vomiting (PONV), 15 = Incision, 16 = Avoiding hypothermia, 17 = Postoperative glycaemic control, 18 = Nasogastric intubation, 19 = Fluid balance, 20 = Perianastomotic drain, 21 = Somatostatin analogs, 22 = Urinary drainage, 23 = Delayed gastric emptying, 24 = Stimulation of bowel movement, 25 = Postoperative artificial nutrition, 26 = Early and scheduled mobilization.

while the remaining study (25) received six stars. Among case-control studies, most articles obtained at least six stars, and only two articles received fewer than six stars. Therefore, most of the studies considered for this meta-analysis were of high quality.

Primary Outcome Measures

Fistula

Our results illustrate the incidence of complications comparing a multimodal ERAS protocol to conventional care. ERAS is associated with a decreased incidence of PF [**Figure 2**; number of comparisons reporting outcome ($n = 16$; OR = 0.79; 95% CI: 0.67–0.95; P for heterogeneity = 0.50, $I^2 = 0\%$)]. However, subgroup analysis of studies for other fistulas showed that the ERAS group did not differ significantly from the control group in the incidence of anastomosis leakage ($n = 1$; OR = 0.96; 95% CI: 0.31–2.99; heterogeneity is not applicable), biliary fistula ($n = 7$; OR = 1.16; 95% CI: 0.69 to 1.97; P for heterogeneity = 0.45, $I^2 = 0\%$), chylous fistula ($n = 3$; OR = 0.91; 95% CI: 0.56 to 1.46; P for heterogeneity = 0.37, $I^2 = 0\%$) and intestinal fistula ($n = 1$; OR = 0.50; 95% CI: 0.03 to 8.19; heterogeneity is not applicable). Sensitive analysis of the quality of the article was performed after removing two articles with less than six stars, and the conclusion is the same as before ($n = 14$; OR = 0.84; 95% CI: 0.72 to 0.98; P for heterogeneity = 0.51, $I^2 = 0\%$).

Infection

Compared to the control group, the incidence of infection (**Figure 3**; OR = 0.63; 95% CI: 0.50 to 0.78) was lower in the ERAS group. Different types of infections were mentioned in the studies, and the data for each infection are different. ERAS was associated with a lower incidence of incision infection ($n = 9$; OR = 0.62; 95% CI: 0.42 to 0.91) and pulmonary infection ($n = 4$; OR = 0.28; 95% CI: 0.12 to 0.66), but there were no significant differences in abdominal infection ($n = 3$; OR = 0.72; 95% CI: 0.52 to 1.00) and urinary infection ($n = 3$; OR = 0.46; 95% CI: 0.14 to 1.49) between the experimental group and the control group. No heterogeneity was found in this subgroup analysis ($I^2 = 0\%$, $P = 0.86$).

Sensitive analysis of the quality of the article was performed after removing two articles with less than six stars, and the conclusion is the same as before ($n = 14$; OR = 0.84; 95% CI: 0.72 to 0.98; P for heterogeneity = 0.51, $I^2 = 0\%$).

Delayed Gastric Emptying

Differences in the rates of DGE (**Figure 4**) were not consistently reduced in the ERAS group. There was also no significant difference between the control group and the experimental group in different grades of DGE. Five studies (7, 8, 24, 38, 39) reported DGE grade A (OR = 0.54; 95% CI: 0.18 to 1.67; $I^2 = 76\%$, $p < 0.01$), grade B (OR = 0.67; 95% CI: 0.37 to 1.20; $I^2 = 0\%$, $p = 0.45$), and grade C (OR = 0.66; 95% CI: 0.35 to 1.24; $I^2 = 33\%$, $p = 0.20$). There was moderate heterogeneity in this subgroup analysis ($I^2 = 46\%$, $p = 0.03$) using the random effects model.

Mortality

Sixteen studies (7, 8, 23–25, 28–32, 34–39) reported mortality as the primary outcome (**Figure 5**). The OR for mortality was 0.96 (95% CI: 0.59 to 1.55). Compared with the control group, the risk of mortality in the ERAS group was not significantly different. The heterogeneity determination of these studies using the fixed effect model was $I^2 = 0\%$, $P = 0.99$; therefore, no heterogeneity was found. After eliminating two articles with less than six stars in their quality scores, the result is as follows: OR = 0.94; 95% CI: 0.58 to 1.55; P for heterogeneity = 0.97, $I^2 = 0\%$.

Readmission

The primary outcome measure readmission **(Figure 6**) was also used in 16 studies (7, 23, 24, 26–37, 39). No significant difference from the control group was found when evaluating the combination of all included studies (OR = 1.02; 95% CI: 0.80 to 1.28). No heterogeneity ($I^2 = 0\%$, P for heterogeneity = 0.86) using the fixed effect model was detected. After eliminating two articles with less than six stars in their quality scores, the result is as follows: OR = 1.03, 95% CI: 0.82 to 1.31; P for heterogeneity = 0.85, $I^2 = 0\%$.

Reoperation

Reoperation data were shown in 8 studies (7, 23, 24, 28–31, 39). We found no evidence that reoperation (**Figure 7**) performed significantly differently between the two groups in the fixed effect model (OR = 0.82; 95% CI: 0.55 to 1.21). No heterogeneity ($I^2 = 0$; $p = 0.80$) was detected.

Secondary Outcome Measures

All studies reported the secondary outcome: LOS (MD = −3.89; 95% CI: −4.98 to −2.81; $I^2 = 78\%$, $p < 0.01$; **Figure 8**). Meta-analysis including 1,087 patients showed that patients in the ERAS group had a shorter postoperative LOS than those in the conventional group (MD = −4.60 days; 95% CI: −5.85 to −3.36), although a moderate degree of heterogeneity was observed ($I^2 = 55\%$, $P = 0.02$). Ten studies (7, 24–26, 28, 31, 34, 35, 37, 39) provided the data total LOS. The estimated mean for the meta-analysis of these studies was −3.12 days (95% CI: −4.81 to −1.42), indicating a significant reduction in the mean of total LOS for the ERAS patients compared with the conventional group. The statistical results of I^2 (83%) showed highly heterogeneous research results in forest plots. Hospitalization costs (**Figure 9**) were reported by five studies and statistical analysis showed that ERAS protocols significantly reduced costs. Only one of the articles showed a lower cost in the control group. Pancreatic surgery can cost up to tens of thousands of dollars and costs at least several thousand dollars.

DISCUSSION

Progress in surgical techniques, improvements in equipment, technology, anesthesia, and perioperative care have contributed significantly to reducing the mortality after pancreatoduodenectomy; in most high-volume centers, the mortality rate is <5% (9). While reducing mortality, the emphasis now is on strengthening rehabilitation and reducing complications (8). Complications are a major reason for longer LOS. Previous studies have shown that reducing complications can reduce LOS. Some controversies

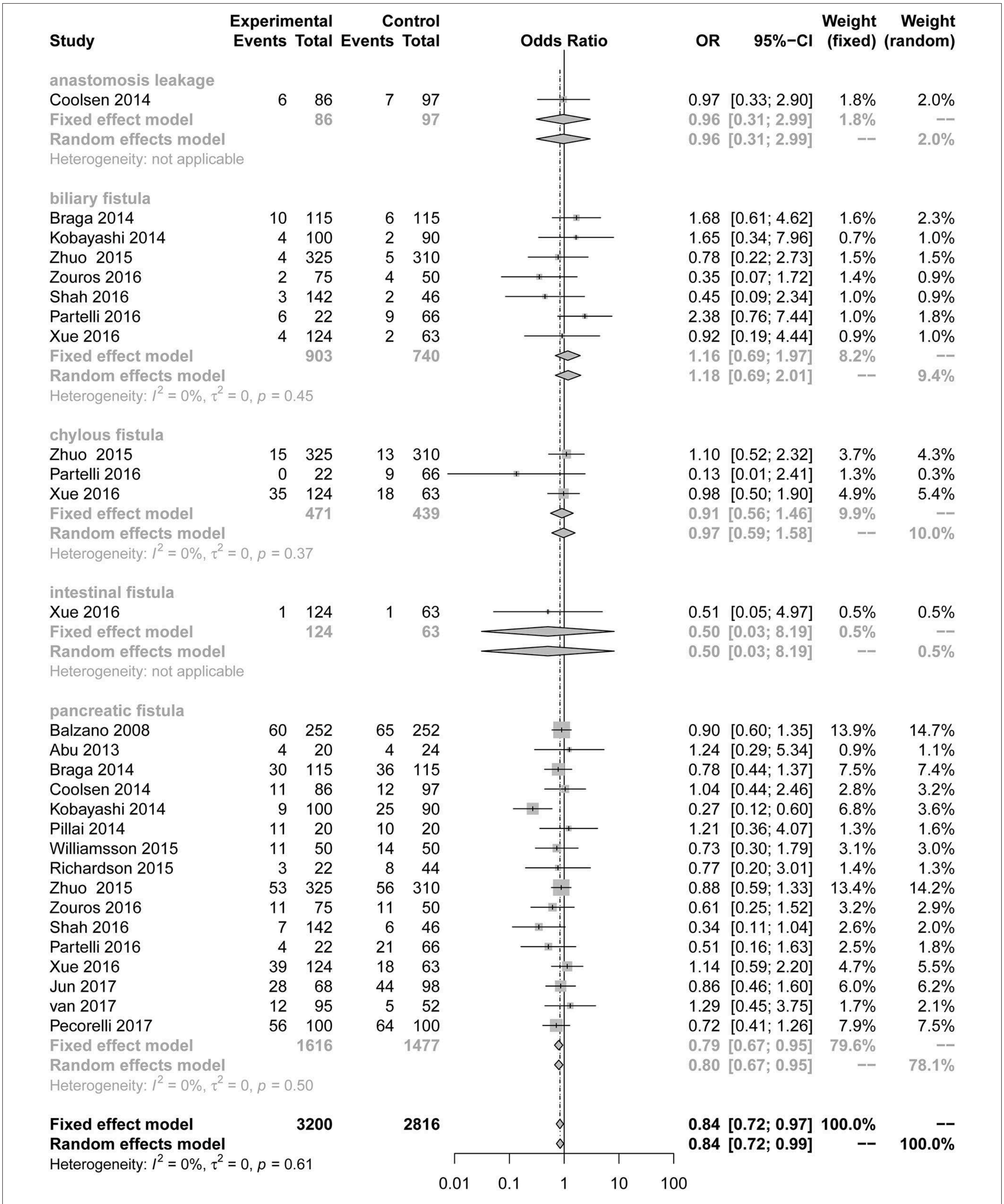


FIGURE 2 | Forest plots demonstrating fistula of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy by subgroup analysis.

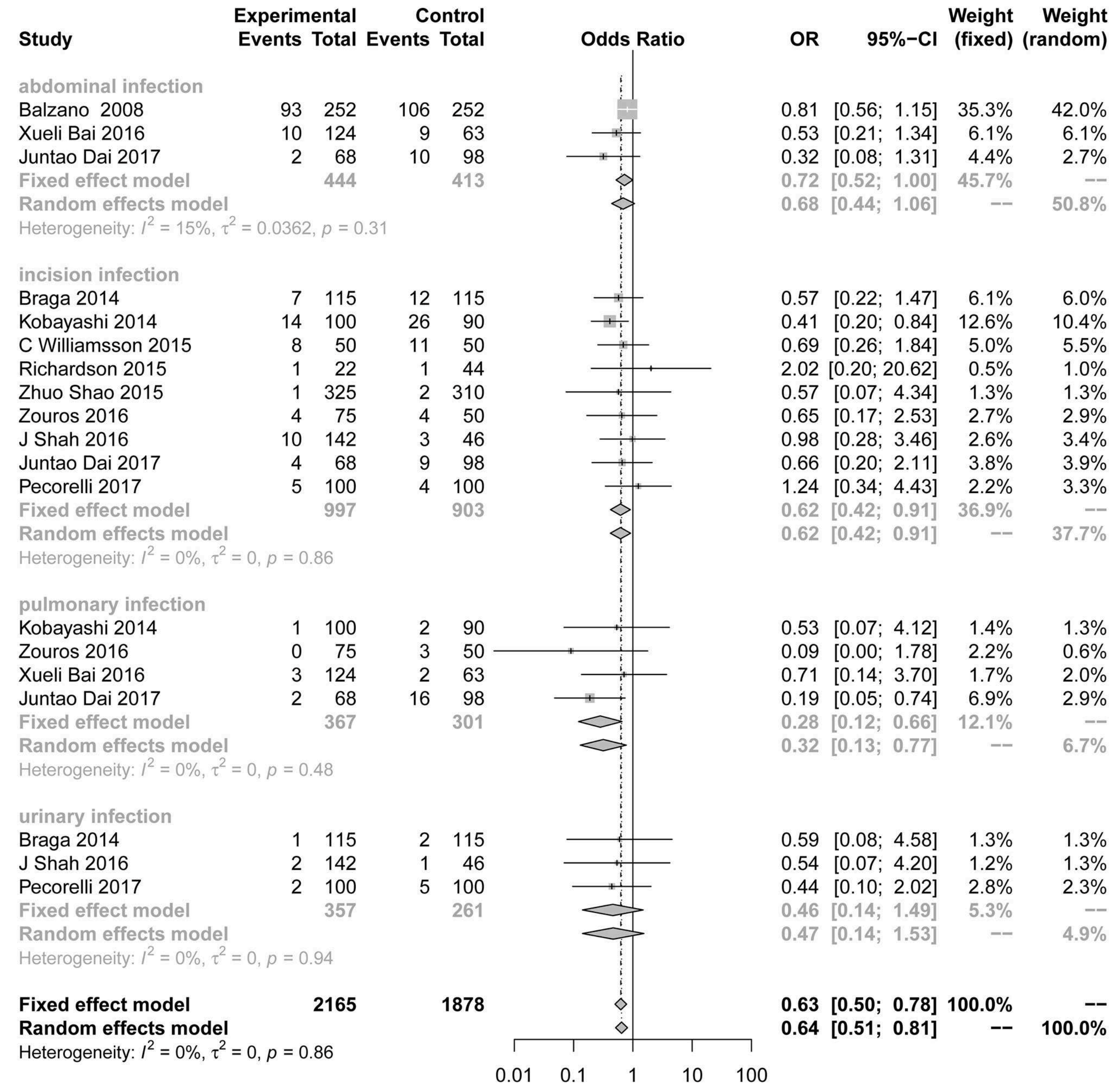


FIGURE 3 | Forest plots demonstrating infection of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy by subgroup analysis.

regarding decreasing complications such as pancreatic fistula, infection and DGE using ERAS protocols after PD still persists.

A large number of data in this meta-analysis showed that ERAS and conventional groups did not significantly differ in the rates of mortality, reoperation, and readmission indicating that earlier discharge after implementation of the ERAS protocol did not affect patient morbidity (24). Most of the readmissions were due to complications, and slightly longer hospital stays can be greatly reduced (37). The results of this study suggest that the number of complications, such as PF and infection, can be safely decreased using ERAS protocols, especially with regard to incision and pulmonary infections. Reducing blood loss during surgery can reduce postoperative complications, especially suppurative infections (40). Because of the electronic laparoscopy used in some surgeries, the incision is smaller, the amount of bleeding is correspondingly reduced, and the chance of incision infection is greatly reduced. The reduction of pulmonary infection may be caused by early mobilization (41) and early removal of nasogastric tubes (42). In most surgeries,

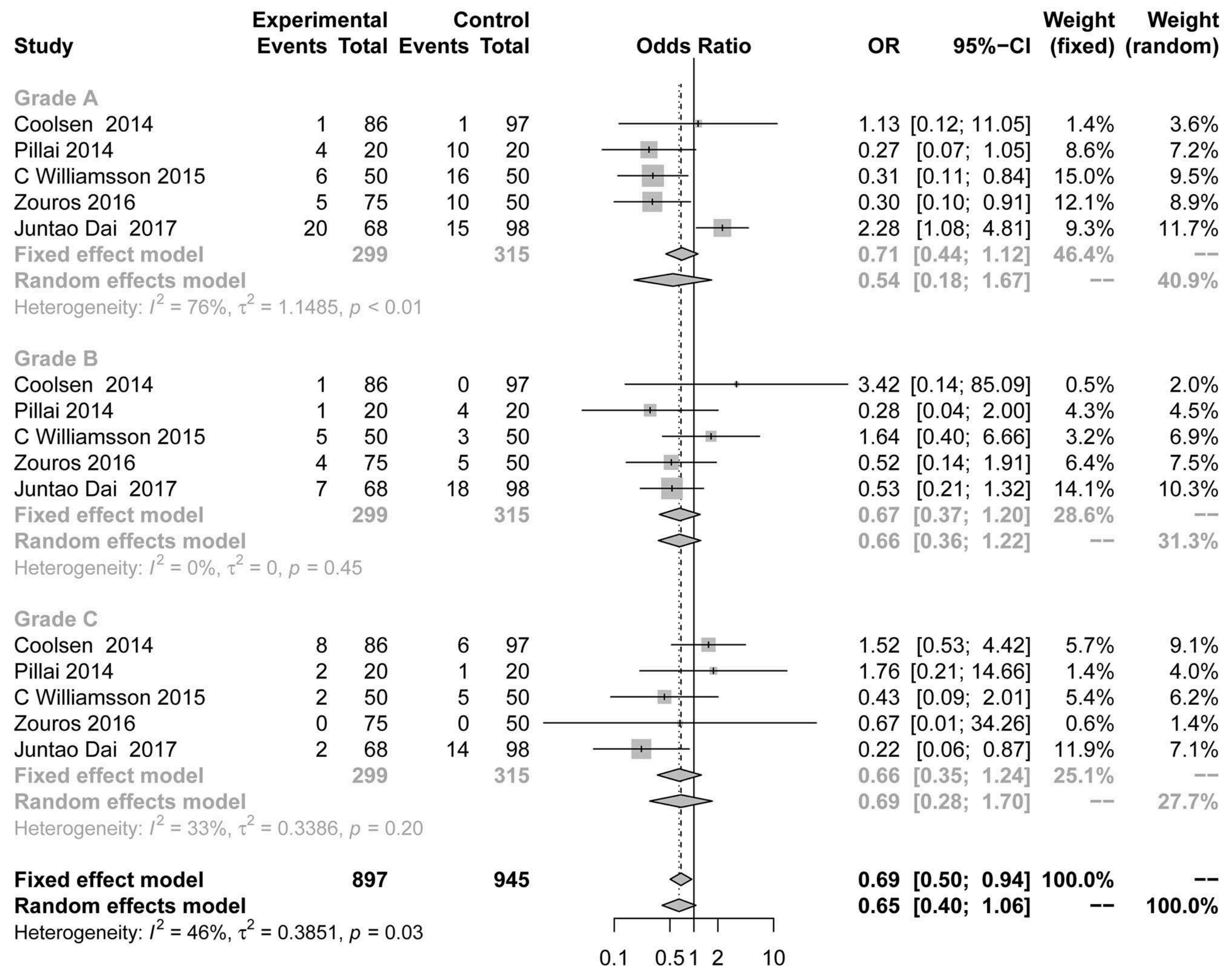


FIGURE 4 | Forest plots demonstrating DGE of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy by subgroup analysis.

the nasogastric tube was removed 1 day after placement to monitor hemorrhage in all types of anastomosis. Prolonged placement of the nasogastric tube can lead to fever, pneumonia and atelectasis (37). The reduction in these complications is desirable because they are the most common complications in patients undergoing PD and constitute the dominant reasons for prolonged LOS and high hospital costs (43). Other types of fistula after operation have been investigated in this meta-analysis, such as anastomotic fistula, biliary fistula, chylous fistula and intestinal fistula. Perhaps owing to the small sample size, no statistical significance could be found. One study suggested early post-operative feeding may improve gastric emptying and peristalsis in the intestine, thereby reducing DGE (44). A subgroup analysis of DGE showed no significant correlation with DGE grade, independent of utilization of the ERAS program. This finding indicated that heterogeneity of DGE was mainly derived from grade A, but such a result did not indicate a limitation of ERAS.

Regarding secondary outcome measures, ERAS programs are associated with shorter LOS, both in the postoperative LOS and total LOS. From a patient perspective, the reduction in postoperative LOS is associated with reduced DGE rates and an earlier return to normal nutrition and enteric function, as well as lower levels of pain and a quicker return to preoperative levels of mobility, resulting in an overall improvement in the postoperative experience. One of the determining factors is the healthcare system depending on different cultural and economic environments. The variable may contribute to the higher heterogeneity observed in our analysis, which was different when analyzing only studies from western centers or Asian countries (13). Some of the reduced LOS is not just improvement of the hospital medical equipment, but includes the patients without the complications (39). The use of laparoscopic technique can make time shorter during operations (27). This result is consistent with a meta-analysis of pancreaticoduodenectomy showing a reduction in the LOS with 4 days (13). Hospitalization costs

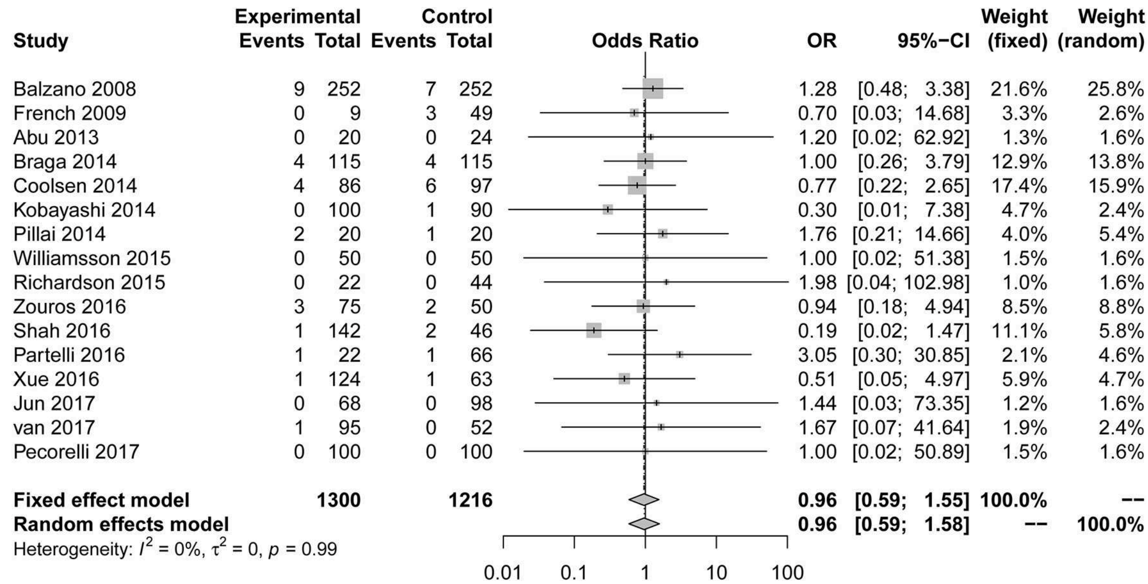


FIGURE 5 | Forest plots demonstrating the mortality of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy.

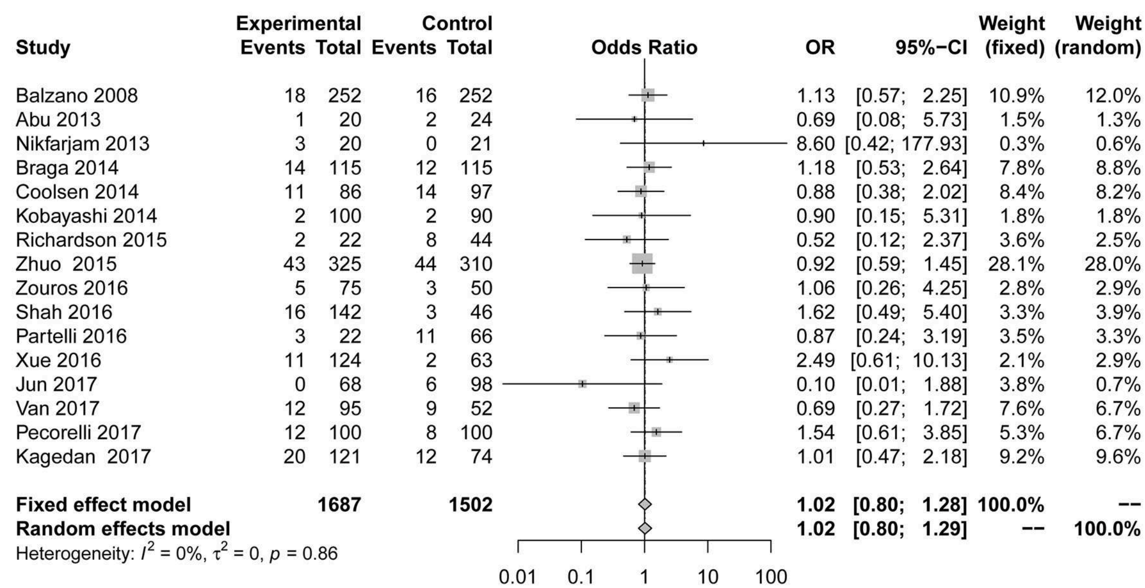


FIGURE 6 | Forest plots demonstrating readmission of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy by subgroup analysis.

were lower in the experimental group than in the control group, independent of the country in which the treatment was received. Fewer complications and LOS correspondingly lead to fewer costs. Sometimes it is undeniable that doctors don't have a uniform level of expertise, and less experienced doctors need more tests to help diagnosis and patients spend more. One of the articles found that the most important economic effect associated with ERAS was the cost reduction in laboratory investigations, medical imaging, pharmaceuticals and patient food (26). There is no denying that laparoscopic surgery, or the use of robotic surgery, can have varying degrees of impact on the cost and recovery time of surgery. In this study, there was only one case of laparoscopic surgery and no robotic surgery.

Compared with the meta-analyses published in 2016 (13) and 2018 (14), we found consistency in LOS, rates of readmission, reoperation, and mortality. However, PF rates were lower for the ERAS group in our study. Additionally, incision infection and pulmonary infection rates were reduced in the ERAS group. DGE rates did not differ between the two groups in our study. According to the guideline for pylorus-preserving PDs, it has

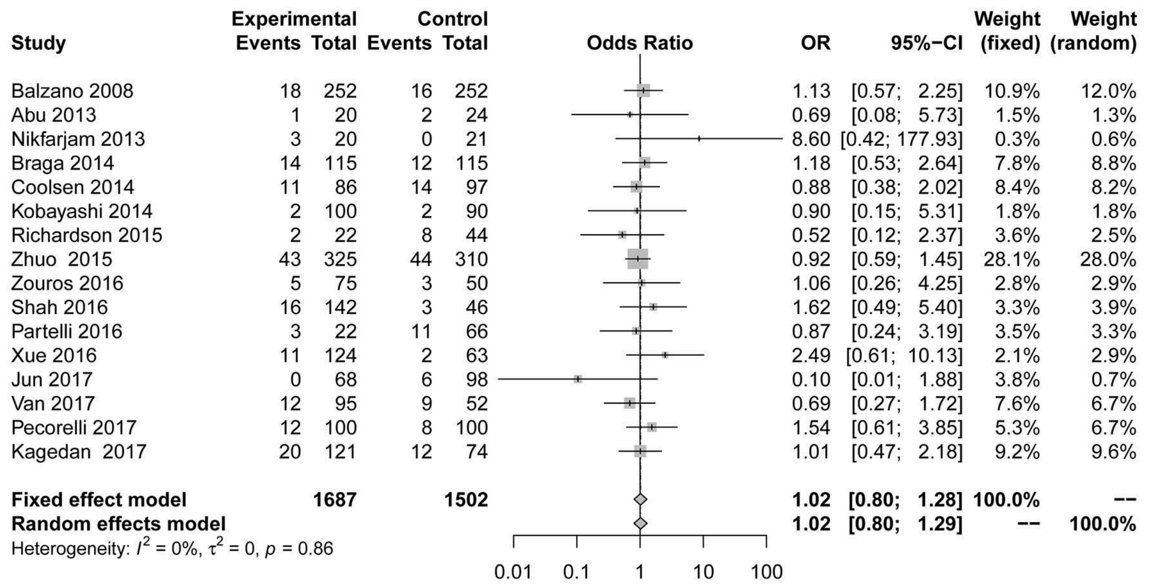


FIGURE 7 | Forest plots demonstrating reoperation of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy by subgroup analysis.

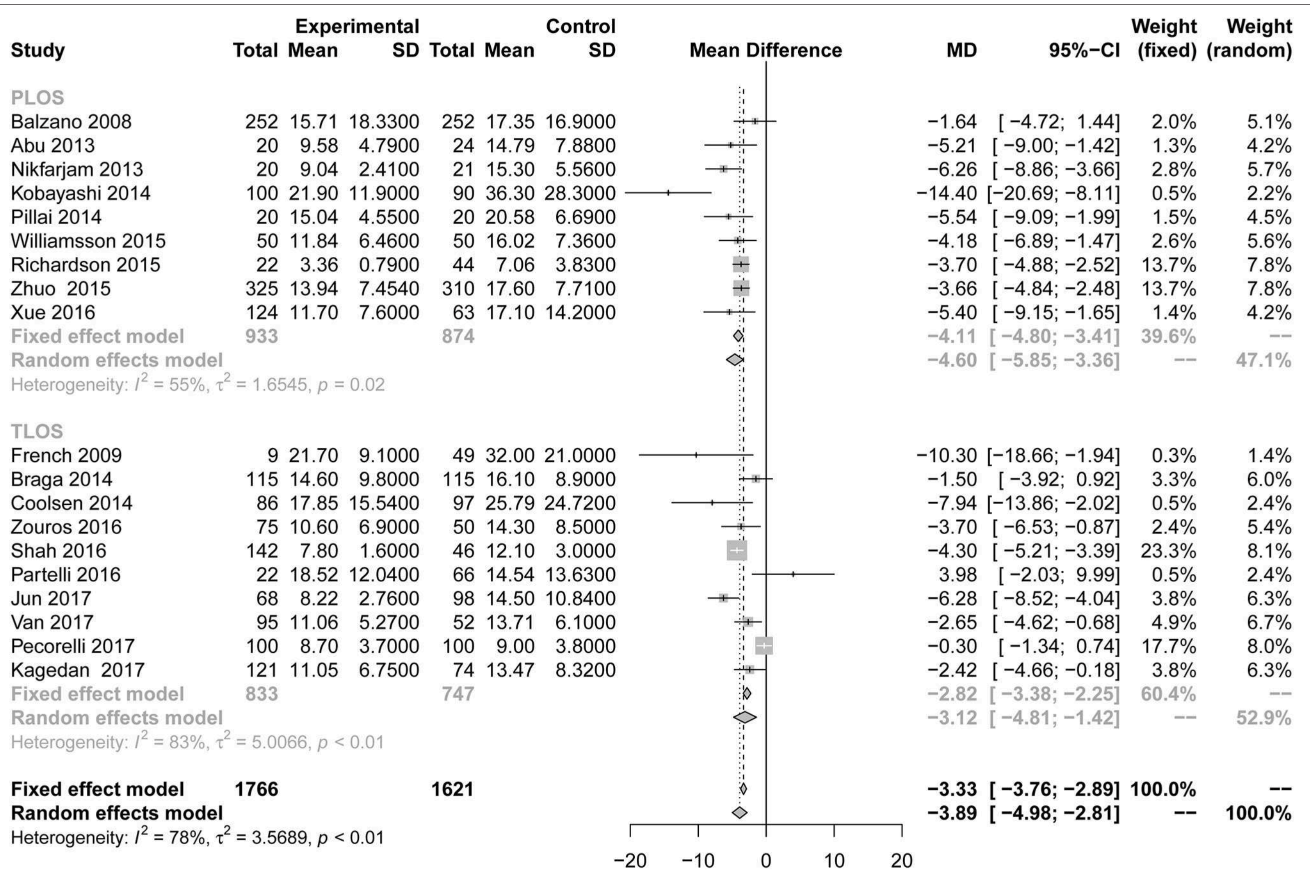


FIGURE 8 | Forest plots demonstrating LOS of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy by subgroup analysis.

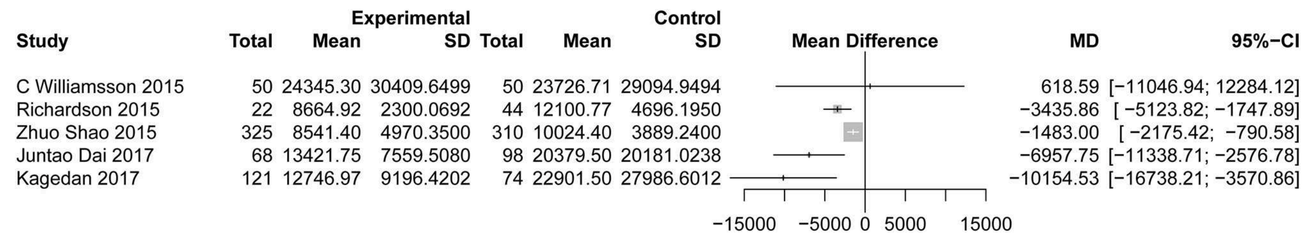


FIGURE 9 | Forest plots demonstrating cost of studies in terms of ERAS vs. CPC after pancreaticoduodenectomy.

been shown that constructing the duodenojejunostomy in an antecolic (as opposed to a retro-colic) fashion results in reduced DGE (6). Thus, we need more data to certify that ERAS can decrease the rate of DGE. It should be noted that early postoperative oral intake does not worsen anastomotic leakage in colorectal surgery (45). Early postoperative oral intake has been avoided in patients undergoing PD with the concern that it may stimulate pancreatic exocrine secretion, resulting in an increased incidence of PF (32).

The purpose of ERAS protocols is to reduce patient stress; so it is important that guidelines mention several major measures: preoperative counseling with various information, avoiding oral bowel preparation and limiting fluid intake. The first measure can eliminate patients' preoperative anxiety (46), and the next one can decrease the incidence of anastomotic insufficiency (47), and liquid management can also reduce anastomotic fistula; this recommendation is also mentioned in the ERAS published in 2018. The included studies did not report the choice of incision at the surgeon's discretion, which should be of a length sufficient to ensure good exposure, so it cannot provide the evidence for clinical treatment. Pre-emptive use of nasogastric tubes postoperatively does not improve outcomes, and their use is not warranted routinely in the guidelines. An important measure is the early removal of the nasogastric duct, which can reduce the incidence of PF, consistently with the outcomes of many studies. Studies have shown that the carbohydrate beverage given to patients on the night before surgery and 2∼4 h before surgery can alleviate the above stress response to some extent. To sum up, the ERAS program appears to be feasible in pancreaticoduodenectomy.

This meta-analysis not only provides evidence for using ERAS guidelines but also shows a new result regarding infection. ERAS can reduce incisions and lung infections. At the same time, the main outcome of this study was not LOS but the effect of the surgery itself, which has significant impact on clinical outcomes. The study incorporated all observational studies that contained large data groups to support the results reported and to increase the accuracy of the results.

This study has three main limitations: (1) it is unlikely that truly blinded, case-control studies regarding ERAS protocols will be performed due to a lack of feasibility. (2) It is very difficult to compare the incidence rates between different treatment centers according to the confirmed case, as the study reported the complication classification scheme (Clavien classification), and a suggestion for grading the complications based on the treatment intervention was to use a compound endpoint, which would reduce the required sample size study and improve objectivity and comparability. (3) Only two studies were randomized controlled trials (48, 49); therefore, data contained in these studies cannot be effectively analyzed.

CONCLUSION

In conclusion, this meta-analysis showed a decrease in the rates of PF, infection, LOS and hospital costs without increasing the incidence of mortality, readmission, or reoperation in patients undergoing pancreatic duodenal surgery when ERAS protocols were applied in the patients' perioperative care. This is the time to promote the use of ERAS pathways as a protocol to restore patients' health after a complex and delicate surgery. With continued improvement in outcome results, ERAS protocols will attain the standard for primary abdominal surgeries.

DATA AVAILABILITY

The datasets for this manuscript are not publicly available because all the data is in the manuscript. Requests to access the datasets should be directed to YF, fuyan_taihe0601@163.com.

AUTHOR CONTRIBUTIONS

CZ and YF had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. JL, YC, and CZ designed the study. JL, YC, and Z-DH developed and tested the data collection forms. H-YG, Y-PW, and QZ acquired the data. YC, H-YG, and Z-DH conducted the analysis and interpreted the data. YC drafted the manuscript. CZ and YF had guarantor. All authors critically revised the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.00687/full#supplementary-material

REFERENCES

1. Basse L, Thorbol JE, Lossl K, Kehlet H. Colonic surgery with accelerated rehabilitation or conventional care. *Dis Colon Rectum.* (2004) 47:271–7. doi: 10.1007/s10350-003-0055-0
2. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg.* (2002) 183:630–41. doi: 10.1016/S0002-9610(02)00866-8
3. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg.* (2008) 248:189–98. doi: 10.1097/SLA.0b013e31817f2c1a
4. Lassen K, Kjaeve J, Fetveit T, Trano G, Sigurdsson HK, Horn A, et al. Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. *Ann Surg.* (2008) 247:721–9. doi: 10.1097/SLA.0b013e31815cca68
5. Malviya A, Martin K, Harper I, Muller SD, Emmerson KP, Partington PF, et al. Enhanced recovery program for hip and knee replacement reduces death rate. *Acta Orthop.* (2011) 82:577–81. doi: 10.3109/17453674.2011.618911
6. Lassen K, Coolsen MM, Slim K, Carli F, de Aguilar-Nascimento JE, Schafer M, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS(R)) society recommendations. *World J Surg.* (2013) 37:240–58. doi: 10.1007/s00268-012-1771-1
7. Coolsen MM, van Dam RM, Chigharoe A, Olde Damink SW, Dejong CH. Improving outcome after pancreaticoduodenectomy: experiences with implementing an enhanced recovery after surgery (ERAS) program. *Dig Surg.* (2014) 31:177–84. doi: 10.1159/000363583
8. Pillai SA, Palaniappan R, Pichaimuthu A, Rajendran KK, Sathyanesan J, Govindhan M. Feasibility of implementing fast-track surgery in pancreaticoduodenectomy with pancreaticogastrostomy for reconstruction–a prospective cohort study with historical control. *Int J Surg.* (2014) 12:1005–9. doi: 10.1016/j.ijsu.2014.07.002
9. de Wilde RF, Besselink MG, van der Tweel I, de Hingh IH, van Eijck CH, Dejong CH, et al. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. *Br J Surg.* (2012) 99:404–10. doi: 10.1002/bjs.8664
10. Berberat PO, Ingold H, Gulbinas A, Kleeff J, Muller MW, Gutt C, et al. Fast track–different implications in pancreatic surgery. *J Gastrointest Surg.* (2007) 11:880–7. doi: 10.1007/s11605-007-0167-2
11. Coolsen MM, van Dam RM, van der Wilt AA, Slim K, Lassen K, Dejong CH. Systematic review and meta-analysis of enhanced recovery after pancreatic surgery with particular emphasis on pancreaticoduodenectomies. *World J Surg.* (2013) 37:1909–18. doi: 10.1007/s00268-013-2044-3
12. Lei Q, Wang X, Tan S, Wan X, Zheng H, Li N. Application of enhanced recovery after surgery program in perioperative management of pancreaticoduodenectomy: a systematic review. *Zhonghua Wei Chang Wai Ke Za Zhi.* (2015) 18:143–9.
13. Xiong J, Szatmary P, Huang W, de la Iglesia-Garcia D, Nunes QM, Xia Q, et al. Enhanced recovery after surgery program in patients undergoing pancreaticoduodenectomy: a PRISMA-compliant systematic review and meta-analysis. *Medicine.* (2016) 95:e3497. doi: 10.1097/MD.0000000000003497
14. Ji HB, Zhu WT, Wei Q, Wang XX, Wang HB, Chen QP. Impact of enhanced recovery after surgery programs on pancreatic surgery: a meta-analysis. *World J Gastroenterol.* (2018) 24:1666–78. doi: 10.3748/wjg.v24.i15.1666
15. Toews LC. Compliance of systematic reviews in veterinary journals with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) literature search reporting guidelines. *J Med Library Assoc.* (2017) 105:233–9. doi: 10.5195/JMLA.2017.246
16. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery.* (2005) 138:8–13. doi: 10.1016/j.surg.2005.05.001
17. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic *Surgery* (ISGPS). *Surgery.* (2007) 142:761–8. doi: 10.1016/j.surg.2007.05.005
18. Margulis AV, Pladevall M, Riera-Guardia N, Varas-Lorenzo C, Hazell L, Berkman ND, et al. Quality assessment of observational studies in a drug-safety systematic review, comparison of two tools: the Newcastle-Ottawa Scale and the RTI item bank. *Clin Epidemiol.* (2014) 6:359–68. doi: 10.2147/CLEP.S66677
19. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* (2010) 25:603–5. doi: 10.1007/s10654-010-9491-z
20. Green S, Higgins J. *Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0.* Cochrane Library, The Cochrane Collaboration, United Kingdom (2011).
21. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ.* (2001) 323:101–5. doi: 10.1136/bmj.323.7304.101
22. Visioni A, Shah R, Gabriel E, Attwood K, Kukar M, Nurkin S. Enhanced recovery after surgery for noncolorectal surgery?: a systematic review and meta-analysis of major abdominal surgery. *Ann. Surg.* (2018) 267:57–65. doi: 10.1097/SLA.0000000000002267
23. Balzano G, Zerbi A, Braga M, Rocchetti S, Beneduce AA, Di Carlo V. Fast-track recovery programme after pancreatico- duodenectomy reduces delayed gastric emptying. *Br J Surg.* (2008) 95:1387–93. doi: 10.1002/bjs.6324
24. Dai J, Jiang Y, Fu D. Reducing postoperative complications and improving clinical outcome: enhanced recovery after surgery in pancreaticoduodenectomy - a retrospective cohort study. *Int J Surg.* (2017) 39:176–81. doi: 10.1016/j.ijsu.2017.01.089
25. French JJ, Mansfield SD, Jaques K, Jaques BC, Manas DM, Charnley RM. Fast-track management of patients undergoing proximal pancreatic resection. *Ann R Coll Surg Engl.* (2009) 91:201–4. doi: 10.1308/003588409X391893
26. Kagedan DJ, Devitt KS, Tremblay St-Germain A, Ramjaun A, Cleary SP, Wei AC. The economics of recovery after pancreatic surgery: detailed cost minimization analysis of an enhanced recovery program. *HPB.* (2017) 19:1026–33. doi: 10.1016/j.hpb.2017.07.013
27. Shao Z, Jin G, Ji W, Shen L, Hu X. The role of fast-track surgery in pancreaticoduodenectomy: a retrospective cohort study of 635 consecutive resections. *Int J Surg.* (2015) 15:129–33. doi: 10.1016/j.ijsu.2015.01.007
28. van der Kolk M, van den Boogaard M, Becking-Verhaar F, Custers H, van der Hoeven H, Pickkers P, et al. Implementation and evaluation of a clinical pathway for pancreaticoduodenectomy procedures: a prospective cohort study. *J Gastrointest Surg.* (2017) 21:1428–41. doi: 10.1007/s11605-017-3459-1
29. Abu Hilal M, Di Fabio F, Badran A, Alsaati H, Clarke H, Fecher I, et al. Implementation of enhanced recovery programme after pancreatoduodenectomy: a single-centre UK pilot study. *Pancreatology.* (2013) 13:58–62. doi: 10.1016/j.pan.2012.11.312
30. Bai X, Zhang X, Lu F, Li G, Gao S, Lou J, et al. The implementation of an enhanced recovery after surgery (ERAS) program following pancreatic surgery in an academic medical center of China. *Pancreatol.* (2016) 16:665–70. doi: 10.1016/j.pan.2016.03.018
31. Braga M, Pecorelli N, Ariotti R, Capretti G, Greco M, Balzano G, et al. Enhanced recovery after surgery pathway in patients undergoing pancreaticoduodenectomy. *World J Surg.* (2014) 38:2960–6. doi: 10.1007/s00268-014-2653-5
32. Kobayashi S, Ooshima R, Koizumi S, Katayama M, Sakurai J, Watanabe T, et al. Perioperative care with fast-track management in patients undergoing pancreaticoduodenectomy. *World J Surg.* (2014) 38:2430–7. doi: 10.1007/s00268-014-2548-5
33. Nikfarjam M, Weinberg L, Low N, Fink MA, Muralidharan V, Houli N, et al. A fast track recovery program significantly reduces hospital length of stay following uncomplicated pancreaticoduodenectomy. *J Pancreas.* (2013) 14:63–70. doi: 10.6092/1590-8577/1223
34. Partelli S, Crippa S, Castagnani R, Ruffo G, Marmorale C, Franconi AM, et al. Evaluation of an enhanced recovery protocol after pancreaticoduodenectomy in elderly patients. *HPB.* (2016) 18:153–8. doi: 10.1016/j.hpb.2015.09.009
35. Pecorelli N, Capretti G, Balzano G, Castoldi R, Maspero M, Beretta L, et al. Enhanced recovery pathway in patients undergoing distal pancreatectomy: a case-matched study. *HPB.* (2017) 19:270–8. doi: 10.1016/j.hpb.2016.10.014
36. Richardson J, Di Fabio F, Clarke H, Bajalan M, Davids J, Abu Hilal M. Implementation of enhanced recovery programme for laparoscopic distal pancreatectomy: feasibility, safety and cost analysis. *Pancreatology.* (2015) 15:185–90. doi: 10.1016/j.pan.2015.01.002

37. Shah OJ, Bangri SA, Singh M, Lattoo RA, Bhat MY, Khan FA. Impact of centralization of pancreaticoduodenectomy coupled with fast track recovery protocol: a comparative study from India. *Hepatobil Pancreat Dis Int*. (2016) 15:546–52. doi: 10.1016/S1499-3872(16)60093-0
38. Williamsson C, Karlsson N, Sturesson C, Lindell G, Andersson R, Tingstedt B. Impact of a fast-track surgery programme for pancreaticoduodenectomy. *Br J Surg*. (2015) 102:1133–41. doi: 10.1002/bjs.9856
39. Zouros E, Liakakos T, Machairas A, Patapis P, Agalianos C, Dervenis C. Improvement of gastric emptying by enhanced recovery after pancreaticoduodenectomy. *Hepatobil Pancreat Dis Int*. (2016) 15:198–208. doi: 10.1016/S1499-3872(16)60061-9
40. Bottger TC, Junginger T. Factors influencing morbidity and mortality after pancreaticoduodenectomy: critical analysis of 221 resections. *World J Surg*. (1999) 23:164–71. doi: 10.1007/PL00013170
41. Yip VS, Dunne DF, Samuels S, Tan CY, Lacasia C, Tang J, et al. Adherence to early mobilisation: Key for successful enhanced recovery after liver resection. *Eur J Surg Oncol*. (2016) 42:1561–7. doi: 10.1016/j.ejso.2016.07.015
42. Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. *Cochrane Database Syst Rev*. (2007) Cd004929. doi: 10.1002/14651858.CD004929.pub3
43. Hanna MM, Gadde R, Allen CJ, Meizoso JP, Sleeman D, Livingstone AS, et al. Delayed gastric emptying after pancreaticoduodenectomy. *J Surg Res*. (2016) 202:380–8. doi: 10.1016/j.jss.2015.12.053
44. Luckey A, Livingston E, Tache Y. Mechanisms and treatment of postoperative ileus. *Arch Surg*. (2003) 138:206–14. doi: 10.1001/archsurg.138.2.206
45. Wind J, Hofland J, Preckel B, Hollmann MW, Bossuyt PM, Gouma DJ, et al. Perioperative strategy in colonic surgery; LAparoscopy and/or FAst track multimodal management versus standard care (LAFA trial). *BMC Surg*. (2006) 6:16. doi: 10.1186/1471-2482-6-16
46. Egbert LD, Battit GE, Welch CE, Bartlett MK. Reduction of postoperative pain by encouragement and instruction of patients. A study of doctor-patient rapport. *N Eng J Med*. (1964) 270:825–7. doi: 10.1056/NEJM196404162701606
47. Roumen RM. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. *Br J Surg*. (2004) 91:1125–30. doi: 10.1002/bjs.4942
48. Deng X, Cheng X, Huo Z, Shi Y, Jin Z, Feng H, et al. Modified protocol for enhanced recovery after surgery is beneficial for Chinese cancer patients undergoing pancreaticoduodenectomy. *Oncotarget*. (2017) 8:47841–8. doi: 10.18632/oncotarget.18092
49. Takagi K, Yoshida R, Yagi T, Umeda Y, Nobuoka D, Kuise T, et al. Effect of an enhanced recovery after surgery protocol in patients undergoing pancreaticoduodenectomy: a randomized controlled trial. *Clin Nutr*. (2018) 38:174–81. doi: 10.1016/j.clnu.2018.01.002

Conflict of Interest Statement: 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.

frontiers in Oncology

SYSTEMATIC REVIEW
published: 30 July 2019
doi: 10.3389/fonc.2019.00675

Enhanced Recovery After Surgery for Breast Reconstruction: Pooled Meta-Analysis of 10 Observational Studies Involving 1,838 Patients

Ya-Zhen Tan[1,2†], Xuan Lu[2†], Jie Luo[2], Zhen-Dong Huang[2], Qi-Feng Deng[2], Xian-Feng Shen[3], Chao Zhang[2] and Guang-Ling Guo[1*]*

[1] Center of Women's Health Sciences, Taihe Hospital, Hubei University of Medicine, Shiyan, China, [2] Center for Evidence-Based Medicine and Clinical Research, Taihe Hospital, Hubei University of Medicine, Shiyan, China, [3] Department of General Surgery, Taihe Hospital, Hubei University of Medicine, Shiyan, China

Edited by:
Aali Jan Sheen, Manchester Royal Infirmary, United Kingdom

Reviewed by:
Laura Kruper, City of Hope National Medical Center, United States
Lunxu Liu, West China Hospital, Sichuan University, China

****Correspondence:***
Guang-Ling Guo
guoguangling1208@163.com
Chao Zhang
zhangchao0803@126.com

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: *28 February 2019*
Accepted: *10 July 2019*
Published: *30 July 2019*

Citation:
Tan Y-Z, Lu X, Luo J, Huang Z-D, Deng Q-F, Shen X-F, Zhang C and Guo G-L (2019) Enhanced Recovery After Surgery for Breast Reconstruction: Pooled Meta-Analysis of 10 Observational Studies Involving 1,838 Patients. Front. Oncol. 9:675. doi: 10.3389/fonc.2019.00675

Purpose: This study aims to explore the effectiveness and safety of the enhanced recovery after surgery (ERAS) protocol vs. traditional perioperative care programs for breast reconstruction.

Methods: Three electronic databases (PubMed, EMBASE, and Cochrane Library) were searched for observational studies comparing an ERAS program with a traditional perioperative care program from database inception to 5 May 2018. Two reviewers independently screened the literature according to the inclusion and exclusion criteria, extracted the data, and evaluated study quality using the Newcastle-Ottawa Scale. Subgroup and sensitivity analyses were performed. The outcomes included the length of hospital stay (LOS), complication rates, pain control, costs, emergency department visits, hospital readmission, and unplanned reoperation.

Results: Ten studies were included in the meta-analysis. Compared with a conventional program, ERAS was associated with significantly decreased LOS, morphine administration (including postoperative patient-controlled analgesia usage rate and duration; intravenous morphine administration on postoperative day [POD] 0, 1, 2, and 4; total intravenous morphine administration on POD 0–3; oral morphine consumption on POD 0–4; and total postoperative oral morphine consumption), and pain scores (postoperative pain score on POD 0 and total pain score on POD 0–3). The other variables did not differ significantly.

Conclusion: Our results suggest that ERAS protocols can decrease LOS and morphine equivalent dosing; therefore, further larger, and better-quality studies that report on bleeding amount and patient satisfaction are needed to validate our findings.

Keywords: breast reconstruction, enhanced recovery after surgery, pain control, flap loss, complication

INTRODUCTION

Breast cancer is the most common cancer diagnosis in women, with 30–40% of patients undergoing mastectomy as treatment (1). Long-term quality of life and cosmetic outcomes after different methods are important considerations for patients that choose breast cancer treatment (2). Research shows that breast reconstruction following surgical treatment for breast cancer improves patient satisfaction and health care-related quality of life (3). Thus, in the United States, breast reconstruction is considered as a standard part of care for breast cancer patients treated with mastectomy (4), with a 39% increase in procedural volume since 2000 (5). However, in most cases, the length of hospital stay (LOS) increases and postoperative complications remains a challenge for patients who have undergone breast reconstruction (6).

Emerging evidence suggests that one effective strategy for reducing postoperative complications may be the adoption of an enhanced recovery after surgery (ERAS) program that uses a transdisciplinary comprehensive approach to perioperative care (7). ERAS is a collective, standardized, evidence-based preoperative, intraoperative, and postoperative multidisciplinary protocol involving the collaboration of several specialties and focuses on engaging patients and their families in their care and ensuring that uniform evidence-based bundled care is delivered with the primary goal of reducing the LOS (1). In the current health care environment, hospitals must achieve a delicate balance between limiting expenses and delivering high-quality care (8). Using evidence-based models, clinicians have successfully tested ERAS protocols to deliver comprehensive perioperative care that is patient-centered and efficient and reduces variations in outcomes such as LOS (9). The important elements of ERAS and similar fast-track surgery (FTS) programs in breast reconstructive surgery included in these studies were factors that improved outcomes; many also addressed traditional outdated treatments. These measures were then amalgamated into treatment programs that included preoperative carbohydrate loading, postoperative nausea and vomiting prophylaxis, and other methods (10).

One systematic review of breast reconstruction published in 2016 also analyzed LOS and postoperative complications (11); in this article, the number of studies included was inadequate at only three. Another study of microsurgical breast reconstruction published in 2017 was the minutes taken during a meeting (12). The third study, published in 2018, included nine systematic reviews and meta-analyses of breast reconstructions (13). Therefore, here we included more studies to confirm our results through detailed systematic reviews and meta-analyses. We conducted a comprehensive and systematic analysis of postoperative complications and added research on pain control and readmission. ERAS protocols have also been implemented in breast reconstruction surgery, but their effectiveness has not been studied extensively. We therefore performed a pooled analysis to investigate the effect of ERAS/FTS pathways compared to conventional programs on decreasing LOS, reducing postoperative complication and readmission rates, and relieving pain.

METHODS

Search Strategy

We systematically searched the PubMed, EMBASE, and Cochrane Library databases from their inception to 5 May 2018. Publication language was restricted to English. Detailed search strategies are shown in **Supplemental Method 1**.

Inclusion and Exclusion Criteria

Studies were considered eligible for inclusion if they met all of following inclusion criteria: (1) Adult patients undergoing breast reconstruction surgery; (2) Perioperative care using ERAS or FTS protocols vs. standard or conventional care; (3) Reported outcomes including at least LOS, complication rates, pain control, emergency department visits, hospital readmission, and unplanned reoperation and costs; and (4) Full-text cohort and case-controlled studies published in English.

A study was excluded if: (1) It did not compare ERAS with a traditional method; (2) Its original research data could not be used, and the consulted authors had not obtained useful results; and (3) It examined aesthetic procedures or mastectomy alone.

Data Extraction and Quality Assessment

Two authors screened the abstracts and titles of the studies identified in the initial search, and independently read the full text of the selected studies. Disagreements were resolved by a third researcher. The data were extracted independently by two authors.

The methodological quality of the included cohort or case-cohort studies was assessed independently by two commentators using the Newcastle-Ottawa Scale (NOS). Studies that achieve six or more stars on the modified NOS were considered high quality (14).

Statistical Analysis

For continuous outcome data, means, and standard deviations were used to calculate mean differences (MD) in the meta-analysis (15); for dichotomous outcomes, relative risk (RR) was calculated (16). Each effect amount gives a 95% confidence interval (CI). Initial analyses were performed using a fixed-effects model. Statistical heterogeneity was tested using I^2 tests (17), which provides an estimate of the percentage of inconsistency thought to be due to chance (18). We determined the use of the model based on the I^2 value, most of which are considered $I^2 > 40\%$ and using a random effects model when $I^2 \leq 40\%$. The level of significance for all tests, including heterogeneous statistics, was set at an alpha level of 0.05. A subgroup analysis was performed of certain factors that may affect overall outcomes, including pain management, hospitalization LOS, and complications. We performed a sensitivity analysis of article types, analyzed the data, and reported the results through relevant experiments. All statistical analyses were performed using R software.

RESULTS

Literature Identification

In the initial literature search, 3,960 studies were identified. After the removal of 981 duplicate studies, 2,979 potentially relevant studies were screened on the basis of citations, of which 2,928 were excluded because they did not meet the inclusion criteria, leading to the evaluation of 51 full texts. Forty-two studies were removed after careful full-text screening; the specific reasons for exclusion are recorded in detail (**Supplemental Table 1**). Ultimately, 10 studies were included in the meta-analysis (**Figure 1**).

Study Characteristics, ERAS Elements, and Quality Evaluation

Ten studies (1, 5, 6, 8, 19–24) included in the review were published between 2015 and 2018, including eight after autologous breast reconstruction surgery and two after implant-based breast reconstruction surgery. Aside from one case-control study, the studies were cohort studies (**Table 1**).

ERAS elements used a consensus review (10) in 2017, with a total of 18 recommended items. A mean of nine (range, 4–12) ERAS elements were clearly shown for each ERAS protocol. Details of the ERAS protocols and conventional recovery regimens across the included studies are shown in **Supplemental Table 2**.

One case-control study and nine cohort studies were evaluated using the NOS. In eight of the cohort studies, the methods for determining exposure factors were reasonable and demonstrated that the outcomes of interest were not present at the start. In addition, the evaluation of the results was sufficient for all studies. Therefore, the number of stars in all studies was six or more. The case-control study also had six stars (**Supplemental Table 3**).

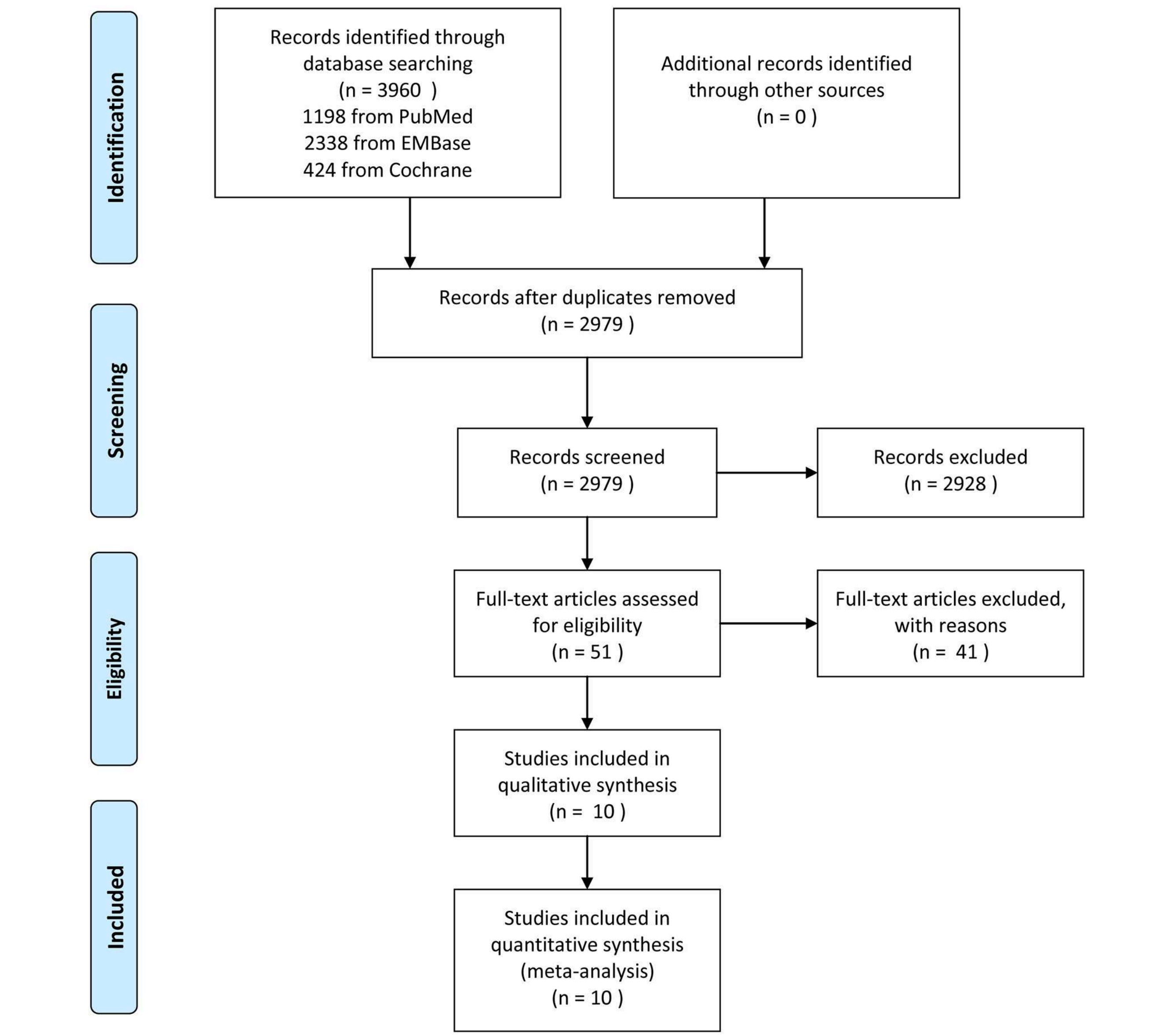


FIGURE 1 | Outline of screening and identification of studies.

TABLE 1 | Patients' and studies' characteristics.

References	Age (T/E)	Study design	Surgery type	Sample		Unilateral (T/E)	Bilateral (T/E)
				T	E		
Afonso et al. (6)	51/50	Cohort study	Immediate or delayed	49	42	29/21	20/21
Astanehe et al. (19)	50.2/52.7	Cohort study	Immediate or delayed	169	72	64/27	105/45
Batdorf et al. (8)	47.5/48.3	Cohort study	Immediate or delayed	51	49	10/9	41/40
Bonde et al. (20)	51/53.9	Case control study	NA	277	177	277/177	0/0
Chiu et al. (1)	48.8/46.9	Cohort study	Immediate or delayed	276	96	111/40	165/56
Dumestre et al. (21)	49/45	Cohort study	Immediate and delayed	78	78	15/35	63/43
Dumestre et al. (22)	48/48	Cohort study	Immediate and delayed	29	29	11/5	18/24
Kaoutzanis et al. (5)	51/51.9	Cohort study	Immediate and delayed	50	50	27/28	23/22
Oh et al. (24)	49.4/49.2	Cohort study	Immediate and delayed	118	82	32/10	86/72
Odom et al. (23)	49.0/49.8	Cohort study	Immediate and delayed	47	19	21/7	26/12

TRAS, Traditional recovery after surgery; ERAS, Enhanced recovery after surgery; T, TRAS; E, ERAS; NA, Not applicable.

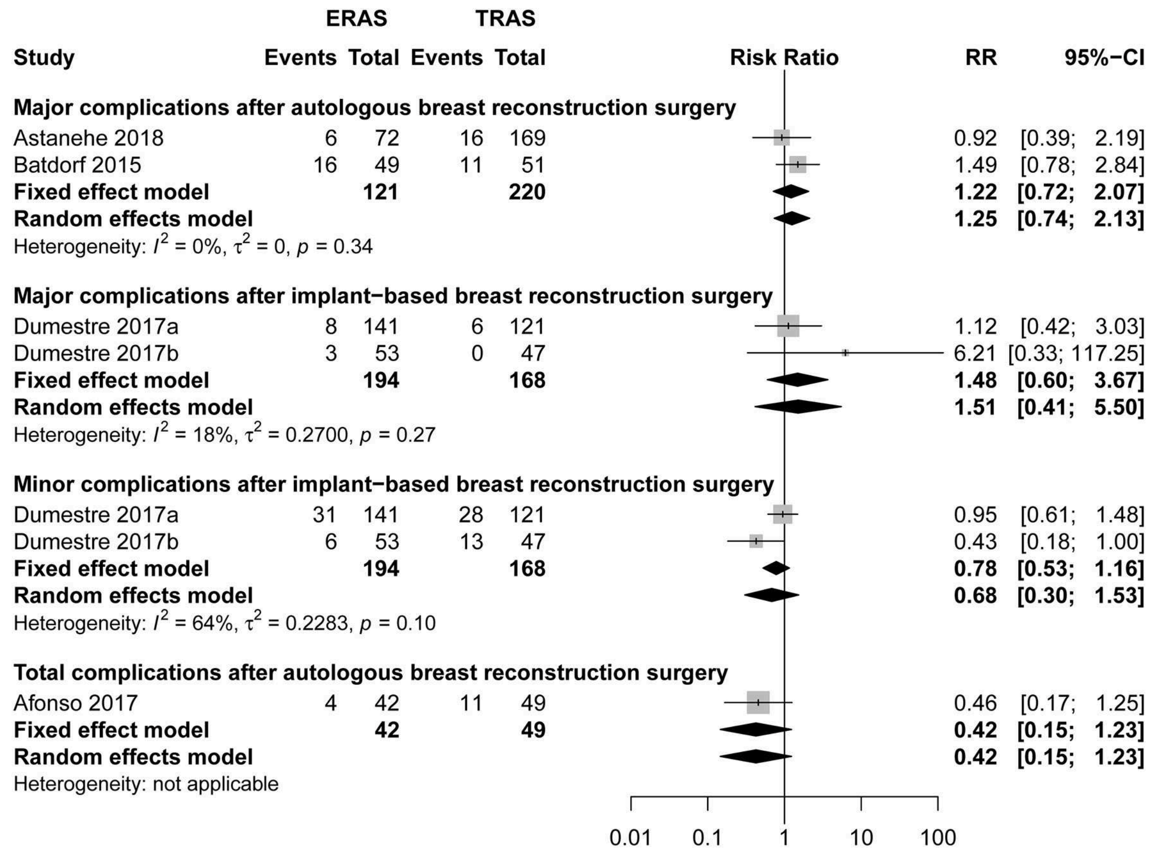


FIGURE 2 | Pooled estimate of the effect of ERAS programs on incidence of total, major, and minor complications within 30 days after autologous and implant-based breast reconstruction surgery compared to conventional perioperative care programs. The incidence is based on number of breast reconstruction in Dumestre et al. (21) and Dumestre et al. (22).

Complications

Complications After Autologous Breast Reconstruction Surgery

There was no significant difference between ERAS/FTS and conventional programs in total or major (**Figure 2**; RR, 1.22; 95% CI, 0.72–2.07; $I^2 = 0\%$) complications within 30 days after surgery.

There was no significant difference between ERAS/FTS and conventional programs in the incidence of breast-related (**Figure 3**; **Table 2**), donor-site (**Supplemental Figure 1**), systemic (**Figure 4**), or opioid-related (**Table 3**; RR, 0.57; 95% CI, 0.28–1.16; $I^2 = 41\%$) complications and urinary tract infection (**Figure 4**; RR, 0.38; 95% CI, 0.06–2.28; $I^2 = 0\%$) within 30 days after surgery.

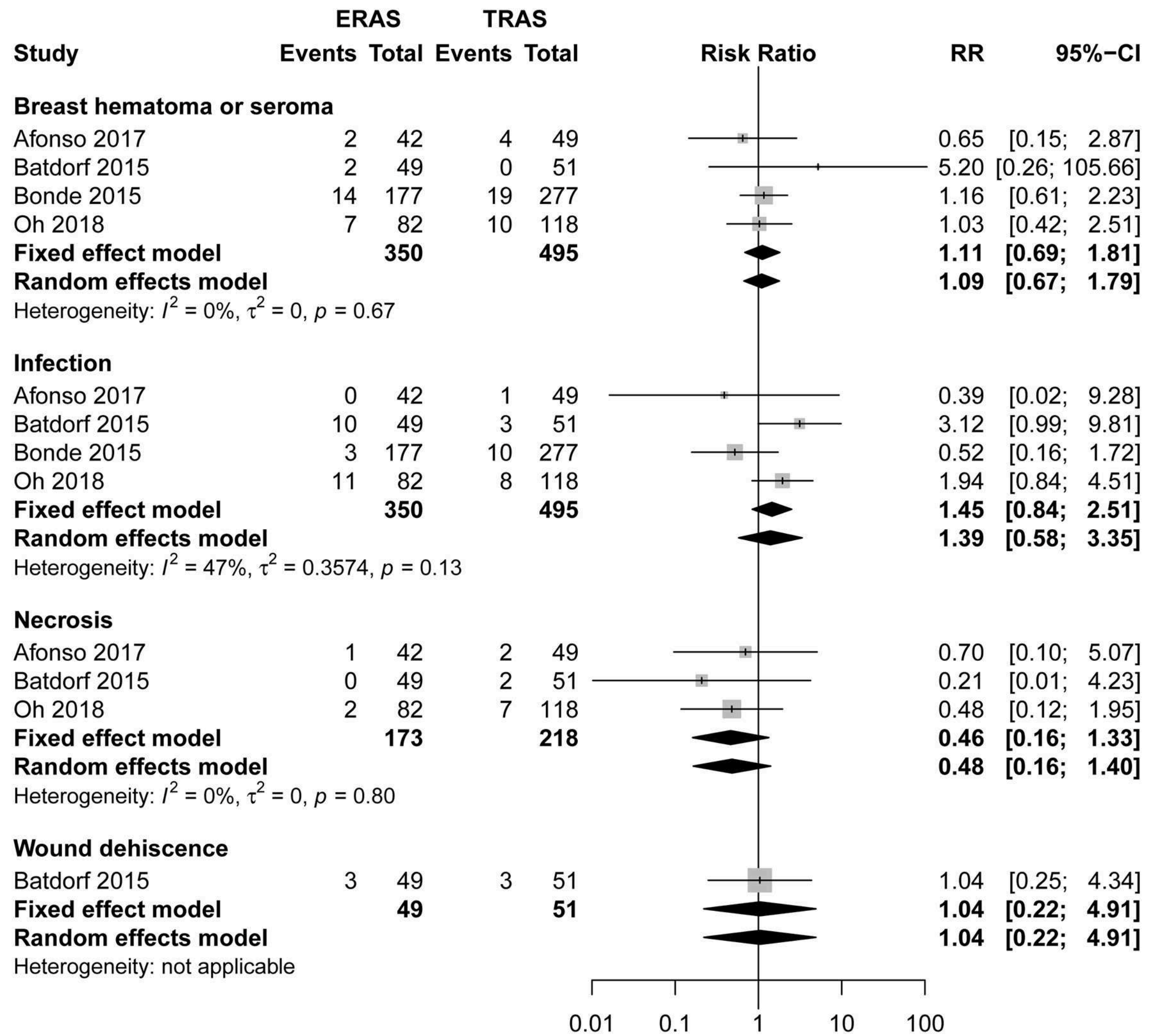


FIGURE 3 | Pooled estimate of the effect of ERAS programs on incidence of breast-related complications within 30 days after autologous breast reconstruction surgery compared to conventional perioperative care programs.

Only one study (3) reported 45-day postoperative complications. The three most common complications in the ERAS/FTS groups were delayed wound healing at the donor site and breast; and hematoma or seroma at the breast requiring drainage in the clinic. Those in the conventional group were delayed wound healing at the donor site; superficial surgical site infection (SSI) requiring antibiotics at the donor site; and necrosis related to the breast (**Figure 5**).

Complications After Implant-Based Breast Reconstruction Surgery

There was no significant differences between the ERAS/FTS and conventional programs in major (**Figure 2**; RR, 1.48; 95% CI, 0.60–3.67; $I^2 = 18\%$), minor (**Figure 2**; RR, 0.68; 95% CI, 0.30–1.53; $I^2 = 64\%$), and breast-related complications (**Supplemental Figure 2**) at POD 30.

Pain Control

Five studies (1, 5, 6, 8, 19) reported the usage rate of analgesics after autologous breast reconstruction surgery. ERAS/FTS was associated with a reduced patient-controlled analgesia (PCA) usage rate (**Table 3**; RR, 0.17; 95% CI, 0.09–0.30; $I^2 = 56\%$) compared to conventional programs, but there was no significant intergroup difference in PCA duration (**Table 3**; MD, −10.56; 95% CI, −20.4 to −0.99; $I^2 = 76\%$]. Pooling of the available data revealed that the ERAS/FTS-treated patients had significantly lower postoperative morphine consumption (**Table 3**).

Emergency Department Visits, Hospital Readmission, and Unplanned Reoperation

Rate After Autologous Breast Reconstruction Surgery

There was no significant difference between the ERAS/FTS and conventional groups in terms of the incidence of hospital readmission (RR, 1.69; 95% CI, 0.99–2.88; $I^2 = 0\%$) or unplanned

TABLE 2 | Pooled estimate of the effect of ERAS programs on incidence of partial, total, and partial & total flap loss within 30 days after autologous and implant-based breast reconstruction surgery compared to conventional perioperative care programs.

References	Number (ERAS/TRAS)	Flap type (ERAS/TRAS)			Partial flap loss		Total flap loss		Partial & Total flap loss (ERAS/TRAS)
		DIEP	MS-TRAM	TRAM	Definition	ERAS/TRAS	Definition	ERAS/TRAS	
Afonso et al. (6)	42/49	28/28	14/16	0/5	NA	NA	NA	NA	1/0
Batdorf et al. (8)	49/51	60/39	25/44	4/9	<40% of the total flap (vascular compromise)	3/0	Complete loss of the flap due to microvascular arterial or venous thrombosis requiring explantation	2/1	5/1
Bonde et al. (20)	177/277	124/44	0/0	53/233	>5% of the total flap	7/9	NA	4/7	11/16
Oh et al. (24)	82/118	NA	NA	NA	NA	3/1	NA	2/1	5/2
Odom et al. (23)	19/47	15/40	NA	NA	NA	0/2	NA	2/1	2/3
Total	369/542	NA	NA	NA	13/12		10/10		24/22
RR (95%CI)	NA	NA	NA	NA	1.67 (0.77, 3.61)		1.55 (0.65, 3.66)		1.67(0.95, 2.95)

ERAS, Enhanced recovery after surgery; TRAS, Traditional recovery after surgery; RR, Relative risk; CI: confidence interval; DIEP, Deep inferior epigastric artery perforator; MS, Muscle-sparing; TRAM, Transverse rectus abdominis myocutaneous; NA, Not applicable.

reoperation (RR, 1.02; 95% CI, 0.30–3.44; $I^2 = 42\%$), within 30 days after surgery (**Supplemental Figure 3**).

Only one study (5) reported this data within 45 days after surgery. No significant difference between ERAS and conventional programs was noted.

Rate After Autologous Breast Reconstruction Surgery

There was no significant difference between the ERAS/FTS and conventional groups in the incidence of hospital readmission or emergency department visits (RR, 0.60; 95% CI, 0.27–1.31; $I^2 = 0\%$] within 30 days after surgery (**Supplemental Figure 3**).

Length of Stay

Eight studies reported LOS in autologous breast reconstruction surgery; of them, two were excluded because the LOS was not defined and contacting the writer was fruitless. Therefore, a total of six studies (1, 5, 6, 8, 19, 20) were included. Pooling of the available data revealed that patients managed with a perioperative ERAS program had mean LOS values that were 1.35-days shorter from admission to discharge (MD, −1.35; 95% CI, −1.75 to −0.95; $I^2 = 83.1\%$), 0.04-days shorter from post-anesthesia care to discharge, and 1.7-nights shorter from admission to discharge than patients in the conventional program (**Supplemental Figure 4**).

Costs

Hospital costs in autologous breast reconstruction surgery were only reported by Oh et al. (24), who considered mean predicted costs and classifications according to Berenson-Eggers Type of Service components (**Supplemental Figure 5**).

Sensitivity Analysis

To explore these results, we performed a stratified analysis across the study strategies. After the exclusion of the case-control study, ERAS/FTS was found to be associated with a statistically significant reduction in the incidence of breast-related infection (RR, 2.18; 95% CI, 1.11–4.27; $I^2 = 0\%$) within 30 days after autologous breast reconstruction surgery. However, there was no significant change in the incidence of breast hematoma or seroma, donor-site infections, LOS (admission to discharge), pneumonia, and urinary tract infection within 30 days after autologous breast reconstruction surgery.

DISCUSSION

Two other recent reviews compared ERAS/FTS with conventional programs in patients undergoing autologous breast reconstruction surgery. However, Gnaneswaran et al. (11) only included three studies, an inadequate number, and only four outcome measures, which was insufficient to assess the safety and effectiveness of the ERAS program for breast reconstruction surgery. Offodile et al. (13) included six observational studies, three-fifths the number of studies our review included. Moreover, Offodile et al. (13) did not report the implementation of ERAS elements in standard perioperative care program; however, it cannot be ignored that it will definitely weaken the effect of the ERAS program in patients undergoing breast reconstruction surgery. In addition, some details were unreasonable, for instance, the meta-analysis of LOS was based on different units of measurement, while the meta-analysis of complications included complications at POD 30 and 45, which inevitably leads to increasing heterogeneity in the statistical analysis. As a result, further research is necessary.

Complications

Complications After Autologous Breast Reconstruction Surgery

It cannot be ignored that most studies included in the meta-analysis reported higher flap loss rates in the ERAS

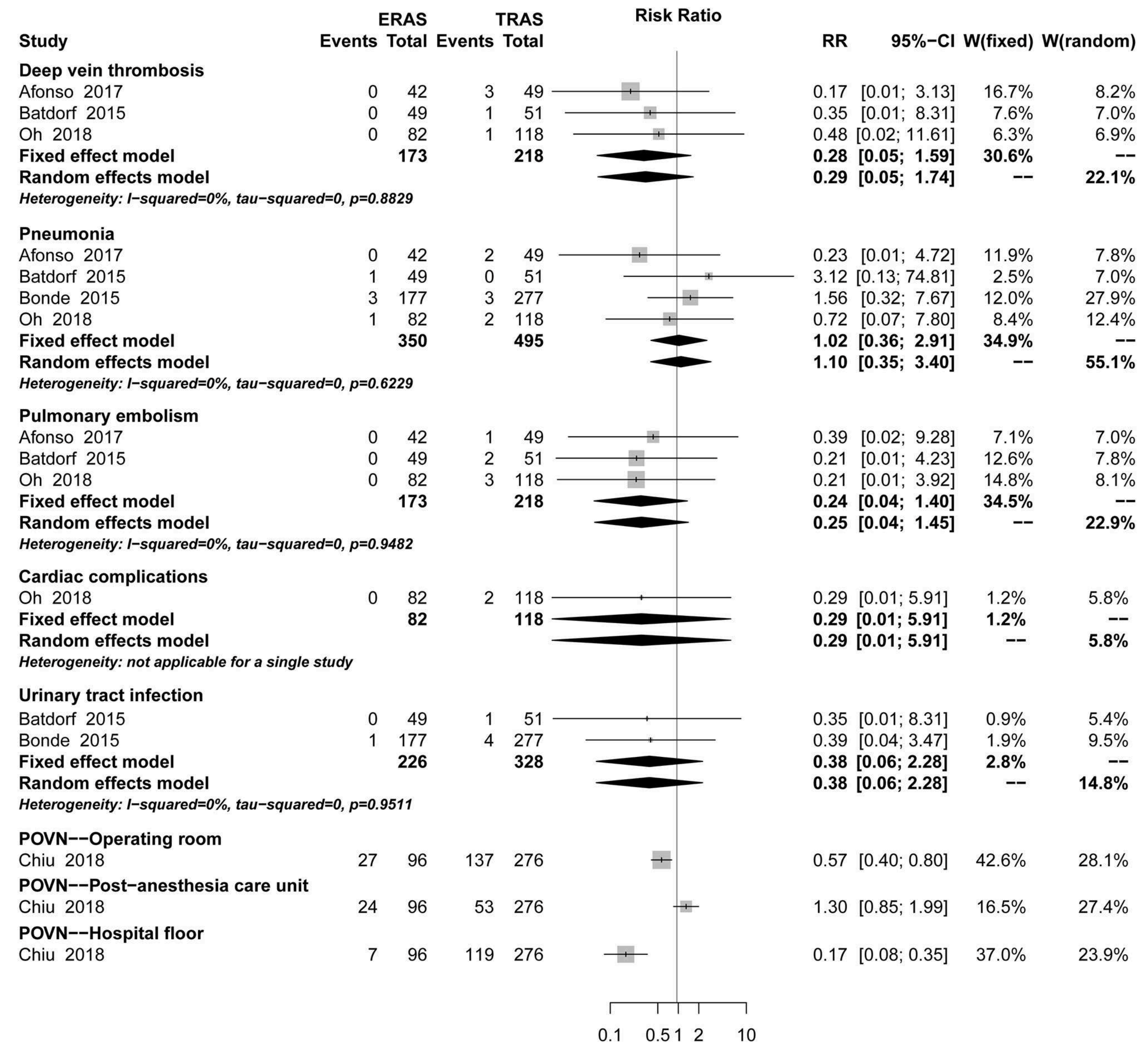


FIGURE 4 | Pooled estimate of the effect of ERAS programs on incidence of systemic complications within 30 days after autologous breast reconstruction surgery compared to conventional perioperative care programs.

protocols. However, results that lack significant differences may be attributed to three reasons. Initially, the great majority of ERAS/FTS protocols employed in the review of flap loss within 30 days after surgery, reported the implementation of venous thromboembolism prophylaxis, perioperative intravenous fluid management, early feeding, postoperative flap monitoring, postoperative wound management, and early mobilization, but preadmission optimization, perforator flap planning, and prevention of intraoperative hypothermia were not reported in any studies. Moreover, an insufficient number of studies were included to support the analysis, making the results unstable, and inaccurate. Finally, the definitions of partial and total flap loss and flap type varied.

The American Society of Anesthesiologists physical status scores (25, 26), reconstruction timing and type (27, 28), and age (29–31) at surgery were potentially associated with the incidence of complications. Further research, including studies using the best practices of ERAS program elements as well as exploring the effects of patients' characteristics and different flap types on the incidence of complications, is needed (32). Additionally, some ERAS/FTS elements have been incorporated in conventional programs, which weakens the impact of an ERAS/FTS program to a certain extent, and the definition of major and minor complications and partial and total flap loss will affect the results of the meta-analysis.

TABLE 3 | The meta-analysis results of PCA usage and duration, intravenous injection, and oral morphine consumption; postoperative pain scores; and antiemetic consumption.

Outcomes		Number	ERAS	TRAS	RR/MD, 95%CI	P for RR/MD	I^2	P for I^2
Use of PCA		3	22	147	0.17 [0.09, 0.30]	<0.00001	56%	0.1
PCA duration		3	22	147	−10.56 [−20.14, −0.99]	0.03	76%	0.02
Morphine equivalents, IV	POD 0	1	42	49	−1.30 [−2.13, −0.47]	0.002	NA	NA
	POD 1	1	42	49	−11.80 [−13.92, −9.68]	<0.00001	NA	NA
	POD 2	1	42	49	−7.30 [−8.62, −5.98]	<0.00001	NA	NA
	POD 3	1	42	49	−0.50 [−1.75, 0.75]	0.43	NA	NA
	POD 4	1	42	49	1.20 [0.40, 2.00]	0.003	NA	NA
	POD 0–3	1	72	169	−99.00 [−117.56, −80.44]	<0.00001	NA	NA
	Total	2	61	96	−14.87 [−47.36, 17.62]	0.37	91%	0.0006
Morphine equivalents, Oral	POD 0	1	50	50	−35.30 [−54.09, −16.51]	0.0002	NA	NA
	POD 1	2	99	101	−141.01 [−239.39, −42.63]	0.005	89%	0.002
	POD 2	2	99	101	−97.64 [−171.24, −24.05]	0.009	86%	0.007
	POD 3	2	99	101	−50.03 [−90.29, −9.77]	0.01	77%	0.04
	POD 4	1	50	50	−14.00 [−21.41, −6.59]	0.0002	NA	NA
	POD 5	1	50	50	−2.60 [−9.30, 4.10]	0.45	NA	NA
	Total	2	99	101	−307.85 [−486.14, −129.57]	0.0007	84%	0.01
Postoperative pain scores	POD 4 h	2	91	100	−0.15 [−1.62, 1.32]	0.84	0.002	0.02
	POD 8 h	2	91	100	−0.26 [−0.86, 0.35]	0.4	0.007	0.2
	POD 12 h	2	91	100	−0.01 [−0.79, 0.77]	0.98	0.04	0.18
	POD 18 h	2	91	100	0.06 [−0.82, 0.95]	0.89	0.002	0.11
	POD 24 h	2	91	100	0.54 [−2.10, 3.19]	0.69	0.007	<0.00001
	POD 48 h	2	91	100	0.30 [−0.68, 1.28]	0.55	0.04	0.06
	POD 72 h	2	91	100	0.72 [−0.16, 1.60]	0.11	0.002	0.06
	POD 0	1	72	169	−1.10 [−1.54, −0.66]	<0.00001	NA	NA
	POD 0-3	1	72	169	−0.70 [−1.09, −0.31]	0.0004	NA	NA
Antiemetics		3	98	215	0.24 [0.15, 0.37]	0.69	98%	<0.00001

ERAS, Enhanced recovery after surgery; TRAS, Traditional recovery after surgery; RR, Relative risk; CI: confidence interval; POD, Postoperative day; MD, Mean difference; PCA, Patient-controlled analgesia; IV, Intravenous injection; NA, Not applicable.

Complications After Implant-Based Breast Reconstruction Surgery

Some ERAS/FTS elements have been incorporated in conventional programs. Dumestre et al. (21) reported a higher incidence of breast hematoma/seroma in an ERAS program, which may be because some ERAS/FTS elements, including perioperative fasting, antimicrobial prophylaxis, preoperative and intraoperative analgesia, perioperative intravenous fluid management, and postoperative analgesia, were only performed by Dumestre et al. (22). Unfortunately, due to the different total number and types of complications at POD 30 between autologous and implant-based breast reconstruction surgery, comparability was impossible. In addition, although our meta-analysis found a decreased breast-related infection rate with the ERAS protocol, the interpretation of this finding should be considered cautiously because of the larger weight demonstrated by Bonde et al. (20) caused by a large sample size and a limited number of studies.

Most importantly, a prolonged indwelling urinary catheter placement might be associated with urinary tract infections following breast reconstruction surgery. The reason for our meta-analysis result of urinary tract infections may be that only two studies (8, 20) were included in the meta-analysis and the evidence was less robust. Although the relative contribution of each of the single elements in the ERAS/FTS program remains uncertain (32); solid evidence indicated that prolonged indwelling urinary catheter placement can increase the incidence of urinary tract infections (33–35). Removing the urinary catheter on POD 1 is the best practice in ERAS methods.

Pain Control

The key factors that keep patients in the hospital after surgery include the need for parenteral analgesia, need for intravenous fluids secondary to gut dysfunction, and bed rest owing to a lack of mobility (36). In addition, pain is an important predictor of postoperative quality of recovery and patient satisfaction. Accordingly, postoperative pain control is essential for early recovery. All studies employed in this review used better practices of venous thromboembolism prophylaxis, preoperative and intraoperative analgesia, perioperative intravenous fluid management, postoperative analgesia, postoperative flap monitoring, and early mobilization, but only Batdorf et al. (8) reported the practice of a standard anesthetic protocol. Surprisingly, ERAS elements were implemented in conventional

Outcomes	ERAS	TRAS	P
Superficial SSI requiring antibiotics	1/50	2/50	0.566
Deep SSI requiring antibiotics	1/50	1/50	1.000
Hematoma/Seroma managed non-operatively	0/50	1/50	0.498
Hematoma/Seroma requiring drainage in clinic	0/50	4/50	0.137
Necrosis	4/50	0/50	0.137
Flap loss	0/50	3/50	0.194
Vascular compromise	1/50	0/50	0.498
Wound dehiscence	0/50	0/50	1.000
Delayed wound healing	0/50	5/50	0.101
Deep vein thrombosis	0/50	0/50	1.000
Pulmonary embolism	0/50	0/50	1.000
Pneumonia	1/50	0/50	0.498
Urinary tract infection	0/50	0/50	1.000
Cardiac complications	0/50	0/50	1.000
Gastrointestinal	0/50	0/50	1.000
Wound dehiscence	0/50	0/50	1.000
Umbilical necrosis	1/50	2/50	0.566
Fat necrosis	2/50	4/50	0.411
Hematoma/Seroma managed non-operatively	1/50	0/50	0.498
Hematoma/Seroma requiring drainage in clinic	0/50	3/50	0.194
Superficial SSI requiring antibiotics	8/50	3/50	0.129
Deep SSI requiring antibiotics	1/50	2/50	0.566
Delayed wound healing	18/50	8/50	0.031

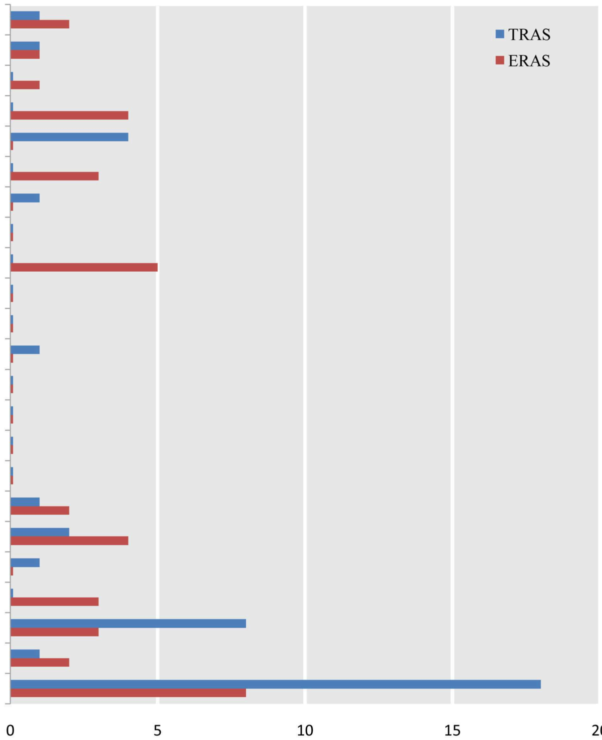


FIGURE 5 | Pooled estimate of the effect of ERAS programs on incidence of breast-related, donor-site, and systemic complications within 45 days after autologous breast reconstruction surgery compared to conventional perioperative care programs.

programs by Kaoutzanis et al. (5), Afonso et al. (6), Batdorf et al. (8), and Odom et al. (23), which weakens the impact of an ERAS/FTS program to a certain extent. Undeniably, the result was not robust owing to the small number of studies included.

LOS, Emergency Department Visits, Hospital Readmission, Unplanned Reoperation, and Costs

Most ERAS/FTS protocols employed in the meta-analysis implemented perioperative fasting, preoperative and intraoperative analgesia, perioperative intravenous fluid management, postoperative analgesia, early feeding, postoperative flap monitoring, and early mobilization. Our meta-analysis results showed that the ERAS program shortened preoperative time to a greater extent. Our review showed that LOS may be related to the number of ERAS elements implemented (6, 8, 19, 20). Therefore, setting strict discharge criteria is also essential in minimizing LOS (37). Furthermore, even if a patient met the predefined discharge criteria, hospital discharge might have been delayed for social reasons (38).

A major concern regarding FTS programs is that reduction of the primary hospital stay might result in an increased readmission rate (24, 37). Intriguingly, our meta-analysis showed a strong trend toward a higher readmission rate within 30 days after autologous breast reconstruction surgery treated with the ERAS/FTS program. All four studies showed a higher incidence of hospital readmission in the ERAS/FTS program but did not provide post-discharge home support and physiotherapy. All studies included in the meta-analysis of emergency department visits and unplanned reoperations reported that different degrees of ERAS elements were implemented in conventional programs, which may weaken the difference between ERAS and conventional programs. Moreover, only Kaoutzanis et al. (5) reported these data on POD 45, so the evidence was not robust.

Our review showed that a LOS reduction was associated with lower hospital costs. Postoperative clinical variables, including laterality, hospital readmission, complications, and the need for postoperative blood transfusion had a statistically significant effect on costs reported by Oh et al. (24) only. Further research including multiple studies on cost is needed.

An ERAS program requires a dedicated and motivated team consisting of an anesthesiologist, surgeon, dietician, physiotherapist, social worker, and nursing team (37). Independent programs to reduce harm are not ideal, and it is unlikely that the improved value of surgical care, a hallmark of ERAS, can be accomplished without this transdisciplinary teamwork and coordination. This bundled approach not only serves to bring the team together but also promotes broad implementation of established best-practice principles in concert rather than one at a time (7). By comparing the meta-analysis results and the first but latest consensus in 2017 (10), our research confirmed that the practices of preadmission optimization, perforator flap planning, preventing intraoperative hypothermia perioperative intravenous fluid management (39, 40), and postoperative flap monitoring (20) were associated with a reduced flap loss rate. The practice of preadmission optimization, perforator flap planning, venous thromboembolism prophylaxis, antimicrobial prophylaxis, and intraoperative hypothermia prevention might lead to fewer complications. In addition, the combined practice of perioperative fasting, preoperative, and intraoperative analgesia, perioperative intravenous fluid management, postoperative analgesia, early feeding, postoperative flap monitoring, and early mobilization resulted in a reduced LOS. Our research showed that the combination of venous thromboembolism prophylaxis, preoperative and intraoperative analgesia, perioperative intravenous fluid management, postoperative analgesia, postoperative flap monitoring, and early mobilization led to a decrease in morphine equivalent dosing. However, we could not prove a correlation between the standard anesthetic protocol and less morphine use. An important finding is that early removal of the urinary catheter is presumably associated with fewer urinary tract infections, which is a suggested practice in ERAS treatment.

There are several important limitations to our review. First, in addition to differences in the particular elements that were included in each ERAS program, the number of elements also varied, which created great heterogeneity. ERAS elements were applied in conventional programs. Second, the practices of prophylaxis against venous thromboembolism and the use of preoperative, intraoperative, and postoperative analgesia may result in a higher bleeding risk. Patient satisfaction is critical to the widespread clinical practice of ERAS programs. Owing to only one study (22) demonstrating patient feedback but no relevant data, further studies are needed that report on the amount of bleeding and the degree of patient satisfaction.

CONCLUSION

Our study found that the ERAS/FTS program was associated with a significant reduction in morphine consumption and LOS compared to conventional programs. However, there was a trend of higher flap loss rates in the ERAS/FTS-treated patients. In addition, decreased LOS may be associated with higher readmission rates. Most importantly, there is a new insight that removing the urinary catheter on POD 1 is a suggested practice in ERAS programs. The implementation of a comprehensive transdisciplinary program promotes patients to quick postoperative recovery. Additionally, there are several risks of harm. ERAS programs in breast reconstruction should be further confirmed and refined with multicenter prospective randomized trials.

DATA AVAILABILITY

No datasets were generated or analyzed for this study.

AUTHOR CONTRIBUTIONS

G-LG had full access to all of the data in the study and took responsibility for the integrity of the data and accuracy of the data analysis. All authors critically revised the manuscript. G-LG had guarantor.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.00675/full#supplementary-material

REFERENCES

1. Chiu C, Aleshi P, Esserman LJ, Inglis-Arkell C, Yap E, Whitlock EL, et al. Improved analgesia and reduced post-operative nausea and vomiting after implementation of an enhanced recovery after surgery (ERAS) pathway for total mastectomy. *J Otolaryngol Head Neck Surg*. (2018) 18:41. doi: 10.1186/s12871-018-0505-9
2. Jagsi R, Li Y, Morrow M, Janz N, Alderman A, Graff J, et al. Patient-reported quality of life and satisfaction with cosmetic outcomes after breast conservation and mastectomy with and without reconstruction: results of a survey of breast cancer survivors. *Ann Surg*. (2015) 261:1198–206. doi: 10.1097/SLA.0000000000000908
3. Garvey PB, Clemens MW, Hoy AE, Smith B, Zhang H, Kronowitz SJ, et al. Muscle-sparing TRAM flap does not protect breast reconstruction from postmastectomy radiation damage compared with the DIEP flap. *Plastic Reconstr Surg*. (2014) 133:223–33. doi: 10.1097/01.prs.0000436845.92623.9a
4. Teo I, Reece GP, Christie IC, Guindani M, Markey MK, Heinberg LJ, et al. Body image and quality of life of breast cancer patients: influence of timing and stage of breast reconstruction. *Psycho-Oncol*. (2016) 25:1106–12. doi: 10.1002/pon.3952
5. Kaoutzanis C, Ganesh Kumar N, O'Neill D, Wormer B, Winocour J, Layliev J, et al. Enhanced recovery pathway in microvascular autologous tissue-based breast reconstruction: should it become the standard of care? *Plastic Reconstr Surg*. (2018) 141:841–51. doi: 10.1097/PRS.0000000000004197
6. Afonso A, Oskar S, Tan KS, Disa JJ, Mehrara BJ, Ceyhan J, et al. Is enhanced recovery the new standard of care in microsurgical breast reconstruction? *Plastic Reconstr Surg*. (2017) 139:1053–61. doi: 10.1097/PRS.0000000000003235
7. Grant MC, Yang D, Wu CL, Makary MA, Wick EC. Impact of enhanced recovery after surgery and fast track surgery pathways on healthcare-associated infections: results from a systematic review and meta-analysis. *Ann Surg*. (2017) 265:68–79. doi: 10.1097/SLA.0000000000001703
8. Batdorf NJ, Lemaine V, Lovely JK, Ballman KV, Goede WJ, Martinez-Jorge J, et al. Enhanced recovery after surgery in microvascular breast reconstruction. *J Plastic Reconstr Aesthet Surg*. (2015) 68:395–402. doi: 10.1016/j.bjps.2014.11.014
9. Paton F, Chambers D, Wilson P, Eastwood A, Craig D, Fox D, et al. Effectiveness and implementation of enhanced recovery after surgery programmes: a rapid evidence synthesis. *BMJ Open*. (2014) 4:e005015. doi: 10.1136/bmjopen-2014-005015
10. Temple-Oberle C, Shea-Budgell MA, Tan M, Semple JL, Schrag C, Barreto M, et al. Consensus review of optimal perioperative care in breast reconstruction: enhanced recovery after surgery (ERAS) society recommendations. *Plastic Reconstr Surg*. (2017) 139:1056e−71e. doi: 10.1097/PRS.0000000000003242

11. Gnaneswaran N, Perera M, Perera N, Peters M. Enhanced recovery after surgery (ERAS) pathways in autologous breast reconstruction: a systematic review. *Eur J Plastic Surg*. (2016) 39:165–72. doi: 10.1007/s00238-016-1189-3
12. Sebai M, Siotos C, Payne C, Seal SM, Habibi M, Broderick K, et al. Enhanced recovery after surgery pathway for microsurgical breast reconstruction: a systematic review and meta-analysis. *Plastic Reconstr Surg Glob Open*. (2017) 5:48. doi: 10.1097/01.GOX.0000516583.55130.f2
13. Offodile AC. II, Gu C, Boukovalas S, Coroneos CJ, Chatterjee A, Largo RD, et al. Enhanced recovery after surgery (ERAS) pathways in breast reconstruction: systematic review and meta-analysis of the literature. *Breast Cancer Res Treat*. (2019) 173:65–77. doi: 10.1007/s10549-018-4991-8
14. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. (2010) 25:603–605. doi: 10.1007/s10654-010-9491-z
15. Higgins JP, Whitehead A, Turner RM, Omar RZ, Thompson SG. Meta-analysis of continuous outcome data from individual patients. *Stat Med*. (2001) 20:2219–41. doi: 10.1002/sim.918
16. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. (2009) 373:31–41. doi: 10.1016/S0140-6736(08)61764-X
17. Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. *Clin Microbiol Infect*. (2014) 20:123–9. doi: 10.1111/1469-0691.12494
18. Speck RM, Courneya KS, Mâsse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Survivorship*. (2010) 4:87–100. doi: 10.1007/s11764-009-0110-5
19. Astanehe A, Temple-Oberle C, Nielsen M, de Haas W, Lindsay R, Matthews J, et al. An enhanced recovery after surgery pathway for microvascular breast reconstruction is safe and effective. *Plast Reconstru Surg Glob Open*. (2018) 6:e1634. doi: 10.1097/GOX.0000000000001634
20. Bonde C, Khorasani H, Eriksen K, Wolthers M, Kehlet H, Elberg J. Introducing the fast track surgery principles can reduce length of stay after autologous breast reconstruction using free flaps: a case control study. *J Plast Surg Hand Surg*. (2015) 49:367–71. doi: 10.3109/2000656X.2015.1062387
21. Dumestre DO, Redwood J, Webb CE, Temple-Oberle C. Enhanced recovery after surgery (eras) protocol enables safe same-day discharge after alloplastic breast reconstruction. *Plastic Surg*. (2017) 25:249–54. doi: 10.1177/2292550317728036
22. Dumestre DO, Webb CE, Temple-Oberle C. Improved recovery experience achieved for women undergoing implant-based breast reconstruction using an enhanced recovery after surgery model. *Plastic Reconstr Surg*. (2017) 139:550–9. doi: 10.1097/PRS.0000000000003056
23. Odom EB, Mehta N, Parikh RP, Guffey R, Myckatyn TM. Paravertebral blocks reduce narcotic use without affecting perfusion in patients undergoing autologous breast reconstruction. *Ann Surg Oncol*. (2017) 24:3180–7. doi: 10.1245/s10434-017-6007-z
24. Oh C, Moriarty J, Borah BJ, Mara KC, Harmsen WS, Saint-Cyr M, et al. Cost analysis of enhanced recovery after surgery in microvascular breast reconstruction. *J Plast Reconstr Aesthet Surg*. (2018) 71:819–26. doi: 10.1016/j.bjps.2018.02.018
25. Woodfield JC, Beshay NMY, Pettigrew RA, Plank LD, van Rij AM. American society of anesthesiologists classification of physical status as a predictor of wound infection. *ANZ J Surg*. (2007) 77:738–41. doi: 10.1111/j.1445-2197.2007.04220.x
26. Yun SS, Hwang DW, Kim SW, Park SH, Park SJ, Lee DS, et al. Better treatment strategies for patients with acute cholecystitis and american society of anesthesiologists classification 3 or greater. *Yonsei Med J*. (2010) 51:540. doi: 10.3349/ymj.2010.51.4.540
27. Hertel R, Lambert SM, Muller S, Ballmer FT, Ganz R. On the timing of soft-tissue reconstruction for open fractures of the lower leg. *Arch Orthop Trauma Surg*. (1999) 119:7–12. doi: 10.1007/s004020050346
28. Weichman KE, Hamill JB, Kim HM, Chen X, Wilkins EG, Pusic AL. Understanding the recovery phase of breast reconstructions: patient-reported outcomes correlated to the type and timing of reconstruction. *J Plastic Reconstr Aesthet Surg*. (2015) 68:1370–8. doi: 10.1016/j.bjps.2015.05.039
29. Bagnall NM, Malietzis G, Kennedy RH, Athanasiou T, Faiz O, Darzi A. A systematic review of enhanced recovery care after colorectal surgery in elderly patients. *Colorect Dis*. (2014) 16:947–56. doi: 10.1111/codi.12718
30. Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW. Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. *Dis Colon Rectum*. (2003) 46:851–9. doi: 10.1007/s10350-004-6672-4
31. Slieker J, Frauche P, Jurt J, Addor V, Blanc C, Demartines N, et al. Enhanced recovery ERAS for elderly: a safe and beneficial pathway in colorectal surgery. *Int J Colorectal Dis*. (2017) 32:215–21. doi: 10.1007/s00384-016-2691-6
32. Gustafsson UO. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. *Arch Surg*. (2011) 146:571–7. doi: 10.1001/archsurg.2010.309
33. Warren JW. Catheter-associated urinary tract infections. *Int J Antimicrob Agents*. (2001) 17:299–303. doi: 10.1016/S0924-8579(00)00359-9
34. Warren JW, Muncie HL Jr, Hall-Craggs M. Acute pyelonephritis associated with bacteriuria during long-term catheterization: a prospective clinicopathological study. *J Infect Dis*. (1988) 158:1341–6. doi: 10.1093/infdis/158.6.1341
35. Warren JW, Muncie HL Jr, Hebel JR, Hall-Craggs M. Long-term urethral catheterization increases risk of chronic pyelonephritis and renal inflammation. *J Am Geriatr Soc*. (1994) 42:1286–90. doi: 10.1111/j.1532-5415.1994.tb06513.x
36. Society E. Enhanced recovery after surgery. ERAS society (2018). Available online at: http://www.erassociety.org
37. Wind J, Polle SW, Fung Kon Jin PH, Dejong CH, von Meyenfeldt MF, Ubbink DT, et al. Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg*. (2006) 93:800–9. doi: 10.1002/bjs.5384
38. Eskicioglu C, Forbes SS, Aarts MA, Okrainec A, McLeod RS. Enhanced recovery after surgery (ERAS) programs for patients having colorectal surgery: a meta-analysis of randomized trials. *J Gastrointest Surg*. (2009) 13:2321–9. doi: 10.1007/s11605-009-0927-2
39. Booi DI. Perioperative fluid overload increases anastomosis thrombosis in the free TRAM flap used for breast reconstruction. *Eur J Plast Surg*. (2011) 34:81–6. doi: 10.1007/s00238-010-0466-9
40. Zhong T, Neinstein R, Massey C, McCluskey SA, Lipa J, Neligan P, et al. Intravenous fluid infusion rate in microsurgical breast reconstruction: important lessons learned from 354 free flaps. *Plastic Reconstr Surg*. (2011) 128:1153–60. doi: 10.1097/PRS.0b013e318221da56

Conflict of Interest Statement: 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.

frontiers in Oncology

METHODS
published: 25 October 2019
doi: 10.3389/fonc.2019.01130

A Standard Algorithm for Reconstruction of Scalp Defects With Simultaneous Free Flaps in an Interdisciplinary Two-Team Approach

Jochen Weitz[1]*, *Christophe Spaas*[1], *Klaus-Dietrich Wolff*[1], *Bernhard Meyer*[2], *Ehab Shiban*[2,3] *and Lucas M. Ritschl*[1]

[1] *Department of Oral and Maxillofacial Surgery, School of Medicine, Technical University of Munich, Klinikum Rechts der Isar, Munich, Germany,* [2] *Department of Neurosurgery, School of Medicine, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany,* [3] *Neurosurgery Department, University Hospital of Augsburg, Augsburg, Germany*

OPEN ACCESS

Edited by:
Marco Rainer Kesting, University Hospital Erlangen, Germany

Reviewed by:
Christian Freudlsperger, Heidelberg University Hospital, Germany
Michael Engel, Heidelberg University Hospital, Germany
Christian Mertens, Heidelberg University Hospital, Germany
Adrien Daigeler, BG University Hospital Bergmannsheil GmbH, Germany
Justus P. Beier, University Hospital RWTH Aachen, Germany

***Correspondence:**
Jochen Weitz
jochen.weitz@tum.de

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: *07 August 2019*
Accepted: *09 October 2019*
Published: *25 October 2019*

Citation:
Weitz J, Spaas C, Wolff K-D, Meyer B, Shiban E and Ritschl LM (2019) A Standard Algorithm for Reconstruction of Scalp Defects With Simultaneous Free Flaps in an Interdisciplinary Two-Team Approach. Front. Oncol. 9:1130. doi: 10.3389/fonc.2019.01130

Reconstructions of complex scalp after ablative resection or by post-traumatic tissue loss, can present difficulties regarding recipient vessel selection, functional, and aesthetic outcome. The harvesting method for many microvascular free flaps requires a need for changing patients position during surgery and makes a simultaneous interdisciplinary two-team approach complicated, which is a major disadvantage regarding safety and operation time. The ideal flap for scalp reconstruction has yet to be described, although the microvascular latissimus dorsi flap is frequently referred to as the first choice in this context, especially after resection of large defects. The purpose of this study is to compare two different microvascular free flaps for a simultaneous scalp reconstruction in an interdisciplinary two-team approach applying a standardized algorithm. All consecutively operated complex scalp defects after ablative surgery from April 2017 until August 2018 were included in this retrospective study. The indications were divided into neoplasm or wound healing disorder. Two microvascular flaps (latissimus dorsi or parascapular flap) were used to cover the soft tissue component of the resulting defects. Seventeen patients met the inclusion criterion and were treated in an interdisciplinary two-team approach. Skull reconstruction with a CAD/CAM implant was performed in 10 cases of which four were in a secondary stage. Nine patients received a parascapular flap and eight patients were treated with latissimus dorsi flap with split thickness skin graft. Anastomosis was performed with no exception to the temporal vessels. One parascapular flap had venous insufficiency after 1 week followed by flap loss. One latissimus dorsi flap had necrosis of the serratus part of the flap. All other flaps healed uneventful and could be further treated with adjuvant therapy or CAD/CAM calvarial implants. Regarding overall complications, flap related complications, flap loss, and inpatient stay no statistical differences were seen between the diagnosis or type of reconstruction. The parascapular flap seems to be a good alternative for reconstruction of complex tumor defects of the scalp besides the latissimus dorsi flap. Stable long-term results and little donor site morbidity are enabled with good aesthetic outcomes and shorter operation time in an interdisciplinary two-team approach.

Keywords: CAD/CAM implant, scalp reconstruction, microvascular free flap, temporal anastomosis, squamous cell carcinoma

INTRODUCTION

Scalp defects often arise after ablative tumor surgery of intra- or extracranial neoplasms or in terms of a wound healing disorder secondarily to previous therapy. Small defects can be reconstructed with local flaps as long as a tension free wound closure is possible, which is one of the most critical risk factor for wound healing disorders and secondary revisions (1). Therefore, larger defects (>25 cm^2) require microvascular free flap transfer for reconstruction with or without computer aided design and computer aided manufactured (CAD/CAM) calvarial implants for accompanying bone defects (2, 3). Craniotomy, to relieve intracranial pressure or to obtain an adequate exposure to certain parts of the cranial vault, is often performed because of brain infarction, intracranial hemorrhages or intracranial disorders caused by tumors and infection (3). Local infection may arise in 1.1–10.0% after reimplantation of the cranial bone flap, which leads to the loss of the bone fragment as well as the covering soft tissue (4, 5). Also tumor invasion of the skull can lead to large cranial bone defects.

The surrounding soft tissues are often inadequate for primary closure apart from reconstruction of the cranial bony contour. In this context vascularized tissue and especially microvascular free flap transfer can overcome this problem. Microsurgical reconstruction is reported to be a save procedure in young and elderly patients (6, 7), but nonetheless the ideal free flap for scalp reconstruction has yet to be described. The common difficulties that accompany and aggravate the soft tissue reconstruction can be subclassified in anatomical, pre-, intra- or postoperative logistics, and patient's and relative's satisfaction. The availability and quality of adequate recipient vessels and surrounding tissue can be altered due to a history of multiple surgical procedures or radiation therapy. For some microvascular free flaps the patient's position must be changed intraoperatively. This maneuver (re-positioning and re-prepping) is time consuming and holds the danger of intubation tube dislocation. Further a simultaneous two-team approach might be hindered.

The purpose of this retrospective analysis is to compare two different microvascular free flaps for a simultaneous scalp reconstruction in an interdisciplinary two-team approach. Further we want to describe our considerations for free flap selection and associated potential pitfalls resulting in a treatment algorithm for clinical practice, as seen for other defect localizations (8, 9).

MATERIALS AND METHODS

Ethical Statement and Enrolled Patients

All clinical investigations and procedures were conducted according to the principles expressed in the Declaration of Helsinki. The study design was reviewed and approved by the ethical committee of the medical faculty of the Technische Universität München. A written informed consent was obtained from all patients.

All patients from April 2017 until August 2018 with a scalp defect that required a microvascular free flap reconstruction in an interdisciplinary approach were included in this retrospective analysis. These were patients with an expected extensive scalp defect or after several unsuccessful attempts of coverage with local flaps. The patients characteristics are summarized in **Table 1**. The medical records were reviewed for gender, age, initial diagnosis which led to the scalp defect, localization of the defect, usage of a CAD/CAM calvarial implant [titanium or polyetheretherketon (PEEK)], type of microvascular free flap (parascapular or latissimus dorsi), recipient vessels selection, inpatient stay, and incidence of short-term complications. Latter was further subclassified in minor (small dehiscence with no need for surgical revision or conversion to the temporal vessels on the opposite site) or major complications (total or partial flap failure, postoperative hematoma of the reconstructed scalp which required surgical intervention, anaphylactic shock, and death of the patient). Additionally, dehiscence, hematoma, and (total or partial) flap loss were rated as flap related complications.

Surgical Procedure and Considerations

Preoperatively, palpation and hand-held doppler measurement were performed in every patient to confirm the availability of the superficial temporal artery and vein (ST A/V). CT-angiography for recipient vessel localization was not needed in any case. The localization of recipient vessel and of the resulting defect determined the positioning side of the patient.

For all included cases the patient was in a right or left lateral decubitus position. A neurosurgeon and maxillofacial surgeon performed the resection of the scalp tumor or the necrotic scalp tissue and preparation of the superficial temporal vessels. A bony defect was immediately reconstructed with a CAD/CAM implant (titanium or PEEK), unless it would have compromised neurological recovery due to increased intracranial pressure. In those cases bony reconstruction was performed in a secondary stage.

As a two team approach, at the same time harvesting of a microvascular parascapular or latissimus dorsi flap was performed by another maxillofacial surgeon in the common techniques as described by others (10, 11). The ST A/V were prepared and a tunnel or an extension incision along the defect was made for the tension free vascular pedicle positioning.

Microvascular anastomosis was performed in end-to-end technique, whereby in the case of two comitant veins, one was anastomosed orthograde, the other retrograde to the temporal vein. Then the flap was positioned onto the defect to allow a tension free wound closure. No drainage was put *in situ*. In case of a latissimus dorsi flap, a meshed split thickness skin graft (STSG) was used as skin layer which was sutured onto the muscle flap (12) and additionally fixed with a fibrin sealant spray application (Tisseel, Baxter, Illinois, U.S.) (**Figure 1**).

Statistical Analyses

Statistical analysis was carried out by using the "Standard Package for the Social Science" (SPSS for Mac, release 22.0.0, 2013; SPSS Inc., Chicago, IL, USA). Comparisons between reconstruction type (parascapular vs. latissimus dorsi flap) and indication (malignancy vs. wound healing disorder) were performed with the Mann–Whitney-U-test. Univariate logistic regression analyses was performed for overall complication rate and

TABLE 1 | Characteristics of analyzed patients.

No.	Gender	Age	Diagnosis	Defect size [cm]	Localization of the defect	CAD/CAM	Scalp reconstruction	Microvascular anastomosis	Complications
1	M	73	Meningioma	≤12	Tempero-parietal left	Secondary phase	Parascapular flap	ST A/V left	None
2	M	62	Meningioma	≤12	Parietal left	Secondary phase	Parascapular flap	ST A/V left	None
3	M	75	SCC scalp	>12	Fronto-temporal left	Secondary phase	Latissimus dorsi flap with STSG	ST A/V left	None
4	F	53	SAB	≤12	Temporal left	Titanium	Parascapular flap	ST A/V right	Conversion from left to right temporal vessels Postoperative dehiscence of the flap
5	M	69	Fibroxanthoma scalp	>12	Occipito-parietal left	Secondary phase	Latissimus dorsi flap with STSG	ST A/V left	None
6	M	28	SAB	≤12	Tempero-parietal left	No skull reconstruction	Parascapular flap	ST A/V left	None
7	M	61	SCC scalp	>12	Fronto-temporal right	PEEK	Latissimus dorsi flap with STSG	ST A/V right	None
8	M	88	SCC scalp	>12	Capitulum	(Titanium mesh)	Latissimus dorsi flap and serratus anterior muscle with STSG	ST A/V left	Necrosis of serratus part of latissimus dorsi flap ALT flap for secondary reconstruction
9	F	68	SCC sinus frontalis	≤12	Fronto-temporal right	Titanium	Parascapular flap	ST A/V right	None
10	M	57	Glioblastoma	≤12	Temporal right	Titanium	Parascapular flap	ST A/V right	Necrosis of the flap Latissimus dorsi flap with STSG for secondary reconstruction
11	M	68	SCC scalp	>12	Parieto-occipital left	No skull reconstruction	Latissimus dorsi flap with STSG	ST A/V left	Sepsis during recovery with dead of the patient
12	M	77	Melanoma scalp	≤12	Fronto-temporal right	No skull reconstruction	Parascapular flap	ST A/V right	Perioperative anaphylactic shock
13	M	51	Dermatofibrosarcoma scalp	>12	Occipital left	No skull reconstruction	Latissimus dorsi flap with STSG	ST A/V left	Postoperative hematoma of the scalp
14	F	54	SAB	≤12	Tempero-parietal left	Titanium	Parascapular flap	ST A/V left	Dehiscence of the flap
15	F	78	SAB	≤12	Parietal left	Titanium	Parascapular flap	ST A/V left	Postoperative hematoma of the scalp
16	M	29	SAB	>12	Fronto-temporal	Secondary phase	Latissimus dorsi flap with STSG	ST A/V left	None
17	M	76	SCC scalp	>12	Occipito-parietal median	No skull reconstruction	Latissimus dorsi flap with STSG	ST A/V right	None

SCC, spinocellular carcinoma; SAB, subarachnoid bleeding; F, Female; M, Male; STSG, split thickness skin graft; ALT, antero-lateral thigh flap; ST A/V, superficial temporal artery/vein.

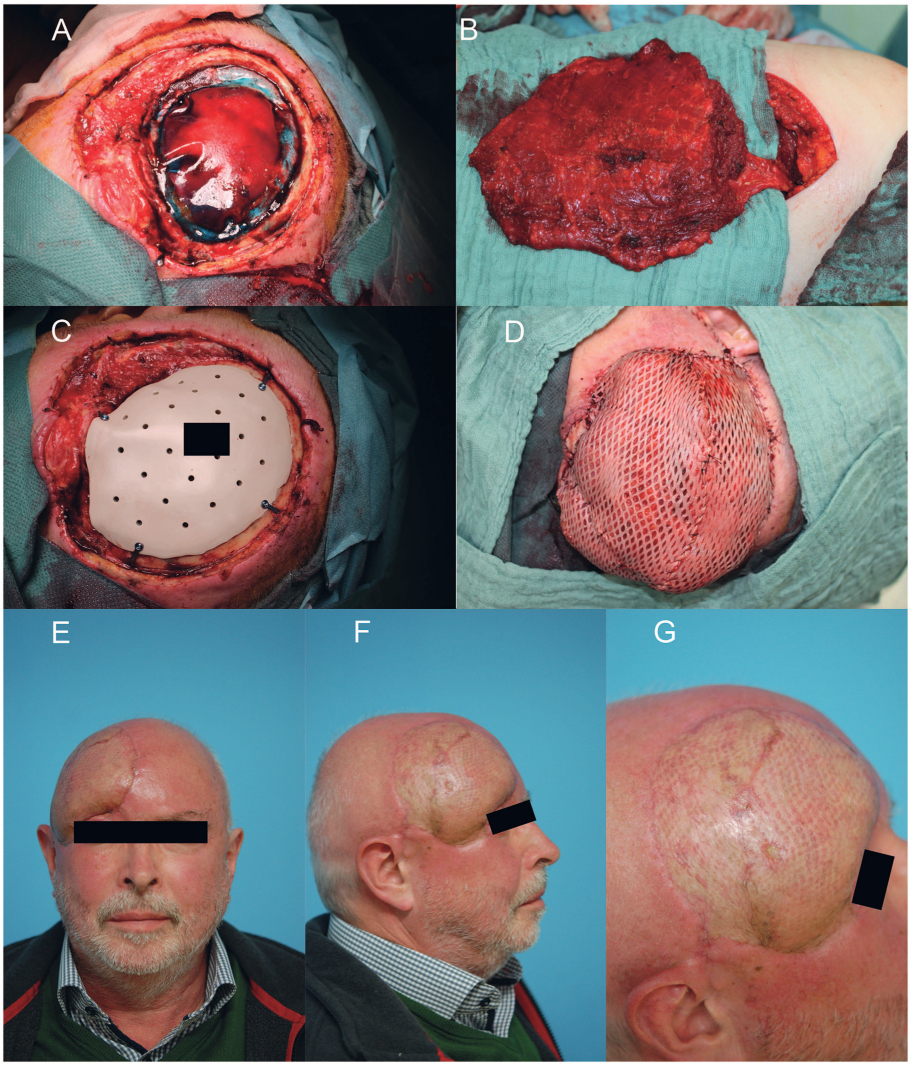


FIGURE 1 | Example of a reconstruction in the fronto-temporal region using a free microvascular latissimus dorsi flap with meshed split thickness skin graft (STSG). **(A)** After interdisciplinary resection of the squamous cell carcinoma and duraplasty of the neurosurgeon. **(B)** Raised free microvascular latissimus dorsi flap in the right decubitus position. **(C)** Bony defect coverage with the patient and defect specific CAD/CAM PEEK-implant. **(D)** Soft tissue coverage with free microvascular latissimus dorsi flap and meshed STSG. **(E–G)** Eighteen months postoperative result. A written informed consent for the publication of the images was obtained from the patient.

inpatient stay. No complementary multivariate logistic regression analysis was performed, because no instance of significance was found in the univariate logistic regression analyses.

All statistical tests were performed at the 0.05 statistical level. *P*-values were two-sided and subjected to a global significance level of 0.05.

RESULTS

Descriptive Analysis

Seventeen consecutively treated cases were included in this retrospective study. Male-to-female distribution was 13/4 and the overall median age was 68 years (28–88). The overall median inpatient stay was 10 days (6–44).

The distribution of age, gender, diagnosis, defect localization, applied technique for calvarial bone reconstruction and complications are presented in **Table 1**.

A comparative descriptive and statistical analysis between parascapular and latissimus dorsi flap is shown in **Table 2**. Nine patients received a parascapular free flap for scalp reconstruction. Herein, necrosis of the flap occurred in one patient after several attempts to salvage the flap such as a conversion to the facial vein with a vein graft and interim recovery after venous congestion. Secondary reconstruction of the defect was done with a microvascular latissimus dorsi flap with a STSG.

Microvascular latissimus dorsi flap with a STSG was used for primary scalp reconstruction in 8 patients in total. There was no total flap failure in this reconstruction group but in case

TABLE 2 | Comparative descriptive and statistical analysis for both reconstruction types.

Parameter	Parascapular (*n* = 9)	Latissimus dorsi (*n* = 8)	*p*-value
Age median (range)	62 (28–78)	68.5 (29–88)	0.665
Diagnosis WHD (%)	8 (88.9)	2 (25.0)	0.01*
Simul. skull reco. (%)	6 (66.7)	2 (25.0)	0.096
Operation time [min.]	445 (300–673)	432 (401–782)	0.847
Overall complications (%)	5 (55.6)	3 (37.5)	0.47
Flap related complications (%)	4 (44.4)	2 (25.0)	0.693
Total flap loss (%)	1 (11.1)	0 (0.0)	0.346
Inpatient stay [days] median (range)	10 (6–44)	11 (6–30)	0.772

WHD, wound healing disorder; simul., simultaneous; reco., reconstruction.
*Mann–Whitney-U-Test; *p-value of <0.05 was considered statistically significant.*

TABLE 3 | Comparative descriptive and statistical analysis for both indications (malignancy vs. wound healing disorder).

Parameter	Malignancy (*n* = 7)	WHD (*n* = 10)	*p*-value
Age median (range)	75 (51–88)	59.5 (28–28)	0.13
Flap type parascapular (%)	1 (14.3)	8 (80.0)	0.01*
Simul. skull reco. (%)	2 (28.6)	6 (60.0)	0.215
Operation time [min.]	430 (401–782)	440 (300–673)	0.626
Overall complications (%)	4 (57.1)	4 (40.0)	0.499
Flap related complications (%)	2 (28.6)	4 (40.0)	0.127
Total flap loss (%)	0 (0.0)	1 (10.0)	0.403
Inpatient stay [days] median (range)	10 (6–30)	11.0 (6–44)	0.845

WHD, wound healing disorder; simul., simultaneous; reco., reconstruction.
*Mann–Whitney-U-Test; *p-value of <0.05 was considered statistically significant.*

TABLE 4 | Univariate logistic regression analyses for the overall incidence of complications and inpatient stay.

	Overall complications		Inpatient stay	
Parameter	*p*-value	95%-CI	*p*-value	95%-CI
Age	0.496	−0.011–0.023	0.479	−0.221–0.449
Gender	0.225	−0.981–0.25	0.985	−12.882–12.651
Diagnosis	0.517	−0.379–0.722	0.894	−11.697–10.297
Flap type	0.488	−0.722–0.361	0.881	−11.619–10.063
Operation time	0.841	−0.002–0.003	0.328	−0.066–0.023
Simultaneous skull reconstruction	0.256	−0.235–0.818	0.097	−1.674–18.063
Overall complications	/	/	0.077	−1.078–18.142

95%-CI, 95% confidence interval.

partial flap loss (serratus anterior muscle part) was registered. The resulting defect was reconstructed with an anterolateral thigh (ALT) flap, which healed uneventful.

In all cases the ST A/V were used as recipient vessels. No difficulties were encountered except for one case, in which conversion to the other side was performed because of insufficient flow of the left ST V.

Minor complications (each small dehiscence) were registered in two patients of the parascapular group. It was treated with re-stitching of the flap under local anesthesia and healed uneventful in the follow-up. Major complications were seen in six patients of which one patient died of multi organ failure, one had a perioperative anaphylactic shock, induced by a hydroxyethyl starch (HES) infusion, which was treated uneventful. Two patients had a hematoma which required surgical exploration, one patient had a complete failure of the flap due to venous congestion and another patient had partial failure of the flap.

Statistical Analysis

The distribution of diagnosis was significantly different in the comparison of the used microvascular flap type ($p = 0.01$, **Table 2**). Wound healing disorder was the leading indication in the parascapular group ($n = 8 = 88.9\%$) and malignancy was the leading indication in the latissimus dorsi group ($n = 6 = 75.0\%$). Flap related complications, total flap loss and inpatient stay varied between both reconstructive methods but showed no significant difference for any parameter ($p = 0.693$, $p = 0.346$, and $p = 0.772$), respectively (**Table 2**).

The distribution of the flap type was significantly different in the comparison of the diagnosis ($p = 0.01$, **Table 3**), respectively. Overall, six out of seven malignancies were reconstructed with the latissimus dorsi flap. Vice-versa eight out of 10 wound healing disorders were reconstructed with the parascapular flap. Bone defects of patients with a wound healing disorder were more often primarily reconstructed (60%) than patients with a malignancy (28.6%; $p = 0.215$, **Table 3**). Flap related complications, total flap loss and inpatient stay varied between both underlaying diagnoses but showed no significant difference for any parameter ($p = 0.\ 127$, $p = 0.\ 403$, and $p = 0.\ 845$), respectively (**Table 2**).

Univariate logistic regression analysis showed no significance for any parameter on the overall complication rate and inpatient stay (**Table 4**).

DISCUSSION

For reconstruction of scalp defects of 25 cm^2 or more, especially if the defect is located close to the hairline or alloplastic materials need to be covered, free tissue transfer is required (12, 13). In the past decades several free flaps were described to reconstruct the scalp. In this context, defect size, recipient vessel, and pedicle length are the main factors, that contribute to the choice of flap type. The latissimus dorsi flap with a STSG is frequently referred to as the first choice in reconstruction of large scalp defects (2, 6, 12, 14). The ALT flap can be used as an alternative, but this microvascular flap is associated with

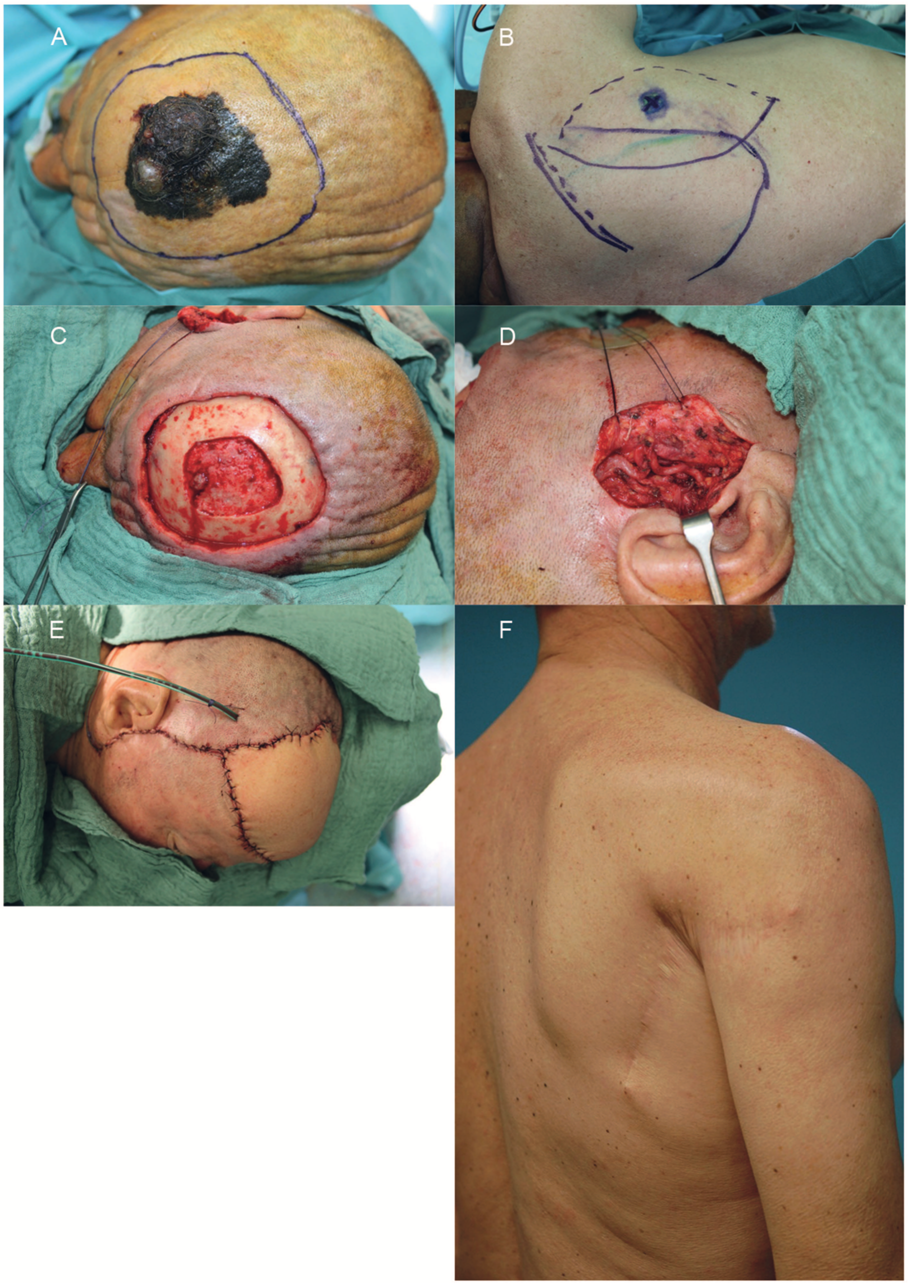


FIGURE 2 | Example of a reconstruction in the fronto-parietal region using a parascapular flap. **(A)** Intended resection margins of melanoma. **(B)** Donor site with marked triangular space. **(C)** Soft and hard tissue defect after interdisciplinary resection. **(D)** Prepared temporal vessels. **(E)** Defect reconstructed with parascapular flap from the ipsilateral side. **(F)** Donor site on the right back 1 year postoperative. A written informed consent for the publication of the images was obtained from the patient.

anatomical variations, bulkiness if it is raised as a non-perforator flap and the patient needs to be re-positioned intraoperatively in many cases, which prevents a two team approach (6, 15). The pedicle length is described to be excellent and also allows microvascular anastomoses to the facial artery and vein (16). Uzun et al. compared musculocutaneous (latissimus dorsi and rectus abdominis) and fasciocutaneous (ALT and radial forearm) flaps for the coverage of composite scalp defects (17). They reported a less atrophy and less blood loss in the fasciocutaneous flap group. For these reasons, we chose the ALT flap for secondary reconstruction, when the latissimus dorsi flap failed partially in one patient. Alternatively, the ALT flap can also be used as a first choice flap in defects with a $\leq$12 cm diameter.

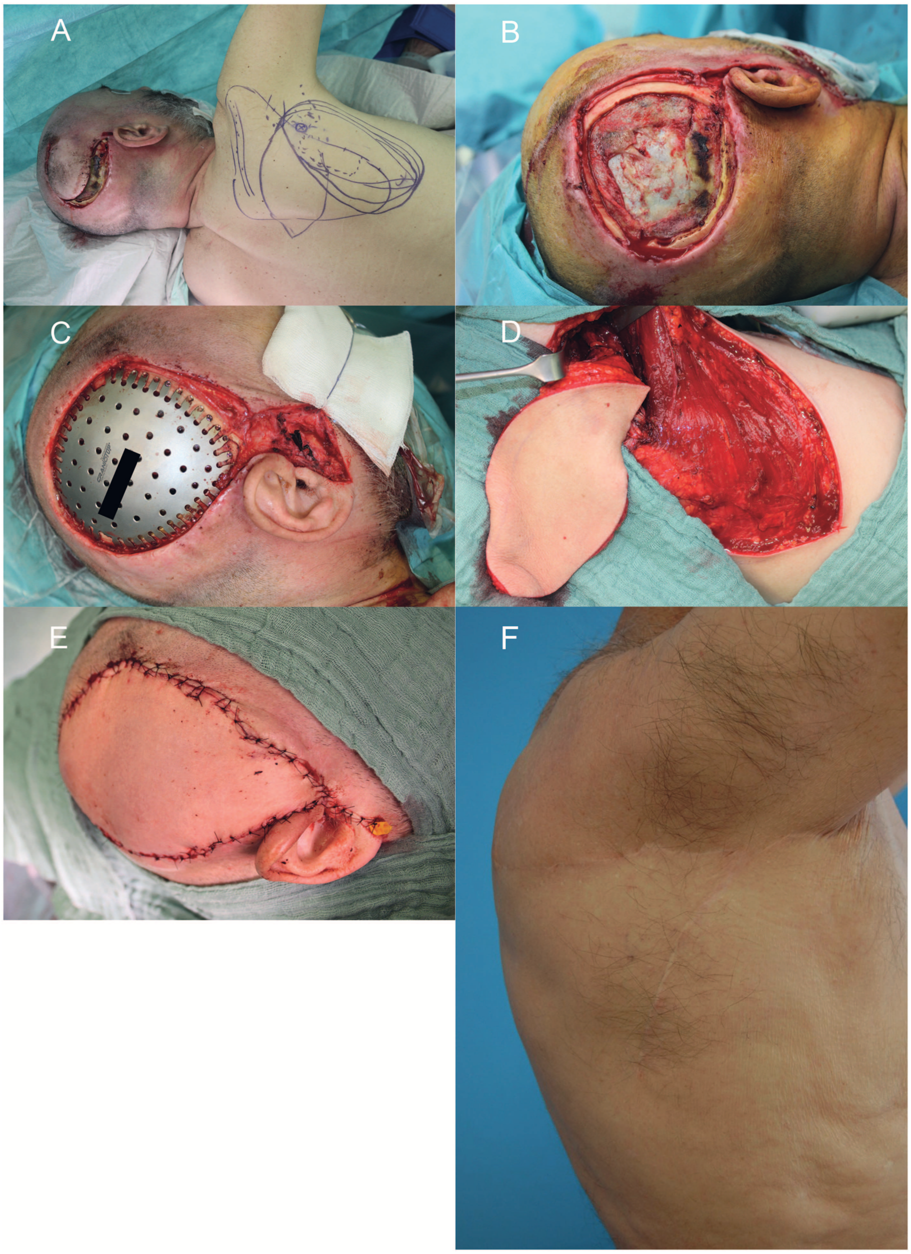


FIGURE 3 | Wound healing disorder after resection of a glioblastoma multiforme relapse in the right temporal region. **(A)** Wound situation and planning of the microvascular parascapular flap in the left decubitus position. **(B)** After debridement of the wound. **(C)** After insertion of the CAD/CAM titanium implant. **(D)** The microvascular parascapular flap with pedicle in the donor site. **(E)** Immediate reconstructive result after soft tissue closure. **(F)** donor site on the right back 1 year postoperative. A written informed consent for the publication of the images was obtained from the patient.

According to our interdisciplinary experience we propose an algorithm for scalp reconstruction where the parascapular flap is the standard flap for reconstruction after wound healing disorders, small neoplasms (diameter ≤12 cm and along oval soft tissue defect), loss of calvarial bone and preparation for calvarial implants (**Figure 5**). We prefer the parascapular flap over the latissimus dorsi free flap due to the reason of maintaining the upper extremity function, which has a significant influence on quality of life, as well as no scaring or muscle atrophy which could jeopardize the scalp and the CAD/CAM-assisted bone reconstruction (18–20) (**Figures 2**, **3**). Klinkenberg et al. described a good patient's satisfaction with the parascapular flap in comparison to the ALT or lateral arm flap (21). Fisher et al. compared patient's satisfaction who received both, ALT and parascapular flap. Herein parascapular flap was also the preferred flap, even though the scar dimensions were greater than with the ALT flap (22). Furthermore, partial flap de-epithelialization can be done (**Figure 4**). The de-epithelized part can be used to treat

FIGURE 4 | Wound healing disorder after two times resection of a meningioma in the left temporo-parietal region. **(A–C)** Preoperative situation of the defect in frontal, side, and back view. **(D)** After microvascular anastomosis and de-epithelialization of the anterior part of the parascapular flap for soft tissue release and to reduce temporal hollowing. **(E)** After wound closure. **(F–H)** Clinical situation on the 7th postoperative day in frontal, side, and back view. A written informed consent for the publication of the images was obtained from the patient.

temporal hollowing, which is often seen as a postsurgical defect due to temporalis muscle disinsertion/atrophy or superficial temporal fat pad atrophy after coronal incision (23). In this context, the usage of muscular latissimus dorsi flap would not need a de-epithelialization with the same effect on avoiding temporal hollowing.

In very large and predominantly round scalp defects a latissimus dorsi flap with STSG is the primary option for reconstruction in our algorithm as described by others (14). The reason therefore is its potentially large surface area, if the transplant is taken as a muscle flap (19). This cannot be achieved by a parascapular flap with a primary closure of the donor site. If even the latissimus flap is insufficient for more extensive defects, Goertz et al. described the combination of LD and PS as a good and reliable option for these cases (24).

In case of flap failure an ALT flap is preferred as secondary reconstruction method due to low donor site morbidity and its favorable pedicle length, which makes the need for an interposition vein graft unnecessary. Disadvantage is the harvesting in supine position of the patient as well as often being

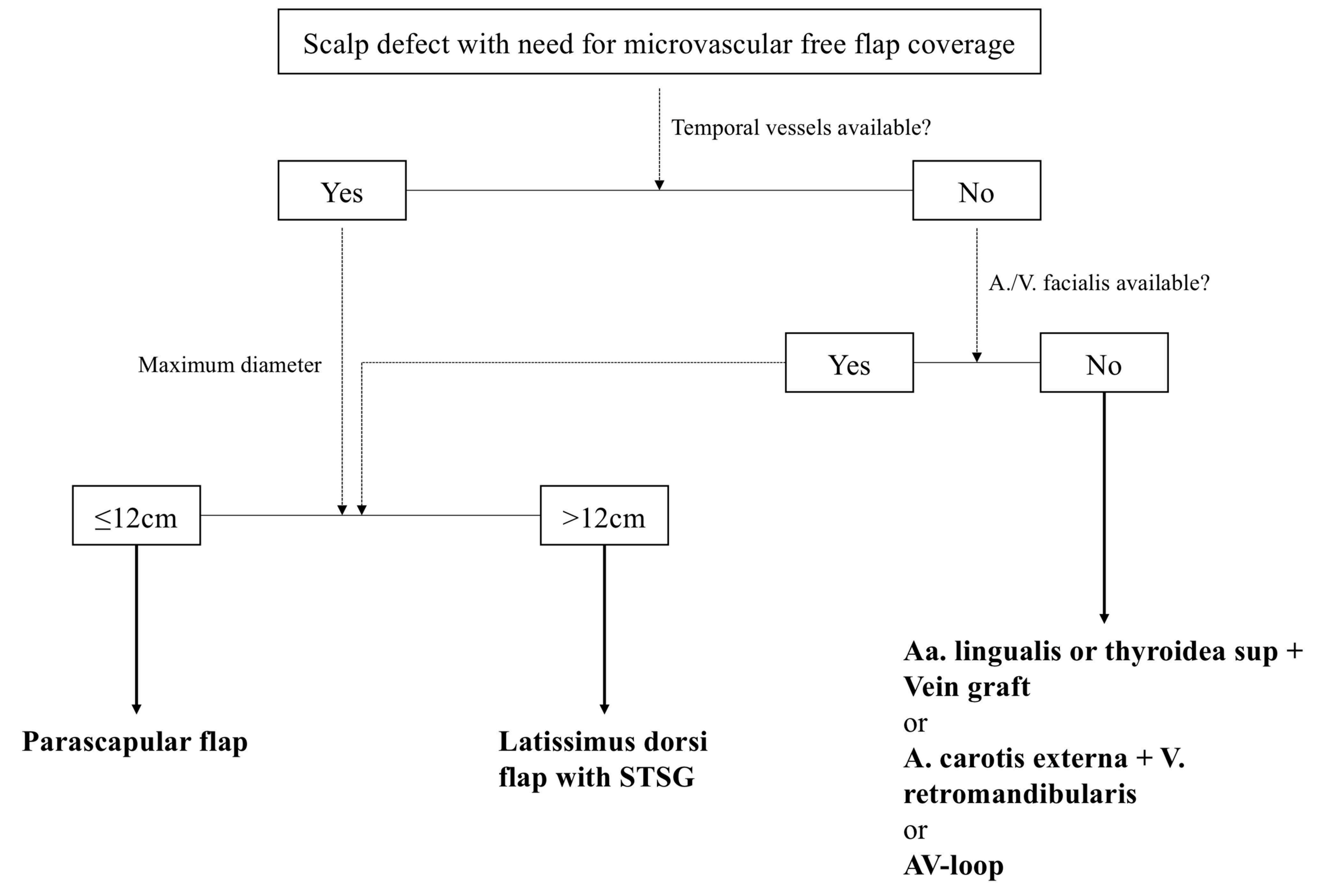


FIGURE 5 | Standardized reconstructive algorithm for scalp defects, that need a defect coverage with a microvascular free flap. STSG, split-thickness skin graft; AV-loop, arteriovenous loop.

bulky. Thinning of the ALT can be done, but might come along with certain risk for flap failure due to vascular compromise because of vasospasm or injury of the perforator, especially in large ALT flaps (25, 26).

In our opinion the parascapular does not oppose any problems due to be bulky or color mismatch, as reported by van Driel et al. (6).

We had one flap loss and the overall flap survival was 94%, which is in line with the reported data in the literature (6, 14). Although in our study it is mainly an elderly population, no adverse effects due to age were seen, as reported by many authors (13, 20).

The ST A/V, if palpable preoperatively (all cases in our study), were the preferred recipient vessel for anastomosis. It is a reliable vascular system because of its consistent anatomy, proximity to the defect, and sufficient vessel caliber for all microvascular flaps (12, 27). Although the caliber of the superficial vessels can be small, especially the distal part, further dissection proximal into the cranial pole of the parotid gland in front of the tragus can be performed to obtain a bigger caliber for vascular anastomosis (6). The temporal vessels are superior to the facial vessels for anastomosis due to the fact that in case of facial recipient vessels and according to the chosen microvascular flap often a interposition vein graft is required, which is known to be a risk factor for flap survival (28, 29). Further, we are able to perform both microvascular anastomoses of the comitant veins to the ST V. Herein we anastomose the better draining comitant vein orthograde to ST V to achieve a drainage to the deep venous system. The weaker comitant vein is anastomosed to the other end of the ST V to achieve a retrograde drainage to the superficial system. In the rare case that the temporal vessels are not suitable for microvascular anastomosis, the neck vessels are a good backup option, especially facial or thyroid artery and vein. In addition, you have the opportunity to raise a vein graft from the external jugular vein via this approach or to include a AV-loop in a single or two-staged regimen, if this should be necessary (**Figure 5**) (30, 31).

LIMITATIONS

According to the nature of a retrospective study, there is a potential for variability in reports of clinical data provided by treating clinicians. The authors attempted to minimize the bias. Secondly, patients were recruited from an inpatient setting only between April 2017 until August 2018 in a single university hospital. The enrolled and analyzed cohort was small. Therefore, the patients might not be representative for the entire population requiring a scalp reconstruction. This rather small patient number guarantees on the other a treatment according to the presented algorithm, that might differ, if we had enrolled more patients from the past years. The statistical results should be interpreted more as a trend. But in summary the cohort meets very well the commonly described underlaying diagnosis and associated comorbidities and history of treatment. Third, records did not comprise radiological or photographic findings to sufficiently describe postoperative morphological and aesthetic changes. We plan to implement this in our pre- and postoperative follow-up for the future, including 3D-photography and a health related questionnaire for quality of life.

CONCLUSIONS

The parascapular flap seems to be a good alternative for microvascular reconstruction of complex composite defects of the scalp ≤12 cm with comparable operation time. Stable results and little donor site morbidity are enabled with subjective satisfying aesthetic outcomes an interdisciplinary two-team approach. A practical treatment algorithm is described.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the manuscript/supplementary files.

AUTHOR CONTRIBUTIONS

JW and LR: study conception, major contributor in writing the manuscript, and operations. CS: data analysis and contributor in writing the manuscript. K-DW and BM: operations and study conception. ES: data acquisition and interpretation, statistical analyses, and writing results section. All authors contributed to manuscript revision, read and approved the submitted version.

FUNDING

This work was supported by the German Research Foundation (DFG) and the Technical University of Munich within the funding programme Open Access Publishing.

ACKNOWLEDGMENTS

All persons who have contributed to the study are listed as authors, since everyone has met the listed criteria for authorship.

REFERENCES

1. Ibrahim Z, Santiago GF, Huang J, Manson PN, Gordon CR. Algorithmic approach to overcome scalp deficiency in the setting of secondary cranial reconstruction. *J Craniofac Surg.* (2016) 27:229–33. doi: 10.1097/SCS.0000000000002289
2. Shonka DC Jr, Potash AE, Jameson MJ, Funk GF. Successful reconstruction of scalp and skull defects: lessons learned from a large series. *Laryngoscope.* (2011) 121:2305–12. doi: 10.1002/lary.22191
3. Gordon CR, Fisher M, Liauw J, Lina I, Puvanesarajah V, Susarla S, et al. Multidisciplinary approach for improved outcomes in secondary cranial reconstruction: introducing the pericranial-onlay cranioplasty technique. *Neurosurgery.* (2014) 10(Suppl 2):179–89; discussion: 189–90. doi: 10.1227/NEU.0000000000000296
4. Baumeister S, Peek A, Friedman A, Levin LS, Marcus JR. Management of postneurosurgical bone flap loss caused by infection. *Plast Reconstr Surg.* (2008) 122:195e–208e. doi: 10.1097/PRS.0b013e3181858eee
5. Bhaskar IP, Inglis TJ, Lee GY. Clinical, radiological, and microbiological profile of patients with autogenous cranioplasty infections. *World Neurosurg.* (2014) 82:e531–4. doi: 10.1016/j.wneu.2013.01.013
6. Van Driel AA, Mureau MA, Goldstein DP, Gilbert RW, Irish JC, Gullane PJ, et al. Aesthetic and oncologic outcome after microsurgical reconstruction of complex scalp and forehead defects after malignant tumor resection: an algorithm for treatment. *Plast Reconstr Surg.* (2010) 126:460–70. doi: 10.1097/PRS.0b013e3181de2260
7. Simunovic F, Eisenhardt SU, Penna V, Thiele JR, Stark GB, Bannasch H. Microsurgical reconstruction of oncological scalp defects in the elderly. *J Plast Reconstr Aesthet Surg.* (2016) 69:912–9. doi: 10.1016/j.bjps.2016.03.021
8. Brown JS, Shaw RJ. Reconstruction of the maxilla and midface: introducing a new classification. *Lancet Oncol.* (2010) 11:1001–8. doi: 10.1016/S1470-2045(10)70113-3
9. Kesting MR, Koerdt S, Rommel N, Mücke T, Wolff K-D, Nobis CP, et al. Classification of orbital exenteration and reconstruction. *J Craniomaxillofac Surg.* (2017) 45:467–73. doi: 10.1016/j.jcms.2017.01.003
10. Watson JS, Craig RD, Orton CI. The free latissimus dorsi myocutaneous flap. *Plast Reconstr Surg.* (1979) 64:299–305. doi: 10.1097/00006534-197909000-00002
11. Nassif TM, Vidal L, Bovet JL, Baudet J. The parascapular flap: a new cutaneous microsurgical free flap. *Plast Reconstr Surg.* (1982) 69:591–600. doi: 10.1097/00006534-198204000-00001
12. Lipa JE, Butler CE. Enhancing the outcome of free latissimus dorsi muscle flap reconstruction of scalp defects. *Head Neck.* (2004) 26:46–53. doi: 10.1002/hed.10338
13. Iblher N, Ziegler MC, Penna V, Eisenhardt SU, Stark GB, Bannasch H. An algorithm for oncologic scalp reconstruction. *Plast Reconstr Surg.* (2010) 126:450–9. doi: 10.1097/PRS.0b013e3181e09515
14. Herrera F, Buntic R, Brooks D, Buncke G, Antony AK. Microvascular approach to scalp replantation and reconstruction: a thirty-six year experience. *Microsurgery.* (2012) 32:591–7. doi: 10.1002/micr.22037
15. Shimizu F, Oatari M, Matsuda K, Uehara M, Sato S, Kato A. Algorithm for reconstruction of composite cranial defects using the fascial component of free anterolateral thigh flaps. *J Craniofac Surg.* (2013) 24:1631–5. doi: 10.1097/SCS.0b013e3182999a33
16. Lamaris GA, Knackstedt R, Couto RA, Abedi N, Durand P, Gastman B. The Anterolateral Thigh Flap as the Flap of Choice for Scalp Reconstruction. *J Craniofac Surg.* (2017) 28:472–6. doi: 10.1097/SCS.0000000000003404
17. Uzun H, Bitik O, Ersoy US, Bilginer B, Aksu AE. Comparison of musculocutaneous and fasciocutaneous free flaps for the reconstruction of the extensive composite scalp and cranium defects. *J Craniofac Surg.* (2018) 29:1947–51. doi: 10.1097/SCS.0000000000005052
18. Krishna BV, Green MF. Extended role of latissimus dorsi myocutaneous flap in reconstruction of the neck. *Br J Plast Surg.* (1980) 33:233–6. doi: 10.1016/0007-1226(80)90018-1
19. Russell RC, Pribaz J, Zook EG, Leighton WD, Eriksson E, Smith CJ. Functional evaluation of latissimus dorsi donor site. *Plast Reconstr Surg.* (1986) 78:336–44. doi: 10.1097/00006534-198609000-00009
20. Sosin M, Chaudhry A, De La Cruz C, Bojovic B, Manson PN, Rodriguez ED. Lessons learned in scalp reconstruction and tailoring free tissue transfer in the elderly: a case series and literature review. *Craniomaxillofac Trauma Reconstr.* (2015) 8:179–89. doi: 10.1055/s-0034-1393725

21. Klinkenberg M, Fischer S, Kremer T, Hernekamp F, Lehnhardt M, Daigeler A. Comparison of anterolateral thigh, lateral arm, and parascapular free flaps with regard to donor-site morbidity and aesthetic and functional outcomes. *Plast Reconstr Surg.* (2013) 131:293–302. doi: 10.1097/PRS.0b013e31827786bc
22. Fischer S, Klinkenberg M, Behr B, Hirsch T, Kremer T, Hernekamp F, et al. Comparison of donor-site morbidity and satisfaction between anterolateral thigh and parascapular free flaps in the same patient. *J Reconstr Microsurg.* (2013) 29:537–44. doi: 10.1055/s-0033-1351394
23. Mericli AF, Gampper TJ. Treatment of postsurgical temporal hollowing with high-density porous polyethylene. *J Craniofac Surg.* (2014) 25:563–7. doi: 10.1097/SCS.0000000000000506
24. Goertz O, Von Der Lohe L, Martinez-Olivera R, Daigeler A, Harati K, Hirsch T, et al. Microsurgical reconstruction of extensive oncological scalp defects. *Front Surg.* (2015) 2:44. doi: 10.3389/fsurg.2015.00044
25. Wolff KD, Kesting M, Loffelbein D, Hölzle F. Perforator-based anterolateral thigh adipofascial or dermal fat flaps for facial contour augmentation. *J Reconstr Microsurg.* (2007) 23:497–503. doi: 10.1055/s-2007-992349
26. Sharabi SE, Hatef DA, Koshy JC, Jain A, Cole PD, Hollier LH Jr. Is primary thinning of the anterolateral thigh flap recommended? *Ann Plast Surg.* (2010) 65:555–9. doi: 10.1097/SAP.0b013e3181cbfebc
27. Hansen SL, Foster RD, Dosanjh AS, Mathes SJ, Hoffman WY, Leon P. Superficial temporal artery and vein as recipient vessels for facial and scalp microsurgical reconstruction. *Plast Reconstr Surg.* (2007) 120:1879–84. doi: 10.1097/01.prs.0000287273.48145.bd
28. Bozikov K, Arnez ZM. Factors predicting free flap complications in head and neck reconstruction. *J Plast Reconstr Aesthet Surg.* (2006) 59:737–42. doi: 10.1016/j.bjps.2005.11.013
29. Preidl RH, Wehrhan F, Schlittenbauer T, Neukam FW, Stockmann P. Perioperative factors that influence the outcome of microsurgical reconstructions in craniomaxillofacial surgery. *Br J Oral Maxillofac Surg.* (2015) 53:533–7. doi: 10.1016/j.bjoms.2015.03.007
30. Oswald TM, Stover SA, Gerzenstein J, Lei MP, Zhang F, Muskett A, et al. Immediate and delayed use of arteriovenous fistulae in microsurgical flap procedures: a clinical series and review of published cases. *Ann Plast Surg.* (2007) 58:61–3. doi: 10.1097/01.sap.0000250743.78576.35
31. Steiner D, Horch RE, Eyupoglu I, Buchfelder M, Arkudas A, Schmitz M, et al. Reconstruction of composite defects of the scalp and neurocranium-a treatment algorithm from local flaps to combined AV loop free flap reconstruction. *World J Surg Oncol.* (2018) 16:217. doi: 10.1186/s12957-018-1517-0

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.

frontiers in Oncology

ORIGINAL RESEARCH
published: 26 November 2019
doi: 10.3389/fonc.2019.01300

Efficacy and Safety of Microsurgery in Interdisciplinary Treatment of Sarcoma Affecting the Bone

Johannes Zeller[1†], Jurij Kiefer[1†], David Braig[1,2,3], Oscar Winninger[1], David Dovi-Akue[4], Georg W. Herget[4], G. B. Stark[1] and Steffen U. Eisenhardt[1*]

[1] Department of Plastic and Hand Surgery, Faculty of Medicine, Medical Center—University of Freiburg, University of Freiburg, Freiburg, Germany, [2] Plastic and Reconstructive Surgery, Sir Charles Gairdner Hospital, Perth, WA, Australia, [3] Division of Hand, Plastic and Aesthetic Surgery, University Hospital, LMU Munich, Munich, Germany, [4] Department of Orthopedics and Trauma Surgery, Faculty of Medicine, Medical Center—University of Freiburg, University of Freiburg, Freiburg, Germany

Edited by:
Raymund E. Horch,
University Hospital Erlangen, Germany

Reviewed by:
Paul Willemsen,
Ziekenhuisnetwerk Antwerpen Middelheim, Belgium
Lee Jae Morse,
Kaiser Permanente Oakland Medical Center, United States

***Correspondence:**
Steffen U. Eisenhardt
steffen.eisenhardt@uniklinik-freiburg.de

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: 07 August 2019
Accepted: 11 November 2019
Published: 26 November 2019

Citation:
Zeller J, Kiefer J, Braig D, Winninger O, Dovi-Akue D, Herget GW, Stark GB and Eisenhardt SU (2019) Efficacy and Safety of Microsurgery in Interdisciplinary Treatment of Sarcoma Affecting the Bone. Front. Oncol. 9:1300. doi: 10.3389/fonc.2019.01300

Background: Sarcomas are tumors of mesenchymal origin with high variation in anatomical localization. Sarcomas affecting the bone often require an interdisciplinary resection and reconstruction approach. However, it is critical that microsurgical reconstruction strategies do not negatively impact tumor safety and overall survival, as limb salvage is only the secondary goal of tumor surgery. Here, we analyzed the efficacy and safety of microsurgery in interdisciplinary treatment of sarcoma affecting the bone.

Patients and Methods: We performed a retrospective chart review of all patients treated for soft-tissue and bone sarcoma at the senior author's institution with a focus on bone affection and microsurgical reconstruction between 2000 and 2019. This particular subgroup was further investigated for tumor resection status, 5-year survival rate, length of hospital stay, as well as overall complication and amputation rates.

Results: Between 2000 and 2019, 803 patients were operated for sarcoma resection and reconstruction by the Department of Plastic and Hand Surgery. Of these, 212 patients presented with sarcoma of the extremity affecting the bone. Within this subgroup, 40 patients required microsurgical reconstruction for limb salvage, which was possible in 38 cases. R0 resection was achieved in 93.8%. The 5-year survival was 96.7%, and the overall complication rate was 25%, of which 40% were microsurgery associated complications.

Conclusion: Safe and function-preserving treatment of soft-tissue and bone sarcoma is challenging. Primary reconstruction with microsurgical techniques of sarcoma-related defects enables limb-sparing and adequate oncosurgical cancer treatment without increasing the risk for local recurrence or prolonged hospital stay. The treatment of sarcoma patients should be reserved to high-volume centers with experienced plastic surgeon embedded in a comprehensive treatment concept.

Keywords: soft tissue sarcoma (STS), microsurgery, interdisciplinary/multidisciplinary, bone sarcoma, free tissue transfer

INTRODUCTION

Sarcomas are a rare and complex entity of tumors arising from tissues of mesodermal origin. With the mesoderm forming both smooth and skeletal muscle, connective tissue, fat, and synovial tissue, sarcomas are not restricted to a specific anatomical location. This highly diverse group of malignancies accounts for <1% of all malignant disorders in adults, yet the current WHO Classification of Diseases and Oncology subdivides sarcomas into more than 100 histologic subtypes (1, 2). Therefore, the variety in localization and histological findings presents a significant challenge for the attending surgeon. For most subtypes, the mainstay of treatment is the surgical excision of the sarcoma. Innovations in reconstructive surgery and interdisciplinary treatment led to safe limb-sparing cancer treatment with amputation rates under ten percent over the last years (3, 4). Improved reconstructive options embedded in a multimodal treatment expanded limb-salvage rates to over 95% of cases (5). Furthermore, recent studies evoke a shift in the paradigm on resection margins in soft tissue sarcoma, with long term safe results in limited sarcoma resection (6). In cases where primary closure after oncological resection is not achievable, microsurgical reconstruction with free tissue transfers allows for sufficient soft tissue coverage and preservation of limb function.

At the Medical Center—University of Freiburg, Germany, patients with localized soft tissue sarcoma are primarily treated by the Department of Plastic and Hand Surgery. Most patients with bone sarcoma or soft tissue sarcoma affecting the bone require an interdisciplinary surgical approach and are, therefore, treated together with the Department of Orthopedics and Trauma Surgery. To optimize all aspects of the cancer treatment, e.g., (neo-)adjuvant and intraoperative radiation therapy, or chemotherapy, every case is discussed in an interdisciplinary tumor board.

Here, we reviewed data from nearly 20 years of multidisciplinary and single-center management of patients with sarcomas regarding surgical treatment modalities and outcome. We further analyzed our results for a subgroup of patients treated in curative intent with bone sarcoma or soft tissue sarcoma affecting the bone, who received microsurgical reconstruction with free tissue transfer.

MATERIALS AND METHODS

We performed a retrospective chart review to analyze all patients treated for sarcoma between January 2000 and July 2019. Within this cohort, we further investigated patients who required complex microsurgical reconstruction for bone sarcoma and soft-tissue sarcoma infiltrating the bone or affecting bone stability after resection for bone sarcoma and soft-tissue sarcoma infiltrating the bone or affecting bone stability after resection. These patients were treated in an interdisciplinary approach by the Department of Plastic and Hand Surgery and the Department of Orthopedics and Trauma Surgery, Medical Center—University of Freiburg. Patients with dermatofibrosarcoma protuberans, pleomorphic dermal sarcoma, and sarcomas of the retroperitoneum were excluded from this study. To reduce heterogeneity, we also excluded sarcoma cases treated with other surgical disciplines, i.e., thoracic or vascular surgery. Clinical notes and pathology reports were reviewed for patient-related data regarding the operative procedure, demographic information, localization of the tumor, histopathological diagnosis, and resection status. Surgical details on flap selection, complications, and further microsurgical information were analyzed from the operative reports.

Statistical analysis was performed using GraphPad Prism v9 for Mac, GraphPad Software, La Jolla California USA (www.graphpad.com). *Fisher's* exact test, *Mann-Whitney* rank-sum, and unpaired t-test (*Student's* test), respectively, were used for statistical analysis. A p-value < 0.05 was regarded as statistically significant.

RESULTS

Patient Characteristics

A total of 803 patients with either soft tissue sarcoma, bone sarcoma, or soft tissue sarcoma infiltrating bones were treated with curative intent between January 2000 and July 2019 by the Department of Plastic and Hand Surgery. Overall, the distribution of sex for our patient population was 46% female and 54% male with a mean age of 58.6 $\pm$ 18 years. Seven cases were excluded due to incomplete or missing data. The further analyzed subgroup of patients with bone-associated sarcoma who received microsurgical reconstruction accounted for 48 patients. The mean age of this cohort was 54.2 $\pm$ 21.7 years (mean $\pm$ SD) with 21 female (43.8%) and 27 male patients (56.2%). Patients of this subgroup underwent tumor surgery, including resection of bone and received microsurgical reconstruction of bone and soft tissue to preserve limb functionality.

Histopathological Characteristics

The anatomical distribution of sarcomas was analyzed based on operative and pathological reports and pre-operative imaging. Overall, sarcomas most frequently affected the lower extremities (51.8% of all patients). Upper extremities, trunk, and head and neck accounted for 19.8, 17.2, and 11.2%, respectively. The most common anatomic location within patients receiving microsurgical coverage was the lower extremities in 32 cases (66.7%). For sarcoma infiltrating bones of the upper extremity, eight patients (16.7%) required microsurgical reconstruction. Sarcoma with bone affection and microsurgical defect coverage located in the trunk comprised of four patients (8.3%), and head and neck sarcoma accounted for four patients (8.3%). In all cases, sarcoma either infiltrated the bone or associated bone tissue had to be resected to ensure cancer-free margins. In nine patients, replacement of the joint with tumor prosthesis had to be performed to achieve limb-salvage, and in 28 patients, extensive bone resection (>3 cm) was performed to ensure tumor-free margins. In 11 cases, limited bone resection was considered sufficient. In patients with oncosurgical bone resections following free tissue transfer, microscopically free

TABLE 1 | Demographic characteristics of sarcoma patients and outcome information.

Age in years	Sex	Entity	Grading	Microsurgical procedure	Resection status	Local recurrence	Radiotherapy	Flap revisions	Flap loss
42	w	Leiomyosarcoma	G2/3	Fibula	R0	No	Neo-adjuvant	None	–
65	m	Undifferentiated liposarcoma	G3	ALT	R1	No	Neo-adjuvant	None	–
83	m	Undifferentiated pleomorphic sarcoma	G3	ALT	R0	No	Adjuvant	None	–
52	w	Fibrobrous synovial sarcoma	G2	ALT	R0	No	Neo-adjuvant	Venous	–
60	m	Undifferentiated pleomorphic sarcoma	G3	ALT	R1	No	Neo-adjuvant	None	–
56	m	Myxofibrosarcoma	G2	ALT	R0	No	No	None	–
72	w	Osteosarcoma	G3	ALT	R0	No	Neo-adjuvant	None	–
29	m	Osteosarcoma	G3	Gracilis	R0	No	No	None	–
17	w	Osteosarcoma	G3	Fibula	R0	No	Neo-adjuvant	Arterial	–
59	w	Sarcoma NOS	G3	Latissimus dorsi	R0	No	Adjuvant	None	–
83	m	Undifferentiated pleomorphic sarcoma	G3	ALT	R0	No	Adjuvant	None	–
52	m	Leiomyosarcoma	G2/3	ALT	R0	No	Adjuvant	None	–
17	w	Osteosarcoma	G3	Gracilis	R0	No	No	None	–
29	m	Osteosarcoma	G3	Gracilis	R0	No	No	None	–
37	m	Undifferenti ated pleomorphic sarcoma	G3	Rectus abdominis	R0	Yes	No	None	–
76	m	Undifferentiated pleomorphic sarcoma	G3	Gracilis	R0	No	Neo-adjuvant	None	–
50	m	Synovial sarcoma	G2	Latissimus dorsi	R0	No	Neo-adjuvant	None	–
59	w	Sarcoma NOS	G3	ALT	R0	No	No	None	–
36	m	Undifferentiated pleomorphic sarcoma	G3	Rectus abdominis	R0	Yes	No	None	–
63	w	Undifferentiated pleomorphi c sarcoma	G3	Latissimus dorsi	R0	No	Adjuvant	None	–
74	w	Sarcoma NOS	G3	Rectus abdominis	R0	No	Adjuvant	None	–
81	m	Myxofibrosarcoma	G3	Latissimus dorsi	R0	No	Adjuvant	None	–
39	m	Myxoid liposarcoma	G1	Parascapular	R0	No	Neo-adjuvant	None	–
88	m	Undifferentiated pleomorphic sarcoma	G3	Radialis	R0	No	No	None	–
77	m	Undifferentiated pleomorphic sarcoma	G3	ALT	R0	Yes	Adjuvant	None	–

(Continued)

TABLE 1 | Continued

Age in years	Sex	Entity	Grading	Microsurgical procedure	Resection status	Local recurrence	Radiotherapy	Flap revisions	Flap loss
68	m	Undifferentiated spindl e cell sarcoma	G3	Latissimus dorsi	R0	No	Adjuvant	None	–
10	m	Alveolar rhabdomyosarcoma	G3	Parascapular	R0	No	No	None	–
71	w	Liposarcoma	G2	Parascapular	R0	No	No	None	–
71	w	Fibrobrous synovial sarcoma	G2	ALT	R1	No	Adjuvant	None	–
52	m	Leiomyosarcoma	G2/3	ALT	R0	No	Adjuvant	None	–
90	m	Sarcoma NOS	G3	ALT	R0	No	No	None	–
74	w	Myxofibrosarcoma	G1	ALT	R0	Yes	No	None	–
46	w	Sarcoma NOS	G3	Rectus abdominis	R0	Yes	Adjuvant	None	–
48	m	Angi osarcoma	G2	Latissimus dorsi	R0	No	Adjuvant	None	–
35	m	Alveolar rhabdomyosarcoma	G3	ALT	R0	No	Adjuvant	None	–
85	w	Sarcoma NOS	G3	Latissimus dorsi	R0	No	No	None	–
53	w	Fibrosarcoma	G3	Rectus	R0	No	No	None	–
56	m	Fibrosarcoma	G3	Lat issimus dorsi	R0	Yes	No	Arterial	–
21	m	Osteosarcoma	G3	ALT	R0	No	No	None	–
21	m	Osteosarcoma	G3	ALT	R0	No	No	None	–
72	w	Dedifferentiated chondrosarcoma	G3	ALT	R0	No	Adjuvant	None	–
77	m	Dedifferentiated chondrosarcoma	G3	Fibula	R0	No	Adjuvant	None	–
65	w	Osteosarcoma	G3	ALT	R0	No	Neo-adjuvant	None	–
44	w	Synovial sarcoma	G2	Rectus abdominis	R0	No	Adjuvant	Arterial	Yes
23	w	Rhabdomyosarcoma	G3	Latissimus dorsi	R0	No	No	Venous	–
15	m	Osteosarcoma	G3	Fibula	R0	No	Neo-adjuvant	None	–
59	w	Myofibroblastic sarcoma	G3	ALT	R0	No	Adjuvant	None	–
49	w	Fibrosarcoma	G3	Fibula	R0	No	No	None	Partial

Grading: G1 Well differentiated (Low grade), G2 Moderately differentiated (Intermediate grade), G3 Poorly differentiated (High grade). ALT, Anterolateral thigh flap.

margins were achieved in 45 cases (93.8%). Three patients were identified as R1 with microscopically residual tumor cells. In two cases, revision surgery had to be performed to achieve tumor-free margins. In one case, the affected limb was amputated to achieve tumor clearance. Overall, sarcomas were located in the limbs in 40 cases. For these patients, limb salvage was achieved in 90%.

The histopathological diagnosis was based on the WHO classification. Osteosarcoma (nine patients), fibrosarcoma (eight patients), and undifferentiated pleomorphic sarcoma (nine patients) were the most common histologic categories. These entities accounted for over 50% of the cases (**Table 1**).

5-Year Survival and Remission Status

Within the observed period, 30 out of 48 patients revealed to be free of sarcoma. Six patients developed local recurrence, and 12 patients presented with distant metastasis. Five years after tumor resection and microsurgical coverage, 30 patients were alive. In 18 cases, tumor surgery was performed within the last 5 years of the study period. Of these patients, 17 were alive. One patient died due to the progression of the disease.

Microsurgical Procedures

The microsurgical procedures performed on sarcoma patients are described hereafter. The most frequently utilized flap was the fasciocutaneos anterolateral thigh flap (ALT), which was utilized in 20 cases (41.7%). The latissimus dorsi flap was the most common muscle flap used for microsurgical reconstruction (nine patients, 18.8%). Minor complications occurred in seven cases (twice seroma and five times wound dehiscence). Five patients had to undergo revision surgery due to insufficient blood flow (three times arterial and twice venous congestion). In two case, total flap loss occurred (**Table 1**).

The following four cases demonstrate study patients treated in an interdisciplinary approach. Each case represents one of the main challenges encountered with bone involvement: prophylactical osteosynthesis in patients with a high risk for secondary fractures, stabilization, and bone bridging with free autografts in primary bone instability, and coverage of tumor endoprosthesis.

Case 1 (**Figure 1**) shows the case of a 52-year old female patient presenting with a G2 synovial sarcoma in the left lower leg (ICD-O M-9040/3., UICC stage IIIA). Sarcoma was infiltrating the posterior compartment of the lower leg and showed contact to both fibula and tibia in the pre-operative imaging. To ensure tumor-free resection margins, the surgical approach included segmental resection of the fibula and wide osteotomy of the dorsolateral cortex of the tibia. Then, a locking compression plate was used to prevent secondary fracture. The transfer of a free ALT flap was performed to cover the resulting defect (8 × 16 cm).

In **Figure 2**, we demonstrate a 42-year-old female patient suffering from a leiomyosarcoma of her lower leg (ICD-O M-8890/3. ypT1, L0, V0, PN0. G2-3, UICC stage II). First, the affected lower leg received neoadjuvant radiation therapy with a total dose of 50 Gy applied. Then, we performed a limb-sparing, wide resection to ensure tumor-free margins. The osteotomy and osteosynthesis of the tibia were performed by the Department for Orthopedics and Trauma Surgery. The resulting bone defect of 8 cm length and soft-tissue defect (7 × 14 cm) was reconstructed with a free osteocutaneous fibula flap.

In case 3 (**Figure 3**), we demonstrate a 15-year old male patient suffering from extensive osteosarcoma in the distal femoral bone (9.1 cm in longitudinal length; ypT2, L0. V0. Pn0). Neoadjuvant chemotherapy was effective and reduced vital tumor cells by 90% while tumor size did not differ to pre-chemotherapy imaging. Consecutively, a 13-cm long segment of the distal femur was resected. For femoral reconstruction, free a fibula graft was harvested from the left limb and used as an intramedullary vascularized graft combined with an allograft as described by Capanna et al. (7) and Ceruso et al. (8). The osteosynthesis was performed using a locking compression plate and a less invasive stabilization system (LISS) plate. Resection margins were microscopically free of tumor cells. The patient presented with normal gait and function and without any difference in leg length 2 months post-operatively.

Case 4 (**Figure 4**) demonstrates a 52-year old male patient presenting with G3 leiomyosarcoma of the distal femur (G2/G3, pT2b, L0, V0, Pn0). Oncological resection included the distal femur and knee joint, which was then reconstructed with a modular endoprosthetic device by the orthopedic surgeons. The resulting soft-tissue defect of 16.5 × 5.5 cm was covered with a free ALT flap from the contralateral thigh performed by the plastic surgeons.

DISCUSSION

We retrospectively analyzed 803 patients treated for soft-tissue and bone sarcoma by the Department of Plastic and Hand Surgery in the observed study period. Within the last 20 years, one-quarter of all sarcoma patients (24.4%) required free tissue transfer after oncosurgical resection. Microsurgical reconstruction was necessary for 48 patients with soft tissue, bone sarcoma, and soft-tissue sarcoma infiltrating bones to restore soft tissue defects or preserve limb functionality. We demonstrated demographic data for this cohort in line with previously published literature. Patients treated with microsurgical techniques for bone affecting sarcomas were evenly distributed between both sexes with a slightly male predilection (1: 1.3 ratio) as reported elsewhere (9). The age distribution of the presented study population is also in line with the available literature on soft-tissue sarcoma (9, 10). Patients who underwent microsurgical coverage for soft-tissue sarcoma affecting the bone and bone sarcoma were slightly younger compared to the overall study population (54.2 ± 21.7 years vs. 58.6 ± 18 years, mean age ± SD).

Besides the extent of the tumor, its localization, and histologic subtype, R0-resection is of utmost importance for local tumor control and mainly predicts the overall survival (11–13). Histopathological evaluation revealed that only 50% of all cases were made up by three sarcoma entities (osteosarcoma, pleomorphic sarcoma, and fibrosarcoma), while the other 50% were divided into another seven subtypes reflecting the inhomogeneity of soft-tissue and bone sarcoma (14). The evaluation of resection margins for the subgroup showed microscopically tumor-free margins in 45 of 48 cases (93.8%). Five-year survival measurement was applicable for 30 patients, of which one patient died due to progressive high-grade liposarcoma, infection, and sepsis. In 620 patients with soft-tissue and bone sarcoma, primary or local defect coverage was possible, compared to 21 cases in which the affected limb had to be amputated ($p = 0.058$). These patients showed local recurrence in 18.2% of all cases (113 cases). The anatomical pattern of cancer localization in both groups showed a predominance of the lower limbs for all sarcoma subtypes combined. With 66.7% of the cases, the analyzed subgroup of soft-tissue sarcomas affecting the bone and bone sarcomas revealed an overrepresentation of the lower extremity compared to the available literature (1). Notably, the often tricky presentation and the relative rareness of soft-tissue sarcomas impede early diagnosis, particularly in the lower extremities, where soft-tissue swelling stays longer unrecognized (15).

We based flap selection on individual parameters such as tumor and defect size, localization, and peri-/intraoperative

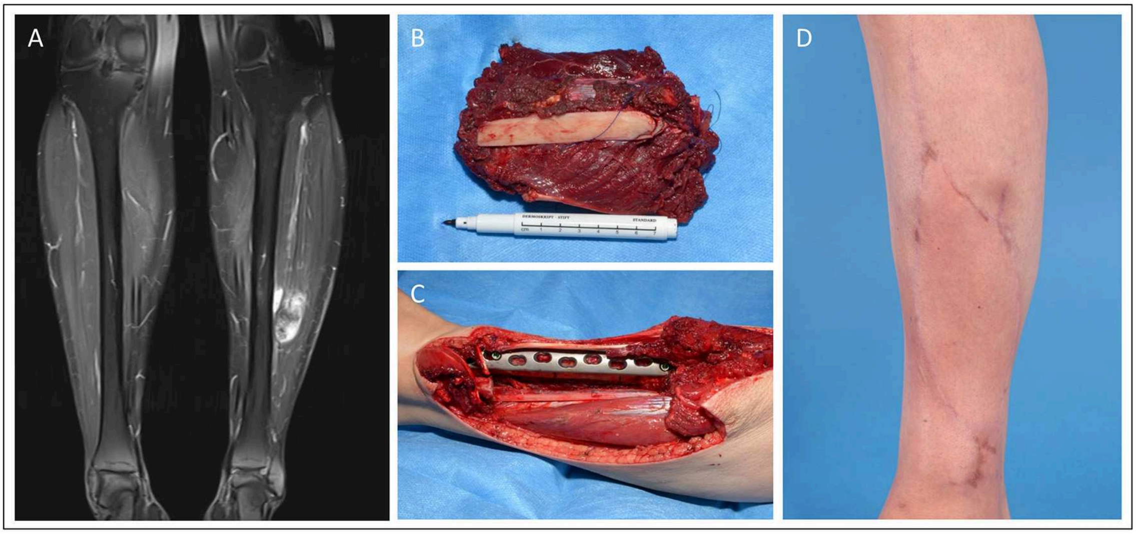


FIGURE 1 | Patient operated in an interdisciplinary approach for synovial sarcoma of the lower extremity. **(A)** Pre-OP MRI of the lower extremity with visible mass in the left lower leg. **(B)** Excised tumor tissue with resected fibula segment. **(C)** Tumor bed with prophylactic plate osteosynthesis on tibia. **(D)** Clinical presentation in the 6 months follow-up.

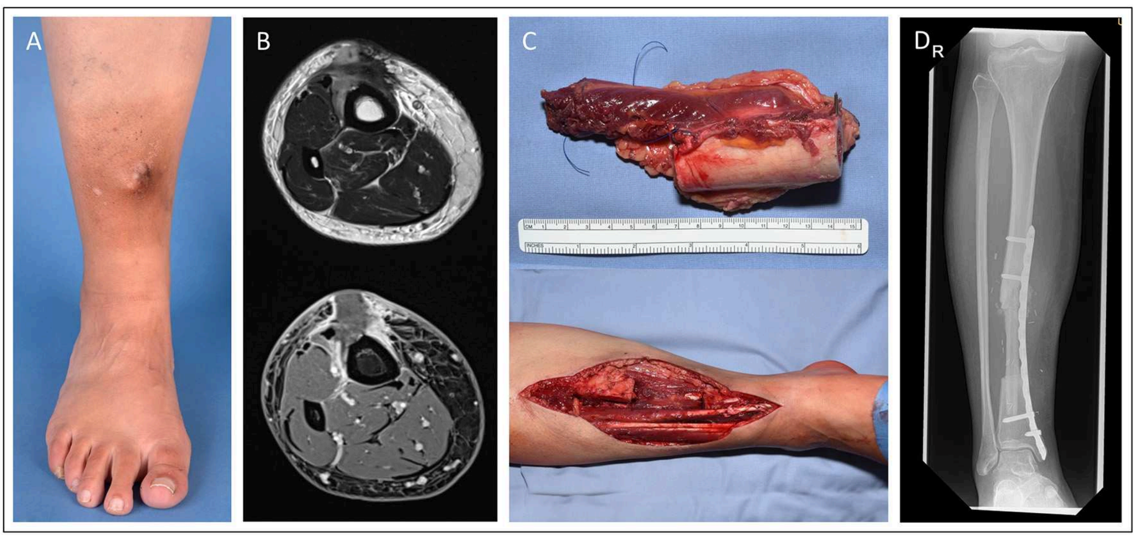


FIGURE 2 | Patient presenting with a tibia-infiltrating leiomyosarcoma. Resulting primary bone defect was bridged by fibula-pro-tibia operation in an interdisciplinary approach. Pre-OP clinical **(A)** and MRI **(B)** presentation of the tumor. **(C)** Excised tumor tissue with affected tibia segment and lower leg during the resection. **(D)** Beginning tibialization of the fibula graft in the 8 months follow-up x-ray.

patient-related conditions, such as patient positioning. If possible, aesthetic principles were also considered. The overall number of major complications was low, with a flap loss rate of 4% and a revision rate of 10.4%. The anterolateral thigh (ALT) flap was the preferred option for soft-tissue defect reconstruction (41.7%). The relative preference in the analyzed cases toward the ALT free flap was due to its high vascular reliability and consistency (16), and the superb experience with this flap in our team (17). The ALT also resembled the plastic surgical principle to replace "like with like" tissue in most cases, resulting in excellent aesthetics at the cost of minimal donor site defects (17, 18). Also, convenient planning for this reconstructive option makes the ALT flap an excellent choice for limited defect sizes. Due to highly trained and organized microsurgeons, the complex reconstruction of the sarcoma-related defects did not prolong hospital stay, which is in line with previously published data (19).

Our findings, as well as extensive retrospective analysis by other groups, undermine that wide excision supersedes

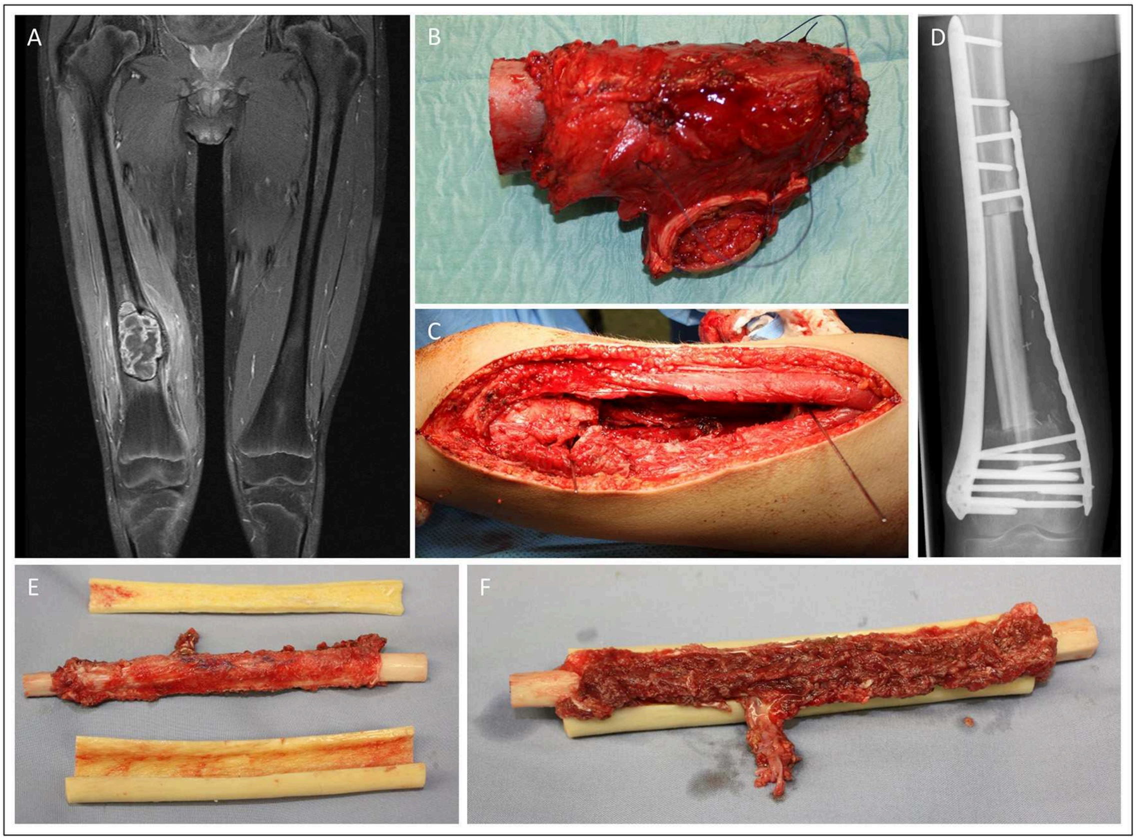


FIGURE 3 | Fifteen-year old male patient presenting with osteosarcoma in the distal femur. Femoral reconstruction was performed with a free fibula graft combined in an allograft as described by Capanna. Pre-OP MRI presentation of the sacroma mass in the distal femur **(A)**. Intraoperative images of the resected tumor (13 cm length) **(B)** and the resulting femoral defect **(C)**. X-ray of the result in the 2 month follow-up **(D)**. **(E)** and **(F)** demonstrate the intraoperative preparation of the microvascular free fibular autograft supported by a peripheral massive allograft shell.

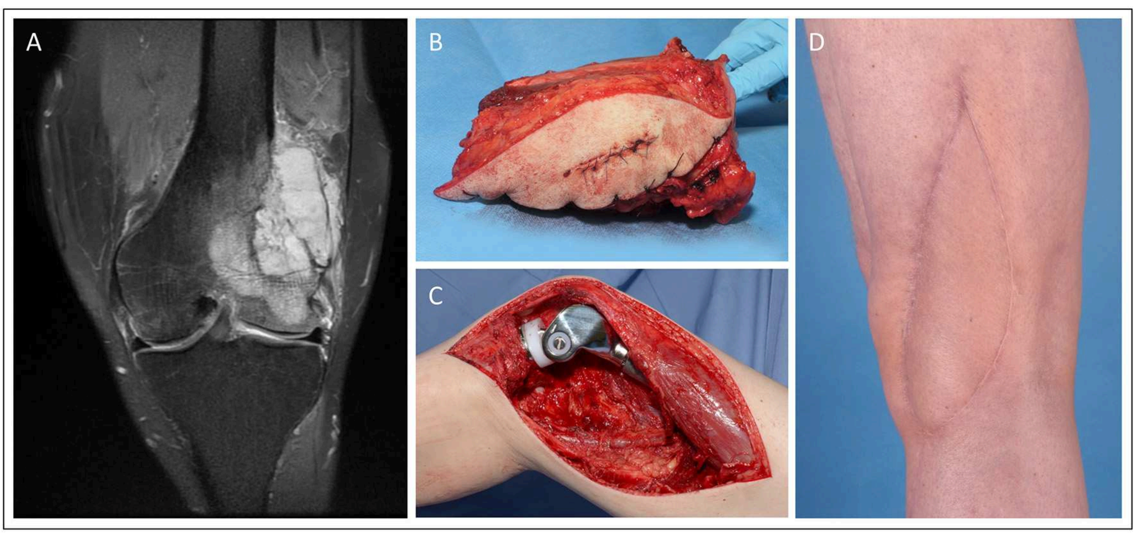


FIGURE 4 | Knee reconstruction with tumor prosthesis and microsurgical soft tissue coverage in a patient presenting with femur-infiltrating leiomyosarcoma. **(A)** Pre-OP MRI of the left knee **(B)** Resected distal femur with tumor free margins **(C)** Intraoperative situation with implanted modular tumor prosthesis after tumor resection. **(D)** Post-operative esthetic outcome in the 6 months follow-up.

compartmental excision (6, 20). Thus, the presented data supports confidence in the efficacy and safety of limb-sparing surgery. Furthermore, the reported 5-year survival rate for the subgroup of complex microsurgical reconstruction (96.7%) is in line with previously published data. Here, limb preservation has shown no disadvantage for the overall survival compared to amputation of the affected (21–23). However, limb-sparing resections might show inferior local control. With 12.5% of the analyzed subgroup cases developed local recurrence, and 25% presented with distant metastasis, patients treated in our department showed risk for tumor recurrence in line with current literature (24). Still, applying plastic surgical principles facilitates limb preservation with the restoration of function even in large tumors. Thus, the utilization of microsurgical reconstruction in sarcoma defects represents a reliable and safe option (25, 26), and is favorable over local options in regards of complication rates and functional outcome (26, 27). By following oncosurgical principles, our results with low amputation rates resembled data published elsewhere (6).

Gutierrez et al. demonstrated the advantages in overall survival and limb-sparing of soft-tissue sarcoma patients treated in high-volume centers over medical centers with a low number of cases (4). The availability of an experienced team of plastic surgeons to guarantee limb-preservation and safe tumor margins and to reduce amputation rates seems vital. However, amputations in complex sarcoma situations involving the limb remains a therapeutic option, and limb-sparing surgery must not be forced at the cost of unsafe tumor margins as limb salvage is only the secondary goal of tumor surgery. Thus, a multidisciplinary tumor board is mandatory to optimize oncological treatment and discuss surgical treatments (28). In critical cases, the impact of amputation on quality of life has to be considered and weigh against declining advantages over limb-spare surgery (29). Surgical treatment should be interdisciplinary in cases where primary instability is inevitable, or resection extent may lead to secondary fracture. Soft-tissue sarcoma patients present initially most often in low volume centers (5), which increases the proportion of previously operated patients and can reduce the operative options for safe tumor resections in the centers, hence creating the requirement for microsurgical defect coverage solutions.

CONCLUSION

Stable oncological outcomes with satisfactory functional results and limb preservation can be achieved even for large sarcoma involving bony tissue if oncological principles for resection are respected and reconstruction is performed according to plastic surgical principles. To handle often large resection-related defects in soft tissue and bone, attending surgeons should provide microsurgical techniques. The heterogeneity and complexity of sarcoma demand an interdisciplinary treatment approach provided by high-volume sarcoma centers.

DATA AVAILABILITY STATEMENT

The datasets analyzed in this manuscript are not publicly available. Requests to access the datasets should be directed to johannes.zeller@uniklinik-freiburg.de.

ETHICS STATEMENT

This study was approved by the ethic committee of the University of Freiburg Medical Center (Nr.: 434/19) and conducted in accordance with the declaration of Helsinki.

AUTHOR CONTRIBUTIONS

JZ conducted main part of the analysis and authored the manuscript with JK. JK authored the manuscript with JZ. DB and OW contributed to the authoring of the manuscript. GS, DD-A, and GH contributed to the interpretation of data, authoring, and final approval of the manuscript. SE planned the analysis, contributed in main parts to the authoring of the manuscript, and interpreted the data.

FUNDING

SE was supported by personal project grants by the German Research Foundation (DFG) (EI 866/1-1, EI 866/1-2, and EI 866/5-1) and a Heisenberg Professorship of the German Research Foundation (EI 866/4-1) which are not related to the research in this manuscript.

REFERENCES

1. Lahat G1, Lazar A, Lev D. Sarcoma epidemiology and etiology: potential environmental and genetic factors. *Surg Clin North Am*. (2008) 88:451–81, v. doi: 10.1016/j.suc.2008.03.006
2. Doyle LA. Sarcoma classification: an update based on the 2013 World Health Organization Classification of tumors of soft tissue and bone. *Cancer*. (2014) 120:1763–74. doi: 10.1002/cncr.28657
3. Canter RJ, Beal S, Borys D, Martinez SR, Bold RJ, Robbins AS. Interaction of histologic subtype and histologic grade in predicting survival for soft-tissue sarcomas. *J Am Coll Surg*. (2010) 210:191–98.e2. doi: 10.1016/j.jamcollsurg.2009.10.007
4. Gutierrez JC, Perez EA, Moffat FL, Livingstone AS, Franceschi D, Koniaris LG. Should soft tissue sarcomas be treated at high-volume centers? An analysis of 4205 patients. *Ann Surg*. (2007) 245:952–8. doi: 10.1097/01.sla.0000250438.04393.a8
5. Steinau HU, Homann HH, Drücke D, Torres A, Soimaru D, Vogt P. [Resection method and functional restoration in soft tissue sarcomas of the extremities]. *Chirurg*. (2001) 72:501–13. doi: 10.1007/s001040051339
6. Harati K, Goertz O, Pieper A, Daigeler A, Joneidi-Jafari H, Niggemann H, et al., Soft tissue sarcomas of the extremities: surgical margins can be close as long as the resected tumor has no ink on it. *Oncologist*. (2017) 22:1400–10. doi: 10.1634/theoncologist.2016-0498
7. Capanna R, Campanacci DA, Belot N, Beltrami G, Manfrini M, Innocenti M, et al. A new reconstructive technique for intercalary defects of long bones: the association of massive allograft with vascularized fibular autograft. Long-term results and comparison with alternative techniques. *Orthop Clin North Am*. (2007) 38:51–60, vi. doi: 10.1016/j.ocl.2006.10.008

8. Ceruso M, Falcone C, Innocenti M, Delcroix L, Capanna R, Manfrini M. Skeletal reconstruction with a free vascularized fibula graft associated to bone allograft after resection of malignant bone tumor of limbs. *Handchir Mikrochir Plast Chir*. (2001) 33:277–82. doi: 10.1055/s-2001-16597
9. Corey RM, Swett K, Ward WG. Epidemiology and survivorship of soft tissue sarcomas in adults: a national cancer database report. *Cancer Med*. (2014) 3:1404–15. doi: 10.1002/cam4.288
10. Gadgeel SM, Harlan LC, Zeruto CA, Osswald M, Schwartz AG. Patterns of care in a population-based sample of soft tissue sarcoma patients in the United States. *Cancer*. (2009) 115:2744–54. doi: 10.1002/cncr.24307
11. Gronchi A, Lo Vullo S, Colombo C, Collini P, Stacchiotti S, Mariani L, Fiore M, et al. Extremity soft tissue sarcoma in a series of patients treated at a single institution: local control directly impacts survival. *Ann Surg*. (2010) 251:506–11. doi: 10.1097/SLA.0b013e3181cf87fa
12. McKee MD, Liu DF, Brooks JJ, Gibbs JF, Driscoll DL, Kraybill WG. The prognostic significance of margin width for extremity and trunk sarcoma. *J Surg Oncol*. (2004) 85:68–76. doi: 10.1002/jso.20009
13. Misra A, Mistry N, Grimer R, Peart F. The management of soft tissue sarcoma. *J Plast Reconstr Aesthet Surg*. (2009) 62:161–74. doi: 10.1016/j.bjps.2008.08.018
14. Jo VY, Doyle LA. Refinements in sarcoma classification in the current 2013 World Health Organization classification of tumours of soft tissue and bone. *Surg Oncol Clin N Am*. (2016) 25:621–43. doi: 10.1016/j.soc.2016.05.001
15. Smolle MA, Andreou D, Tunn P-U, Szkandera J, Liegl-Atzwanger B, Leithner A. Diagnosis and treatment of soft-tissue sarcomas of the extremities and trunk. *EFORT Open Rev*. (2017) 2:421–31. doi: 10.1302/2058-5241.2.170005
16. Wei FC, Jain V, Celik N, Chen HC, Chuang DC, Lin CH. Have we found an ideal soft-tissue flap? An experience with 672 anterolateral thigh flaps. *Plast Reconstr Surg*. (2002) 109:2219–26; discussion: 2227–30. doi: 10.1097/00006534-200206000-00007
17. Momeni A, Kalash Z, Stark GB, Bannasch H. The use of the anterolateral thigh flap for microsurgical reconstruction of distal extremities after oncosurgical resection of soft-tissue sarcomas. *J Plast Reconstr Aesthet Surg*. (2011) 64:643–8. doi: 10.1016/j.bjps.2010.08.005
18. Geddes CR, Morris SF, Neligan PC. Perforator flaps: evolution, classification, and applications. *Ann Plast Surg*. (2003) 50:90–9. doi: 10.1097/00000637-200301000-00016
19. Busse JW, Jacobs CL, Swiontkowski MF, Bosse MJ, Bhandari M, Evidence-Based Orthopaedic Trauma Working Group. Complex limb salvage or early amputation for severe lower-limb injury: a meta-analysis of observational studies. *J Orthop Trauma*. (2007) 21:70–6. doi: 10.1097/BOT.0b013e31802cbc43
20. Bannasch H, Haivas I, Momeni A, Stark GB. Oncosurgical and reconstructive concepts in the treatment of soft tissue sarcomas: a retrospective analysis. *Arch Orthop Trauma Surg*. (2009) 129:43–9. doi: 10.1007/s00402-008-0576-z
21. Alamanda VK, Crosby SN, Archer KR, Song Y, Schwartz HS, Holt GE. Amputation for extremity soft tissue sarcoma does not increase overall survival: a retrospective cohort study. *Eur J Surg Oncol*. (2012) 38:1178–83. doi: 10.1016/j.ejso.2012.08.024
22. Rosenberg SA, Tepper J, Glatstein E, Costa J, Baker A, Brennan M, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Ann Surg*. (1982) 196:305–15. doi: 10.1097/00000658-198209000-00009
23. Williard WC, Hajdu SI, Casper ES, Brennan MF. Comparison of amputation with limb-sparing operations for adult soft tissue sarcoma of the extremity. *Ann Surg*. (1992) 215:269–75. doi: 10.1097/00000658-199203000-00012
24. Cahlon O, Brennan MF, Jia X, Qin LX, Singer S, Alektiar KM. A postoperative nomogram for local recurrence risk in extremity soft tissue sarcomas after limb-sparing surgery without adjuvant radiation. *Ann Surg*. (2012) 255:343–7. doi: 10.1097/SLA.0b013e3182367aa7
25. Koulaxouzidis G, Simunovic F, Bannasch H. Soft tissue sarcomas of the arm - oncosurgical and reconstructive principles within a multimodal, interdisciplinary setting. *Front Surg*. (2016) 3:12. doi: 10.3389/fsurg.2016.00012
26. Vinals JM, Rodrigues TA, Sildenikova DP, Payro JM, Porté JA, Suñe CH, et al., Indications of microsurgery in soft tissue sarcomas. *J Reconstr Microsurg*. (2012) 28:619–25. doi: 10.1055/s-0032-1326740
27. Barner-Rasmussen I, Popov P, Böhling T, Blomqvist C, Tukiainen E. Microvascular reconstructions after extensive soft tissue sarcoma resections in the upper limb. *Eur J Surg Oncol*. (2010) 36:78–83. doi: 10.1016/j.ejso.2009.08.003
28. Stevenson MG, Musters AH, Geertzen JHB, van Leeuwen BL, Hoekstra HJ, Been LB. Amputations for extremity soft tissue sarcoma in an era of limb salvage treatment: local control and survival. *J Surg Oncol*. (2018) 117:434–442. doi: 10.1002/jso.24881
29. Mason GE, Aung L, Gall S, Meyers PA, Butler R, Krüg S, et al. Quality of life following amputation or limb preservation in patients with lower extremity bone sarcoma. *Front Oncol*. (2013) 3:210. doi: 10.3389/fonc.2013.00210

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.

frontiers in Oncology

ORIGINAL RESEARCH
published: 05 March 2020
doi: 10.3389/fonc.2020.00177

Interdisciplinary Treatment of Breast Cancer After Mastectomy With Autologous Breast Reconstruction Using Abdominal Free Flaps in a University Teaching Hospital—A Standardized and Safe Procedure

Dominik Steiner[1]*, *Raymund E. Horch*[1], *Ingo Ludolph*[1], *Marweh Schmitz*[1], *Justus P. Beier*[1,2] and *Andreas Arkudas*[1]

[1] *Department of Plastic and Hand Surgery, University Hospital of Erlangen, Friedrich-Alexander University of Erlangen-Nuernberg, Erlangen, Germany,* [2] *Department of Plastic Surgery, Hand Surgery, Burn Center, University Hospital RWTH Aachen, Aachen, Germany*

OPEN ACCESS

Edited by:
Brian J. Czerniecki, Moffitt Cancer Center, United States

Reviewed by:
John Fischer, University of Pennsylvania, United States
Jaume Masia Ayala, Hospital de la Santa Creu i Sant Pau, Spain

***Correspondence:**
Dominik Steiner
dominik.steiner@uk-erlangen.de

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: *09 August 2019*
Accepted: *31 January 2020*
Published: *05 March 2020*

Citation:
Steiner D, Horch RE, Ludolph I, Schmitz M, Beier JP and Arkudas A (2020) Interdisciplinary Treatment of Breast Cancer After Mastectomy With Autologous Breast Reconstruction Using Abdominal Free Flaps in a University Teaching Hospital—A Standardized and Safe Procedure. Front. Oncol. 10:177. doi: 10.3389/fonc.2020.00177

Background: Breast cancer is the most common malignancy in women. The interdisciplinary treatment is based on the histological tumor type, the TNM classification, and the patient's wishes. Following tumor resection and (neo-) adjuvant therapy strategies, breast reconstruction represents the final step in the individual interdisciplinary treatment plan. Although manifold flaps have been described, abdominal free flaps, such as the deep inferior epigastric artery perforator (DIEP) or the muscle-sparing transverse rectus abdominis myocutaneous (ms-TRAM) flap, are the current gold standard for autologous breast reconstruction. This retrospective study focuses on the safety of autologous breast reconstruction upon mastectomy using abdominal free flaps.

Methods: From April 2012 until December 2018, 193 women received 217 abdominal free flaps for autologous breast reconstruction at the University Hospital of Erlangen. For perforator mapping, we performed computed tomography angiography (CTA). Venous anastomosis was standardized using a ring pin coupler system, and flap perfusion was assessed with fluorescence angiography. A retrospective analysis was performed based on medical records, the surgery report, and follow-up of outpatient course.

Results: In most cases, autologous breast reconstruction was performed as a secondary reconstructive procedure after mastectomy and radiotherapy. In total, 132 ms1-TRAM, 23 ms2-TRAM, and 62 DIEP flaps were performed with 21 major complications (10%) during hospital stay including five free flap losses (2.3%). In all cases of free flap loss, we found an arterial thrombosis as the main cause. In 24 patients a bilateral breast reconstruction was performed without free flap loss. The majority of free flaps (96.7%) did not need additional supercharging or turbocharging to improve venous outflow. Median venous coupler size was 2.5 mm (range, 1.5–3.5 mm).

Conclusion: Using CTA, intraoperative fluorescence angiography, titanized hernia meshes for rectus sheath reconstruction, and venous coupler systems, autologous breast reconstruction with DIEP or ms-TRAM free flaps is a safe and standardized procedure in high-volume microsurgery centers.

Keywords: breast reconstruction, ms-TRAM, DIEP, CTA, venous coupler, interdisciplinary

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer type in women (24.2%) with an annual incidence and mortality of 11.6 and 15%, respectively (1). As previously reported, autologous breast reconstruction upon mastectomy improves quality of life and is superior to alloplastic methods (2). In the past 40 years, autologous breast reconstruction went through a consequent development. Starting with the rediscovery and popularization of the pedicled latissimus dorsi flap for thoracic wall defects by Olivari in the early 1970s, the invention of muscle-sparing free TRAM flaps by Holmström and later the description of the pedicled transverse rectus abdominis myocutaneous (TRAM) flap by Hartrampf et al. (3) were the next evolutionary steps (4). Nowadays, the reconstructive surgeon can rely on a broad spectrum of free flaps such as the transverse myocutaneous gracilis, superior/inferior gluteal artery perforator, or abdominal free flaps (5). The later ones experienced a further refinement starting from the TRAM over the muscle-sparing variants (ms-TRAM) to the deep inferior epigastric artery perforator (DIEP) flap. Because of their low donor site morbidity, ms-TRAM and DIEP flaps represent the gold standard in autologous breast reconstruction (6–9).

In the past years, many high-volume microsurgery centers have established and improved several methods regarding perforator mapping, quantitative flap perfusion assessment, or donor site morbidity reduction, to make autologous breast reconstruction a standardized and safe procedure. Unlike centers, where one or two surgeons perform breast reconstruction with abdominal free flaps, we tried to answer the question if in an academic university hospital setting with a high number of various surgeons and teaching tasks this procedure is still safe and if there is a difference to published series from single surgeon's experiences.

In this retrospective analysis, we therefore analyzed the various factors that might be relevant in autologous breast reconstruction using abdominal free flaps, computed tomography angiography (CTA) for perforator mapping, venous coupler devices, intraoperative fluorescence angiography, and rectus sheath reconstruction with titanized hernia meshes.

METHODS

Prior to surgery, all patients underwent CTA of the abdomen for perforator mapping (**Figure 1**). Based on the perforator anatomy (size, course, number), the patients were elected for autologous breast reconstruction with either DIEP or ms-TRAM free flaps. Moreover, only patients suitable for free tissue transfer (without morbid obesity or coagulation disorders) and with anesthesiologic acceptable risks underwent autologous breast reconstruction. No further exclusion criteria were defined. Seven senior surgeons performed autologous breast reconstruction in a 2-team approach. Flap harvest and vessel preparation

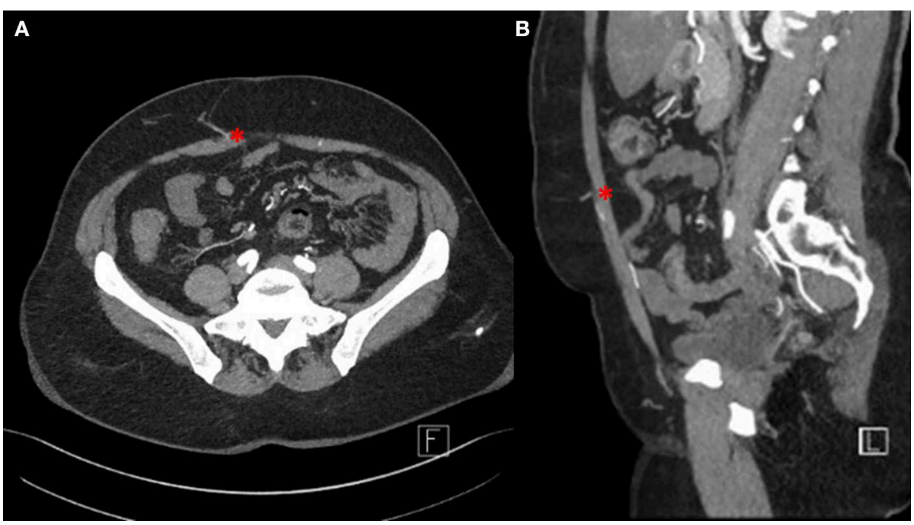


FIGURE 1 | Perforator mapping using computed tomographic angiography (CTA) of the abdomen. **(A)** Transversal view. **(B)** Sagittal view.

occurred simultaneously. Flap harvest was performed by one of the senior surgeons. The internal mammary artery and vein were chosen as the primary recipient vessels. Mostly, a resident prepared the recipient vessels and assisted the senior surgeon during the microvascular anastomosis. Venous anastomoses were performed using a ring-pin coupler system from Synovis (St. Paul, MN, USA). Arterial anastomoses were hand-sewn with Ethilon 8-0 (Ethicon Inc., Somerville, NJ, USA). As previously reported, flap perfusion was assessed with fluorescence angiography using the SPY Elite Imaging System (Stryker, Kalamazoo, MI, USA) (10, 11). In case of fragile and/or recurrent thrombotic internal mammary artery, the vascular surgeons performed bypass extensions using the subclavian or thoracoacromial artery and a vein graft. In terms of primary breast reconstruction ($n = 8$), five prophylactic mastectomies and three mastectomies upon breast conserving therapy were performed. Rectus sheath closure or reconstruction and abdominal wound closure were performed using a TiMESH graft (pfm medical ag, Köln, Germany) in all cases. In case of postoperative hernia, four patients underwent laparoscopic ($n = 3$) or open ($n = 1$) hernia repair. For the retrospective analysis, we reviewed the complete medical charts and surgery reports. We used GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA) for statistical analysis. Normal distribution was assessed with Shapiro-Wilk test. Further analysis was performed with multiple comparisons (using Tukey or Kruskal-Wallis test), Mann-Whitney U test, and Fisher exact test. $p \leq 0.05$ are considered as statistically significant. This study was approved by the ethical review committee of the Friedrich-Alexander-University of Erlangen-Nuremberg (AZ 291_19 Bc).

RESULTS

During the period between 2012 and 2018, 193 women received 217 abdominal free flaps for autologous breast reconstruction at the Department of Plastic and Hand Surgery of the University Hospital of Erlangen. Thereof 24 patients underwent bilateral breast reconstruction (BBR). Average follow-up time was 41.2 months. Mostly, the patients were elected for secondary breast reconstruction (96%). Mean age of the patients was 50.5 ± 8.15 years. Compared to the patients receiving a unilateral ms-TRAM free flap, we found statistically significant younger patients in the bilateral reconstruction group (47.42 ± 16.04, $p \leq 0.05$) (**Figure 2**). Most patients ($n = 122$) displayed a body mass index (BMI) of <30 kg/m^2 in contrast to 50 women with a BMI of >30 kg/m^2; 114 patients (59%) were irradiated, and 55 patients (28.5%) received chemotherapy. In total, 132 ms1-TRAM (60.8%), 23 ms2-TRAM (10.6%), and 62 DIEP flaps (28.6%) were used. Mean operation time for unilateral breast reconstruction was 315.18 ± 32.47 min without statistically significant differences between ms-TRAM and DIEP flaps (**Figure 3**). Obviously, the mean operation time was longer

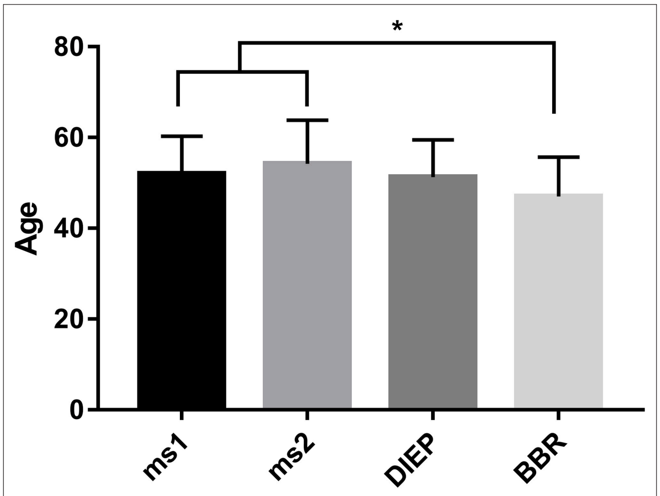


FIGURE 2 | Statistically significant younger patients underwent bilateral breast reconstruction (BBR) compared to unilateral breast reconstruction using muscle-sparing transverse rectus abdominis myocutaneous flap. *$p \leq 0.05$.

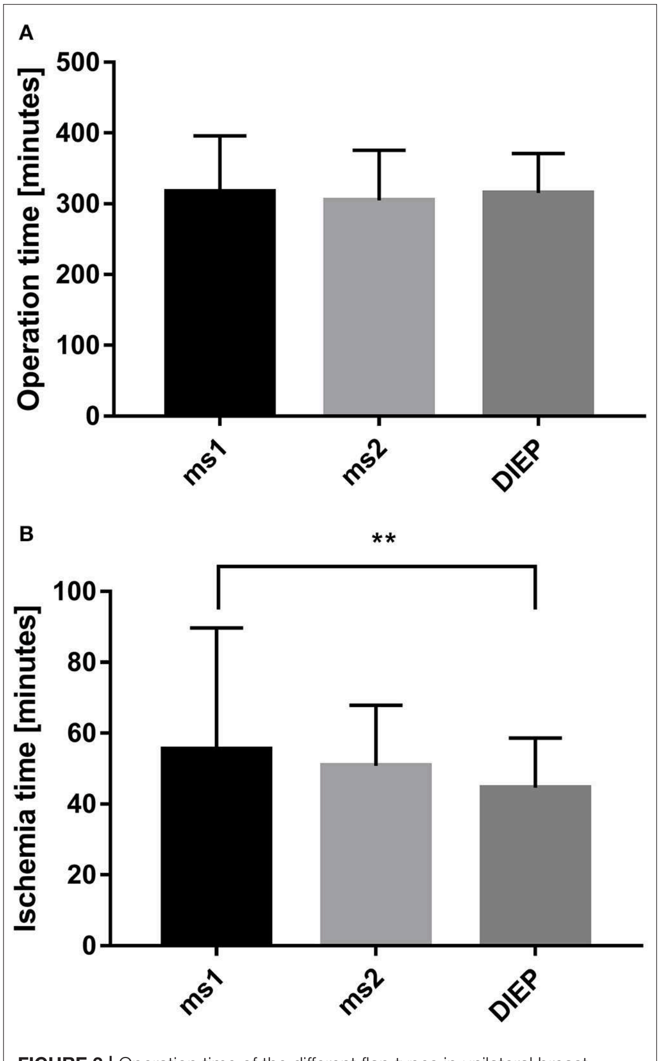


FIGURE 3 | Operation time of the different flap types in unilateral breast reconstruction did not demonstrate statistically significant differences **(A)**. Comparing the ischemia time with the flap type, we found the shortest ischemia time in the deep inferior epigastric artery perforator (DIEP) group **(B)**. **$p \leq 0.01$.

in the bilateral reconstruction group (455.7 ± 99.2; $p \leq 0.001$). Mean flap ischemia time was 52.2 ± 29.4 min with the shortest ischemia times in the DIEP group (44.6 ± 14; $p \leq 0.01$) (**Figure 3**). Next, we compared the operation time from 2012 until 2018. Operation time was defined as the interval between the first skin incision until complete wound closure. We analyzed the operation times from three senior surgeons who performed 149 of 169 unilateral breast reconstructions (88%). In this context, each senior surgeon reached a relatively stable minimum operation time (range, 247–309) after 5 years (**Figure 4**).

In order to improve venous outflow, additional turbocharging or supercharging was necessary in 2.3 and 1%, respectively. For turbocharging, additional anastomoses were performed between the superficial epigastric inferior and the deep inferior epigastric vein ($n = 5$). In case of supercharging, the ipsilateral cephalic vein was used additionally to the internal mammary vein ($n = 2$).

Most commonly, DIEP flaps required additional turbocharging or supercharging ($n = 4$) followed by ms1-TRAM flaps ($n = 3$). Flap characteristics are shown in **Tables 1**, **2**.

Mostly, the internal mammary artery was used for arterial anastomosis (98.2%). Because of recurrent intraoperative thrombosis, a vascular bypass using the subclavian ($n = 2$) or thoracoacromial ($n = 2$) artery and a vein graft was necessary in four patients. In two patients, the cephalic vein was used because of insufficient venous drainage of the internal mammary vein.

In our patient cohort, the internal mammary artery was mostly accompanied by one vein (81%). If one venous anastomosis was performed, the coupler diameter varied between 2.5 and 3.0 mm (48.8 and 34.6%, respectively). In 22 patients, a secondary venous anastomosis was performed with a median coupler diameter of 2.0 mm (range, 1.5–2.5 mm) (**Figures 5A,B**). Comparing the diameter of the venous coupler device, we were able to prove smaller diameters of the first venous anastomosis if a second anastomosis was additionally performed (2.55 ± 0.342 vs. 2.7 ± 0.371 mm; $p \leq 0.05$). Considering the coupler size for the first venous anastomosis, the diameter varied between 2 and 3.5 mm without statistically significant differences between ms1-TRAM, ms2-TRAM, or DIEP flaps. Regarding the coupler size for the second venous anastomosis, ms2-TRAM group displayed smaller coupler diameters (range, 1.5–2.0 mm) compared to the ms1-TRAM or DIEP group (range, 2.0–2.5 mm) (**Figures 5C,D**). In case of secondary venous anastomosis, the medial and lateral internal mammary vein ($n = 14$) or the cranial and the

TABLE 1 | Flap characteristics in unilateral breast reconstruction.

	ms1	ms2	DIEP
Number	100	16	53
Primary reconstruction	2	1	0
Secondary reconstruction	98	15	53
Turbocharging	3	0	2
Supercharging	0	0	2
Complications	15	3	3
Flap loss	3	1	1
Radiation therapy	63	11	31
Chemotherapy	24	4	16

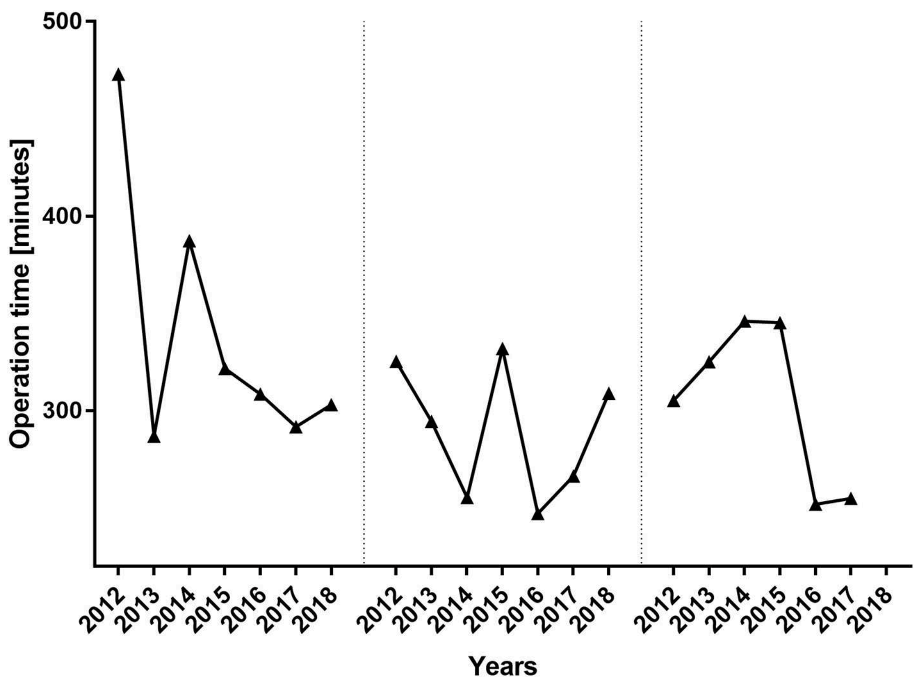


FIGURE 4 | Operation time per surgeon from 2012 until 2018. The operation times of the three major surgeons who performed 88% of the unilateral breast reconstructions are depicted. Despite the years 2012 and 2014, the operation times did not differ significantly between the three senior surgeons.

caudal part of a solitary internal mammary vein was used for anastomosis ($n = 8$).

Considering the need of an additional charging procedure (turbocharging or supercharging; $n = 7$), we did not find a correlation between BMI of <30 kg/m^2 ($p = 0.3230$), radiation therapy ($p > 0.9999$), or flap choice (muscle-sparing TRAM vs. DIEP; $p = 0.2292$).

TABLE 2 | Flap characteristics in bilateral breast reconstruction (BBR).

	ms1	ms2	DIEP
Number	32	7	9
Primary reconstruction	0	1	0
Secondary reconstruction	32	6	9
Turbocharging	2	0	0
Supercharging	1	0	1
Complications	0	0	1
Flap loss	0	0	0
Radiation therapy		8	
Chemotherapy		11	

DIEP, deep inferior epigastric artery perforator.

Twenty-one major complications during hospital stay were registered. In most cases, secondary bleeding or hematoma ($n = 6$) was the main reason for revision surgery. Venous congestion ($n = 3$) and arterial thrombosis ($n = 4$) were the second leading cause for flap revision. Other major complications were umbilicus necrosis ($n = 4$), wound infection ($n = 1$), and abdominal wound healing disorder ($n = 2$). Five free flap losses were found (2.3%). In four patients, an arterial thrombosis was the cause for flap loss, whereas in the fifth case a disorder of cutaneous microcirculation led to partial flap loss ($n = 1$). In three of four cases, in which arterial reconstruction was necessary using the subclavian or thoracoacromial artery and a vein graft, flap loss was observed in the postoperative period. Regarding major complications during hospital stay associated with arterial or venous thrombosis, we did not find a correlation with BMI of >30 kg/m^2 ($p > 0.9999$) or radiation therapy ($p = 0.4716$).

In four patients (2%), we found abdominal hernia in the postoperative aftercare (11–30 months after free flap harvest) requiring hernia repair. In these cases, a ms1-TRAM abdominal free flap was used for breast reconstruction with a tension-free

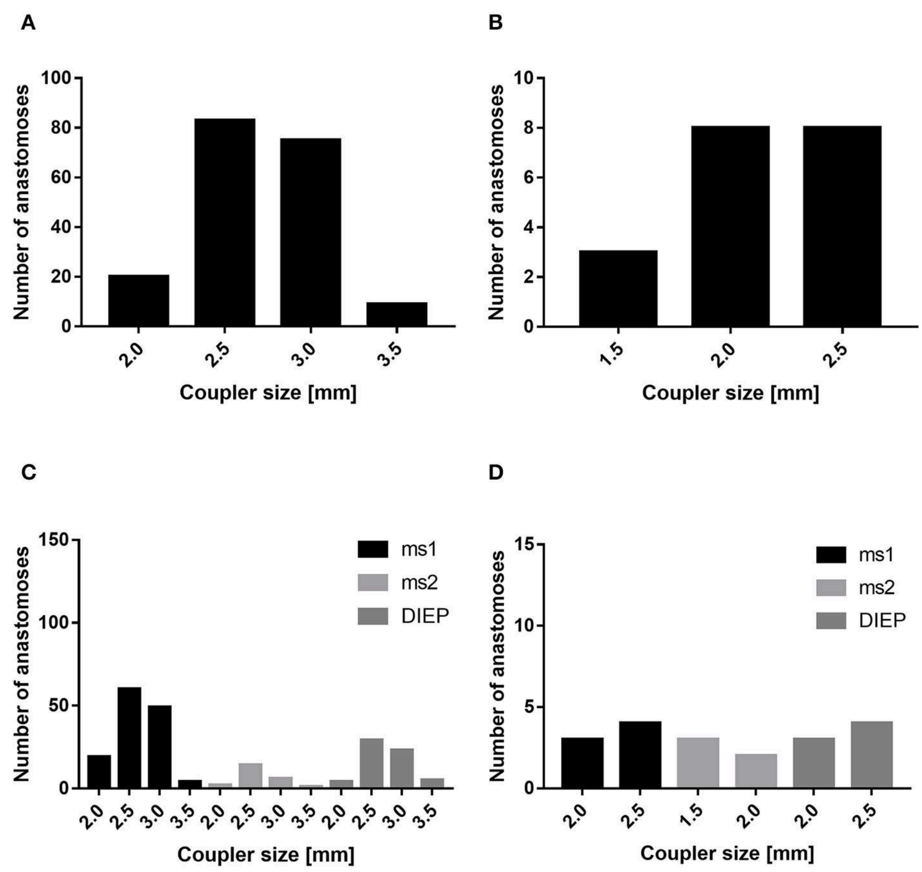


FIGURE 5 | Mostly, the coupler diameter varied between 2.5 and 3.0 mm **(A)**. If a second venous anastomosis was performed, the coupler size varied between 1.5 and 2.5 mm **(B)**. The coupler size did not differ between muscle-sparing transverse rectus abdominis myocutaneous (ms-TRAM) and deep inferior epigastric artery perforator. (DIEP) flaps **(C)**. In case of a second venous anastomosis, the coupler size was smaller in the ms2-TRAM group **(D)**.

anatomical reconstruction of the anterior rectus sheath using titanized hernia meshes in sublay technique.

DISCUSSION

Free microsurgical breast reconstruction with autologous tissue remains the gold standard in modern therapeutic strategies following mastectomy and especially when irradiation was performed during cancer treatment. Other techniques, such as tissue engineering and regenerative medicine, also including the prospect of three-dimensional printing, seem promising but have not reached the clinical applicability so far (12–14). In this retrospective study, we analyzed the outcome of 217 abdominal free flaps for autologous breast reconstruction in 193 patients with respect to the multisurgeon teaching aspect in a university hospital. Herein, we describe our approach including preoperative CTA, venous coupler systems, rectus sheath reconstruction, and intraoperative fluorescence angiography to assess flap perfusion, as well as the inclusion of other medical disciplines such as radiologists, gynecologists, and vascular or general surgeons. Nearly all women underwent secondary breast reconstruction. In 4%, our patients underwent primary breast reconstruction. In these selected cases, the oncological gynecologists performed mastectomy prior to autologous breast reconstruction.

For perforator as well as pedicle mapping, a preoperative CTA was performed. Of course, the preoperative use of CTA might display a certain risk of selection bias concerning the low major complication rate in our series. On the other hand, consistent with the pertinent literature, we believe that CTA enhances the inclusion of appropriate perforators while reducing the operation time and donor site morbidity (15–19). Computed tomography angiography does not only offer the possibility to visualize the architecture of the deep inferior artery and its perforators but also detects anomalous connections between the superficial and deep inferior epigastric venous system (20). The latter ones can affect venous outflow requiring additional charging procedures (supercharging or turbocharging) or the use of another flap type to prevent flap failure (21).

In 1962, Nakayama introduced the first vascular coupler system (22). From then on, the devices were consequently further developed in order to improve their efficacy and safety. Since 2009, our clinic uses venous coupler systems for free tissue transfer. In our cohort, median coupler size was 2.5 mm, without any statistically significant differences between ms1-TRAM, ms2-TRAM, and DIEP flaps. In accordance with other groups, the coupler size varied between 2.5 and 3.0 mm for most abdominal free flaps (23–26). We believe that venous coupler systems reduce the operation time, flap ischemia, venous thrombosis, and consequently flap failure. In the pertinent literature, venous thrombosis rate using venous coupler devices ranges between 0 and 4% (23–25, 27–30). In our cohort, we encountered three cases (1.4%) in which venous congestion was the main cause for revision surgery. In one case, venous congestion occurred intraoperatively during BBR, due to insufficient venous flow in the ipsilateral internal mammary vein after thrombosis of a subclavian port system in the medical history. We solved this problem using a venous crossover bypass to the contralateral caudal internal mammary vein (31). In the other two cases, a postoperative venous congestion occurred. In these two cases, venous coupler size was 2.5 mm. Bearing in mind that smaller diameters of the coupler device can affect venous congestion, we believe that a coupler size of $<$2.5 mm is associated with a higher risk of venous congestion (26). Supercharging and turbocharging procedures were necessary in 1 and 2.3%, respectively.

Although other risk factors, such as radiotherapy or obesity, are discussed in the literature, we could not prove an influence of previous radiation therapy or a BMI of $>$30 kg/m^2 on vessel-associated complications (32–35). Furthermore, flap failure was not associated with venous thrombosis underlining the superiority of venous coupler systems compared to hand-sewn anastomoses (23, 30, 36). As a preliminary finding, the combination of venous coupler anastomosis and preoperative CTA is a valuable tool to enhance the safety of autologous breast reconstruction using abdominal free flaps (37).

In most cases, the internal mammary vessels were used as recipient vessels. Because of fragile and/or recurrent thrombotic internal mammary artery, arterial reconstruction was necessary in four patients using the thoracoacromial or subclavian artery and vein grafts. Although thoracodorsal vessels are discussed as recipient vessels, we believe that the internal mammary artery and vein are the gold standard for autologous breast reconstruction (38–41). The main reasons are the easy preparation of the internal mammary vessels, their good blood flow and diameter, and the preservation of the latissimus dorsi in case of required secondary reconstruction upon free flap failure.

Originating from the TRAM flap, equally whether the pedicled or free flap version, abdominal flaps for breast reconstruction experienced a consequent further development (3, 4, 42). In this regard, Koshima and Soeda (8) introduced the DIEP flap, whereas Nahabedian et al. (43) popularized the muscle-sparing TRAM. The latter ones preserve the anterior rectus sheath, especially (parts of) the rectus muscle with its remaining laterally based innervation and blood supply. Both components, the anterior rectus sheath and the remaining neurovascular supply, play a major role in abdominal wall stabilization after flap harvest (44, 45). In the literature, hernia rates of approximately 10% for pedicled TRAM (range, 0–21.1%), 6% for free TRAM, 2% for ms-TRAM (range, 0–5%), and 3% for DIEP flaps (range, 0–7.1%) were found (46–50). In our study, we found four abdominal hernias (2%), which is comparable to the pertinent literature. Nevertheless, one has to bear in mind that not all surgeons perform anterior rectus sheath reconstruction in the same manner, especially with mesh materials. Besides rectus sheath reconstruction, preoperative CTA can help to preserve the remaining lateral abdominal wall perfusion (51). Taken together, the combination of preoperative CTA and anterior rectus sheath reconstruction may reduce abdominal hernia (47, 52, 53). In the rare event of a true postoperative hernia, we advocate abdominal wall reconstruction together with hernia surgeons.

Besides the clinical evaluation of the flap perfusion, we performed intraoperative fluorescence angiography. The routine use of this imaging tool and early adoption of this technique in a university setting may be an explanation for the excellent performance and the high success rate despite the various surgeons and their individual learning curves (54).

From our point of view, intraoperative fluorescence angiography helps to objectively assess flap perfusion and individually tailor the optimally perfused tissue parts (10, 11, 55). Consequently, insufficiently perfused flap parts can safely be discarded right away. This limits and reduces the rate of postoperative skin and fat necrosis or wound healing disorders. As most of the abdominal free flaps were performed by three senior surgeons, one has to bear in mind that always two to three residents were involved in the operation. The residents prepared the recipient vessels and assisted during the flap harvest and anastomosis, as well as rectus sheath/abdominal closure. Regardless the heterogeneous education year of the residents (range, 1–6 years), we did not observe any statistical difference of the operation time.

Although this is a retrospective single-center study, our results and the pertinent literature prove that autologous breast reconstruction, using abdominal free flaps, is a safe procedure in high-volume microsurgery centers, even following a previous radiation and regardless of patient's age (42, 56–58). Preoperative CTA visualizes abdominal wall vasculature, thereby minimizing operation time and morbidity. In case of arterial reconstruction, one has to bear in mind an increased thrombosis and consequently flap loss rate. However, the interdisciplinary approach together with radiologists, gynecologists, and general and vascular surgeons ensures the success in complex cases.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethical review committee of the Friedrich-Alexander-University of Erlangen-Nuremberg (AZ 291_19 Bc). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DS, RH, and AA made substantial contributions to the study conception and design. DS, RH, AA, IL, JB, and MS made primary contributions to acquisition of data, analysis and interpretation. All authors participated in drafting or revising the article for important intellectual content and gave final approval of the manuscript.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2018) 68:394–424. doi: 10.3322/caac.21492
2. Ludolph I, Horch RE, Harlander M, Arkudas A, Bach AD, Kneser U, et al. Is there a Rationale for autologous breast reconstruction in older patients? A retrospective single center analysis of quality of life, complications and comorbidities after DIEP or ms-TRAM flap using the BREAST-Q. *Breast J*. (2015) 21:588–95. doi: 10.1111/tbj.12493
3. Hartrampf CR, Scheflan M, Black PW. Breast reconstruction with a transverse abdominal island flap. *Plast Reconstr Surg*. (1982) 69:216–25. doi: 10.1097/00006534-198202000-00007
4. Holmstrom H. The free abdominoplasty flap and its use in breast reconstruction. an experimental study and clinical case report. *Scand J Plast Reconstr Surg*. (1979)13:423–27. doi: 10.3109/02844317909013092
5. Seth AK, Allen RJ Jr. Modern techniques and alternative flaps in microsurgical breast reconstruction. *J Surg Oncol*. (2018) 118:768–79. doi: 10.1002/jso.25198
6. Jeong W, Lee S, Kim J. Meta-analysis of flap perfusion and donor site complications for breast reconstruction using pedicled versus free TRAM and DIEP flaps. *Breast*. (2018) 38:45–51. doi: 10.1016/j.breast.2017.12.003
7. Nahabedian MY, Momen B, Galdino G, Manson PN. Breast reconstruction with the free TRAM or DIEP flap: patient selection, choice of flap, and outcome. *Plast Reconstruc Surg*. (2002) 110:466–75; discussion 76–7. doi: 10.1097/00006534-200208000-00015
8. Koshima I, Soeda S. Inferior epigastric artery skin flaps without rectus abdominis muscle. *Br J Plast Surg*. (1989) 42:645–8. doi: 10.1016/0007-1226(89)90075-1
9. Nahabedian MY, Tsangaris T, Momen B. Breast reconstruction with the DIEP flap or the muscle-sparing (MS-2) free TRAM flap: is there a difference. *Plast Reconstruc Surg*. (2005) 115:436–44; discussion 45–6. doi: 10.1097/01.PRS.0000149404.57087.8E
10. Ludolph I, Arkudas A, Schmitz M, Boos AM, Taeger CD, Rother U, et al. Cracking the perfusion code?: Laser-assisted Indocyanine green angiography and combined laser doppler spectrophotometry for intraoperative evaluation of tissue perfusion in autologous breast reconstruction with DIEP or ms-TRAM flaps. *J Plast Reconstr Aesthet Surg*. (2016) 69:1382–8. doi: 10.1016/j.bjps.2016.07.014
11. Buehrer G, Taeger CD, Ludolph I, Horch RE, Beier JP. Intraoperative flap design using ICG monitoring of a conjoined fabricated anterolateral thigh/tensor fasciae latae perforator flap in a case of extensive soft tissue reconstruction at the lower extremity. *Microsurgery*. (2016) 36:684–8. doi: 10.1002/micr.22424
12. Steiner D, Lang G, Fischer L, Winkler S, Fey T, Greil P, et al. Intrinsic vascularization of recombinant eADF4(C16) spider silk matrices in the arteriovenous loop model. *Tissue Eng A*. (2019) 25:1504–13. doi: 10.1089/ten.tea.2018.0360
13. Weigand A, Horch RE, Boos AM, Beier JP, Arkudas A. The arteriovenous loop: engineering of axially vascularized tissue. *Eur Surg Res*. (2018) 59:286–99. doi: 10.1159/000492417
14. Horch RE, Weigand A, Wajant H, Groll J, Boccaccini AR, Arkudas A. [Biofabrication: new approaches for tissue regeneration]. *Handchir Mikrochir Plast Chir*. (2018) 50:93–100. doi: 10.1055/s-0043-124674
15. Fitzgerald O'Connor E, Rozen WM, Chowdhry M, Band B, Ramakrishnan VV, Griffiths M. Preoperative computed tomography angiography for planning DIEP flap breast reconstruction reduces operative time and overall complications. *Gland Surg*. (2016) 5:93–8. doi: 10.3978/j.issn.2227-684X.2015.05.17
16. Boer VB, van Wingerden JJ, Wever CF, Kardux JJ, Beets MR, van der Zaag-Loonen HJ, et al. Concordance between preoperative computed tomography angiographic mapping and intraoperative perforator selection for deep inferior epigastric artery perforator flap breast reconstructions. *Gland Surg*. (2017) 6:620–9. doi: 10.21037/gs.2017.09.13

17. Wade RG, Watford J, Wormald JCR, Bramhall RJ, Figus A. Perforator mapping reduces the operative time of DIEP flap breast reconstruction: a systematic review and meta-analysis of preoperative ultrasound, computed tomography and magnetic resonance angiography. *J Plast Reconstr Aesthet Surg*. (2018) 71:468–77. doi: 10.1016/j.bjps.2017.12.012
18. Rozen WM, Anavekar NS, Ashton MW, Stella DL, Grinsell D, Bloom RJ, et al. Does the preoperative imaging of perforators with CT angiography improve operative outcomes in breast reconstruction? *Microsurgery*. (2008) 28:516–23. doi: 10.1002/micr.20526
19. Ngaage LM, Hamed R, Oni G, Di Pace B, Ghorra DT, Koo BBC, et al. The role of CT angiography in assessing deep inferior epigastric perforator flap patency in patients with pre-existing abdominal scars. *J Surg Res*. (2019) 235:58–65. doi: 10.1016/j.jss.2018.09.059
20. Davis CR, Jones L, Tillett RL, Richards H, Wilson SM. Predicting venous congestion before DIEP breast reconstruction by identifying atypical venous connections on preoperative CTA imaging. *Microsurgery*. (2019) 39:24–31. doi: 10.1002/micr.30367
21. Schaverien MV, Ludman CN, Neil-Dwyer J, Perks AG, Raurell A, Rasheed T, et al. Relationship between venous congestion and intraflap venous anatomy in DIEP flaps using contrast-enhanced magnetic resonance angiography. *Plast Reconstr Surg*. (2010) 126:385–92. doi: 10.1097/PRS.0b013e3181de2313
22. Nakayama K, Tamiya T, Yamamoto K, Akimoto S. A simple new apparatus for small vessel anastomosisi (free autograft of the sigmoid included). *Surgery*. (1962) 52:918–31.
23. Kulkarni AR, Mehrara BJ, Pusic AL, Cordeiro PG, Matros E, McCarthy CM, et al. Venous thrombosis in handsewn versus coupled venous anastomoses in 857 consecutive breast free flaps. *J Reconstr Microsurg*. (2016) 32:178–82. doi: 10.1055/s-0035-1563737
24. Bodin F, Brunetti S, Dissaux C, Erik AS, Facca S, Bruant-Rodier C, et al. Venous coupler use for free-flap breast reconstructions: specific analyses of TMG and DIEP flaps. *Microsurgery*. (2015) 35:295–9. doi: 10.1002/micr.22350
25. Jandali S, Wu LC, Vega SJ, Kovach SJ, Serletti JM. 1000 consecutive venous anastomoses using the microvascular anastomotic coupler in breast reconstruction. *Plast Reconstr Surg*. (2010) 125:792–8. doi: 10.1097/PRS.0b013e3181cb636d
26. Broer PN, Weichman KE, Tanna N, Wilson S, Ng R, Ahn C, et al. Venous coupler size in autologous breast reconstruction–does it matter? *Microsurgery*. (2013) 33:514–8. doi: 10.1002/micr.22169
27. Rozen WM, Whitaker IS, Acosta R. Venous coupler for free-flap anastomosis: outcomes of 1,000 cases. *Anticancer Res*. (2010) 30:1293−4.
28. Ardehali B, Morritt AN, Jain A. Systematic review: anastomotic microvascular device. *J Plast Reconstr Aesthet Surg*. (2014) 67:752–5. doi: 10.1016/j.bjps.2014.01.038
29. Zhang T, Lubek J, Salama A, Caccamese J, Coletti D, Dyalram D, et al. Venous anastomoses using microvascular coupler in free flap head and neck reconstruction. *J Oral Maxillofac Surg*. (2012) 70:992–6. doi: 10.1016/j.joms.2011.02.111
30. Fitzgerald O'Connor E, Rozen WM, Chowdhry M, Patel NG, Chow WT, Griffiths M, et al. The microvascular anastomotic coupler for venous anastomoses in free flap breast reconstruction improves outcomes. *Gland Surg*. (2016) 5:88–92. doi: 10.3978/j.issn.2227-684X.2015.05.14
31. Steiner D, Horch RE, Ludolph I, Arkudas A. Successful free flap salvage upon venous congestion in bilateral breast reconstruction using a venous cross-over bypass: a case report. *Microsurgery*. (2019) 40:74–8. doi: 10.1002/micr.30423
32. Berry T, Brooks S, Sydow N, Djohan R, Nutter B, Lyons J, et al. Complication rates of radiation on tissue expander and autologous tissue breast reconstruction. *Ann Surg Oncol*. (2010) 17(Suppl. 3):202–10. doi: 10.1245/s10434-010-1261-3
33. McAllister P, Teo I, Chin K, Makubate B, Alexander Munnoch D. Bilateral breast reconstruction with abdominal free flaps: a single centre, single surgeon retrospective review of 55 consecutive patients. *Plast Surg Int*. (2016) 2016:6085624. doi: 10.1155/2016/6085624
34. Lee KT, Mun GH. Effects of obesity on postoperative complications after breast reconstruction using free muscle-sparing transverse rectus abdominis myocutaneous, deep inferior epigastric perforator, and superficial inferior epigastric artery flap: a systematic review and meta-analysis. *Annal plast Surg*. (2016) 76:576–84. doi: 10.1097/SAP.0000000000000400
35. Parikh RP, Odom EB, Yu L, Colditz GA, Myckatyn TM. Complications and thromboembolic events associated with tamoxifen therapy in patients with breast cancer undergoing microvascular breast reconstruction: a systematic review and meta-analysis. *Breast Cancer Res Treat*. (2017) 163:1–10. doi: 10.1007/s10549-017-4146-3
36. Zhang A, Dayicioglu D. Outcomes of 270 consecutive deep inferior epigastric perforator flaps for breast reconstruction. *Ann Plast Surg*. (2018) 80(6S Suppl. 6):S388–94. doi: 10.1097/SAP.0000000000001341
37. Ngaage LM, Oni G, Di Pace B, Hamed RR, Fopp L, Koo BC, et al. The effect of CT angiography and venous couplers on surgery duration in microvascular breast reconstruction: a single operator's experience. *Gland Surg*. (2018) 7:440–8. doi: 10.21037/gs.2018.07.11
38. Santanelli Di Pompeo F, Longo B, Sorotos M, Pagnoni M, Laporta R. The axillary versus internal mammary recipient vessel sites for breast reconstruction with diep flaps: a retrospective study of 256 consecutive cases. *Microsurgery*. (2015) 35:34–8. doi: 10.1002/micr.22266
39. Saint-Cyr M, Youssef A, Bae HW, Robb GL, Chang DW. Changing trends in recipient vessel selection for microvascular autologous breast reconstruction: an analysis of 1483 consecutive cases. *Plast Reconstr Surg*. (2007) 119:1993–2000. doi: 10.1097/01.prs.0000260636.43385.90
40. Moon KC, Lee JM, Baek SO, Jang SY, Yoon ES, Lee BI, et al. Choice of recipient vessels in muscle-sparing transverse rectus abdominis myocutaneous flap breast reconstruction: a comparative study. *Arch Plast Surg*. (2019) 46:140–6. doi: 10.5999/aps.2018.00913
41. Venturi ML, Poh MM, Chevray PM, Hanasono MM. Comparison of flow rates in the antegrade and retrograde internal mammary vein for free flap breast reconstruction. *Microsurgery*. (2011) 31:596–602. doi: 10.1002/micr.20928
42. Cai A, Suckau J, Arkudas A, Beier JP, Momeni A, Horch RE. Autologous breast reconstruction with Transverse Rectus Abdominis Musculocutaneous (TRAM) or Deep Inferior Epigastric Perforator (DIEP) flaps: an analysis of the 100 most cited articles. *Med Sci Monit*. (2019) 25:3520–36. doi: 10.12659/MSM.914665
43. Nahabedian MY, Dooley W, Singh N, Manson PN. Contour abnormalities of the abdomen after breast reconstruction with abdominal flaps: the role of muscle preservation. *Plast Reconstr Surg*. (2002) 109:91–101. doi: 10.1097/00006534-200201000-00016
44. Hartrampf CR Jr. Abdominal wall competence in transverse abdominal island flap operations. *Ann Plast Surg*. (1984) 12:139–46. doi: 10.1097/00000637-198402000-00008
45. Nahabedian MY, Manson PN. Contour abnormalities of the abdomen after transverse rectus abdominis muscle flap breast reconstruction: a multifactorial analysis. *Plast Reconstr Surg*. (2002) 109:81–7; discussion 8–90. doi: 10.1097/00006534-200201000-00014
46. Knox AD, Ho AL, Leung L, Tashakkor AY, Lennox PA, Van Laeken N, et al. Comparison of outcomes following autologous breast reconstruction using the DIEP and pedicled TRAM flaps: a 12-year clinical retrospective study and literature review. *Plast Reconstr Surg*. (2016) 138:16–28. doi: 10.1097/PRS.0000000000001747
47. Wan DC, Tseng CY, Anderson-Dam J, Dalio AL, Crisera CA, Festekjian JH. Inclusion of mesh in donor-site repair of free TRAM and muscle-sparing free TRAM flaps yields rates of abdominal complications comparable to those of DIEP flap reconstruction. *Plast Reconstr Surg*. (2010) 126:367–74. doi: 10.1097/PRS.0b013e3181de1b7e
48. Bajaj AK, Chevray PM, Chang DW. Comparison of donor-site complications and functional outcomes in free muscle-sparing TRAM flap and free DIEP flap breast reconstruction. *Plast Reconstr Surg*. (2006) 117:737–46; discussion 47–50. doi: 10.1097/01.prs.0000200062.97265.fb
49. Egeberg A, Rasmussen MK, Sorensen JA. Comparing the donor-site morbidity using DIEP, SIEA or MS-TRAM flaps for breast reconstructive surgery: a meta-analysis. *J Plast Reconstr Aesthet Surg*. (2012) 65:1474–80. doi: 10.1016/j.bjps.2012.07.001
50. Shubinets V, Fox JP, Sarik JR, Kovach SJ, Fischer JP. Surgically treated hernia following abdominally based autologous breast reconstruction: prevalence, outcomes, and expenditures. *Plast Reconstr Surg*. (2016) 137:749–57. doi: 10.1097/01.prs.0000479931.96538.c5
51. Ghattaura A, Henton J, Jallali N, Rajapakse Y, Savidge C, Allen S, et al. One hundred cases of abdominal-based free flaps in breast reconstruction. the

impact of preoperative computed tomographic angiography. *J Plast Reconstr Aesthet Surg*. (2010) 63:1597–601. doi: 10.1016/j.bjps.2009.10.015

52. Ireton JE, Kluft JA, Ascherman JA. Unilateral and bilateral breast reconstruction with pedicled TRAM flaps: an outcomes analysis of 188 consecutive patients. *Plast Reconstr Surg Glob Open*. (2013) 1:1–7. doi: 10.1097/GOX.0b013e3182944595
53. Chatterjee A, Ramkumar DB, Dawli TB, Nigriny JF, Stotland MA, Ridgway EB. The use of mesh versus primary fascial closure of the abdominal donor site when using a transverse rectus abdominis myocutaneous flap for breast reconstruction: a cost-utility analysis. *Plast Reconstr Surg*. (2015) 135:682–9. doi: 10.1097/PRS.0000000000000957
54. Ludolph I, Cai A, Arkudas A, Lang W, Rother U, Horch RE. Indocyanine green angiography and the old question of vascular autonomy - long term changes of microcirculation in microsurgically transplanted free flaps. *Clin Hemorheol Microcirc*. (2019) 72:421–30. doi: 10.3233/CH-180544
55. Ludolph I, Horch RE, Arkudas A, Schmitz M. Enhancing safety in reconstructive microsurgery using intraoperative indocyanine green angiography. *Front Surg*. (2019) 6:39. doi: 10.3389/fsurg.2019.00039
56. Hauck T, Horch RE, Schmitz M, Arkudas A. Secondary breast reconstruction after mastectomy using the DIEP flap. *Surg Oncol*. (2018) 27:513. doi: 10.1016/j.suronc.2018.06.006
57. Eisenhardt SU, Momeni A, von Fritschen U, Horch RE, Stark GB, Bannasch H, et al. [Breast reconstruction with the free TRAM or DIEP flap - what is the current standard? Consensus statement of the German speaking working group for microsurgery of the peripheral nerves and vessels]. H*andchir Mikrochir Plast Chir*. (2018) 50:248–55. doi: 10.1055/a-0631-9025
58. Ludolph I, Lehnhardt M, Arkudas A, Kneser U, Pierer G, Harder Y, et al. [Plastic reconstructive microsurgery in the elderly patient - consensus statement of the German speaking working group for microsurgery of the peripheral nerves and vessels]. *Handchir Mikrochir Plast Chir*. (2018) 50:118–25. doi: 10.1055/s-0043-115730

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.

frontiers in Oncology

ORIGINAL RESEARCH
published: 31 March 2020
doi: 10.3389/fonc.2020.00399

Comparative Effectiveness of Radiofrequency Ablation vs. Surgical Resection for Patients With Solitary Hepatocellular Carcinoma Smaller Than 5 cm

Lei Zheng[1†], Chi-Hao Zhang[1†], Jia-Yun Lin[1†], Chen-Lu Song[2†], Xiao-Liang Qi[1] and Meng Luo[1*]*

[1] Department of General Surgery, School of Medicine, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University, Shanghai, China, [2] Department of Burns and Plastic Surgery, School of Medicine, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University, Shanghai, China

Background: This study aims to compare survival outcome after receiving radiofrequency ablation (RFA) and surgical resection (SR) for solitary hepatocellular carcinoma (HCC) with size large as 5 cm.

Methods: The SEER database was queried for patients with HCC tumors who were treated with RFA or SR between 2004 and 2015. Univariate and multivariate Cox analysis was used to assess the influence of potential variables on the patients' outcome. Additionally, propensity score matching (PSM) and multiple imputations (MI) were used as sensitivity analyses.

Results: Of 1,985 cases, 934 patients received RFA treatment, while the rest underwent surgical resection. The patients in the RFA group had poorer overall survival (OS) and cancer-specific survival (CSS) than those in the SR group regardless of the tumor size before matching and MI. By using PSM analysis at a 1:1 ratio, 1,302 cases were paired and we have found that SR had a positive impact on OS and CSS of patients with tumors measuring from 3.1 to 5 cm. However, when the tumor size was <3 cm, patients undergoing SR had similar survival benefit with those after RFA. The above results were confirmed after performing PSM analysis at a 1:2 and 1:3 ratio.

Conclusion: By applying several effective sensitivity analyses, we demonstrated that OS and CSS were similar between the patients with tumors smaller than 3 cm receiving RFA and SR. But SR may be a superior treatment option with better long-term outcome than RFA in patients with tumor measuring 3.1–5 cm.

Keywords: hepatocellular carcinoma, radiofrequency ablation, surgical resection, overall survival, disease-free survival

OPEN ACCESS

Edited by:
Raymund E. Horch,
University Hospital Erlangen, Germany

Reviewed by:
Zahir Soonawalla,
Oxford University Hospitals NHS Trust, United Kingdom
Stephan Kersting,
University Hospital Erlangen, Germany
Georg F. Weber,
University of Erlangen Nuremberg, Germany

***Correspondence:**
Xiao-Liang Qi
billroth@163.com
Meng Luo
luosh9hospital@sina.com

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

***Received:** 09 July 2019*
***Accepted:** 05 March 2020*
***Published:** 31 March 2020*

Citation:
Zheng L, Zhang C-H, Lin J-Y, Song C-L, Qi X-L and Luo M (2020) Comparative Effectiveness of Radiofrequency Ablation vs. Surgical Resection for Patients With Solitary Hepatocellular Carcinoma Smaller Than 5 cm. Front. Oncol. 10:399. doi: 10.3389/fonc.2020.00399

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most frequent cancer and the third most common cause leading to cancer-related mortality worldwide (1, 2). It is estimated that ~500,000 deaths from HCC occur per year. At diagnosis, no more than 20% of patients are ultimately eligible for curative treatments, such as liver transplantation, surgical removal, and radiofrequency ablation (RFA), mainly due to the presence of metastatic sites or heavy tumor burden (3). Liver transplantation is regarded as the best choice of therapy if possible, as it also treats the remaining liver that is most often cirrhotic. The Milan criteria (4–6), the standard for liver transplant eligibility, are defined as a solitary nodule $\leq$ 5 cm, or up to 3 nodules $\leq$ 3 cm, with no evidence of vascular invasion, and enough liver functional reserve. But owing to the shortage of available liver donors, this technique is limited in clinical practice and only a few patients have the chance to accept this kind of treatment. For those with one tumor $\leq$ 5 cm, who are suitable for transplants but with a low likelihood of receiving an organ, surgical resection (SR) and radiofrequency ablation (RFA) have been suggested as a first-line treatment option.

Currently, there are many studies that have investigated the efficacy of these two therapies (2, 4, 7, 8). But it is still controversial whether RFA or SR results in more favorable treatment outcomes for patients with small lesions. To the best of our knowledge, three randomized trials have been conducted on this issue and the results were discordant. Two of them have reported that SR was similar to RFA in terms of overall survival (OS) (9, 10), while the third one demonstrated that SR offered better OS and disease-free survival (DFS) (6). These results could be explained by the different tumor sizes chosen for RFA and SR treatment.

Although RFA is proposed as preferred therapy in treating small HCC, it is still unclear the maximum HCC tumor size at which RFA continues to be safe and effective. Some proposed that tumor size measuring up to 3 cm was an indication for RFA treatment for HCC (11). However, a multi-center study conducted by Italian scientists found that for tumors smaller than 2 cm, there is no significant survival difference between RFA and SR (5). Furthermore, another study found that even for tumors up to 5 cm, RFA is still effective and can be applied as the first-line treatment (12). Because the therapeutic efficiency of RFA and SR are different in the setting of different tumor size, there is clinical confusion when considering which approach is better for patients. Therefore, to clarify this issue, we stratified patients based on the above tumor size cut-off values and compared the effect of RFA and SR on the survival outcomes of HCC with a single lesion.

Abbreviations: HCC, Hepatocellular carcinoma; RFA, Radiofrequency ablation; SR, Surgical resection; OS, Overall survival; DFS, Disease-free survival; SEER, Surveillance Epidemiology and End Results; AFP, Alpha-fetoprotein; PSM, Propensity score matching; MI, Multiple imputations; CSS, Cancer-specific survival; Cis, Confidence intervals; HRs, Hazard ratios; sdHRs, Subdistribution hazard ratios; INR, International normalized ratio.

MATERIALS AND METHODS

Data Source

Data was retrieved from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database between 2004 to 2015 using SEER*Stat 8.3.5. The SEER database provides information on cancer statistics in an effort to reduce the cancer burden among the U.S. population. The information on type of cancer, tumor size, alpha-fetoprotein (AFP), marital status, gender, age, race, differential degree, survival time, survival status, treatment type of primary cancer, and vascular invasion were retrospectively collected.

Inclusion and Exclusion Criteria

Patients were enrolled into this study if they met the following inclusion criteria: (1) a histological diagnosis of HCC with ICD-O-3 code 8170; (2) 18 years of age or older; (3) follow-up time longer than 3 months; (4) only one lesion measuring <5 cm in size; (5) absence of intrahepatic vascular invasion; (6) underwent RFA or SR. The exclusion criteria included: (1) not the first tumor (occurring simultaneously with or following another tumor); (2) no known survival related information; (3) presence of intra- or extra-hepatic metastases.

Propensity Score Matching (PSM)

Because this is a retrospective study, the included patients were not randomly distributed between RFA and SR group. The unbalanced patient characteristics may result in selection bias, which can distort the real impact of RFA or SR on patients' outcome. To reduce this effect, we first calculated the propensity score using logistic regression modeling of the probability of a patient undergoing RFA or SR on the basis of age, gender, race, marital status, differentiate degree, tumor size, and AFP. Then we used the propensity score to match patients who underwent RFA or SR at a 1:1, 1:2, and 1:3 fixed ratio with no replacement, respectively. In the whole analysis, we used the method of the nearest available matching with the caliper of 0.05. After matching, standardized difference was generated and the value < 0.1 was taken as an indication of the covariates which were well balanced between the two groups.

Multiple Imputations

To alleviate potential biases caused by the missing values in covariates, multiple imputations (MI) method was used with the **mice** function from the **mice** R package. This procedure starts with building a regression model for target variables with missing values based on all other variables. Through this approach, we created 5 sets of complete datasets and then analyzed them using different statistical methods.

Statistical Analysis

In this study, OS and cancer-specific survival (CSS) were defined as the main outcome. Categorial variables were expressed as frequency (percentages) and evaluated using the χ^2 test. The Kaplan-Meier method was used to generate OS and CSS. The survival difference was tested by a log-rank test. To identify potential prognostic variables, Cox univariate analysis was performed and any variables with *p*-values smaller than 0.2

were subsequently included in the Cox multivariate analysis. The results were reported as hazard ratios (HRs) with their 95% confidence intervals (CIs). In addition, death due to causes other than HCC was considered to compete with the event of interest, which may underestimate the incidence of CSS. Therefore, when we estimated the cumulative cancer-specific mortality, death due to other causes needed to be taken into account. In order to examine the association of HCC with mortality, the Fine-Gray proportional hazard models were used and the results were represented as subdistribution hazard ratios (sdHRs) and their 95% CIs. A sdHR of 1 implies no association, an sdHR <1 implies a decreased risk compared with the reference category, and a sdHR >1 implies an increased risk compared with the reference category.

To make our conclusions more robust, sensitivity analyses were performed including deletion of missing values and PSM at different ratios (detailed in the above description). All the statistic tests were two-sided. A p-value smaller than 0.05 was regarded as statistically significant. All the above analyses were performed using R software version 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

A total of 1,985 eligible patients were enrolled in this study, of which 934 were treated with RFA and the others were treated with SR. The median follow-up period of patients in the RFA group was 30 months (range 15–53 months) compared with 34 months (range 16–61 months) in the SR group. The gender and age were similar between the two groups. More patients were married in the RFA group. Fifty-four percent of patients in the RFA group had AFP positive compared with 46% in the SR group. The number of tumors with size smaller than 3 cm were higher in the RFA group. In addition, the SR group tended to have more patients with relatively poorly differentiated tumors. More detailed information can be found in **Table 1**.

TABLE 1 | Baseline demographic and clinical characteristics.

Variables	RFA (n = 934)	SR (n = 1,051)	p
Age			
≤65	596 (63.81)	690 (65.65)	0.418
>65	338 (36.19)	361 (34.35)	0.418
Gender			
Male	701 (75.05)	763 (72.6)	0.234
Female	233 (24.95)	288 (27.4)	0.234
Race			
White	563 (60.28)	564 (53.66)	<0.001
Black	118 (12.63)	124 (11.8)	<0.001
Others	247 (26.45)	359 (34.16)	<0.001
Unknown	6 (0.64)	4 (0.38)	<0.001
Marital status			
Married	504 (53.96)	626 (59.56)	0.009
Unmarried	404 (43.25)	386 (36.73)	0.009
Unknown	26 (2.78)	39 (3.71)	0.009
Grade			
Well differentiated	257 (27.52)	269 (25.59)	<0.001
Moderately differentiated	256 (27.41)	502 (47.76)	<0.001
Poorly differentiated	66 (7.07)	162 (15.41)	<0.001
Undifferentiated	2 (0.21)	13 (1.24)	<0.001
Unknown	353 (37.79)	105 (9.99)	<0.001
Tumor size (cm)			
≤2	216 (23.12)	219 (20.84)	<0.001
≤3	379 (40.58)	332 (31.59)	<0.001
≤5	339(36.30)	500 (47.57)	<0.001
AFP			
Positive	509 (54.50)	488 (46.43)	<0.001
Negative	279 (29.87)	325 (30.92)	<0.001
Unknown	146 (15.63)	238 (22.65)	<0.001
Follow-up time (month)	30 (15.53)	34 (16.61)	0.001

RFA, radiofrequency ablation; SR, surgical removal.

Comparison of Survival Outcomes Before Matching

Before matching, the patients in the RFA group had poorer OS and CSS than those in the SR group regardless of the tumor size. On multivariate analysis, a worse OS (HR: 0.593, 95% CI: 0.285–0.737, $p = 0.012$) and CSS (HR: 0.444, 95% CI: 0.265–0.623, $p < 0.001$) was observed in patients with RFA with tumors ≤ 2 cm before MI (**Figures 1**, **2**). For tumors measuring 2.1–3 cm, the CSS tended to be similar in patients undergoing RFA compared with those receiving SR (HR: 0.919, 95% CI: 0.547–1.291, $p = 0.656$), while the OS is still better in SR group than in RFA group (HR: 0.759, 95% CI: 0.498–0.961, $p = 0.038$). When the tumor size exceeded 3 cm, the SR group had a higher OS (HR: 0.502, 95% CI: 0.263–0.741, $p < 0.001$) and CSS (HR: 0.575, 95% CI: 0.258–0.892, $p < 0.001$) than the RFA group. Furthermore, the competing risk model was built with death caused by cancer-unrelated diseases as a competing event (**Figure 5**). For tumors measuring 2.1 to 3 cm, patients receiving RFA treatment had a similar risk of cancer-related mortality compared to those undergoing SR, with SHR of 0.842 (95% CI: 0.627-1.130). However, the outcome of the SR group was more favorable then the RFA group with tumors measuring either 3.1 to 5 cm (HR: 0.615, 95% CI: 0.451–0.839, $p = 0.002$) or ≤ 2 cm (HR: 0.484, 95% CI: 0.333–0.703, $p < 0.001$).

Because the results may be affected by the variables with missing values, MI was applied to impute the missing values and the complete data was then generated. In this analysis, we found that the patients undergoing RFA had a better OS with tumors ≤ 2 cm (HR: 0.509, 95% CI: 0.273–0.744, $p < 0.001$), ≤ 3 cm (HR: 0.736, 95% CI: 0.501–0.972, $p = 0.011$) and ≤ 5 cm (HR: 0.489, 95% CI: 0.273–0.704, $p < 0.001$) (**Figure 1**). However, the CSS time for RFA was similar to SR for tumors measuring 2.1–3 cm (HR: 0.751, 95% CI: 0.481–1.022, $p = 0.059$). For those whose tumors measured 3.1–5 cm (HR: 0.488, 95% CI: 0.243–0.733, $p < 0.001$) or ≤ 2 cm (HR: 0.436, 95% CI: 0.254–0.618, $p < 0.001$), no significant different was observed in CSS between RFA and SR after MI (**Figure 2**).

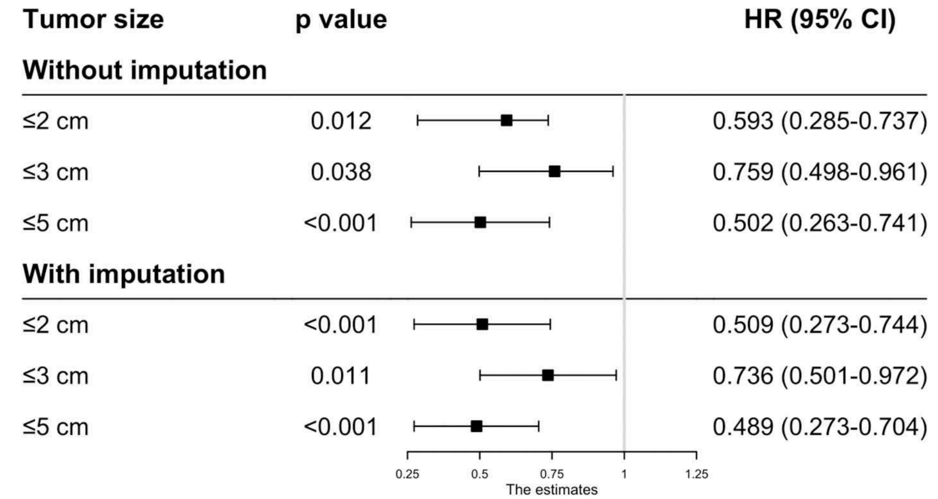


FIGURE 1 | The effect of RFA and surgery on HCC patients' OS with different tumor size before PSM.

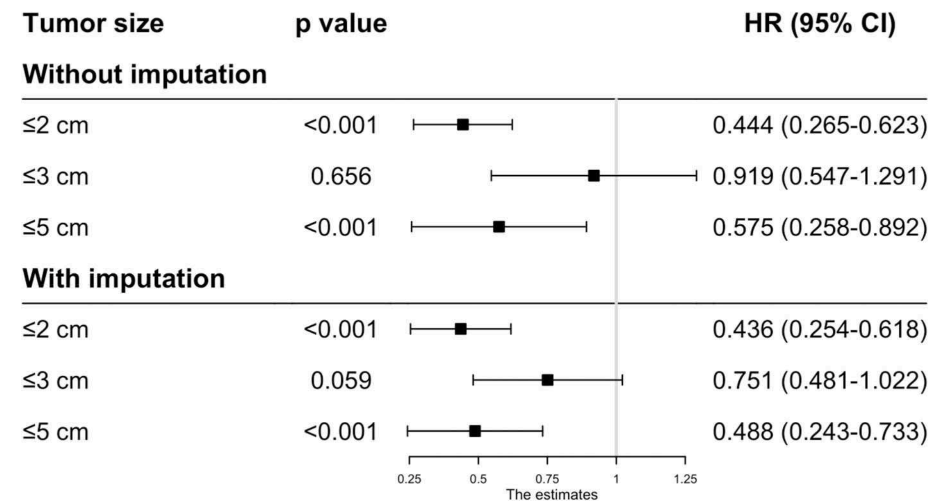


FIGURE 2 | The effect of RFA and surgery on HCC patients' CSS with different tumor size before PSM.

Comparison of Survival Outcomes After Matching

As the baseline characteristics between the RFA and SR group were not the same in the original data, which may lead to inaccurate conclusions, we therefore performed PSM analysis to balance the covariate variables except for therapeutic options. To enhance the validity of our results, we conducted PSM at a 1:1, 1:2, and 1:3 ratio, respectively, and standard difference <0.1 was taken as an indication of well-balanced variables between the two groups. Univariate and multivariate Cox analyses were carried out stratified by tumor size. The results show that RFA and SR were correlated with similar OS (HR: 0.637, 95% CI: 0.249–1.024, $p = 0.526$; HR: 0.865, 95% CI: 0.505–1.225, $p = 0.431$) and CSS (HR: 0.618, 95% CI: 0.111–1.224, $p = 0.121$; HR: 0.874, 95% CI: 0.444–1.304, $p = 0.539$) with tumor size ≤2 and ≤3 cm (**Figures 3**, **4**). Whereas for tumors measuring 3.1 to 5 cm, patients after SR had a significant improvement in OS (HR: 0.549, 95% CI: 0.197–0.900, $p < 0.001$) and CSS (HR: 0.544, 95% CI: 0.139–0.850, $p = 0.023$) compared with those after RFA. This result was maintained after PSM analysis at a 1:2 and 1:3 ratio. A similar trend was also observed in the Fine-Gray proportional hazard model (**Figure 5**).

DISCUSSION

The purpose of this study was to investigate the therapeutic effect of SR and RFA on HCC patients with a solitary lesion measuring ≤5 cm. By applying several effective sensitivity analyses, we have demonstrated that SR had a positive impact on OS and CSS of patients with tumors measuring 3.1–5 cm. However, when the tumor size ≤3 cm, patients had a similar survival benefit from SR as from RFA.

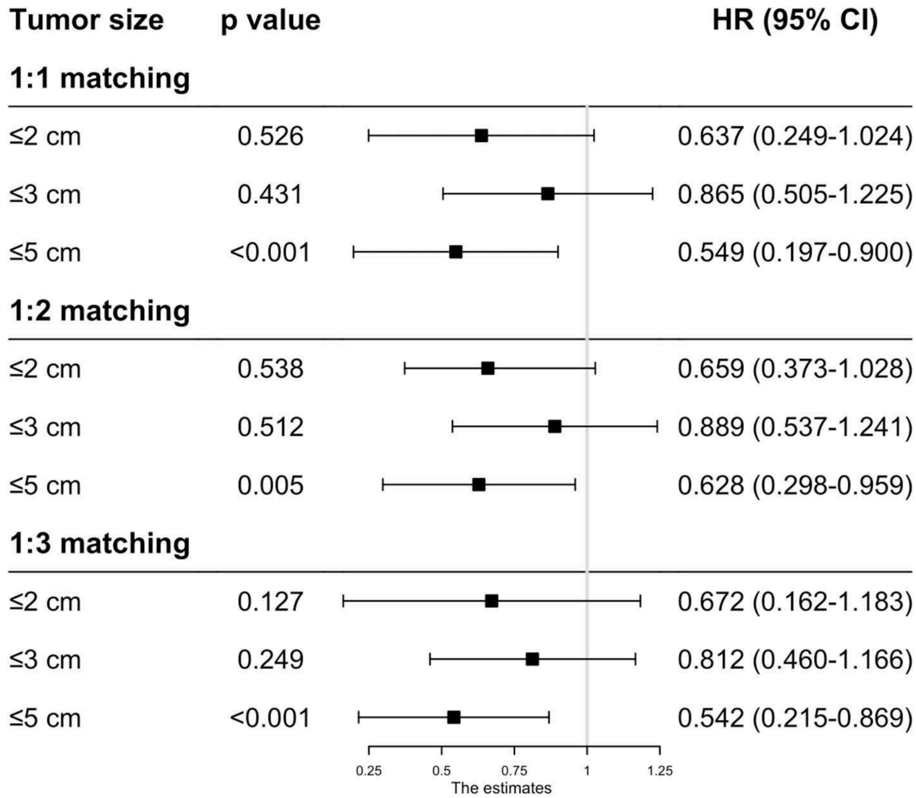


FIGURE 3 | The effect of RFA and surgery on HCC patients' OS with different tumor size after PSM.

Our findings are in agreement with the study by Kutlu et al. (8), which is also conducted based on the SEER database. But our study differs from theirs in three aspects: (1) There are a significant proportion of patients with data missing in this database. The authors chose to delete these missing data and it may result in inaccuracy of the analyses that follow. Therefore, in order to solve this problem, we performed MI analysis in this study, which is an effective approach in dealing with missing data, and the results remained consistent before and after MI analysis. (2) Given potential confounders differed between the SR and RFA group, we also performed propensity score matching to mitigate biases caused by these unadjusted valuables. (3) In the study by Kutlu et al. (8), OS and CSS were considered as the primary event of interest. However, they did not account for the fact that this could result in a bias when using the Kaplan-Meier method in the presence of competing risks, because in this case, the competing risk events are treated as censored data. Non-cancer deaths as a competing event may mislead one to accurately estimate the real mortality rate of HCC. Thus, the Fine-Gray model was also constructed to determine whether or not the therapeutic approach was an independent prognostic factor. Through these methodological improvements, we believe the conclusions will be more reliable.

There have been some reports comparing the efficacy of RFA with SR in small, solitary HCC, however the results proved to be contradictory (2, 4, 6, 7, 13). In the analysis of patients with HCC measuring ≥3 cm, SR was shown to be superior to RFA with respect to OS and CSS in our study regardless of PSM, whereas several studies reported that the effect of RFA on HCC ≥3 cm was comparable to that of SR. For example, the results of a study from France including 281 patients with HCC measuring ≤5 cm have shown no survival difference between the RFA and SR group (5). In addition, another study involving 152 cirrhotic patients undergoing either RFA or SR demonstrated that these two therapies had similar survival rates for single HCC nodules measuring ≤5 cm (14). The discrepancy of these results may be partly due to the type of RFA device used. For example, multipolar devices, which offer better outcomes for HCC patients, have stronger capacity for destroying large tumors than multi-tined expandable monopolar devices. Therefore, some authors pointed that it could result in a bias if several kinds of devices were applied (15). In addition to different types of devices, RFA can be carried out by percutaneous, laparoscopic, or open approaches. It is reported that laparoscopic RFA (LRFA) exerted better therapeutic efficacy than percutaneous approach, especially for those lesions close to the gallbladder, stomach, colon, or other visceral structures (16, 17). So bias might also occur with the application of different RFA approaches. As the RFA probe type is unknown in this database, and multipolar devices, as a newly-invented

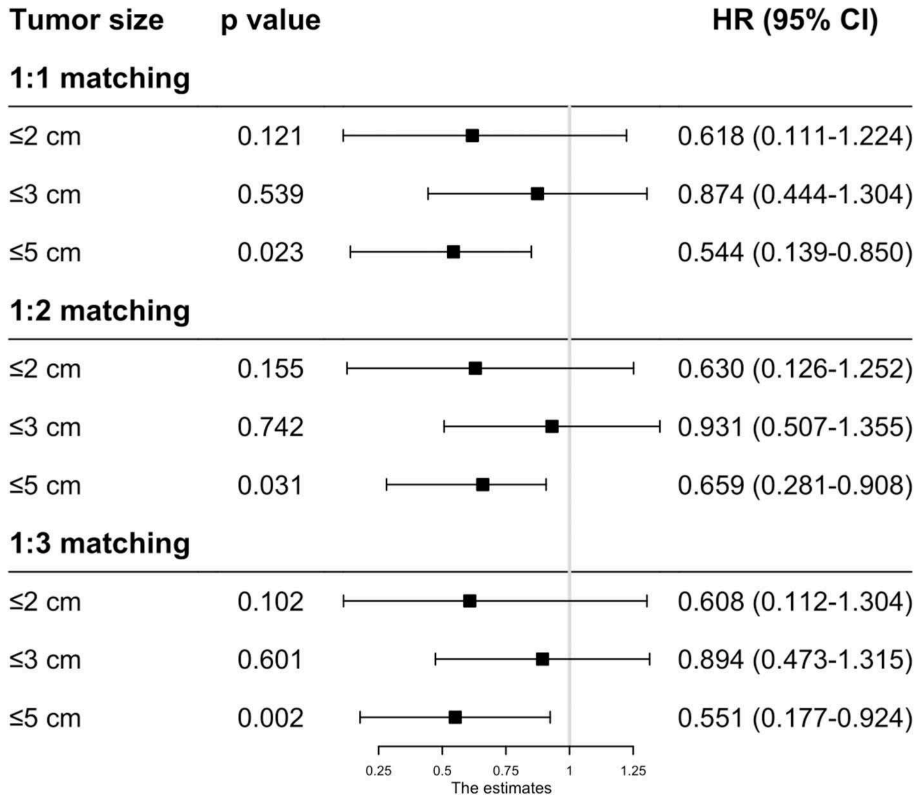


FIGURE 4 | The effect of RFA and surgery on HCC patients' CSS with different tumor size after PSM.

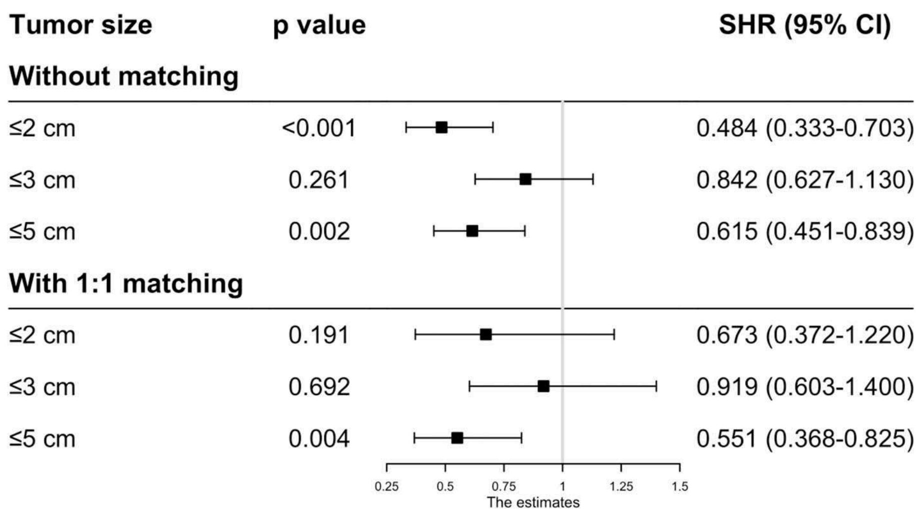


FIGURE 5 | Adjusted HRs for the mortality of HCC patients receiving RFA and surgery before/after PSM.

technique, have only recently entered clinical practice, we think in our study the patients receiving monopolar RFA treatment are more numerous than those receiving multipolar treatment. We believe that is why we found patients in the SR group had a better prognosis.

With regard to HCC ≤3 cm, our results show that there is no significant difference in survival rate between the RFA and SR group, which is similar to several previous studies (7, 18–20). It has been proven that the advantage of SR lies in the complete removal of tumor tissue and hepatic parenchyma around the tumor, which might contain undetectable micrometastases and microvascular invasion. When the tumor is small, it is relatively less likely to have satellite nodules, and therefore, it is possible for RFA to erase the lesion. If the size of tumor exceeds 3 cm, it becomes difficult for clinicians to remove the microlesions completely using the RFA method. So, the effectiveness of RFA vs. SR for HCC (< 5 cm) is expected to be different when the 3 cm cutoff value is considered.

However, according to the published reports, the efficacy of the two therapies in HCC with size 2–3 cm is quite controversial. In a work conducted by Cucchetti et al. (21), it was shown that surgery might provide a better prognosis than RFA in 2–3 cm HCC. Normally during the RFA procedure, in order to overlap target regions in a large tumor, the needle electrodes need to be placed more than one time, and thus it is not easy to reach the desired temperature throughout all the areas of the nodule (9). Therefore, the efficacy of RFA is considered to be highly size dependent. Some studies have reported that a higher incidence of local recurrence was observed in patients following RFA (22, 23). This may be explained by the fact that the procedure of thermal ablation can increase intratumoral pressure and thus promote the spread of tumor cells into the adjacent portal vein (17). Other factors such as the heat-sink effect or microscopic satellites and emboli in adjacent vasculature may also contribute to this phenomenon (19). In spite of the tendency to relapse, Hung et al. (22) found those in the RFA group still have satisfactory survival outcomes comparable to the SR group. One reason for this is that most of the patients underwent close surveillance after RFA, so the recurrent tumor is detected easily and treated completely by subsequent local ablation (22). Therefore, it is believed that the higher risk of recurrence is not a major obstacle to apply RFA as first-line treatment for solitary small HCCs. In addition, over the last decade, due to the advances in RFA devices and needle electrode technology, clinicians have been able to apply RFA to larger tumors. The current RFA system is able to destroy areas of liver parenchyma with diameters of more than 5 cm in a single application (9). Therefore, from our point of view, RFA is recommend as an effective and safe treatment option for single HCC ≤3 cm (24).

But one thing should arise our attention that treatment strategy is also dependent on patients' fitness condition.

Because sometimes patients' physical condition is not allowed to endure the surgical intervention. Under those circumstances, SR may not be the optimal option even if the tumor grows beyond 3 cm.

Our study has several limitations. First, due to its retrospective nature, potential bias still possibly exists. The selection bias, for example, might not be completely avoided even after careful PSM analysis. Second, our study also has limitations specific to the SEER database. Information such as underlying liver disease, liver function, the presence of portal hypertension, surgical margin status, and RFA approaches are not provided, and these variables may be different between both groups and have effects on the patients' prognosis. Additionally, indices such as international normalized ratio (INR), creatinine, and bilirubin could be filled in the database, but often such information was not submitted. As a result, the Child-Pugh or MELD Score could not be calculated for further investigation. Thus, randomized-controlled studies in multiple centers are necessary to help further clarify this question.

CONCLUSION

In summary, by using PSM analysis to mitigate the selection bias between the RFA and SR group, patient outcomes were reanalyzed using comparable clinicopathologic characteristics. As a result, we have better defined the actual effectiveness of RFA and SR in treating solitary HCC. We have verified our results with further analysis by the use of multiple imputations of missing data and a competing risk model. We found that OS and CSS were similar between both treatments with tumors ≤3 cm, and thus both RFA and SR are highly recommended in this situation. While surgery may be a superior treatment option with better long-term outcome than RFA in patients with tumors measuring 3.1–5 cm.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

The study was approved by the Ethics Committee of Shanghai Ninth People's Hospital. As this is a retrospective study in nature, the informed consent was not required in this study.

AUTHOR CONTRIBUTIONS

LZ, C-LS, C-HZ, and J-YL contributed to data acquisition. LZ, C-LS, and J-YL performed the statistical analysis and prepared the manuscript. LZ and C-HZ drafted this manuscript. X-LQ and ML supervised the study. All authors read and approved the final manuscript.

FUNDING

This study was supported by National Natural Science Foundation of China (81770599), Clinical Research Program of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (JYLJ021). The authors would like to acknowledge them for financial support.

ACKNOWLEDGMENTS

We have great respect for the work that goes into compiling and maintaining the Surveillance, Epidemiology, and End Results Program (SEER) tumor registries, including the interpretation and reporting of these data and so on.

REFERENCES

1. Sherman M. Hepatocellular carcinoma: epidemiology, surveillance, and diagnosis. *Semin Liver Dis*. (2010) 30:3–16. doi: 10.1055/s-0030-1247128
2. Jiang YQ, Wang ZX, Deng YN, Yang Y, Wang GY, Chen GH. Efficacy of hepatic resection vs. radiofrequency ablation for patients with very-early-stage or early-stage hepatocellular carcinoma: a population-based study with stratification by age and tumor size. *Front Oncol*. (2019) 9:113. doi: 10.3389/fonc.2019.00113
3. Kanwal F, Singal AG. Surveillance for hepatocellular carcinoma: current best practice and future direction. *Gastroenterology*. (2019) 157:56–64. doi: 10.1053/j.gastro.2019.02.049
4. Min JH, Kang TW, Cha DI, Song KD, Lee MW, Rhim H, et al. Radiofrequency ablation versus surgical resection for multiple HCCs meeting the Milan criteria: propensity score analyses of 10-year therapeutic outcomes. *Clin Radiol*. (2018) 73:676.e615–24. doi: 10.1016/j.crad.2018.02.007
5. Hocquelet A, Balageas P, Laurent C, Blanc JF, Frulio N, Salut C, et al. Radiofrequency ablation versus surgical resection for hepatocellular carcinoma within the Milan criteria: a study of 281 Western patients. *Int J Hyperther*. (2015) 31:749–57. doi: 10.3109/02656736.2015.1068382
6. Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg*. (2010) 252:903–12. doi: 10.1097/SLA.0b013e3181efc656
7. Fang Y, Chen W, Liang X, Li D, Lou H, Chen R, et al. Comparison of long-term effectiveness and complications of radiofrequency ablation with hepatectomy for small hepatocellular carcinoma. *J Gastroenterol Hepatol*. (2014) 29:193–200. doi: 10.1111/jgh.12441
8. Kutlu OC, Chan JA, Aloia TA, Chun YS, Kaseb AO, Passot G, et al. Comparative effectiveness of first-line radiofrequency ablation versus surgical resection and transplantation for patients with early hepatocellular carcinoma. *Cancer*. (2017) 123:1817–27. doi: 10.1002/cncr.30531
9. Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol*. (2012) 57:794–802. doi: 10.1016/j.jhep.2012.05.007
10. Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg*. (2006) 243:321–8. doi: 10.1097/01.sla.0000201480.65519.b8
11. Pompili M, Saviano A, De Matthaeis N, Cucchetti A, Ardito F, Federico B, et al. Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma </=3 cm. Results of a multicenter Italian survey. *J Hepatol*. (2013) 59:89–97. doi: 10.1016/j.jhep.2013.03.009
12. Lee SH, Jin YJ, Lee JW. Survival benefit of radiofrequency ablation for solitary (3-5 cm) hepatocellular carcinoma: an analysis for nationwide cancer registry. *Medicine*. (2017) 96:e8486. doi: 10.1097/MD.0000000000008486
13. Zhang L, Ge NL, Chen Y, Xie XY, Yin X, Gan YH, et al. Long-term outcomes and prognostic analysis of radiofrequency ablation for small hepatocellular carcinoma: 10-year follow-up in Chinese patients. *Med Oncol*. (2015) 32:77. doi: 10.1007/s12032-015-0532-z
14. Santambrogio R, Bruno S, Kluger MD, Costa M, Salceda J, Belli A, et al. Laparoscopic ablation therapies or hepatic resection in cirrhotic patients with small hepatocellular carcinoma. *Dig Liver Dis*. (2016) 48:189–96. doi: 10.1016/j.dld.2015.11.010
15. Topal B, Hompes D, Aerts R, Fieuws S, Thijs M, Penninckx F. Morbidity and mortality of laparoscopic vs. open radiofrequency ablation for hepatic malignancies. *Eur J Surg Oncol*. (2007) 33:603–7. doi: 10.1016/j.ejso.2007.02.031
16. Mulier S, Ni Y, Jamart J, Ruers T, Marchal G, Michel L. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. *Ann Surg*. (2005) 242:158–71. doi: 10.1097/01.sla.0000171032.99149.fe
17. Li C, Wen TF. Does surgical resection provide better outcomes than radiofrequency ablation in patients with BCLC very early-stage hepatocellular carcinoma? *Ann Surg*. (2017) 266:e54–5. doi: 10.1097/SLA.0000000000001357
18. Zhou Z, Lei J, Li B, Yan L, Wang W, Wei Y, et al. Liver resection and radiofrequency ablation of very early hepatocellular carcinoma cases (single nodule <2 cm): a single-center study. *Eur J Gastroenterol Hepatol*. (2014) 26:339–44. doi: 10.1097/MEG.0000000000000012
19. Kim GA, Shim JH, Kim MJ, Kim SY, Won HJ, Shin YM, et al. Radiofrequency ablation as an alternative to hepatic resection for single small hepatocellular carcinomas. *Br J Surg*. (2016) 103:126–35. doi: 10.1002/bjs.9960
20. Ng KKC, Chok KSH, Chan ACY, Cheung TT. Randomized clinical trial of hepatic resection versus radiofrequency ablation for early-stage hepatocellular carcinoma. *Br J Surg*. (2017) 104:1775–84. doi: 10.1002/bjs.10677
21. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Ercolani G, Bolondi L, et al. Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. *J Hepatol*. (2013) 59:300–7. doi: 10.1016/j.jhep.2013.04.009
22. Hung HH, Chiou YY, Hsia CY, Su CW, Chou YH, Chiang JH, et al. Survival rates are comparable after radiofrequency ablation or surgery in patients with small hepatocellular carcinomas. *Clin Gastroenterol Hepatol*. (2011) 9:79–86. doi: 10.1016/j.cgh.2010.08.018
23. Xu XL, Liu XD, Liang M, Luo BM. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma: systematic review of randomized controlled trials with meta-analysis and trial sequential analysis. *Radiology*. (2018) 287:461–72. doi: 10.1148/radiol.2017162756
24. Lei JY, Wang WT, Yan LN, Wen TF, Li B. Radiofrequency ablation versus surgical resection for small unifocal hepatocellular carcinomas. *Medicine*. (2014) 93:e271. doi: 10.1097/MD.0000000000000271

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.

frontiers in Oncology

ORIGINAL RESEARCH
published: 06 May 2020
doi: 10.3389/fonc.2020.00668

Reconstruction of Perineal Defects: A Comparison of the Myocutaneous Gracilis and the Gluteal Fold Flap in Interdisciplinary Anorectal Tumor Resection

Jan R. Thiele[1], *Janick Weber*[1], *Hannes P. Neeff*[2], *Philipp Manegold*[2], *Stefan Fichtner-Feigl*[2], *G. B. Stark*[1] and *Steffen U. Eisenhardt*[1]*

[1] *Department of Plastic and Hand Surgery, Medical Center, University of Freiburg, Freiburg, Germany,* [2] *Department of General and Visceral Surgery, Medical Center, University of Freiburg, Freiburg, Germany*

Introduction: Resection of anorectal malignancies may result in extensive perineal/pelvic defects that require an interdisciplinary surgical approach involving reconstructive surgery. The myocutaneous gracilis flap (MGF) and the gluteal fold flap (GFF) are common options for defect coverage in this area. Here we report our experience with the MGF/GFF and compare the outcome regarding clinical key parameters.

Methods: In a retrospective chart review, we collected data from the Department of Plastic Surgery of the University of Freiburg from December 2008–18 focusing on epidemiological, oncological, and therapy-related data including comorbidities (ASA Classification) and peri-/postoperative complications (Clavien-Dindo-System).

Results: Twenty-nine patients were included with a mean follow-up of 17 months. Of the cases, 19 (65.5%) presented with recurrent disease, 21 (72.4%) received radiochemotherapy preoperatively, 2 (6.9%) received chemotherapy alone. Microscopic tumor free margins were achieved in 25 cases (86.2%). 17 patients (7 men, 10 women, rectal adenocarcinoma $n = 11$; anal squamous cell carcinoma $n = 6$; mean age 58.5 ± 10.68, mean BMI 23.1, mean ASA score 2.8) received a MGF (unilateral $n = 10$; bilateral $n = 7$). Twelve patients (7 men, 5 women, rectal adenocarcinoma $n = 7$; anal squamous cell carcinoma $n = 4$, proctodeal gland carcinoma $n = 1$, mean age 66.2 ± 9.2, mean BMI 23.6, mean ASA score 2.6) received coverage with a GFF (unilateral $n = 4$; bilateral $n = 8$). Mean operation time of coverage was 105 ± 9 min for unilateral and 163 ± 11 for bilateral MGFs, 70 ± 13 min for unilateral and 107 ± 14 for bilateral GFFs. Complications affected 62%. There was no significant difference in the complication rate between the MGF- and GFF-group. Complications were mainly wound healing disorders that did not extend the hospital stay. No flap loss and no complication that lead to long-lasting disability was documented (both groups). Pain-free sitting took more time in the GFF-group due to the location of the donor site.

Conclusion: MG-flaps and GF-flaps prove to be reliable and robust techniques for perineal/pelvic reconstruction. Though flap elevation is significantly faster for GF-flaps,

OPEN ACCESS

Edited by:
Adrien Daigeler,
BG University Hospital Bergmannsheil GmbH, Germany

Reviewed by:
Kaartinen Ilkka,
Tampere University Hospital, Finland
Paolo Persichetti,
Campus Bio-Medico University, Italy

***Correspondence:**
Steffen U. Eisenhardt
jan.thiele@ortenau-klinikum.de

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: *02 August 2019*
Accepted: *09 April 2020*
Published: *06 May 2020*

Citation:
Thiele JR, Weber J, Neeff HP, Manegold P, Fichtner-Feigl S, Stark GB and Eisenhardt SU (2020) Reconstruction of Perineal Defects: A Comparison of the Myocutaneous Gracilis and the Gluteal Fold Flap in Interdisciplinary Anorectal Tumor Resection. Front. Oncol. 10:668. doi: 10.3389/fonc.2020.00668

preoperative planning and intraoperative Doppler confirmation are advisable. With comparable complication rates, we suggest a decision-making based on distribution of adipose tissue for dead space obliteration, intraoperative patient positioning, and perforator vessel quality/distribution.

Keywords: reconstructive surgery, gracilis flap, gluteal fold flap, perineal defect, anorectal tumors

INTRODUCTION

Surgical treatment of rectal and anal diseases may result in perineal defects that affect the surface and lead to loss of volume in the lesser pelvis, following abdominoperineal resection of the rectum (APR) or pelvic exenteration (PE) (1). The vertical rectus abdominis myocutaneous (VRAM) flap is a commonly used reconstructive option and widely reported in the literature (2–4). However, abdominal myocutaneous flaps may be unavailable because of pre-existing abdominal scars, the need for colostomy/urostomy or unacceptable abdominal wall sequelae (2, 5–7). The surgeon is therefore required to consider alternative reconstructive strategies that should involve the following: (1) Provision of a flap with a safe vascularization as recruitment of well-vascularized tissue into a complex wound is crucial and main parts of the flap will not be accessible for perfusion monitoring. (2) Dead space obliteration to prevent the risk of intestinal prolapse, which depends on tumor dimension and location. (3) Accessibility of the donor site, which depends on patient positioning for oncosurgery to minimize the operation time. (4) Keeping donor site morbidity to a minimum, as patients present with significant comorbidity, preoperative radio- and chemotherapy, and a high risk for wound complications (8).

Numerous alternative techniques to the VRAM flap have been described, predominantly using abdominal, pudendal, gluteal, and thigh donor sites (2, 9, 10). Among those, is the myocutaneous gracilis flap (MGF), a well-described alternative to the VRAM flap for genital and perineal reconstruction (11, 12). Functional donor site morbidity of the MGF is advantageous and flap elevation can easily be performed. Recently, perforator based local flaps of the perineal and gluteal region have been introduced in perineal coverage. One of those is the fasciocutaneous gluteal fold flap (GFF) that is based on perforators of the internal pudendal artery (13). First described by Yii and Niranjan in 1996, the flap has been well-described in vulval and vaginal reconstruction and gradually gains popularity for perineal defect coverage (14, 15). Here we present our experience of using the MGF and the GFF uni- and bilaterally for reconstructing perineal defects after resection of anorectal malignancies and compare the outcome regarding clinical key parameters.

PATIENTS AND METHODS

Data Collection

In a retrospective chart analysis, we evaluated all patients that underwent APR or PE at our institution referred for plastic surgery closure between December 2008 and 2018. Data were categorized as demographic, therapy-related, or outcome-related. Patients with the need for vaginal wall reconstruction and patients that received a VRAM flap for defect coverage were excluded. Demographic data included age at the time of surgery, gender, body mass index (BMI), and concomitant diseases. The latter were summarized using the American Society of Anesthesiologists Physical Status Classification System (ASA), a six-point scale to measure the patients' preoperative global health (16). Oncosurgical data consisted of tumor histology, stage of disease, presentation status (primary or recurrent disease), the initial oncological treatment performed (radiotherapy and chemotherapy), the oncosurgical resection procedure (APR or PE), and the achieved resection margins (R0, R1, R2). Reconstructive data included the flap type (MGF or GFF, unilateral or bilateral) and operation time for defect coverage. Postoperative outcome data included all complications or adverse events occurring within 30 days of the operation (classified according to the Clavien-Dindo system), hospital stay, complications that were seen in the period 30 days after the operation until the last follow-up with the potential for long-term disability, and last follow-up. Oncological outcome data such as recurrent disease, distant metastasis and survival status were not included in the study. Informed consent and approval for the publication of photographs were obtained from the patients. The study was approved by the University of Freiburg Ethics Committee, Germany (approval number 357/19). The design and performance of the study are in accordance with the Declaration of Helsinki.

Statistical Analysis

Analyses of data were performed with GraphPad Prism version 5.0 software (GraphPad Software, San Diego, CA). For comparison of 2 groups, a 2-tailed t-test was used. Surgical complications of different grades were analyzed in a 2-way repeated-measure ANOVA. Contingency tables were analyzed by the fisher's exact test. All groups and prognostic factors (gender, age, BMI, comorbidities, preoperative radiotherapy, preoperative chemotherapy, primary disease, recurrent disease, number of flaps, and complications) were analyzed by univariate analysis. A $p < 0.05$ was considered statistically significant.

Surgical Technique

Myocutaneous Gracilis Flap

With the patient in frog leg position, the adductor longus muscle was palpated and a line was marked right behind the adductor longus along the axis of the gracilis muscle on both sides. A mark was made 1 hand-breadth below the inguinal crease, which approximates the location of the primary vascular pedicle (5). Following oncosurgical resection, the left thigh was addressed preferentially in case of a right-handed surgeon. The skin paddle was outlined over the muscle and over the posterior edge of the adductor longus muscle where the intermuscular septum is located and carries vessels to supply the overlying skin. The lengths of the skin paddle can safely comprise the proximal two-thirds of the underlying muscle. Regarding width, the "pinch test" allowed for direct donor site closure; in our patients, about 7 cm could be safely closed primarily. A skin bridge was left between the locations of skin the island and the perineal defect. Preparation of the flap was started from distally, in order to confirm the gracilis muscle and locate its skin territory. Afterwards, the muscle fascia of the adductor longus muscle was exposed via the anterior incision. The fascia was incised and elevated posteriorly in order to incorporate and protect the intermuscular septum. The main vascular pedicle was visualized and freed from its surrounding tissue to the end. Branches to the adductor longus muscle were thereby identified, clipped, and divided. The obturator nerve to the gracilis was identified and divided. The gracilis muscle was freed from the surrounding tissue. Sutures between the muscle and its skin paddle prevented tension forces to the perforators. The flap was then cut distally and tunneled into the defect. Dead space obliteration was evaluated with the colorectal surgeon. In cases of insufficiency, the right sided flap was elevated, and in most cases deepithelialized and buried. The donor site was closed primarily.

Gluteal Fold Flap

With the patient in the standing position, the gluteal fold was marked (2). The patient was then put in the lithotomy position to identify the pudendal artery perforators along the medial pole of the gluteal fold using a hand-held Doppler probe or color duplex imaging in the region of the ischial tuberosity on both sides. Following the oncosurgical resection, the perforators were reevaluated intraoperatively. In case of a satisfying distribution and signal, the flap dimensions were outlined, centered on the gluteal fold, and extending for 3–4 cm on either side of it, depending on the "pinch" (to allow direct donor site closure) and ensuring an adequate size to cover the anticipated perineal defect (2). The flap was then raised along a subfascial plane under careful preservation of the perforators through intra-operative Doppler assistance. In this respect, the fibrofatty tissue of ischiorectal fossa was preserved, as it contains the rich network of perforators of the internal pudendal artery and the accompanying vein (13). Skeletonization of the perforators was avoided. The flap was then transposed into the defect as a propeller flap (Type I-1 propeller flap according to Hashimoto et al.) as this allowed a wider arc of rotation than a type I-2 transposition flap (17). The sufficiency of dead space obliteration was re-evaluated with the colorectal surgeon, resulting in uni- or bilateral flap elevation. In cases of bilateral coverage, one flap was deepithelialized and buried. Inset was without tension and the donor site was closed primarily.

RESULTS

In a 10 years period, 24 myocutaneous gracilis flaps (unilateral MGF $n = 10$; bilateral $n = 7$) and 20 gluteal fold flaps (unilateral $n = 4$; bilateral $n = 8$) were performed for perineal defects following anorectal tumor excision in 29 patients. Fifteen out of 29 patients were female (MGF $n = 10$, 58.8%; GFF $n = 5$, 41.7%). The mean age at the time of surgery was 58.5 ± 10.68 in the MGF group and 66.2 ± 9.2 in the GFF group ($p = 0.61$), with a mean BMI of 23.1 kg/m² $\pm$ 4.7 in the MGF- and a mean BMI of 23.6 kg/m² $\pm$ 2.7 in the GFF group ($p = 0.94$). Mean ASA score was 2.75 ± 0.43 in the MGF group and 2.58 ± 0.64 in the GFF group ($p = 0.82$). Hypertension ($n = 8$), coronary heart disease ($n = 8$), and smoking ($n = 8$) were the most frequent comorbidities, followed by diabetes ($n = 6$), malignancies other than anorectal ($n = 5$), thyroid disorders ($n = 5$), chronic inflammatory bowel disease ($n = 5$), atrial fibrillation ($n = 4$), pulmonary embolism ($n = 4$), chronic liver disease ($n = 4$), and obesity ($n = 1$). Tumor histology revealed an anal squamous cell carcinoma in six patients in the MGF group (35.3%) and in four patients in the GFF group (33.3%). Rectal adenocarcinomas were seen in 11 patients in the MGF group (64.7%) and in seven patients (58.3%) in the GFF group. One patient of the GFF group (8.3%) was diagnosed with a proctodeal gland carcinoma. Primary disease was diagnosed in just 10 out of 29 cases ($n = 6$ in the MGF group, 35.3%; $n = 4$ in the GFF group, 33.3%). Of those, six ($n = 4$ in the MGF group, 66.7% and $n = 2$ in the GFF group, 50.0%) were additionally treated by radiotherapy and chemotherapy; one patient of the GFF group received chemotherapy alone. In the cases presenting with a recurrent tumor ($n = 11$ in the MGF group, 64.7%; $n = 8$ in the GFF group 66.7%) 13 patients ($n = 8$ in the MGF group, 72.7%; $n = 5$ in the GFF group, 66.6%) were preoperatively treated with radiotherapy and chemotherapy; one patient of the MGF group (9.1%) received neoadjuvant chemotherapy alone. In the MGF group, 11 patients received PE (64.7%) and six patients received APR (35.3%). In the GFF group 11 patients received APR (91.7%) and only one patient received PE (83.3%). The choice of oncosurgical procedure led to no significant difference in the frequency of bilateral or unilateral MGF/GFF for defect reconstruction ($p = 0.6437$ in the MGF group and $p = 0.3333$ in the GFF group, Fisher's exact test). In all but four cases, microscopic complete tumor resection was achieved (R0; MGF group: $n = 14$, 82.35%; GFF group: $n = 11$, 91.67%). In cases of perineal herniation, omentoplasty was used as first choice for stabilization. In cases where neither vesicopexy nor uteropexy were feasible as second choice options, a resorbable mesh was utilized for reconstruction. In our study, omentoplasty was conducted in a total of 13 cases (MGF group: $n = 4$, 23.53%; GFF group: $n = 9$, 75%), a vesicopexy in two cases (MGF group: $n = 1$, 5.88%; GFF group: $n = 1$, 8.33%) and a mesh in 11 cases (MGF group: $n = 7$, 41.18%; GFF group: $n = 4$, 33.33%; **Tables 1**, **2**).

Concerning defect coverage and obliteration of dead space, 10 patients received unilateral flaps in the MGF group (58.82%). Among those receiving GF-flaps, only four patients (33.33%) were treated with unilateral flaps ($p = 0.2635$, Fisher's exact test). Taken together, a close majority of 15 patients was treated with bilateral flap coverage. Mean operation time of flap coverage for unilateral flaps was 105 ± 9 min in the MGF group and 70 ± 13 min in the GFF group ($p = 0.0497$). For bilateral flaps, flap coverage took 163 ± 11 min in the MGF group and 107 ± 14 min in the GFF group ($p = 0.0077$).

TABLE 1 | Demographic and oncosurgical data of the MGF group.

Pat.- no.	Age	Sex	BMI	Comor-bidities (ASA)	Indication	Re-current disease	Stage	Pre-OP		Oncosurgical Proc.
								RT	CT	
1	69	M	24	4	Rectal AC	+	ypT3,pN0,L0,V0,Pn0.R0	+	+	PE, OP, M
2	67	F	26	3	Rectal AC	+	rpT4b, pN1,L0,V0,Pn0.R0	+	+	PE, OP
3	52	M	20	3	Rectal AC	-	ypT3,pN0,L0,V0,Pn0.R0	+	+	APR
4	61	F	20	3	Rectal AC	+	ypT3,pN0,L0,V0,Pn0.R0	+	+	APR, OP
5	74	M	28	2	Rectal AC	+	rpT4,pN1,L0, V0,Pn1.R0	-	+	PE, OP
6	69	F	26	3	Anal SCC	+	rpT2,pN1,L0,V0.Pn1.R0	+	+	PE, M
7	*51*	*F*	*20*	3	Rectal AC	+	pT4,pN1,L0,V0,Pn0.R0	+	+	PE
8	*48*	*F*	*24*	3	Rectal AC	-	pT4,N2,L0,V0,Pn0.R0	-	-	APR, VP
9	*63*	*F*	*22*	3	Rectal AC	+	pT4,pN1,L0,V0,Pn1.R0	-	-	APR
10	50	M	16	3	Anal SCC	-	ypT4,pN0,L0,V1,Pn1.R1	+	+	PE, M
11	70	M	21	3	Rectal AC	-	ypT4,pN1,L0,V1,Pn1.R0	+	+	PE, M
12	36	F	16	3	Anal SCC	+	pT4,N2.L1V1,Pn1.R0	+	+	PE, M
13	59	F	20	2	Anal SCC	+	pT3,pN1, L1,V1,Pn0.R1	+	+	PE, M
14	66	M	20	3	Anal SCC	+	pT4b,pN1,L1,V0,Pn1.R1	+	+	PE
15	54	F	29	3	Anal SCC	+	rpT2,pN1,L0,V0.Pn0.R0	+	+	APR
16	64	F	25	2	Rectal AC	-	ypT3,pN0,L0,V0,Pn0.R0	-	-	PE, M
17	43	M	35	2	Rectal AC	-	rpT4b, pN1,L0,V0,Pn0.R0	+	+	APR

M, male; F, female; BMI, body mass index in kg/m²; ASA, American Society of Anesthesiologists Physical Status Classification System; AC, adenocarcinoma; SCC, squamous cell carcinoma; RT, radiotherapy; CT, chemotherapy; APR, abdominoperineal resection of the rectum, PE, pelvic exenteration; OP, omentoplasty; VP, vesicopexy; M, mesh.

TABLE 2 | Demographic and oncosurgical data of the GFF group.

Pat.- no.	Age	Sex	BMI	Comor-bidities (ASA)	Indication	Re-current disease	Stage	Pre-OP		Oncosurgical Proc.
								RT	CT	
1	74	M	27	2	Rectal AC	+	pT4,pN1, L0,V0,Pn0.R0	+	+	APR, OP
2	52	M	27	2	Rectal AC	+	ypT3,pN0,L0,V0,Pn0.R0	+	+	APR, OP
3	66	F	24	3	Rectal AC	-	pT3,pN0,L1,V0,Pn1.R0	-	+	APR, OP
4	68	F	25	2	Rectal AC	+	ypT2,pN0,L0,V0,Pn0.R0	+	+	EALPE, OP
5	73	M	22	3	Rectal AC	-	pT4b, pN0,L1,V0,Pn1.R0	-	+	APR, OP, M
6	58	M	27	2	Rectal AC	-	ypT1,pN0,L0,V0,Pn0.R0	+	+	APR, M
7	*72*	*M*	*21*	3	Rectal AC	+	rpT3,pN0,L0,V0,Pn0. R0	-	-	APR, VP
8	*62*	*M*	*19*	4	Anal SCC	+	ypT3,pN0,L0,V0,Pn1.R0	+	+	APR, OP
9	*69*	*F*	*25*	3	Anal SCC	+	pT4,pN0, L1,V1,Pn1. R1	-	-	APR, OP
10	49	F	20	3	Anal SCC	+	pT4,pN0,L1V1,Pn0. R0	+	+	APR, M
11	83	M	22	2	Anal SCC	+	ypT3,pN0,L0,V0,Pn0.R0	-	-	APR, OP, M
12	68	F	24	2	Proctideal gland C	-	ypT3,pN0,L0,V0,Pn0.R0	+	+	EP, OP

M, male; F, female; BMI, body mass index in kg/m²; ASA, American Society of Anesthesiologists Physical Status Classification System; AC, adenocarcinoma; SCC, squamous cell carcinoma; C, carcinoma; RT, radiotherapy; CT, chemotherapy; APR, abdominoperineal resection of the rectum, PE, pelvic exenteration; OP, omentoplasty; VP, vesicopexy; M, mesh.

In 11 patients, we saw no complication (37.93%) at all. According to the Clavien-Dindo classification for surgical complications, the were 4 grade II, 3 type IIIa, 3 type IIIb, and one type 4a complication among MGFs. In the GFF group, one type II, 2 type IIIa, and 4 type IIIb complications were observed. There was no significant difference between the two groups. Type II complications were postoperative infections that could be treated with antibiotic therapy. Type IIIa complications included wound healing disorders of the donor site or defect site and local infections or seroma formation resulting in bed site debridement or drainage. Type IIIb complications included wound dehiscence and partial flap loss (<30%) that had to be treated by debridement, vacuum assisted closure (VAC) or secondary suture under general anesthesia. There was one grade IVa complication (intraoperative ventricular fibrillation) that resulted in a staged though successful defect coverage in the MGF group. We saw no breakdown of enteric anastomoses, no formation of vascular or visceral fistulae, and no instances of deep pelvic abscess formation. The time from reconstruction to discharge was 23 ± 4.7 days for MGFs and 24 ± 9.7

days for GFFs ($p = 0.9002$). Regarding both groups, we found no significant difference in the time to discharge between patients with complications of any grade and those who were unaffected ($p = 0.9190$) (**Tables 3**, **4**). Analyzation of relevant risk factors (gender, age, BMI, comorbidities, preoperative radio-/chemotherapy, primary, or recurrent disease, and number of flaps) for complications or delayed discharge by univariate analysis revealed no single significant factor. With a mean follow-up of 17 ± 9.20 months among MGFs and 16 ± 8.88 months among GFFs ($p = 0.9203$), flap-related complications were documented. In the GFF group 5 (29.41%) patients had pain under mobilization and 2 (11.77%) patients complained about pain at the donor site when sitting within the first 30 postoperative days. Among GFFs, 3 (25.0%) patients felt pain under mobilization and 7 (58.33%) patients complained about pain at the donor site when sitting. Thus, significantly more patients felt sitting-related pain at the donor site in the GFF group ($p = 0.0104$, Fisher's exact test). No long-lasting (>30 days) flap related disability was documented in both groups.

DISCUSSION

Abdominoperineal resections create a wound that is intrinsically poor at healing due to the location, frequent bacterial

TABLE 3 | Reconstructive and postoperative data of the MGF group.

Pat.- no.	Re-constr. Proc.	Time for defect coverage (min)	Complications			Post-op stay (days)	Follow-up (months)
			CD-Class.	Type	Management		
1	Bilateral	191	Iva	Intraoperative ventricular fibrillation	Reanimation, staged coverage	33	25
2	Unilateral	91	-			21	5
3	Unilateral	84	II	Postoperative infection	Antibiotic therapy	25	16
4	Unilateral	131	IIIa	Wound healing disorder (defect site)	Debridement, VAC	26	32
5	Bilateral	209	IIIa	Seroma formation (donor site)	Puncture	20	7
6	Bilateral	125	IIIb	Wound dehiscence (defect site)	Debridement, VAC	28	6
7	Unilateral	97	IIIa	Local Infection (defect site)	Drainage	22	13
8	Unilateral	131	-			24	12
9	Bilateral	121	-			16	25
10	Unilateral	97	IIIb	Wound healing disorder (defect site)	Debridement, VAC	21	21
11	Bilateral	177	II	Postoperative infection	Antibiotic therapy	19	15
12	Unilateral	101	II	Postoperative infection	Antibiotic therapy	23	24
13	Unilateral	86	-			25	3
14	Unilateral	122	-			13	34
15	Bilateral	152	IIIb	Partial flap loss (<30%)	Debridement, flap repositiong	28	18
16	Bilateral	162	-			21	27
17	Unilateral	116	-			19	12

Proc, Procedure; min, minutes; CD-Class, Clavien-Dindo classification; VAC, vacuum assisted closure; Post-op stay time from reconstruction to discharge in days.

TABLE 4 | Reconstructive and postoperative data of the GFF group.

Pat.- no.	Re-constr. Proc.	Time for defect coverage (min)	Complications			Post-op stay (days)	Follow-up (months)
			CD-Class.	Type	Management		
1	Unilateral	53	-			11	4
2	Bilateral	103	II	Postoperative infection	Antibiotic therapy	24	28
3	Unilateral	110	-			33	16
4	Bilateral	98	II	Postoperative infection	Antibiotic therapy	21	12
5	Bilateral	187	IIIb	Wound dehiscence (defect site)	Debridement, VAC	21	21
6	Bilateral	168	-			22	12
7	Bilateral	125	IIIb	Wound dehiscence (defect site)	Debridement, VAC	25	6
8	Bilateral	97	-			14	9
9	Bilateral	106	IIIb	Wound dehiscence (donor site)	Debridement, secondray suture	28	31
10	Unilateral	87	IIIa	Local abscess formation	Drainage	13	28
11	Bilateral	135	IIIb	Wound healing disorder (defect site)	Debridement, secondary suture	25	7
12	Unilateral	75	IIIa	Wound dehiscence (defect site)	Debridement	49	14

Proc, Procedure; min, minutes; CD-Class, Clavien-Dindo classification; VAC, vacuum assisted closure; Post-op stay time from reconstruction to discharge in days.

contamination, and dead space prone to fluid collection (5). Preoperative chemoradiation, associated comorbidities, and pressure created by sitting upright complicate the healing process. As such, wound complication rate of up to 60% are reported in the literature (5, 8, 18, 19). A flap-based wound closure is the idea to obliterate dead space and to recruit well-vascularized tissue into the irradiated wound bed, thereby improving blood-flow, antibiotic delivery and healing (11, 20–22). Several series have demonstrated the beneficial effect of immediate defect reconstruction with regional flaps when compared with primary closure however, the exact indications for flap closure vs. direct closure are still debated (11, 20, 22–25). In the past, pelvic defects have commonly been reconstructed with vertical rectus abdominis myocutaneous (VRAM) flaps, as the large-volume bulk effectively obliterates pelvic dead space (3, 5, 21, 26). However, harvest of the rectus abdominis muscle can result in weakening of the abdominal wall, abdominal bulge or hernia, mesh-related complications, if a mesh is required, and in many cases the flap may be unavailable because of pre-existing abdominal scars or the need for colostomy/urostomy or both (5, 27–29).

We here compare two well-described concurrent techniques that are used in our department. The gracilis muscle is the most superficial adductor of the thigh and harvest of the myocutaneous flap paddle results in minimal functional deficit (5, 30). To date, there are conflicting reports in terms of reliability of the flap for pelvic reconstruction as high (31) and very low complication rates (32) have been reported. This warrants further investigation as addressed in this study. Regional alternatives to muscle-based flaps represent perforator-based flaps of the internal pudendal artery (terminal branch of the internal iliac artery) (14, 17, 33). Though the initial description of the gluteal fold flap dates back to 1996 (14), reports of its use in anorectal resection for malignancy are relatively sparse (2, 13, 34). This may reflect the uncertainty about the residual blood supply following extensive pelvic dissection or the habitus-dependent limitation of tissue

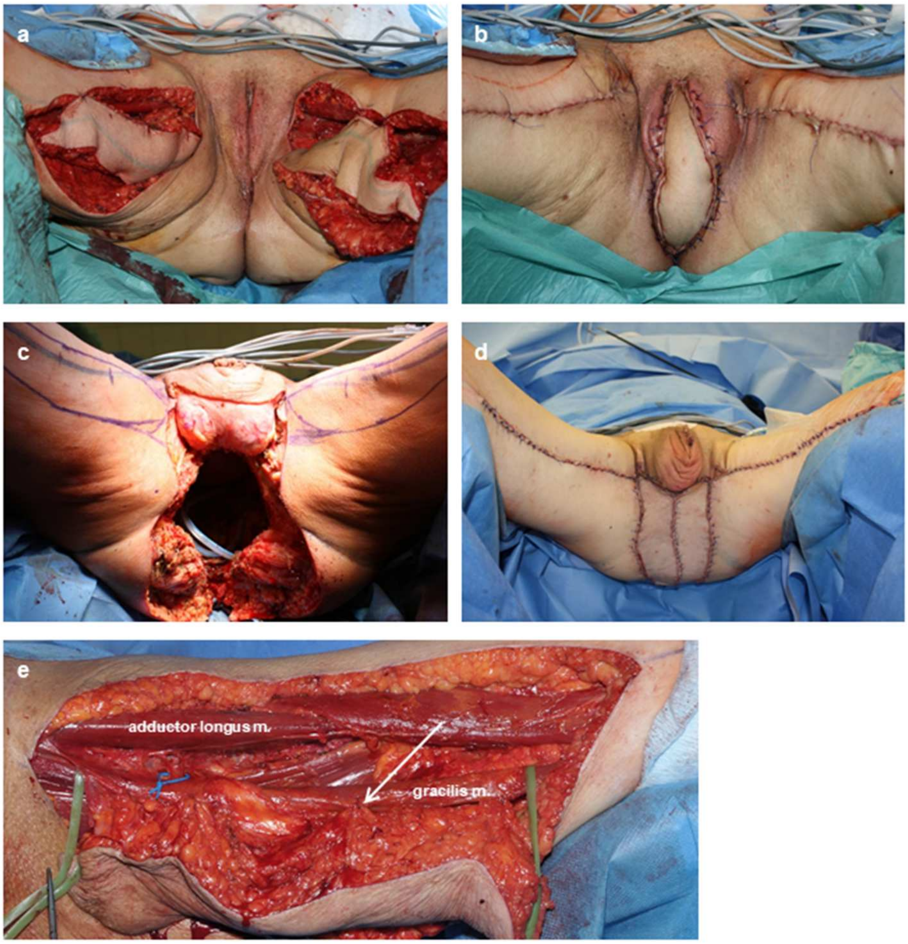


FIGURE 1 | Intra- and postoperative documentation of MGFs. **(a,b)** Bilateral defect coverage after PE with vulvectomy in a case of advanced recurrent rectal AC. **(c,d)** Bilateral defect coverage after extended PE with amputation of the penis and testecomy in a case of recurrent anal SCC. The extended cutaneous defect resulted in a cutaneous coverage through both skin islands. **(e)** Flap elevation. Sutures (arrow) between the muscle and its skin paddle prevented tension forces to the perforators. The main vascular pedicle (loop) is freed to its junction for maximal mobility of the flap.

bulk to fill dead space in the pelvis. Among others, the MGF and the GFF are well-described alternatives to the VRAM flap in the literature. However, there is to date no comparative outcome study that compares the flaps types in terms of clinical outcome parameters.

This study illustrates the limitations and benefits of the muscle based MGF and the perforator based GFF in a comparable patient collective. In a close majority of our patients, defect coverage with obliteration of dead space could only be achieved through bilateral flap elevation. There was no significant difference between MGFs and GFFs, which allows the conclusion that mobilization of tissue bulk is comparable for both flaps even though substantial inter-individual differences in the distribution of subcutaneous body fat in the region of the thigh and gluteal fold could be observed. In this respect, a BMI >25 did not increase the chance for unilateral flap coverage. The obliteration of dead space is effective with single VRAM flaps, however, as defect size reduces; the ability to fit a large VRAM (especially in obese patients with thick abdominal tissue) gets more difficult (5). Even if bilateral myocutaneous gracilis or gluteal fold mobilization is needed, morbidity to the patient is reduced compared to VRAM flaps (5).

Skin perfusion problems, resulting in skin necrosis in the distal part because of inconsistent perforator blood supply is a well-documented complication of the MGF (6, 35). Anatomic studies of the proximal gracilis pedicle illustrated both septocutaneous and myocutaneous perforators traveling in a transverse direction, suggesting the skin island for the MGF should be redesigned in a horizontal fashion (6, 36). To date, several authors prefer the horizontal skin island design (transverse myocutaneous gracilis flap, TMG flap) and achieve flap dimensions that are comparable to the vertical flap design (37). Further developments included a bilobed design of the MGF for perineal reconstruction (6). Studies reexamining the

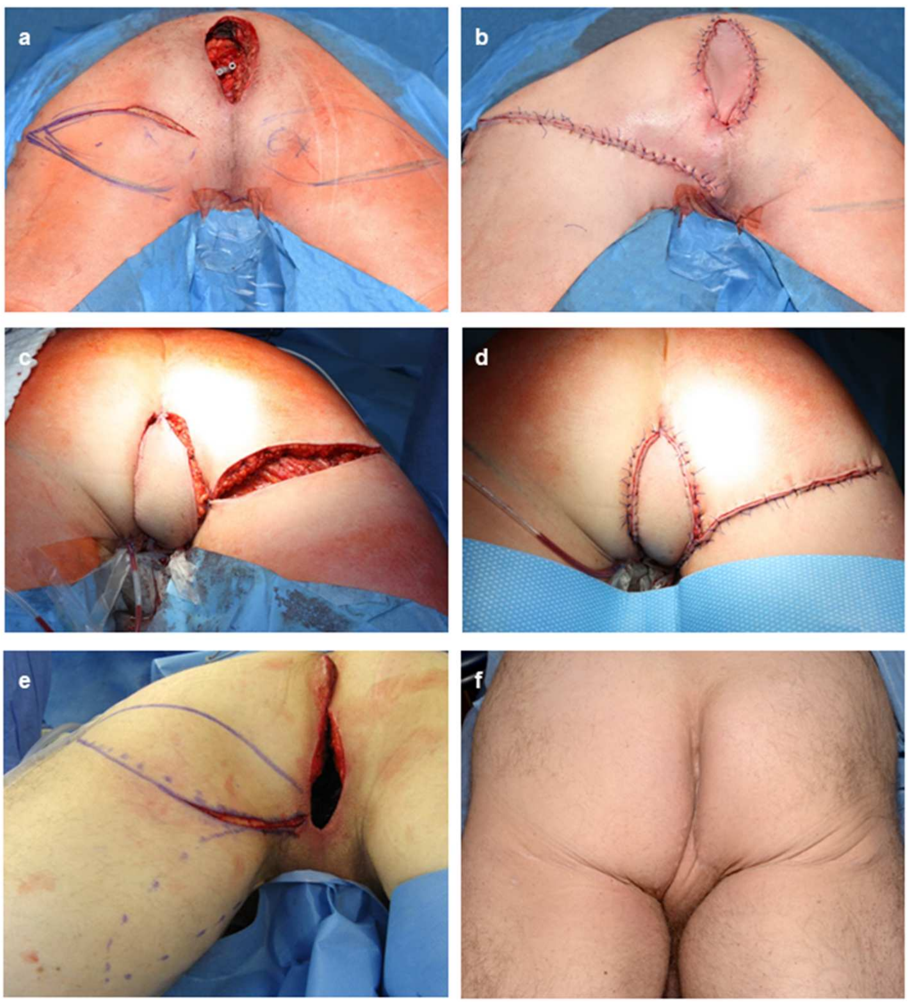


FIGURE 2 | Intra- and postoperative documentation of GFFs. **(a)** Perineal defect after APR for recurrent rectal AC with the potential for a bilateral flap desgin. **(b)** flap insertion after tunneling of the GFF and primary closure of the defect. **(c,d)** Right sided GFF without skin bridge to the perineal defect after APR for a recurrent anal SCC. **(e)** Intraoperative markings of either usage of the left sided MGF or GFF. Here, the GFF was used. **(f)** Posoperative result after bilateral GFF.

perforator anatomy and cutaneous vascular supply of MGFs found a variable quantity of gracilis perforators perfuse a nearly circular shaped angiosome centered over the proximal muscle (6, 38, 39). A circular design of the skin island would therefore be preferable, though unacceptable in terms of donor site mortality.

In our experience, the skin island of the MGF is reliable as long as it is centered over the superior two-thirds of the muscle. This results in flap dimensions that are comparable to the TMG flap design. Suturing the skin island to the gracilis muscle with resorbable sutures during flap elevation is effective taking traction forces from the perforators (**Figure 1**). Inspection of the skin island in the distal part before flap insertion is mandatory to identify and remove insufficiently perfused cutaneous and subcutaneous tissue. Alternatively, indocyanine green (ICG) imaging can be performed to evaluate tissue perfusion intraoperatively and may be superior to sole inspection of the skin (40). Under those measures, the MGF is a reliable flap and flap necrosis is reduced to a minimum. Here, we saw only one partial flap necrosis (<30%) in the MGF group that could be attributed to perfusion problems and resulted in operative debridement and repositioning of the flap. The rates of partial flap loss among MGF (6%) are comparable to those that have been reported for TMG flaps (Kaartinen et al. 6%; Kiiski et al. 4%) (37, 41).

Elevation of gluteal fold perforator flaps has been described in a sub-fascial and epi-fascial plane with or without strict identification of the pedicle, the latter with the idea to prevent pedicle torsion (**Figure 2**) (7, 14). We here avoided to skeletonize the pedicle in order to overcome previously described venous congestion of the GFF (42) which also contributed to minimize the operation time of the reconstructive part. The flap was designed to contain the Doppler signal in

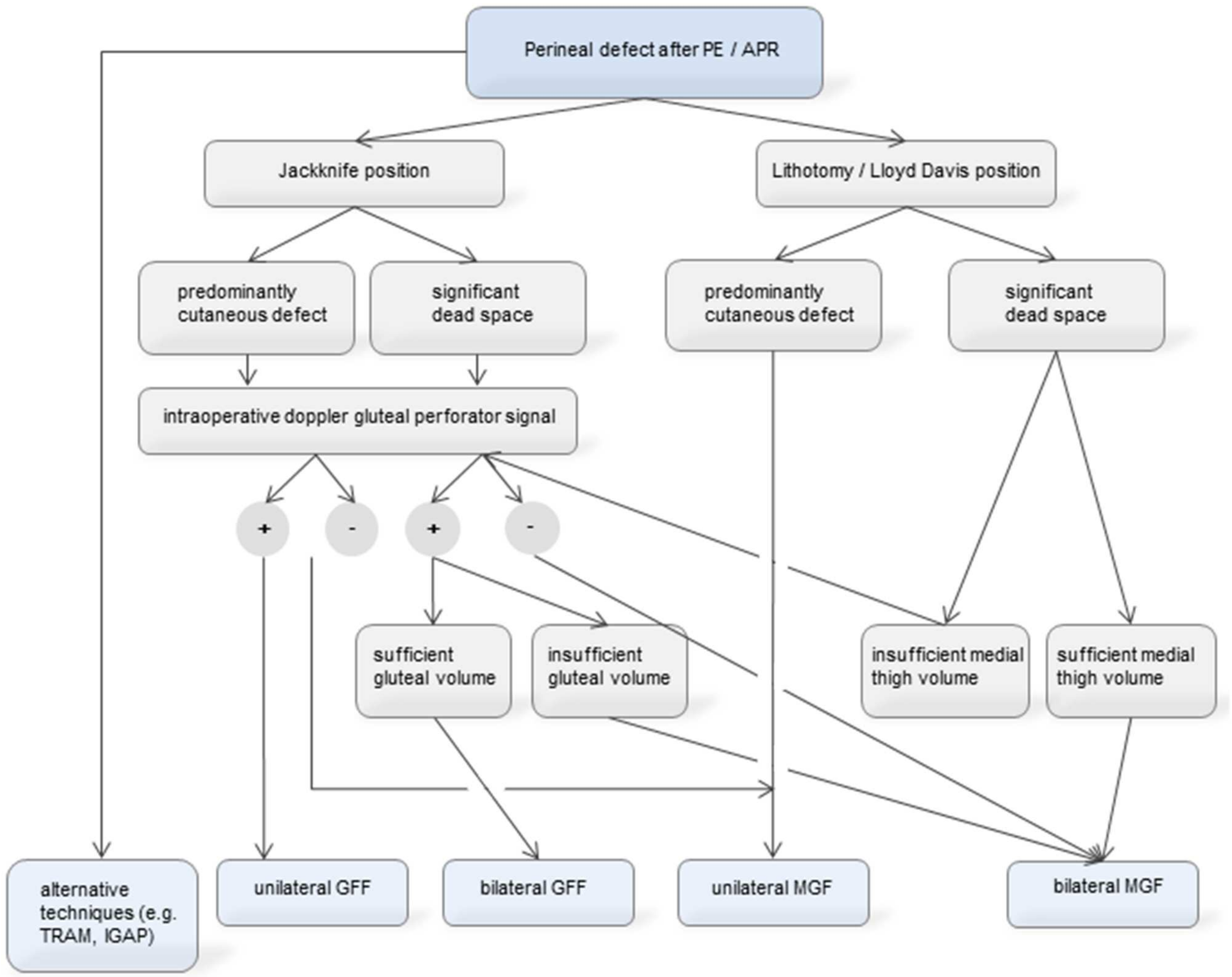


FIGURE 3 | Proposed algorithm for decision-making in perineal defect reconstruction through MGF and GFF. As MGFs and GFFs are equally effective and safe, the decision can be based on individual factors. These are patient positioning, gluteal perforator quality and body habitus (distribution of subcutaneous fat and skin laxity at the thigh and the gluteal fold). The algorithm focuses on the MGF and GFF, we however emphasize that alternative techniques such as TRAM flap or IGAP flap can be used and are not included in the decision making presented herein.

the rotation axis (type I-1 pattern according to Hashimoto et al.). The propeller design allowed easy movement of the entire flap and avoided dog ear formation around the flap that can occur with larger transposition flaps (type I-2 pattern according to Hashimoto et al.). Defect coverage was significantly faster with GFFs compared to MGFs, either uni- or bilaterally. In this respect, the GFF is superior to the MGF as it reduces the time for the patient in surgery. However, planning for GFFs including Doppler examination is more time consuming than for MGF. Also, intraoperative confirmation of the preoperative Doppler examination is advisable, as gluteal perforators can be weakened through extensive tumor resection. Elevation of the GFF is also possible in lithotomy or Lloyd Davis positioning, however it is significantly more complex. Conversely, Jackknife positioning complicates elevation of gracilis based flaps, thus prolonging operation time.

An equivalent surgical complication rate in patients receiving MGFs and those receiving GFFs is a significant finding of our study. Most of the patients had complications (62.07%) however, the vast majority was of minor degree and treatable with minimal intervention. There was no complete flap loss and complication rates of GFFs are in line with those reported in the literature (2, 7, 13, 42). Different experience is reported on MGFs for perineal defect coverage, complicating the assessment of our own results. Chong et al. (32) reported lower complication rates whereas others (31) saw distinctly higher complication rates with myocutaneous gracilis flaps. Our report clearly demonstrates that the GFF is not superior to the MGF, as reported by others (13). The previously reported limitation of the MGF in terms of tissue bulk and mobility can be overcome by generous planning of flap dimensions, complete dissection of the vascular pedicle and bilateral flap elevation if necessary.

In either using the MGF or the GFF for defect coverage uni- or bilaterally, discharge was not significantly influenced by complications. Besides, we found no independent risk factor among patients for complications or time to discharge, although this may be due to the small number of cases in our series. Morbidity of MGFs and GFFs is low, even when raised bilaterally. No long-lasting flap related disability was documented in both groups which is in contract to the VRAM flap, where rates of incisional hernia have been reported to be as high as 10% after flap harvest (27–29). Sitting associated pain is an issue among patients after gluteal fold flap harvest. This is well-explained by the postoperative position of the scar. However, when clearly communicated preoperatively, this is well-tolerated by most patients as a temporary discomfort.

Although no complication could be attributed to the utilization of a mesh, we try to avoid this technique and rather use the greater omentum for the closure of the pelvic entrance. Only sometimes, fully resorbable Polyglactin mesh had to be used in order to prevent a small bowel herniation into the deep pelvic at early postoperative stages. We are strongly opposed to non-resorbable or synthetic meshes in the pelvis, especially because the surgeries described here are "clean-contaminated" at best.

This study compares two alternative techniques for perineal defect reconstruction with the intention to provide a comparable patient collective and a comparable patient number. Concurrent techniques such as IGAP advancement flap or the posterior thigh flap are therefore not included (9, 10, 43).

CONCLUSION

Our study demonstrates the safety and efficacy of gracilis based myocutaneous flaps as well as gluteal fold flaps to reconstruct perineal defects secondary the abdominoperineal excision of the rectum and pelvic exenteration. The overall complication rate is equivalent for both types of flaps. Beneficial effects of each flap such as operation time and postoperative rehabilitation will even out at the end, so that we propose the equal application. Decision-making should be based on individual factors such as body habitus (distribution of subcutaneous fat and skin laxity at the thigh and the gluteal fold), intraoperative patient positioning (dependent on colorectal surgeon preference), and gluteal perforator distribution and quality (**Figure 3**).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Freiburg Ethics Committee Engelberger Strasse 21 79106 Freiburg Germany. 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

SE and JT conceived of the presented idea. JT and JW developed the theory and performed the computations. HN, PM, SE, and SF-F verified the analytical methods. GS and SE encouraged JT to investigate the therapy-related data and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript and gave their final approval of the version to be submitted.

REFERENCES

1. West NP, Finan PJ, Anderin C, Lindholm J, Holm T, Quirke P. Evidence of the oncologic superiority of cylindrical abdominoperineal excision for low rectal cancer. *J Clin Oncol.* (2008) 26:3517–22. doi: 10.1200/JCO.2007.14.5961
2. Pantelides NM, Davies RJ, Fearnhead NS Malata CM. The gluteal fold flap: a versatile option for perineal reconstruction following anorectal cancer resection. *J Plast Reconstr Aesthet Surg.* (2013) 66:812–20. doi: 10.1016/j.bjps.2013.02.010
3. Horch RE, Hohenberger W, Eweida A, Kneser U, Weber K, Arkudas A, et al. A hundred patients with vertical rectus abdominis myocutaneous (VRAM) flap

for pelvic reconstruction after total pelvic exenteration. *Int J Colorectal Dis*. (2014) 29:813–23. doi: 10.1007/s00384-014-1868-0

4. Sunesen KG, Buntzen S, Tei T, Lindegaard JC, Nørgaard M, Laurberg S. Perineal healing and survival after anal cancer salvage surgery: 10-years experience with primary perineal reconstruction using the vertical rectus abdominis myocutaneous (VRAM) flap. *Ann Surg Oncol*. (2009) 16:68–77. doi: 10.1245/s10434-008-0208-4
5. Singh M, Kinsley S, Huang A, Ricci JA, Clancy TE, Irani J, et al. Gracilis flap reconstruction of the perineum: an outcomes analysis. *J Am Coll Surg*. (2016) 223:602–10. doi: 10.1016/j.jamcollsurg.2016.06.383
6. Vyas RM, Pomahac B. Use of a bilobed gracilis myocutaneous flap in perineal and genital reconstruction. *Ann Plast Surg*. (2010) 65:225–7. doi: 10.1097/SAP.0b013e3181c9c434
7. Winterton RI, Lambe GF, Ekwobi C, Oudit D, Mowatt D, Murphy JV, et al. Gluteal fold flaps for perineal reconstruction. *J Plast Reconstr Aesthet Surg*. (2013) 66:397–405. doi: 10.1016/j.bjps.2012.09.026
8. Farid H, O'Connell TX. Methods to decrease the morbidity of abdominoperineal resection. *Am Surg*. (1995) 61:1061–4.
9. Mughal M, Baker RJ, Muneer A, Mosahebi A. Reconstruction of perineal defects. *Ann R Coll Surg Engl*. (2013) 95:539–44. doi: 10.1308/rcsann.2013.95.8.539
10. Higgins JP, Orlando GS, Blondeel PN. Ischial pressure sore reconstruction using an inferior gluteal artery perforator (IGAP) flap. *Br J Plast Surg*. (2002) 55:83–5. doi: 10.1054/bjps.2001.3713
11. Burke TW, Morris M, Roh MS, Levenback C, Gershenson DM. Perineal reconstruction using single gracilis myocutaneous flaps. *Gynecol Oncol*. (1995) 57:221–5. doi: 10.1006/gyno.1995.1129
12. Persichetti P, Cogliandro A, Marangi GF, Simone P, Ripetti V, Vitelli CE, et al. Pelvic and perineal reconstruction following abdominoperineal resection: the role of gracilis flap. *Ann Plast Surg*. (2007) 59:168–72. doi: 10.1097/01.sap.0000252693.53692.e0
13. Koulaxouzidis G, Penna V, Bannasch H, Neeff HP, Manegold P, Aigner F, et al. The adipofasciocutaneous gluteal fold perforator flap a versatile alternative choice for covering perineal defects. *Int J Colorectal Dis*. (2019) 34:501–11. doi: 10.1007/s00384-018-03222-w
14. Yii NW, Niranjan NS. Lotus petal flaps in vulvo-vaginal reconstruction. *Br J Plast Surg*. (1996) 49:547–54. doi: 10.1016/S0007-1226(96)90132-0
15. Salgarello M, Farallo E, Barone-Adesi L, Cervelli D, Scambia G, Salerno G, et al. Flap algorithm in vulvar reconstruction after radical, extensive vulvectomy. *Ann Plast Surg*. (2005) 54:184–90. doi: 10.1097/01.sap.0000141381.77762.07
16. Sankar A, Johnson SR, Beattie WS, Tait G, Wijeysundera DN. Reliability of the American society of anesthesiologists physical status scale in clinical practice. *Br J Anaesth*. (2014) 113:424–32. doi: 10.1093/bja/aeu100
17. Hashimoto I, Abe Y, Nakanishi H. The internal pudendal artery perforator flap: free-style pedicle perforator flaps for vulva, vagina, and buttock reconstruction. *Plast Reconstr Surg*. (2014) 133:924–33. doi: 10.1097/PRS.0000000000000008
18. Wiatrek RL, Thomas JS, Papaconstantinou HT. Perineal wound complications after abdominoperineal resection. *Clin Colon Rectal Surg*. (2008) 21:76–85. doi: 10.1055/s-2008-1055325
19. Luna-Perez P, Rodriguez-Ramirez S, Vega J, Sandoval E, Labastida S. Morbidity and mortality following abdominoperineal resection for low rectal adenocarcinoma. *Rev Invest Clin*. (2001) 53:388−95.
20. Buchel EW, Finical S, Johnson C. Pelvic reconstruction using vertical rectus abdominis musculocutaneous flaps. *Ann Plast Surg*. (2004) 52:22–6. doi: 10.1097/01.sap.0000099820.10065.2a
21. Butler CE, Rodriguez-Bigas MA. Pelvic reconstruction after abdominoperineal resection: is it worthwhile? *Ann Surg Oncol*. (2005) 12:91–4. doi: 10.1245/ASO.2005.11.923
22. Chessin DB, Hartley J, Cohen AM, Mazumdar M, Cordeiro P, Disa J, et al. Rectus flap reconstruction decreases perineal wound complications after pelvic chemoradiation and surgery: a cohort study. *Ann Surg Oncol*. (2005) 12:104–10. doi: 10.1245/ASO.2005.03.100
23. Butler CE, Gundeslioglu AO, Rodriguez-Bigas MA. Outcomes of immediate vertical rectus abdominis myocutaneous flap reconstruction for irradiated abdominoperineal resection defects. *J Am Coll Surg*. (2008) 206:694–703. doi: 10.1016/j.jamcollsurg.2007.12.007
24. Galandiuk S, Jorden J, Mahid S, McCafferty MH, Tobin G. The use of tissue flaps as an adjunct to pelvic surgery. *Am J Surg*. (2005) 190:186–90. doi: 10.1016/j.amjsurg.2005.05.009
25. Khoo AK, Skibber JM, Nabawi AS, Gurlek A, Youssef AA, Wang B, et al. Indications for immediate tissue transfer for soft tissue reconstruction in visceral pelvic surgery. *Surgery*. (2001) 130:463–9. doi: 10.1067/msy.2001.116416
26. Horch RE, D'Hoore A, Holm T, Kneser U, Hohenberger W, Arkudas A. Laparoscopic abdominoperineal resection with open posterior cylindrical excision and primary transpelvic VRAM flap. *Ann Surg Oncol*. (2012) 19:502–3. doi: 10.1245/s10434-011-1977-8
27. Daigeler A, Simidjiiska-Belyaeva M, Drücke D, Goertz O, Hirsch T, Soimaru C, et al. The versatility of the pedicled vertical rectus abdominis myocutaneous flap in oncologic patients. *Langenbecks Arch Surg*. (2011) 396:1271–9. doi: 10.1007/s00423-011-0823-6
28. Soper JT, Secord AA, Havrilesky LJ, Berchuck A, Clarke-Pearson DL. Rectus abdominis myocutaneous and myoperitoneal flaps for neovaginal reconstruction after radical pelvic surgery: comparison of flap-related morbidity. *Gynecol Oncol*. (2005) 97:596–601. doi: 10.1016/j.ygyno.2005.01.032
29. Deo SV, Nootan KS, Niranjan B, Dinesh K. Vertical rectus abdominis myocutaneous flap cover for lower abdomen, chest wall, groin and thigh defects following resection of malignant tumours. *Indian J Cancer*. (2001) 38:33–7.
30. Nisar PJ, Scott HJ. Myocutaneous flap reconstruction of the pelvis after abdominoperineal excision. *Colorectal Dis*. (2009) 11:806–16. doi: 10.1111/j.1463-1318.2008.01743.x
31. Nelson RA. Butler CE. Surgical outcomes of VRAM versus thigh flaps for immediate reconstruction of pelvic and perineal cancer resection defects. *Plast Reconstr Surg*. (2009) 123:175–83. doi: 10.1097/PRS.0b013e3181904df7
32. Chong TW, Balch GC, Kehoe SM, Margulis V, Saint-Cyr M. Reconstruction of large perineal and pelvic wounds using gracilis muscle flaps. *Ann Surg Oncol*. (2015) 22:3738–44. doi: 10.1245/s10434-015-4435-1
33. Abood A, Niranjan NS. Perineal reconstruction: from lotus petal to "canopy." An alternative to the standard surgical algorithm. *J Plast Reconstr Aesthet Surg*. (2014) 67:738–9. doi: 10.1016/j.bjps.2013.12.012
34. Hashimoto I, Nakanishi H, Nagae H, Harada H, Sedo H. The gluteal-fold flap for vulvar and buttock reconstruction: anatomic study and adjustment of flap volume. *Plast Reconstr Surg*. (2001) 108:1998–2005. doi: 10.1097/00006534-200112000-00025
35. Whetzel TP, Lechtman AN. The gracilis myofasciocutaneous flap: vascular anatomy and clinical application. *Plast Reconstr Surg*. (1997) 99:1642–52. doi: 10.1097/00006534-199705010-00026
36. Yousif NJ, Matloub HS, Kolachalam R, Grunert BK, Sanger JR. The transverse gracilis musculocutaneous flap. *Ann Plast Surg*. (1992) 29:482–90. doi: 10.1097/00000637-199212000-00002
37. Kiiski J, Räikkönen K, Vuento MH, Hyöty MK, Kallio J, Kuokkanen HO, et al. Transverse myocutaneous gracilis flap reconstruction is feasible after pelvic exenteration: 12-years surgical and oncological results. *Eur J Surg Oncol*. (2019) 45:1632–7. doi: 10.1016/j.ejso.2019.04.021
38. Coquerel-Beghin D, Milliez PY, Auquit-Auckbur I, Lemierre G, Duparc F. The gracilis musculocutaneous flap: vascular supply of the muscle and skin components. *Surg Radiol Anat*. (2006) 28:588–95. doi: 10.1007/s00276-006-0150-8
39. Kappler UA, Constantinescu MA, Buchler U, Vogelin E. Anatomy of the proximal cutaneous perforator vessels of the gracilis muscle. *Br J Plast Surg*. (2005) 58:445–8. doi: 10.1016/j.bjps.2004.11.021
40. Ludolph I, Arkudas A, Schmitz M, Boos AM, Taeger CD, Rother U, et al. Cracking the perfusion code?: laser-assisted indocyanine green angiography and combined laser doppler spectrophotometry for intraoperative evaluation of tissue perfusion in autologous breast reconstruction with DIEP or ms-TRAM flaps. *J Plast Reconstr Aesthet Surg*. (2016) 69:1382–8. doi: 10.1016/j.bjps.2016.07.014

41. Kaartinen IS, Vuento MH, Hyoty MK, Kallio J, Kuokkanen HO. Reconstruction of the pelvic floor and the vagina after total pelvic exenteration using the transverse musculocutaneous gracilis flap. *J Plast Reconstr Aesthet Surg*. (2015) 68:93–7. doi: 10.1016/j.bjps.2014.08.059
42. Ragoowansi R, Yii N, Niranjan N. Immediate vulvar and vaginal reconstruction using the gluteal-fold flap: long-term results. *Br J Plast Surg*. (2004) 57:406–10. doi: 10.1016/j.bjps.2004.02.022
43. Hurwitz DJ, Swartz WM, Mathes SJ. The gluteal thigh flap: a reliable, sensate flap for the closure of buttock and perineal wounds. *Plast Reconstr Surg*. (1981) 68:521–32. doi: 10.1097/00006534-198111000-00008

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.

frontiers in Oncology

ORIGINAL RESEARCH
published: 23 June 2020
doi: 10.3389/fonc.2020.00745

Craniofacial Osteosarcoma—Pilot Study on the Expression of Osteobiologic Characteristics and Hypothesis on Metastasis

Manuel Weber[1]*, *Stephan Söder*[2], *Janina Sander*[1], *Jutta Ries*[1], *Carol Geppert*[3], *Marco Kesting*[1] and *Falk Wehrhan*[1]

[1] Department of Oral and Maxillofacial Surgery, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Erlangen, Germany, [2] Institute of Pathology, Fürth, Germany, [3] Institute of Pathology, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Erlangen, Germany

Background: Craniofacial osteosarcomas (COS) and extracranial osteosarcomas (EOS) show distinct clinical differences. COS show a remarkably lower incidence of metastases and a better survival. However, in contrast to EOS, they show a poor response to neoadjuvant chemotherapy. Tumor-associated macrophages and their polarization as well as developmental biological signaling pathways are possible candidates for explaining the clinical differences between COS and EOS. The aim of the study was to analyze differential expression of macrophage markers and important regulators of these pathways.

Methods: Twenty osteosarcoma cases (10 COS and 10 EOS) were immunohistochemically stained to assess CD68, CD11c, CD163, MRC1, Gli1, and Gli2 expression. Statistical differences between COS and EOS were tested using the Mann–Whitney *U* test. Additionally, the paper describes an example of multidisciplinary treatment of a patient suffering from COS and discusses the surgical challenges in treatment and rehabilitation of COS.

Results: COS showed a significantly ($p < 0.05$) increased infiltration of CD11c-positive M1 macrophages and a shift toward M1 polarization compared to EOS. Additionally, COS revealed a significantly ($p < 0.05$) lower Gli1 expression than EOS.

Conclusion: The reduced Gli1 expression in COS can be interpreted as reduced activation of the Hedgehog (Hh) signaling pathway. The increased M1 polarization and reduced Hh activation in COS could explain the low incidence of metastases in these osteosarcomas.

Keywords: craniofacial osteosarcoma, osteosarcoma of the jaw, hedgehog, macrophage polarization, Gli1, M1, M2

OPEN ACCESS

Edited by:
Raymund E. Horch, University Hospital Erlangen, Germany

Reviewed by:
Jürgen Hoffmann, Heidelberg University Hospital, Germany
Joerg Schipper, University Hospital of Düsseldorf, Germany

***Correspondence:**
Manuel Weber
manuel.weber@uk-erlangen.de

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: *07 August 2019*
Accepted: *20 April 2020*
Published: *23 June 2020*

Citation:
Weber M, Söder S, Sander J, Ries J, Geppert C, Kesting M and Wehrhan F (2020) Craniofacial Osteosarcoma—Pilot Study on the Expression of Osteobiologic Characteristics and Hypothesis on Metastasis. Front. Oncol. 10:745. doi: 10.3389/fonc.2020.00745

INTRODUCTION

Osteosarcomas are the most frequent primary bone tumors (1). Osteosarcomas are affecting predominantly young people and are characterized by a poor prognosis and yet unsatisfying therapeutic options. The early formation of metastases is the outstanding clinical problem and, in many cases, the limiting factor for the patient (2, 3).

Craniofacial osteosarcomas (COS) represent an exception in this regard. Although, due to local progression, they are also characterized by an unfavorable prognosis, formation of metastases is an extremely rare event in these tumors (1, 4–6). Besides the different metastatic behavior, there are several other clinical differences between craniofacial (COS) and extracranial osteosarcomas (EOS). While the 5-year survival of COS is ~77%, EOS show a worse 5-year survival of only about 55–70% (1, 4). The introduction of neoadjuvant chemotherapy 30 years ago revolutionized the treatment of EOS. Before the introduction of chemotherapy, over 90% of patients with extracranial osteosarcoma died from distant metastases (7). With polychemotherapy, an increase in cure rates from only ~10 to 60–70% could be achieved (4). In contrast, the role of chemotherapy in craniofacial osteosarcomas is still unclear, and meta-analyses have reported conflicting results (3, 4). There are also data showing that treatment with surgery alone was associated with significantly longer survival rates than surgery with adjuvant chemotherapy in COS (1, 3, 8). With a typical occurrence in the third and fourth decade of life, COS patients are usually older than EOS cases (4). The most frequent COS are osteosarcomas of the jaw (3, 4).

Compared to extracranial bone, craniofacial bone shows several special characteristics: A faster turnover and remodeling and the relative absence of osteoporosis can be observed in craniofacial bone (9, 10). Furthermore, a different expression of osseous differentiation markers was reported by several studies (10–12). To understand the special features of the craniofacial bone, the special embryologic development has to be considered. In contrast to the axial skeleton, craniofacial bone does not derive from mesenchymal progenitor cells. Instead, craniofacial bone derives from the cranial neural crest, which represents neuroectodermal tissue (13, 14) (**Figure 1**).

This different embryologic origin of craniofacial and extracranial bones could explain clinically observed differences between COS and EOS. The Hedgehog (Hh) pathway plays a critical role in embryonic development and in pathogenesis of human tumors (15). Loss-of-function mutations in the Hedgehog receptor Patched (PCT) or gain-of-function mutations in the signal transduction protein Smoothened (SMO) activate Hh signaling. Smoothened inhibitors like Vismodegib are already used in the routine therapy of advanced basal cell carcinoma (16). Hh signaling finally leads to the activation of the transcription factors Gli1, Gli2, and Gli3, which are differentially expressed in different tissues.

A high Gli2 expression could be shown in osteosarcoma cell lines, and a correlation of Gli2 expression with the prognosis of osteosarcoma patients was reported (15). *In vitro*, Gli2 inhibition led to a reduced proliferation of tumor cells and an increased sensitivity to chemotherapeutic agents (15). In chondrosarcomas and Ewing sarcomas, the involvement of the Hh pathway in tumorigenesis is also shown (16). The role of the Hh signaling pathway in COS is not yet investigated. However, Hh signaling plays a critical role in craniofacial embryologic development. It is shown that patterning of the cranial neural crest and facial morphogenesis require Hh signaling (17).

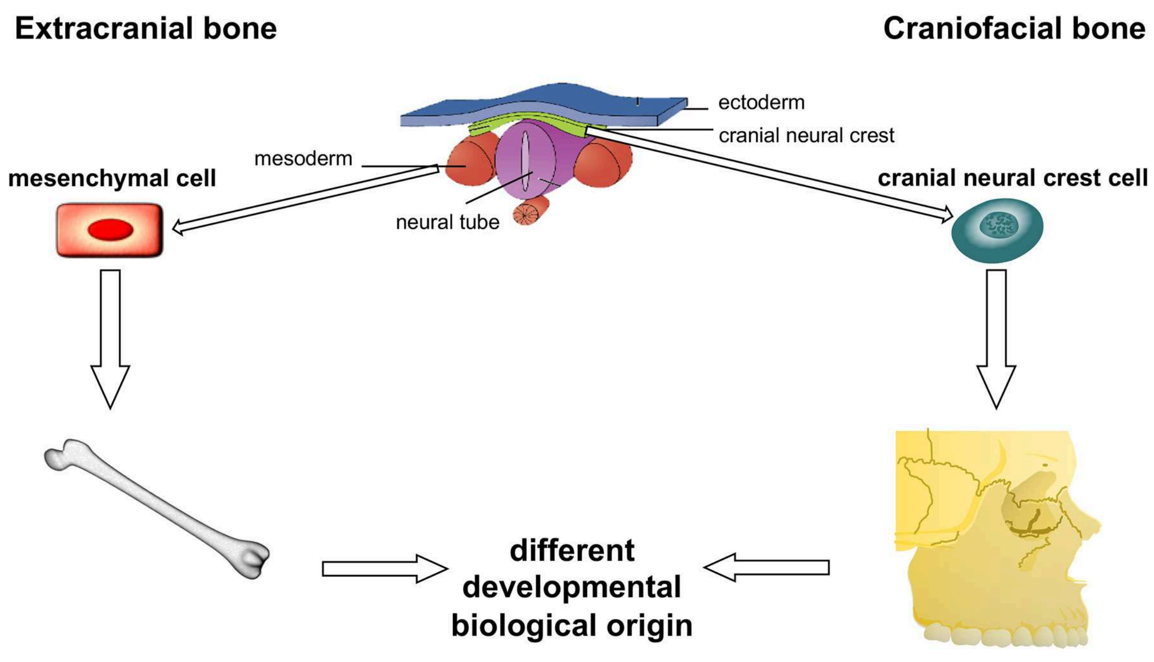


FIGURE 1 | Developmental biological origin of craniofacial and extracranial bone. The figure shows the different developmental biological origin of the craniofacial and extracranial bones. Extracranial bone is derived from the mesenchyme, whereas the craniofacial bone originates the cranial neural crest. The cranial neural crest is of ectodermal origin. (The figure was created adopting the neurulation scheme from Anatomy & Physiology, Connections: Web site. http://cnx.org/content/col11496/1.6/, Jun 19, 2013 and using the software tool powerpathways, 2010; source: epath3d San Diego, epath3d.com).

Differences in tumor immunology are another possible explanation for the diverse clinical behavior of COS and EOS. In this regard, tumor-associated macrophages could be of particular relevance, as they account for up to 50% of the tumor volume in some malignancies (2). An explorative gene expression analysis showed that EOS cases with and those without metastasis within 5 years differ regarding the expression of genes associated with regulation of macrophage functions (18). Macrophages play a key role in the progression and metastasis of most solid tumors (19–22). In breast cancer, for example,

TABLE 1 | Demographic parameters of the patient cohort.

Description of the patient collective; total number of cases: 20					
		COS		EOS	
		n	% of cases	*n*	% of cases
Number of cases		10		10	
Gender	Male	5	50%	4	40%
	Female	5	50%	6	60%
Mean age		40.6 years (SD 18.2)		26.5 years (SD 19.2)	
Age range		19–75 years		5–63 years	
Analyzed specimen	Primary tumor	8	80%	10	100%
	Recurrence	2	20%	0	
Metastatic disease	Yes	1	10%	8	80%
	No	9	90%	2	20%
Grading	G1	1	10%	0	0%
	G2	2	20%	1	10%
	G3	4	40%	7	70%
	Unknown	3	30%	2	20%

Gender, age at diagnosis, grading, and presence of metastatic disease are displayed.
COS, craniofacial osteosarcomas; EOS, extracranial osteosarcomas.

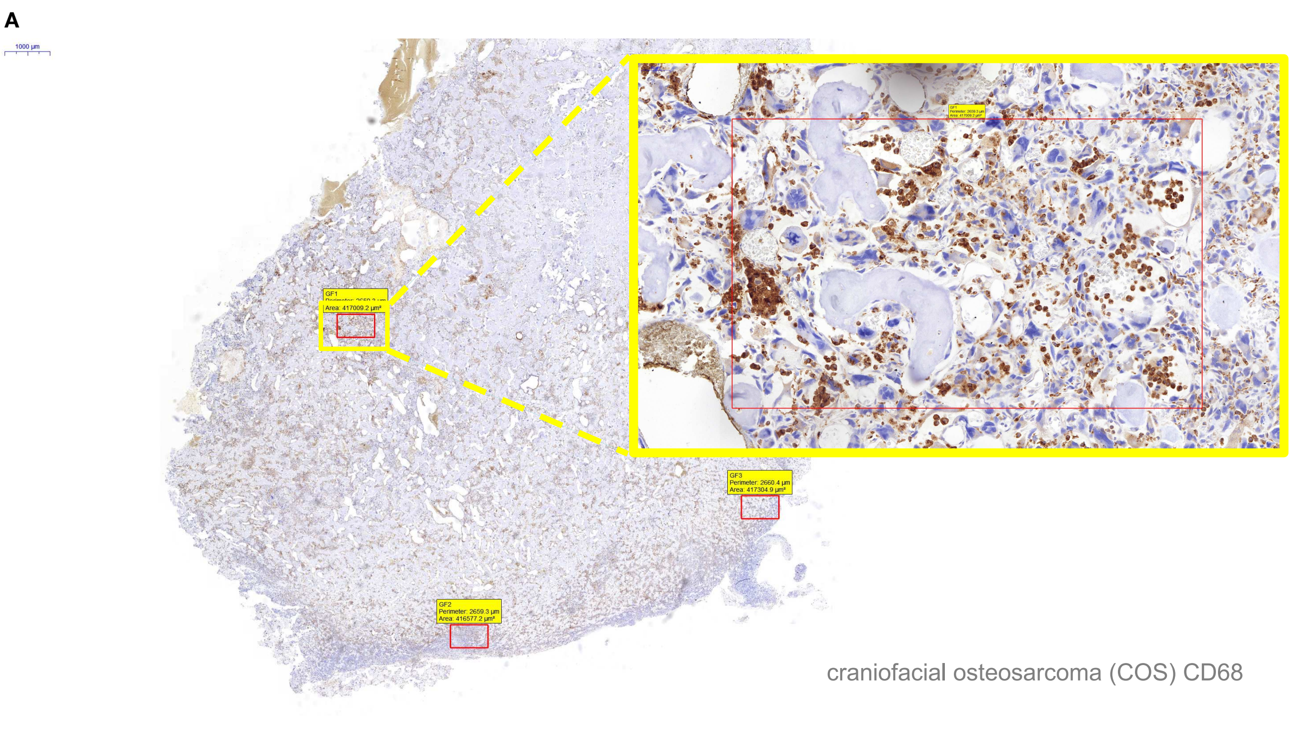


FIGURE 2 | Continued

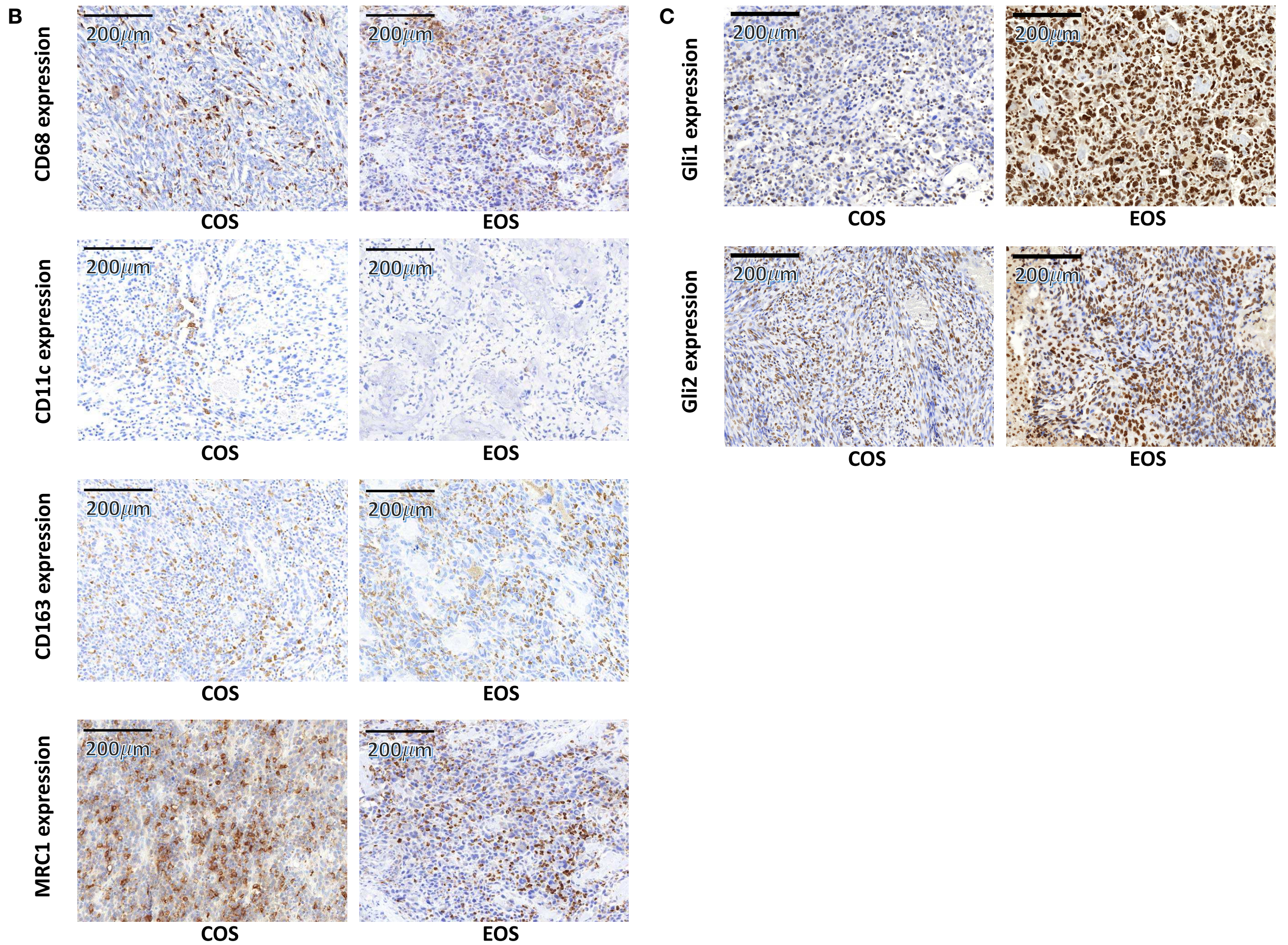


FIGURE 2 | Typical macrophage marker and Gli staining pattern. **(A)** shows exemplarily the typical expression pattern of the generic macrophage marker CD68 in a craniofacial osteosarcoma. CD68-positive cells are stained in brown. A panoramic view (2× magnification) is given on the left side, and a magnification of the indicated region (25× magnification) is displayed on the right side. Three fields of view are marked in the panoramic micrograph for cell counting. **(B)** shows high power micrographs (35× magnification) of CD68, CD11c, CD163, and MRC1-positive macrophages in COS and EOS. All macrophage markers reveal acytoplasmic and membranous expression pattern. **(C)** shows high power micrographs (35× magnification) of Gli1- and Gli2-positive tumor cells in COS and EOS. Both markers reveal a nuclear expression pattern. COS, craniofacial osteosarcomas; EOS, extracranial osteosarcomas.

macrophages are involved in the growth of bone metastases (2) and may influence chemotherapy response (23). The influence of macrophages on osteosarcomas has not yet been conclusively understood. There are studies showing an association between high macrophage infiltration and unfavorable prognosis (24). Other studies, however, come to the opposite conclusion (18). Studies regarding tumor-associated macrophages in COS are lacking so far.

Currently, there are no data available in the literature, describing the different tumor biological behavior of osteosarcomas depending on their primary location (craniofacial vs. extracranial).

The exception of craniofacial osteosarcomas could help identifying the molecular factors facilitating the metastases of osteosarcomas and may lead to new therapeutic interventions. The current pilot study aims to test if COS and EOS differ regarding macrophage infiltration, macrophage polarization, and activation of Hedgehog signaling.

MATERIALS AND METHODS

Patients and Tissue Harvesting

For this retrospective analysis, tissue specimens of 10 cases of craniofacial osteosarcomas (COS) and 10 cases of extracranial osteosarcomas (EOS) treated at the university hospital of Erlangen during 2005 and 2015. The study was approved by the ethics committee of the Friedrich-Alexander University Erlangen–Nürnberg (70_15 Bc) and performed in accordance with the Declaration of Helsinki. There was an equal distribution between male and female patients. The mean age was 40.6 years in the COS group and 26.5 years in the EOS group. Metastatic disease was present at the time of surgery or in the follow-up in one COS case and in eight EOS cases. Most

TABLE 2 | Macrophage cell count (positive cells/mm^2) and the macrophage marker expression ratio in craniofacial (COS) and extracranial osteosarcomas (EOS).

		Macrophage infiltration, macrophage expression ratios, and Gli expression in craniofacial osteosarcomas (COS) and extracranial osteosarcomas (EOS)			
		n	Median	SD	*p* value
Macrophage infiltration					
CD68	COS	10	858	449	0.243
(cells/mm^2)	EOS	10	500	429	
CD11c	COS	10	173	211	0.022
(cells/mm^2)	EOS	10	34	261	
CD163	COS	10	828	637	0.739
(cells/mm^2)	EOS	10	480	609	
MRC1	COS	10	580	456	0.400
(cells/mm^2)	EOS	10	370	480	
Macrophage expression ratios					
Ratio	COS	10	0.27	0.13	0.014
CD11c/CD68	EOS	10	0.09	0.48	
Ratio	COS	10	1.04	0.55	0.447
CD163/CD68	EOS	10	1.48	1.03	
Ratio	COS	10	3.75	3.53	0.035
CD163/CD11c	EOS	10	18.54	28.36	
Ratio	COS	10	3.43	1.88	0.182
MRC1/CD11c	EOS	10	6.04	26.19	
Gli expression					
Gli1	COS	10	1,102	676	0.035
(cells/mm^2)	EOS	10	2,883	1,307	
Gli1	COS	10	0.24	0.21	0.028
Labeling index	EOS	10	0.72	0.23	
Gli2	COS	10	3,217	1,441	0.829
(cells/mm^2)	EOS	10	3,319	1,510	
Gli2	COS	10	0.65	0.14	0.101
Labeling index	EOS	10	0.84	0.24	

Additionally, the Gli1 and Gli2 expression (positive cells/mm^2 and labeling index) in COS and EOS is given. Values represent the median, standard deviation (SD), and p value (Mann–Whitney U test).
n, number of cases.

osteosarcomas were high-grade sarcomas. Five COS cases were osteosarcomas of the mandible and five cases osteosarcomas of the maxilla. The demographic characteristics are given in **Table 1**.

Immunohistochemical Staining and Quantitative Analysis

Established antibodies were used to detect macrophage infiltration and macrophage polarization. CD68 is an established pan-macrophage marker to detect macrophages independent of their polarization (25–27). M1-polarized macrophages express the CD11c antigen (27–29). M2-polarized macrophages express the CD163 (25, 26, 30, 31) and the MRC1 antigen (28, 30, 32). The immunohistochemical staining procedure was performed as previously described (21, 33). Gli1 and Gli2 staining was performed after samples were treated for 20 min with the detergent TritonX (Merck, Darmstadt, Germany) to enable better nuclear penetration of the antibodies. The following primary antibodies were used: anti-CD68 (11081401, clone KP1, Dako, Hamburg, Germany), anti-CD11c (ab52632, clone EP1347y, Abcam, Cambridge, UK) anti-CD163 (NCL-CD163, 6027910, Novocastra, Newcastle, USA), anti-MRC1 (H00004360-1102, clone 5C11, Abnova), anti-Gli1 (ab151796, 1:200, Abcam, Cambridge, UK), and anti-Gli2 (ab7181, 1:200, Abcam, Cambridge, UK).

An appropriate positive control was included in each series.

The tumor and biopsy sections were completely scanned and digitized using the method of "whole slide imaging." The scanning procedure was performed in cooperation with the Institute of Pathology of the University of Erlangen–Nürnberg using a Pannoramic 250 Flash III Scanner (3D Histech, Budapest, Hungary) and in 40× magnification mode. All samples were digitally analyzed (Case viewer, 3D Histech, Budapest, Hungary). Quality controls were performed under a bright-field microscope (Zeiss Axioskop and Axiocam 5, at 10–40× magnification). H&E-stained sections of all samples were examined together with a pathologist to ensure that all samples contained representative osteosarcoma tissue.

For each sample and each marker, three visual fields showing the highest infiltration rate of positive cells were selected (hot spot analysis). The complete area of all three visual fields of one specimen was between 1.1 and 1.5 mm^2 (Case viewer, 3D Histech, Budapest, Hungary).

Micrographs of the selected areas were imported into the BioMas analysis software (modular systems of applied biology, Erlangen, Germany) for cell counting.

A quantitative analysis was performed to determine the numbers of CD68-, CD11c-, CD163-, MRC1-, Gli1- and Gli2-positive cells in the osteosarcoma tissue. Assessment of the cell density per square millimeter was performed as previously described (22, 33).

Statistical Analysis

To analyze the immunohistochemical staining, the cell count per square millimeter was determined as the number of positive cells per square millimeter of the specimen. Labeling index was calculated by dividing the number of positive cells by the number of all cells (positive + negative). The results are expressed as the median and standard deviation (SD). Box plot diagrams represent the median, the interquartile range, minimum (Min), and maximum (Max).

Two-sided, adjusted $p \leq 0.05$ were considered to be significant. The analyses were performed using the Mann–Whitney *U* test with SPSS 22 for Mac OS (IBM Inc., New York, USA).

RESULTS

Macrophage Infiltration and Polarization in COS and EOS

The analyzed macrophage markers CD68, CD11c, CD163, and MRC1 showed a staining of the plasma membrane and the

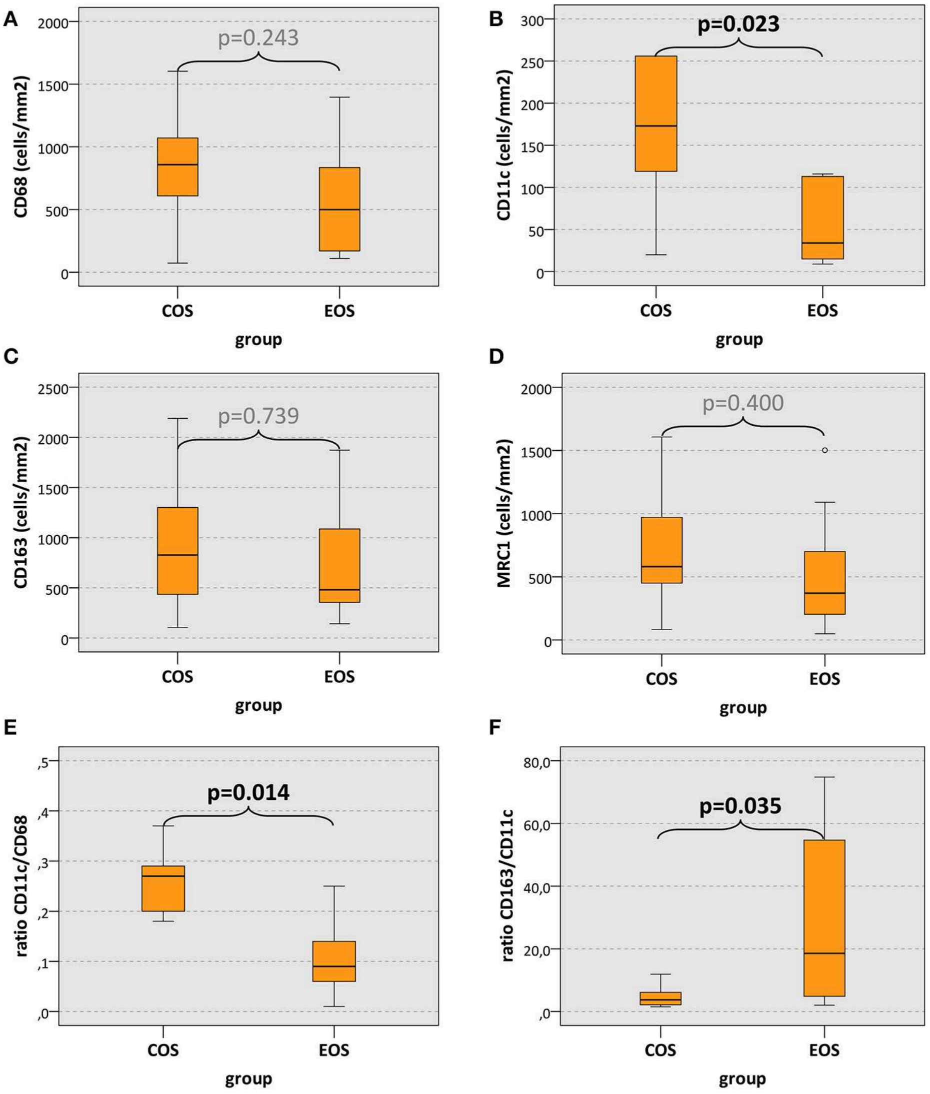


FIGURE 3 | Macrophage cell count and macrophage expression ratios. **(A–D)** The box plots show macrophage infiltration (positive cells/mm^2) and **(E,F)** macrophage expression ratios in craniofacial osteosarcomas (COS) and extracranial osteosarcomas (EOS). *p* values generated by the Mann–Whitney *U* test are given. Significant *p* values are printed in "bold" letters.

cytoplasm, as it was already described (33). In addition to mononucleated cells, polynuclear osteoclasts also expressed macrophage markers. An example of the staining pattern of macrophage markers is given in **Figures 2A,B**.

CD68 cell count in COS was increased compared to EOS without reaching statistical significance (median, 858 and 500 cells/mm^2, respectively) ($p = 0.243$) (**Table 2**, **Figure 3A**). However, CD11c expression in COS cases was significantly higher than in EOS (median, 173 and 34 cells/mm^2, respectively) ($p = 0.022$) (**Table 2**, **Figure 3B**). There was no significant difference in CD163 and MRC1 expression between COS and EOS (**Table 2**, **Figures 3C,D**).

The ratio between CD11c-expressing cells and CD68-positive cells (CD11c/CD68 ratio; indicator of M1 polarization) in COS cases was significantly higher (median value, 0.27) than in EOS cases (median value, 0.09) ($p = 0.014$) (**Table 2**, **Figure 3E**). Accordingly, the CD163/CD11c ratio (indicator of M2 polarization) in COS was significantly lower than in EOS (median value, 3.75 and 18.54, respectively) ($p = 0.035$) (**Table 2**, **Figure 3F**). The MRC1/CD11c ratio and the CD163/CD68 showed no statistically significant difference (**Table 2**).

Gli Expression in COS and EOS

Gli1 and Gli2 showed expression predominantly in the nuclear compartment of osteosarcoma tumor cells (**Figure 2C**).

Gli1 cell count (positive cells/mm^2) in COS was significantly lower compared to EOS (median, 1,102 and 2,883 cells/mm^2, respectively) ($p = 0.035$) (**Table 2**, **Figure 4A**). Additionally, the Gli1 labeling index (positive cells/all cells) in COS was significantly lower than in EOS (median value, 0.24 and 0.72,

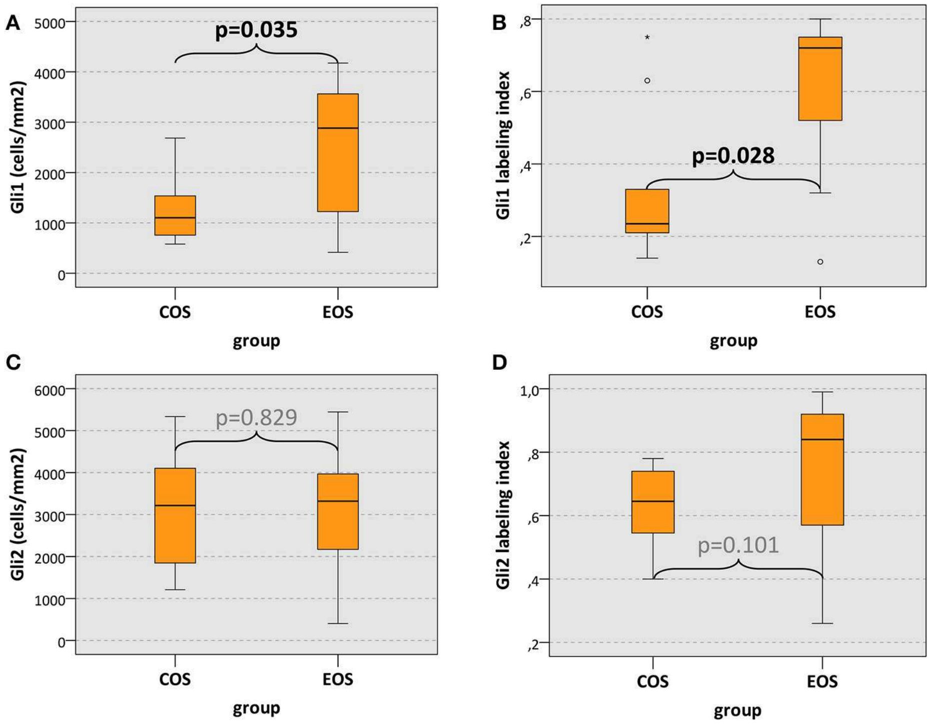


FIGURE 4 | Gli1 and Gli2 expression. **(A,C)** The box plots show Gli1 and Gli2 expression displayed as cell density (positive cells/mm^2) and **(B,D)** labeling index (percentage of expressing cells). Values for craniofacial osteosarcomas (COS) and extracranial osteosarcomas (EOS) are given. *p* values are generated by the Mann–Whitney *U* test. Significant *p* values are printed in "bold" letters.

respectively) ($p = 0.028$) (**Table 2**, **Figure 4B**). In contrast, there was no significant difference in Gli2 expression between COS and EOS (**Table 2**, **Figures 4C,D**).

DISCUSSION

Role of Macrophage Polarization in COS and EOS

COS cases showed an increased infiltration of macrophages. However, only the M1 macrophage marker CD11c (27–29) showed significantly increased cell density in COS cases. Macrophages can have two different activation sets or polarizations: M1 and M2 (34–36). M1 macrophages promote inflammatory reactions, are capable of antigen presentation and T-cell activation, and have therefore antitumor and antimetastatic effects (34–36). M2 macrophages have immunoregulatory properties and are associated with wound healing, immunosuppression, tumor progression, and metastatic spread (20, 21, 25, 28, 34–39).

In addition to the significantly increased CD11c cell density in COS, we could show a significantly increased CD11c/CD68 ratio in COS cases. The CD11c/CD68 ratio can be seen as indicator of M1 polarization (40). Accordingly, the CD163/CD11c ratio—as indicator of M2 polarization—was significantly higher in EOS. These results suggest that there might be an increased degree of M1 polarization of macrophages in COS compared to EOS. In EOS, an association of M1 polarization of macrophages and high macrophage infiltration with low incidence of metastases and better outcome was already shown (41). These data are in accordance with the results of the current study in which we could show an increased degree of M1 polarization and a tendency towards increased macrophage infiltration in COS.

It is shown that muramyl tripeptide phosphatidyl ethanolamine (MTP-PE) can be used for the adjuvant treatment of osteosarcoma (42, 43). MTP-PE acts by increasing M1 polarization of macrophages (43). While meta-analyses showed no clear benefit for adjuvant MTP-PE treatment for overall survival, there was a positive effect for cases with absence of metastases reported (44). This indicates a potential metastasis preventing effect through M1-polarized macrophages. A combination of MTP-PE with bisphosphonates was shown to be a potential candidate for adjuvant EOS treatment (42). This is interesting as bisphosphonates also have M1 polarizing properties (45). Additionally, a prevention of osteosarcoma metastases by antagonizing M2 polarization of macrophages with all-trans-retinoic acid was shown (46).

If the increased degree of M1 polarization in COS suggested by this pilot study can be verified in confirmatory analyses, it needs to be assessed if macrophage modulating treatments are exclusively beneficial for EOS cases or if COS with an inherent increase in M1 polarization can also profit from such immune modulatory approaches.

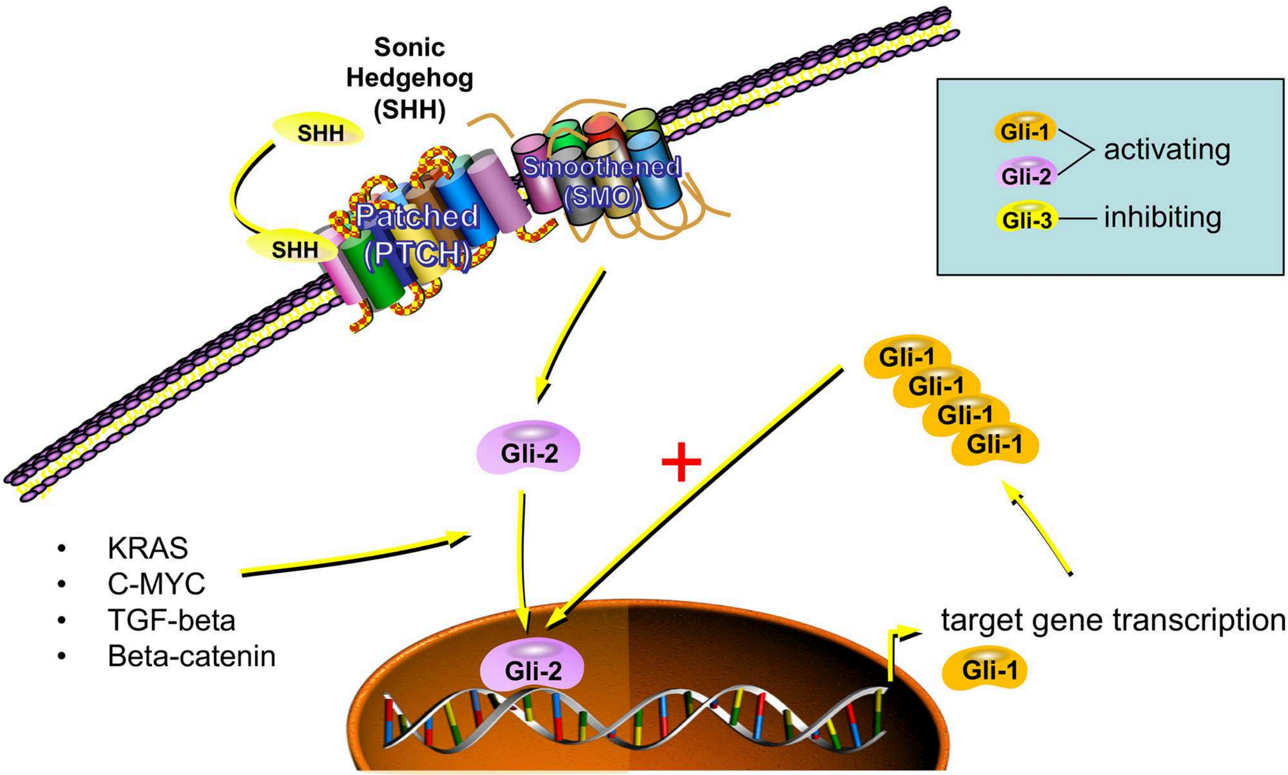


FIGURE 5 | Interpretation of increased Gli1 expression as indicator of increased hedgehog signaling. Binding of a hedgehog ligand-like sonic hedgehog (SHH) to the transmembrane receptor Patched (PTCH) leads to the dissociation of PTCH from Smoothened (SMO). Thereby signal transduction to the cytoplasm is initiated, and Gli transcription factors are translocated to the nucleus. Gli2 is the main factor responsible for the transcription of hedgehog target genes. Gli1 is one of the hedgehog target genes and its transcription is increased by hedgehog signaling. Gli1 augments the transcription activation of Gli2. In this context, Gli1 expression can be interpreted as surrogate marker of hedgehog activation. Besides the described canonical hedgehog activation through extracellular ligand-like sonic hedgehog (SHH), a noncanonical hedgehog activation via oncogenic pathways like KRAS, C-MYC, transforming growth factor beta (TGF-beta), or beta-catenin can also be observed (The figure was created using the software tool powerpathways, 2010; source: epath3d San Diego, epath3d.com).

Hedgehog Signaling in COS and EOS

The Hedgehog (Hh) pathway plays a relevant role in the progression and metastatic spread of several cancers including osteosarcomas (47). Hh target genes are involved in proliferation, survival, stem cell formation, and invasion (47). Increased Hh signaling in osteosarcomas was associated with inferior survival and metastatic disease (47, 48).

The endpoint of intracellular Hh signaling is the activation of Gli transcription factors. Gli1 and Gli2 act as transcriptional activators, while Gli3 is a transcriptional repressor (48). The current pilot study could show that COS have a significantly reduced Gli1 expression compared to EOS. However, there was no significant difference regarding Gli2 expression detected. In this regard, it needs to be noted that Gli1 is one of the target genes of the Hh pathway and therefore can act as indicator of Hh activation (48, 49). The increased Gli1 expression in cells with activated Hh signaling can then be detected by immunohistochemical staining. An overview of Hh signaling in osteosarcoma cells is given in **Figure 5**.

It was shown that an inhibition of Hh signaling inhibits proliferation, migration, and invasion of osteosarcoma cells *in vitro* (50). As a result of Hh inhibition a decreased cellular Gli1 expression was reported (50). An antimetastatic effect of Hh inhibition was verified in an animal model in which lung metastases and tumor growth were inhibited (50). A combination of standard chemotherapy with Hh inhibitors was shown to synergistically prevent osteosarcoma progression *in vivo* and could also be used for human treatment (51). In this regard, the rare occurrence of metastatic disease could be associated with the decreased degree of Hh activation in COS compared to EOS. These data indicate that Hh inhibition might be a promising therapeutic approach for EOS.

However, an increased radioresistance of osteosarcoma cells was reported to be associated with high Hh activation and could be reversed by Hh inhibition (52, 53). In this regard, Hh inhibition might also be considered for new studies evaluating multimodal treatment including radiotherapy in COS.

Besides the canonical Hedgehog activation via extracellular ligands like Sonic Hedgehog (SHH), there is also a noncanonical Hedgehog activation via oncogenic pathways like KRAS, C-MYC, transforming growth factor beta (TGF-beta), or beta-catenin described (**Figure 5**) (54). In this regard, it needs to be evaluated if Hh inhibition on the level of the transmembrane receptors is sufficient for osteosarcoma therapy. However, it could be shown that several Smoothened inhibitors are sufficient to inhibit Gli1 expression and proliferation in osteosarcoma cell lines (55).

The results of the current pilot study indicate that Hh activation in COS might be reduced compared to EOS. This could explain the low incidence of metastases in COS and supports the investigation of Hh inhibitors in osteosarcoma treatment.

Limitations of the Study

The main limitation of the study is the low number of analyzed cases. In this regard, it needs to be considered that COS are relatively rare tumors. Most centers in Germany treat about one case a year. The current pilot study could motivate a larger multicenter analysis in the future.

A further limitation is the lack of specificity of the available macrophage marker. This aspect is already discussed elsewhere (33). The current study uses the Gli transcription factors as surrogate markers for the activation of the hedgehog signaling pathway. An analysis of hedgehog ligands, receptors, and further target genes would be desirable in future analyses.

CONCLUSION

The current pilot study could show that Hedgehog activation in COS is significantly lower than in EOS. This finding could be caused by the different developmental biological origin of craniofacial and extracranial bone and could contribute to the low incidence of metastases in COS. The shift of macrophage polarization towards the antimetastatic M1 type could also contribute to the uncommon metastatic spread in COS.

Based on these tumor biological differences, the diverse metastatic behavior, and the clinical response to chemotherapy, COS and EOS should be considered as different tumor entities that also require a specific treatment regime. Thus, the therapeutic concept of EOS cannot simply be transferred to COS. Prospective studies are needed to evaluate the value of adjuvant therapy in COS treatment. For COS, surgical resection with wide margins is currently the only available treatment with a high level of evidence. As a result, functionally important anatomical structures of the orofacial tissue often have to be sacrificed. Therefore, the anatomic reconstruction is essential to preserve the quality of life of patients.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethics committee of the Friedrich-Alexander University Erlangen-Nürnberg. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. 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

MW formulated the hypothesis, applied for grant support (VFWZ Germany), initiated and conducted the study, interpreted the data and wrote the manuscript. FW formulated the hypothesis, created the **Figures 1**, **5**, interpreted the data and contributed relevantly to the manuscript. SS selected the patients, performed the histologic analysis of all samples, helped to validate the markers, contributed to the discussion and critically reviewed the manuscript. JS collected the tissue samples, performed the macrophage stainings, interpreted the data, and contributed to the manuscript. JR and MK contributed to the discussion and critically reviewed the manuscript. CG performed the digitalization of the specimens, helped with cell counting and critically reviewed the manuscript. All authors read and approved the final manuscript.

FUNDING

This study was financially supported by the foundation Verein zur Förderung der wissenschaftlichen Zahnheilkunde in Bayern e.V. (VFWZ) (grant to MW in 2015).

ACKNOWLEDGMENTS

The authors thank Luitpold Distel for providing the Biomas Software. We also like to thank Susanne Schoenherr and Elke Diebel for technical assistance. Further thanks to the dental student Ellen Sonntag for the evaluation of Gli staining. Parts of the results were published in the dissertation of JS, published in German language at the University Library of the Friedrich-Alexander University Erlangen–Nürnberg (FAU). **Figures 1**, **5** were drawn by FW using the commercially available software tool powerpathways, version 2010, powerpathways, 2010; source: epath3d San Diego, epath3d.com (www.motifolio.com).

REFERENCES

1. Thariat J, Julieron M, Brouchet A, Italiano A, Schouman T, Marcy PY, et al. Osteosarcomas of the mandible: are they different from other tumor sites? *Crit Rev Oncol Hematol.* (2012) 82:280–95. doi: 10.1016/j.critrevonc.2011.07.001
2. Endo-Munoz L, Evdokiou A, Saunders NA. The role of osteoclasts and tumour-associated macrophages in osteosarcoma metastasis. *Biochim Biophys Acta.* (2012) 1826:434–42. doi: 10.1016/j.bbcan.2012.07.003
3. Mendenhall WM, Fernandes R, Werning JW, Vaysberg M, Malyapa RS, Mendenhall NP. Head and neck osteosarcoma. *Am J Otolaryngol.* (2011) 32:597–600. doi: 10.1016/j.amjoto.2010.09.002
4. Jasnau S, Meyer U, Potratz J, Jundt G, Kevric M, Joos UK, et al. Cooperative Osteosarcoma Study Group, Craniofacial osteosarcoma Experience of the cooperative German-Austrian-Swiss osteosarcoma study group. *Oral Oncol.* (2008) 44:286–94. doi: 10.1016/j.oraloncology.2007.03.001

5. Laskar S, Basu A, Muckaden MA, D'Cruz A, Pai S, Jambhekar N, et al. Osteosarcoma of the head and neck region: lessons learned from a single-institution experience of 50 patients. *Head Neck.* (2008) 30:1020–6. doi: 10.1002/hed.20820
6. Guadagnolo BA, Zagars GK, Raymond AK, Benjamin RS, Sturgis EM. Osteosarcoma of the jaw/craniofacial region: outcomes after multimodality treatment. *Cancer.* (2009) 115:3262–70. doi: 10.1002/cncr.24297
7. Ritter J, Bielack SS. Osteosarcoma. *Ann Oncol.* (2010) 21(Suppl. 7):vii320–5. doi: 10.1093/annonc/mdq276
8. Kassir RR, Rassekh CH, Kinsella JB, Segas J, Carrau RL, Hokanson JA. Osteosarcoma of the head and neck: meta-analysis of nonrandomized studies. *Laryngoscope.* (1997) 107:56–61. doi: 10.1097/00005537-199701000-00013
9. Finkelman RD, Eason AL, Rakijian DR, Tutundzhyan Y, Hardesty RA. Elevated IGF-II and TGF-beta concentrations in human calvarial bone: potential mechanism for increased graft survival and resistance to osteoporosis. *Plast Reconstr Surg.* (1994) 93:732–8. doi: 10.1097/00006534-199404000-00012
10. Wehrhan F, Hyckel P, Ries J, Stockmann P, Nkenke E, Schlegel KA, et al. Expression of Msx-1 is suppressed in bisphosphonate associated osteonecrosis related jaw tissue-etiopathology considerations respecting jaw developmental biology-related unique features. *J Transl Med.* (2010) 8:96. doi: 10.1186/1479-5876-8-96
11. Wehrhan F, Hyckel P, Amann K, Ries J, Stockmann P, Schlegel K, et al. Msx-1 is suppressed in bisphosphonate-exposed jaw bone analysis of bone turnover-related cell signalling after bisphosphonate treatment. *Oral Dis.* (2011) 17:433–42. doi: 10.1111/j.1601-0825.2010.01778.x
12. Matsubara T, Suardita K, Ishii M, Sugiyama M, Igarashi A, Oda R, et al. Alveolar bone marrow as a cell source for regenerative medicine: differences between alveolar and iliac bone marrow stromal cells. *J Bone Miner Res.* (2005) 20:399–409. doi: 10.1359/JBMR.041117
13. Yamaguchi DT. "Ins" and "Outs" of mesenchymal stem cell osteogenesis in regenerative medicine. *World J Stem Cells.* (2014) 6:94–110. doi: 10.4252/wjsc.v6.i2.94
14. Bronner ME, LaBonne C. Preface: the neural crest–from stem cell formation to migration and differentiation. *Dev Biol.* (2012) 366:1. doi: 10.1016/j.ydbio.2012.03.011
15. Nicholas S, Mathios D, Ruzevick J, Jackson C, Yang I, Lim M. Current trends in glioblastoma multiforme treatment: radiation therapy and immune checkpoint inhibitors. *Brain Tumor Res Treat.* (2013) 1:2–8. doi: 10.14791/btrt.2013.1.1.2
16. Kelleher FC, Cain JE, Healy JM, Watkins DN, Thomas DM. Prevailing importance of the hedgehog signaling pathway and the potential for treatment advancement in sarcoma. *Pharmacol Ther.* (2012) 136:153–68. doi: 10.1016/j.pharmthera.2012.08.004
17. Swartz ME, Nguyen V, McCarthy NQ, Eberhart JK. Hh signaling regulates patterning and morphogenesis of the pharyngeal arch-derived skeleton. *Dev Biol.* (2012) 369:65–75. doi: 10.1016/j.ydbio.2012.05.032
18. Buddingh EP, Kuijjer ML, Duim RA, Burger H, Agelopoulos K, Myklebost O, et al. Tumor-infiltrating macrophages are associated with metastasis suppression in high-grade osteosarcoma: a rationale for treatment with macrophage activating agents. *Clin Cancer Res.* (2011) 17:2110–9. doi: 10.1158/1078-0432.CCR-10-2047
19. Allavena P, Mantovani A. Immunology in the clinic review series; focus on cancer: tumour-associated macrophages: undisputed stars of the inflammatory tumour microenvironment. *Clin Exp Immunol.* (2012) 167:195–205. doi: 10.1111/j.1365-2249.2011.04515.x
20. Kurahara H, Shinchi H, Mataki Y, Maemura K, Noma H, Kubo F, et al. Significance of M2-polarized tumor-associated macrophage in pancreatic cancer. *J Surg Res.* (2011) 167:e211–9. doi: 10.1016/j.jss.2009.05.026
21. Weber M, Buttner-Herold M, Hyckel P, Moebius P, Distel L, Ries J, et al. Small oral squamous cell carcinomas with nodal lymphogenic metastasis show increased infiltration of M2 polarized macrophages–an immunohistochemical analysis. *J Craniomaxillofac Surg.* (2014) 42:1087–94. doi: 10.1016/j.jcms.2014.01.035
22. Weber M, Iliopoulos C, Moebius P, Buttner-Herold M, Amann K, Ries J, et al. Prognostic significance of macrophage polarization in early stage oral squamous cell carcinomas. *Oral Oncol.* (2016) 52:75–84. doi: 10.1016/j.oraloncology.2015.11.001
23. DeNardo DG, Brennan DJ, Rexhepaj E, Ruffell B, Shiao SL, Madden SF, et al. Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. *Cancer Discov.* (2011) 1:54–67. doi: 10.1158/2159-8274.CD-10-0028
24. Koirala P, Roth ME, Gill J, Piperdi S, Chinai JM, Geller DS, et al. Immune infiltration and PD-L1 expression in the tumor microenvironment are prognostic in osteosarcoma. *Sci Rep.* (2016) 6:30093. doi: 10.1038/srep30093
25. Cao X, Shen D, Patel MM, Tuo J, Johnson TM, Olsen TW, et al. Macrophage polarization in the maculae of age-related macular degeneration: A pilot study. *Pathol Int.* (2011) 61:528–35. doi: 10.1111/j.1440-1827.2011.02695.x
26. Kawamura K, Komohara Y, Takaishi K, Katabuchi H, Takeya M. Detection of M2 macrophages and colony-stimulating factor 1 expression in serous and mucinous ovarian epithelial tumors. *Pathol Int.* (2009) 59:300–5. doi: 10.1111/j.1440-1827.2009.02369.x
27. Cho KY, Miyoshi H, Kuroda S, Yasuda H, Kamiyama K, Nakagawara J, et al. The phenotype of infiltrating macrophages influences arteriosclerotic plaque vulnerability in the carotid artery. *J Stroke Cerebrovasc Dis.* (2013) 22:910–18. doi: 10.1016/j.jstrokecerebrovasdis.2012.11.020
28. Hirata Y, Tabata M, Kurobe H, Motoki T, Akaike M, Nishio C, et al. Coronary atherosclerosis is associated with macrophage polarization in epicardial adipose tissue. *J Am Coll Cardiol.* (2011) 58:248–55. doi: 10.1016/j.jacc.2011.01.048
29. Pejnovic N, Pantic J, Jovanovic I, Radosavljevic G, Milovanovic M, Nikolic I, et al. Galectin-3 deficiency accelerates high-fat diet induced obesity and amplifies inflammation in adipose tissue and pancreatic islets. *Diabetes.* (2013) 62:1932–44. doi: 10.2337/db12-0222
30. Aron-Wisnewsky J, Tordjman J, Poitou C, Darakhshan F, Hugol D, Basdevant A, et al. Human adipose tissue macrophages: m1 and m2 cell surface markers in subcutaneous and omental depots and after weight loss. *J Clin Endocrinol Metab.* (2009) 94:4619–23. doi: 10.1210/jc.2009-0925
31. Hasan D, Chalouhi N, Jabbour P, Hashimoto T. Macrophage imbalance (M1 vs. M2) and upregulation of mast cells in wall of ruptured human cerebral aneurysms: preliminary results. *J Neuroinflammation.* (2012) 9:222. doi: 10.1186/1742-2094-9-222
32. van Putten SM, Ploeger DT, Popa ER, Bank RA. Macrophage phenotypes in the collagen-induced foreign body reaction in rats. *Acta Biomater.* (2013) 9:6502–10. doi: 10.1016/j.actbio.2013.01.022
33. Weber M, Moebius P, Buttner-Herold M, Amann K, Preidl R, Neukam FW, et al. Macrophage polarisation changes within the time between diagnostic biopsy and tumour resection in oral squamous cell carcinomas-an immunohistochemical study. *Br J Cancer.* (2015) 113:510–9. doi: 10.1038/bjc.2015.212
34. Mantovani A, Sica A, Locati M. New vistas on macrophage differentiation and activation. *Eur J Immunol.* (2007) 37:14–6. doi: 10.1002/eji.200636910
35. Mantovani A, Biswas SK, Galdiero MR, Sica A, Locati M. Macrophage plasticity and polarization in tissue repair and remodelling. *J Pathol.* (2013) 229:176–85. doi: 10.1002/path.4133
36. Sica A, Mantovani A. Macrophage plasticity and polarization: *in vivo* veritas. *J Clin Invest.* (2012) 122:787–95. doi: 10.1172/JCI59643
37. Murray PJ, Wynn TA. Obstacles and opportunities for understanding macrophage polarization. *J Leukoc Biol.* (2011) 89:557–63. doi: 10.1189/jlb.0710409
38. Lan C, Huang X, Lin S, Huang H, Cai Q, Wan T, et al. Expression of M2-polarized macrophages is associated with poor prognosis for advanced epithelial ovarian cancer. *Technol Cancer Res Treat.* (2013) 12:259–67. doi: 10.7785/tcrt.2012.500312
39. Hao NB, Lu MH, Fan YH, Cao YL, Zhang ZR, Yang SM. Macrophages in tumor microenvironments and the progression of tumors. *Clin Dev Immunol.* (2012) 2012:948098. doi: 10.1155/2012/948098
40. Weber M, Schlittenbauer T, Moebius P, Buttner-Herold M, Ries J, Preidl R, et al. Macrophage polarization differs between apical granulomas, radicular cysts, dentigerous cysts. *Clin Oral Investig.* (2018) 22:385–394. doi: 10.1007/s00784-017-2123-1
41. Dumars C, Ngyuen JM, Gaultier A, Lanel R, Corradini N, Gouin F, et al. Dysregulation of macrophage polarization is associated with the metastatic process in osteosarcoma. *Oncotarget.* (2016) 7:78343–54. doi: 10.18632/oncotarget.13055

42. Biteau K, Guiho R, Chatelais M, Taurelle J, Chesneau J, Corradini N, et al. L-MTP-PE and zoledronic acid combination in osteosarcoma: preclinical evidence of positive therapeutic combination for clinical transfer. *Am J Cancer Res.* (2016) 6:677–89.
43. Kelleher FC, O'Sullivan H. Monocytes, Macrophages, and Osteoclasts in Osteosarcoma. *J Adolesc Young Adult Oncol.* (2017) 6:396–405. doi: 10.1089/jayao.2016.0078
44. Jimmy R, Stern C, Lisy K, White S. Effectiveness of mifamurtide in addition to standard chemotherapy for high-grade osteosarcoma: a systematic review. *JBI Database System Rev Implement Rep.* (2017) 15:2113–52. doi: 10.11124/JBISRIR-2016-003105
45. Rogers TL, Holen I. Tumour macrophages as potential targets of bisphosphonates. *J Transl Med.* (2011) 9:177. doi: 10.1186/1479-5876-9-177
46. Zhou Q, Xian M, Xiang S, Xiang D, Shao X, Wang J, et al. All-Trans retinoic acid prevents osteosarcoma metastasis by inhibiting M2 polarization of tumor-associated macrophages. *Cancer Immunol Res.* (2017) 5:547–59. doi: 10.1158/2326-6066.CIR-16-0259
47. Yao Z, Han L, Chen Y, He F, Sun B, Kamar S, et al. Hedgehog signalling in the tumourigenesis and metastasis of osteosarcoma, and its potential value in the clinical therapy of osteosarcoma. *Cell Death Dis.* (2018) 9:701. doi: 10.1038/s41419-018-0647-1
48. Lo WW, Pinnaduwage D, Gokgoz N, Wunder JS, Andrulis IL. Aberrant hedgehog signaling and clinical outcome in osteosarcoma. *Sarcoma.* (2014) 2014:261804. doi: 10.1155/2014/261804
49. Lee J, Platt KA, Censullo P, Ruiz i Altaba A. Gli1 is a target of Sonic hedgehog that induces ventral neural tube development. *Development.* (1997) 124:2537–52.
50. Zhao Z, Jia Q, Wu MS, Xie X, Wang Y, Song G, et al. Degalactotigonin, a natural compound from *Solanum nigrum L.*, inhibits growth and metastasis of osteosarcoma through GSK3beta inactivation-mediated repression of the hedgehog/Gli1 pathway. *Clin Cancer Res.* (2018) 24:130–44. doi: 10.1158/1078-0432.CCR-17-0692
51. Saitoh Y, Setoguchi T, Nagata M, Tsuru A, Nakamura S, Nagano S, et al. Combination of Hedgehog inhibitors and standard anticancer agents synergistically prevent osteosarcoma growth. *Int J Oncol.* (2016) 48:235–42. doi: 10.3892/ijo.2015.3236
52. Qu W, Wang Y, Wu Q, Hao D, Li D. Emodin impairs radioresistance of human osteosarcoma cells by suppressing sonic hedgehog signaling. *Med Sci Monit.* (2017) 23:5767–73. doi: 10.12659/MSM.907453
53. Qu W, Li D, Wang Y, Wu Q, Hao D. Activation of sonic hedgehog signaling is associated with human osteosarcoma cells radioresistance characterized by increased proliferation, migration, and invasion. *Med Sci Monit.* (2018) 24:3764–71. doi: 10.12659/MSM.908278
54. Palle K, Mani C, Tripathi K, Athar M. Aberrant GLI1 activation in DNA damage response, carcinogenesis and chemoresistance. *Cancers (Basel).* (2015) 7:2330–51. doi: 10.3390/cancers7040894
55. Bernardini G, Geminiani M, Gambassi S, Orlandini M, Petricci E, Marzocchi B, et al. Novel smoothened antagonists as anti-neoplastic agents for the treatment of osteosarcoma. *J Cell Physiol.* (2018) 233:4961–71. doi: 10.1002/jcp.26330

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.

The handling editor declared a shared affiliation, though no other collaboration, with the authors at the time of review.

frontiers in Oncology

ORIGINAL RESEARCH
published: 04 November 2020
doi: 10.3389/fonc.2020.599097

Time to Local Recurrence as a Predictor of Survival in Patients With Soft Tissue Sarcoma of the Extremity and Abdominothoracic Wall

Yao Liang[1,2†], *Tianhui Guo*[1,3†], *Dongchun Hong*[1,3†], *Wei Xiao*[1,3], *Zhiwei Zhou*[1,2*] *and Xing Zhang*[1,3*]

[1] State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China, [2] Department of Gastric Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China, [3] Department of Medical Melanoma and Sarcoma, Sun Yat-sen University Cancer Center, Guangzhou, China

OPEN ACCESS

Edited by:
Raymund E. Horch,
University Hospital Erlangen, Germany

Reviewed by:
Matthew Tristan Wallace,
MedStar Franklin Square Medical Center, United States
Ziv Radisavljevic,
Brigham and Women's Hospital and Harvard Medical School, United States

***Correspondence:**
Zhiwei Zhou
zhouzhw@sysucc.org.cn
Xing Zhang
zhangxing@sysucc.org.cn

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: 26 August 2020
Accepted: 09 October 2020
Published: 04 November 2020

Citation:
Liang Y, Guo T, Hong D, Xiao W, Zhou Z and Zhang X (2020) Time to Local Recurrence as a Predictor of Survival in Patients With Soft Tissue Sarcoma of the Extremity and Abdominothoracic Wall. Front. Oncol. 10:599097. doi: 10.3389/fonc.2020.599097

Objective: The purpose of this retrospective study was to identify the prognostic significance of time to local recurrence (TLR) with regard to overall survival (OS) and survival after local recurrence (SAR) in patients with soft tissue sarcoma (STS) of the extremity and abdominothoracic wall.

Methods: We identified 477 patients who underwent R0 resection for localized STS of the extremity and abdominothoracic wall, from January 1995 to December 2016, of whom 190 patients developed local recurrence as their first recurrent event. Based on TLR, patients were divided into two groups: early local recurrence (ELR, <12 months) and late local recurrence (LLR, ≥12 months). The Kaplan–Meier method and Cox regression analysis were used to estimate the OS and SAR, and to identify factors associated with patient outcomes.

Results: The median follow-up time for the entire cohort was 118.4 months, and was 118.5 months for the 190 patients who developed local recurrence. Deep tumor location (HR 1.73, 95% CI 1.27–2.37, $P = 0.001$) and tumor grade ≥2 (G2 vs. G1: HR 1.75, 95% CI 1.21–2.53, G3 vs. G1: HR 2.57, 95% CI 1.66–3.98, $P < 0.001$) were associated with a higher rate of local recurrence. There were 99 patients in the ELR group and 91 in the LLR group, with a median TLR of 10.8 months for the entire cohort. Patients from the ELR group had a shorter OS and a lower 5-year OS rate than the LLR group. Univariate and multivariate analyses demonstrated TLR as an independent prognostic factor for SAR and OS, in addition to tumor grade. Also, surgical treatment and absence of metastasis after local recurrence were associated with longer SAR.

Conclusions: In patients with STS of the extremity and abdominothoracic wall, ELR after R0 resection indicated a worse prognosis than those with LLR, and TLR can be considered an independent prognostic factor for OS and SAR. Furthermore, local recurrence was significantly influenced by the depth and the histopathological grading of the primary tumor, and reoperation after local recurrence could improve survival, which means salvage surgery may still be the preferred treatment when there are surgical indications after recurrence.

Keywords: time to local recurrence, soft tissue sarcoma, extremity and abdominothoracic wall, survival, prognostic factors

INTRODUCTION

Soft tissue sarcomas (STSs) are a heterogeneous group of malignancies with a low incidence, accounting for approximately 1% of all adult malignancies (1). STSs may arise in different body sites, including the head or neck, extremity, trunk, retroperitoneum, or chest wall, with local aggressiveness. Among all of STS, about 80% of tumors locate in the extremities and superficial trunk. There are more than 50 different histologic subtypes identified, each with distinct biologic behavior and clinical manifestation. The anatomic sites and pathologic subtypes of these tumors are crucial for their treatments and outcomes. Despite the established role of radical or wide surgical resection as a standard of treatment, 15%–40% of patients with localized STS tumors develop recurrence and have a dismal 5-year survival rate ranging between 55% and 70% (2, 3). Thus, tumor local relapse remains one of the major problems in managing STS, and can be defined as early or late recurrence. In breast adenocarcinoma, renal cell carcinoma, and gastric cancer, it was previously reported that patients with late recurrence had better prognosis than those with early recurrence (4–6). However, to the best of our knowledge, neither significant factors affecting the survival after recurrence (SAR) for STS patients nor information concerning the prognostic significance of time to local recurrence (TLR) in STS patients have been reported.

Therefore, we performed this retrospective study to determine the clinicopathological factors affecting local recurrence (LR), and the prognostic significance of TLR, with regard to overall survival (OS) and SAR, in patients with STS of the extremity and abdominothoracic wall.

METHODS

Study Population

The data of 769 patients who underwent R0 resection for primary STS at the Sun Yat-sen University Cancer Center (SYSUCC, Guangzhou, China), from January 1995 to December 2016, were retrieved. As there is no clear standard for defining radical or extensive resection of STS, due to the existing different tumor types, tumor volume, and location, here, we used the standardized classifications (R0, R1, R2) of the International Union Against Cancer (UICC) for surgery to classify the radicality of the surgical resections performed (7). R0 was defined as the microscopic absence of malignant cells at the resection margin. Patients with R1 or R2 resection were excluded as they comprised of a very small proportion of the retrieved cases. Seventy-seven of the 769 (10%) patients were lost to follow-up and were excluded. Patients with inadequate medical records (5 patients) and distant metastasis at the time of initial diagnosis (82 patients) were also excluded. Although the proportion is low, patients who received the adjuvant treatments (23.9%), including chemotherapy (mostly doxorubicin-based), radiotherapy, or chemoradiotherapy, were included for the analysis. All adjuvant treatments were planned based on the patients' disease stage and willingness to abide to treatment, and the regimen prescribed was based on the treating oncologist's discretion. Finally, 477 patients were included in this study (**Additional File 1: Figure S1**).

Local recurrence was defined as tumor relapse in the operative field following R0 resection according to follow-up radiographic evidence, physical exam, or self-reported symptoms. Among the 477 patients, 190 patients were diagnosed with local recurrence as their first recurrent event, which was then histologically confirmed. Most of the patients with local recurrences underwent secondary resection, except for a small percentage of patients who received chemotherapy (n = 6) or radiotherapy (n = 1) only. The 190 patients were then classified into two groups according to their TLR, which was calculated from the date of R0 resection to the date of initial local recurrence. Patients who were diagnosed with TLR within 12 months (n = 99) were grouped into an early local recurrence (ELR) group while those diagnosed with TLR no less than 12 months (n = 91) were included in a late local recurrence (LLR) group. As there is no standard definition for early and late local recurrence, the 12 months cutoff value was determined based on published literatures (8, 9).

This study was approved by the institutional review board of SYSUCC (No. B2020-008-01), and the ethics committee waived the need for informed consent as this was retrospective study. All patients' data used was anonymously analyzed.

Data Collection

Clinical and pathological data of the included patients were retrospectively obtained from the patient's medical records. Tumor stage was classified using the AJCC 8th Edition (10), and the tumors were graded according to the Fédération Française des Centres de Lutte Contre le Cancer (FNCLCC) grading system (11).

The authenticity of this article was validated by uploading the key raw data to the Research Data Deposit public platform (www.researchdata.org.cn) with the approval RDD number of RDDA2019001332.

Follow-Up

All patients were routinely followed with physical examination, computerized tomography or magnetic resonance imaging every 3 to 6 months for the first 2 years after resection, then annually *via* outpatient visits or telephone interviews by the independent follow-up department of SYSUCC. The minimum follow-up time was 6 months. The final survival follow-up time was considered the latest follow-up date of this study (October 1, 2019) or death. OS was defined as the time between the R0 resection and death of any cause or the last follow-up. SAR was defined as the time from the date of diagnosis of local recurrence to the last follow-up date or the date of death.

Statistical Analysis

The chi-square test of independence was used to test the distributive correlations between the clinicopathological variables and local recurrence. Survival curves were analysed by Kaplan-Meier method, and differences between survival rates were compared by using the log-rank test (12). The Cox proportional hazard model with the stepwise forward selection algorithm was used to find out independent prognostic variables associated with LR, OS, and SAR, and the results are presented as hazard ratios (HR) and 95% confidence intervals (95% CI). Two-sided *P* values < 0.05 were considered statistically significant. All data were analyzed using the IBM SPSS software, version 20.0 (SPSS, Inc., and IBM Company, Armonk, New York).

RESULTS

Baseline Patient Characteristics

The patients' baseline characteristics are shown in **Table 1**. The median age of the 477 patients was 42 years (range: 6–85 years). There were 284 male patients and 193 female patients in a ratio of 1.47:1. Fibrosarcoma (137, 28.7%) and undifferentiated pleomorphic sarcoma (104, 21.8%) were the most common pathological types. G1 tumors were identified in 135 (28.3%) patients, G2 in 226 (47.4%) patients, and G3 in 72 (15.1%) patients. Most patients had stage II disease (177, 37.1%). In addition, 135 (28.3%) patients had stage I disease and 121 (25.4%) had stage III disease. Due to the lack of understanding of the disease and standard treatment, only a small percentage of the STS patients received postoperative therapy, including chemotherapy (28, 5.9%), radiotherapy (67,14.0%) and chemoradiotherapy (19, 4.0%), spanning a period of 21 years. By comparisons, patients with deep tumor depth, G2-G3 tumor grade and II-III AJCC stage are more likely to receive adjuvant therapy (all P < 0.001).

Local Recurrence Rate and Influencing Factors

Over a median follow-up time of 118.4 months (range 9.6–368.8 months), 73 (15.3%) patients died, and 190 (39.8%) experienced local recurrence. Fifty-four (28.4%) of the 190 patients with local recurrence developed distant metastasis. A total of 46 patients had grade 3 sarcomas, 105 had grade 2, and 39 had grade 1. In 61 patients the depth of the tumor was superficial and in 129 it was deep. The recurrence rates observed in patients classified as stage I, II, and III were 29.6% (40/135), 44.1% (78/177), and 59.5% (72/121), respectively. However, there were no differences in the

TABLE 1 | >Baseline characteristics of the entire study cohort (n = 477).

Characteristics	Cases	Percentage (%)
Sex	477	
Male	284	59.5
Female	193	40.5
Age at operation (years)		
<50	300	62.9
≥50	177	37.1
Body mass index (kg/m^2)		
<18.5	53	11.1
≥18.5 to <25.0	299	62.7
≥25.0	125	26.2
Pathological types		
Fibrosarcoma	137	28.7
Liposarcoma	65	13.6
Undifferentiated pleomorphic sarcoma/MFH	104	21.8
Leiomyosarcoma	12	2.5
Synovial sarcoma	63	13.2
Rhabdomyosarcoma	19	4.0
Alveolar soft part sarcoma	6	1.3
Angiosarcoma	6	1.3
Malignant peripheral nerve sheath tumor	31	6.5
Mesenchymal chondrosarcoma	14	2.9
Others	20	4.2
Tumor size (cm)		
<5	262	54.9
≥5	215	45.1
Tumor site		
Upper extremity	117	24.5
Lower extremity	182	38.2
Thoracic/trunk/abdominal wall	178	37.3
Tumor depth		
Superficial	211	44.2
Deep	266	55.8
Tumor grade		
G1	135	28.3
G2	226	47.4
G3	72	15.1
Missing	44	9.2
AJCC stage		
IA	91	19.1
IB	44	9.2
II	177	37.1
IIIA	91	19.1
IIIB	30	6.3
Missing	44	9.2
End-point		
Alive	404	84.7
Dead	73	15.3
Local Recurrence		
Yes	190	39.8
No	287	60.2
Metastasis after recurrence		
Yes	54	11.3
No	423	88.7
Adjuvant therapy		
None	363	76.1
Chemotherapy	28	5.9
Radiotherapy	67	14
Combined chemoradiotherapy	19	4
Therapy after recurrence		
None	7	3.7
Surgery alone	108	56.8
Chemotherapy alone	6	3.2
Radiotherapy alone	1	0.5

(Continued)

TABLE 1 | Continued

Characteristics	Cases	Percentage (%)
Surgery + Chemotherapy	23	12.1
Surgery + Radiotherapy	24	12.6
Surgery + chemoradiotherapy	17	8.9
Combined chemoradiotherapy	3	1.6
Radiofrequency	1	0.5

incidence of local recurrence between the patients with or without postoperative treatments (P = 0.096), and this might be on account of the small sample. Histological subtype (e.g., fibrosarcoma, undifferentiated pleomorphic sarcoma, liposarcoma and synovial sarcoma) did not affect the local recurrence in this study. Furthermore, the 5- and 10-year OS rates of patients who did not develop local recurrence were significantly higher than those who developed local recurrence (97.9% vs. 75.7%; 96.6% vs. 63.4%; p < 0.001; **Figure 1A**). Deep tumor location (deep vs. superficial: HR 1.73, 95% CI 1.27–2.37, P = 0.001) and tumor grade ≥ 2 (G2 vs. G1: HR 1.75, 95% CI 1.21–2.53, G3 vs. G1: HR 2.57, 95% CI 1.66–3.98, P < 0.001) were significantly associated with a higher rate of local recurrence (**Table 2**).

Association Between TLR and Survival

The median TLR was 10.8 months (range 1.4–190.7 months). Patients in the ELR group had a shorter median OS time and lower 5-year OS rate than those in the LLR group (P = 0.008; 64.4% vs. 87.9%, P < 0.001; **Figure 1B**). Patients with LLR had a longer SAR than patients with ELR (P = 0.036; **Figure 1C**).

To determine the factors affecting the prognosis of ELR and LLR patients, the prognostic relevance of TLR and the patients' clinicopathological parameters were analyzed using the Cox proportional hazards model (**Figure 2**). Our results demonstrated that LLR patients had better OS than ELR patients in both gender (male, female), the presence of metastasis, and the performance of surgery after local recurrence. Furthermore, there were significant differences in OS between the two groups for patients with tumor grade ≥ 2 (G2: HR 2.21, 95% CI 1.02–4.79, P = 0.044; G3: HR 2.14, 95% CI 1.01–4.54, P = 0.047), with stage III disease (HR 2.99, 95% CI 1.40–6.38, P = 0.005), and without adjuvant therapy after initial R0 surgery (HR 3.01, 95% CI 1.55-5.84, P = 0.001) (**Figure 2A**).

In addition, there were no statistically significant differences in SAR between the two groups regardless of sex, tumor depth, tumor grade, AJCC stage, and adjuvant therapies. However, it was worth noting that patients without metastases (HR 3.01, 95% CI 1.06–8.56, P = 0.039) or with surgery (HR 1.77, 95% CI 1.00–3.14, P = 0.015) after local recurrence in the LLR group exhibited a better SAR than those in the ELR group (**Figure 2B**).

Multivariate analyses revealed that TLR and tumor grade were independent prognostic factors for both OS (P = 0.014, P < 0.001) and SAR (P = 0.006, P = 0.022). Moreover, for the 190 patients with local recurrence, non-surgical treatment and metastases after recurrence were negative prognostic factors for SAR, with HRs of 1.94 (95% CI 1.06–3.57, P = 0.033) and 0.12 (95% CI 0.07–0.23, P < 0.001), respectively (**Tables 3** and **4**).

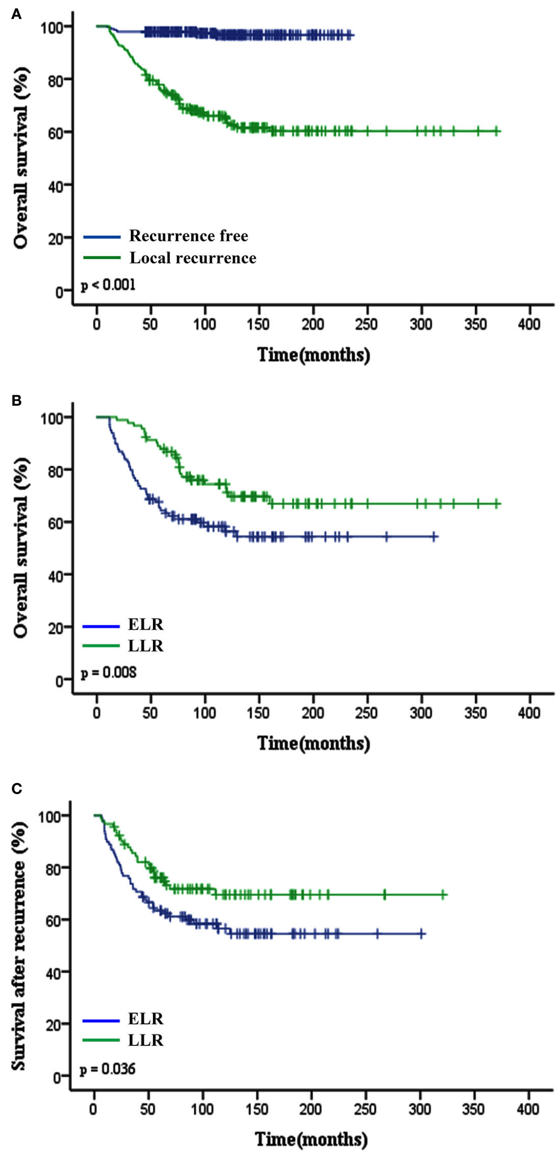


FIGURE 1 | Impact of local recurrence and TLR (ELR vs. LLR) on clinical outcomes of patients with STS of extremity and abdominothoracic wall. **(A)** Overall survival in recurrent free and local recurrent patients (p < 0.001). **(B)** Overall survival (p = 0.008) and **(C)** Survival after recurrence (p = 0.036) curves showed that patients in the ELR group had a worse prognosis than those in the LLR group. TLR, time to local recurrence; ELR, early local recurrence (<12 months after primary surgery); LLR, late local recurrence (≥12 months after primary surgery).

DISCUSSION

Local recurrence is a common reason for treatment failure after R0 surgery in STS (13). To assess the effects of local recurrence and other clinicopathological factors on survival, especially TLR, in patients with STS of the extremity and abdominothoracic wall, we performed a retrospective study based on data from 477 patients from the SYSUCC. This study is—to our best

TABLE 2 | Univariate and multivariate analyses of variables for local recurrence in STS patients.

Variables	LR Univariate analysis		LR Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Sex		0.416		
Male	1 (referent)			
Female	0.89 (0.66–1.19)			
Age (years)		0.048		
<50	1 (referent)			
≥50	1.34 (1.00–1.79)			
Tumor size (cm)		0.007		
<5	1 (referent)			
≥5	1.48 (1.12–1.97)			
Tumor depth		<0.001		0.001
Superficial	1 (referent)		1 (referent)	
Deep	1.95 (1.43–2.64)		1.73 (1.27–2.37)	
Tumor Grade		<0.001		<0.001
G1	1 (referent)		1 (referent)	
G2	1.88 (1.30–2.72)		1.75 (1.21–2.53)	
G3	3.08 (2.01–4.73)		2.57 (1.66–3.98)	
AJCC stage		<0.001		
IA + IB	1 (referent)			
II	1.69 (1.15–2.47)			
IIIA + IIIB	1.79 (1.83–3.97)			
Adjuvant therapy		0.111		
Yes	1 (referent)			
No	0.77 (0.56–1.06)			

LR, local recurrence; HR, hazard ratio; CI, confidence interval.

knowledge—the largest study to analyze the association between the TLR and survival in patients with STS.

In this study, a high local recurrence rate was found in STS (n = 190, 39.8%), which was slightly above other relevant literatures (14–16). There can be several reasons for this. First, although the tumor treatment condition has been improved in the past years in China, patients usually come to the hospital in a comparatively later stage or when their symptoms have been aggravated. Most of the patients included in this study had advanced tumor grade (G2-G3) or stage (II-III) with deep location at the time of initial diagnosis. And also, the percentage (only 23.9%) of patients who received postoperative adjuvant treatment was low due to clinical, financial, or personal reasons. Second, all of the patients included in this study had received the R0 resection, but the distance between the tumor and the surgical margins was not clear completely owing to the long retrospective span. As we all know that those patients who presented with a surgical margin of 2 mm or less might have a worse survival and a higher local recurrence rate (9). Moreover, this article involved a cohort of patients with long follow-up time (some for more than 15 years), based on which the risk for local recurrence was observed to increase accordingly.

Tumor recurrence is a well-known factor for poor prognosis of STS. Zhao et al. (17) and Eilber et al. (18) reported respectively in 133 and 753 STS patients groups that there was a lower 5-year OS rate in the local recurrence group than in the no local recurrence group. Posch et al. (19) observed that patients with local recurrence were more likely to develop distant metastasis (HR = 8.4; 95% CI, 4.3–16.5; P < 0.001). Another study demonstrated that 17% of patients with extremity STS after R1 resection died of local recurrence without any distant metastasis (20). All of these studies illustrated that local recurrence had a negative effect on the survival of patients with STS, which was in accordance with our study findings.

Some investigators reported that prognostic factors such as surgical margin and location played an important role in local control and were associated with the local recurrence in STS (15, 21, 22). In addition, high tumor grade, larger tumor size, and deep tumor location were also considered as predictors of local recurrence in STS (17, 19, 23, 24). Consistent with other studies (20), tumor depth and tumor grade were identified as significant prognostic factors affecting local recurrence by multivariate analysis in our study. Since early diagnosis of STS recurrence is important to offer the patient a realistic second treatment chance, an adequate identification of patients at higher risk, those with a deep tumor location and higher tumor grade, can promote the development of individualized surveillance programs. These patients may require more extensive resection and closer postoperative follow-up, and may be considered for additional preoperative therapy or more intense adjuvant chemotherapy to reduce the risk of recurrence. However, AJCC stage were not independent predictors of local recurrence, OS and SAR in our analysis, which is similar to a previous large-scale study (25). This could be due to the staging defects of human subjectivity and the heterogeneity of STS. The 8th AJCC stage system illustrated an unprecedented change for risk stratification by redefining the T-stage categories (26), which disregarding the independent prognostic information provided by tumor depth. Superficial tumors are associated with better outcomes than deep ones, even after controlling for tumor size and histologic grade (27, 28). Our data suggest that the system still needs further investigation to improve risk stratification.

TLR as a predictior for survival in patients with various cancers has been researched with divergent results. Several studies have suggested that TLR is a prognostic factor for survival in primary breast sarcoma, renal cell carcinoma and gastric cancer (4, 6, 29), while others have not found TLR of significant importance (8, 30). Sugiura et al. found the survival rate was lower in STS patients with local recurrence developing within 2 years than after 2 years (46% vs. 83%, P = 0.01) (31). Our study confirmed that TLR in patients with STS of the extremity and abdominothoracic wall was associated with survival and was considered an independent prognostic factor for OS and SAR, and patients with ELR (TLR within 12 months) indicated worse prognosis compared with those with LLR (TLR no less than 12 months). In addition, our research included 54 patients who developed distant metastasis after the local recurrence. We found that patients without metastases after local recurrence in the LLR group also exhibited a better SAR than those in the ELR group, but there was no difference in patients with distant metastases between two groups. The study from Posch (19) demonstrated that patients who suffered a local recurrence were more likely to develop distant matastasis and patients with distant metastasis after a long tumor-free interval did not show a better survival prognosis compared to those with

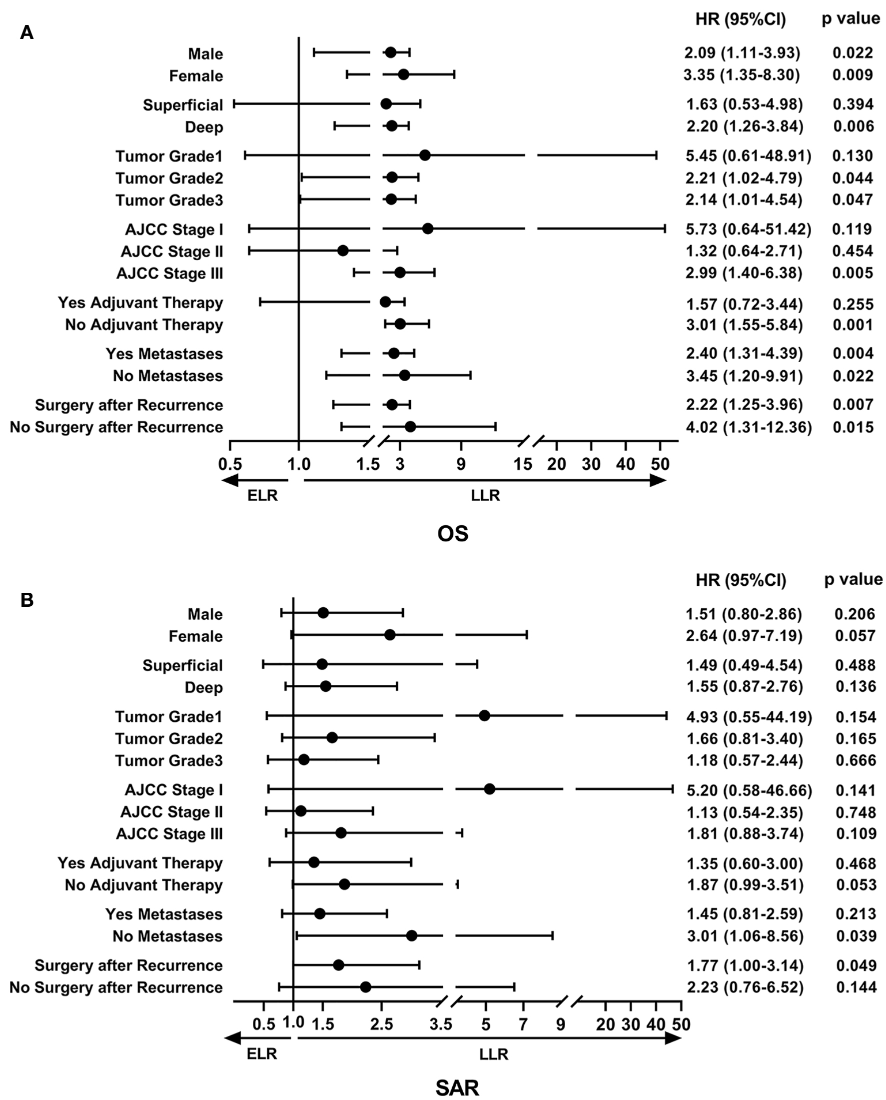


FIGURE 2 | The forest plot of prognostic relevance of TLR and relevant clinicopathological parameters using the Cox proportional hazards model. **(A)** Overall survival curve showed that there were significant differences between the ELR and LLR groups for patients with tumor grade ≥ 2, stage III disease and without adjuvant therapy after initial R0 surgery. **(B)** Survival after recurrence curve showed that patients without metastases or with surgery after local recurrence in the LLR group exhibited a better SAR than those in the ELR group. OS, overall survival; SAR, survival after recurrence; ELR, early local recurrence (<12 months after primary surgery); LLR, late local recurrence (≥12 months after primary surgery); HR, hazard ratio; CI, confidence interval.

distant metastasis occurring early after primary surgery, which had similar views with our research.

Moreover, though there is no concrete proof, it is generally accepted that STS patients with local recurrence need another resection with a goal of negative margins. A previous study reported that local recurrence in retroperitoneal STS patients was amenable to surgery, which could improve survival (32). Our results confirmed that operation after recurrence was also strongly associated with better SAR in STS of the extremity and abdominothoracic wall, indicating that salvage surgery may still be the preferred treatment when there are surgical indications after recurrence. This observation supports the mainstream view nowadays.

There were some limitations of the analyses in this study that should be noted. First, this was a retrospective study which could have inherent sources of transfer bias (i.e., loss to follow-up) and selection bias (i.e., clinical decision based on economic condition by patients), and we enrolled consecutive patients to reduce the influence of possible selection bias. Second, all patients enrolled in this study were selected from one hospital, the SYSUCC and therefore, the investigated patients' characteristics and the study results may not be generalizable to other populations. Our

TABLE 3 | Univariate and multivariate analyses of variables for overall survival in STS patients.

Variables	OS Univariate analysis		OS Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Sex		0.531		
Male	1 (referent)			
Female	1.16 (0.74–1.82)			
Age (years)		0.534		
<50	1 (referent)			
≥50	1.16 (0.73–1.83)			
Tumor size (cm)		0.002		
<5	1 (referent)			
≥5	2.05 (1.29–3.26)			
Tumor depth		<0.001		
Superficial	1 (referent)			
Deep	2.80 (1.65–4.76)			
Tumor Grade		<0.001		<0.001
G1	1 (referent)		1 (referent)	
G2	5.20 (2.02–13.38)		2.98 (1.17-7.67)	
G3	8.95 (3.51–22.82)		9.04 (3.50-23.34)	
AJCC stage		<0.001		
IA + IB	1 (referent)			
II	4.33 (1.70–11.06)			
IIIA + IIIB	16.79 (6.53–43.15)			
Recurrence		<0.001[a] 0.009[b]		<0.001[a] 0.014[b]
Free	1 (referent)		1 (referent)	
LLR	9.96 (4.47–21.79)		13.03 (4.53–37.48)	
ELR	18.67 (8.76–39.78)[a] 1.92 (1.18–3.13)[b]		23.90 (8.53–67.00)[a] 1.85 (1.13-3.02)[b]	
Adjuvant therapy		0.039		
Yes	1 (referent)			
No	0.61 (0.38–0.98)			

[a]Recurrence-free group as the referent;
[b]Late local recurrence group as the referent.
OS, overall survival; HR, hazard ratio; CI, confidence interval; LLR, late local recurrence; ELR, early local recurrence.

TABLE 4 | Univariate and multivariate analyses of variables for SAR in STS patients.

Variables	SAR Univariate analysis		SAR Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Sex		0.400		
Male	1 (referent)			
Female	1.23 (0.76–2.00)			
Tumor depth		0.006		
Superficial	1 (referent)			
Deep	2.34 (1.28–4.30)			
Tumor Grade		<0.001		0.006
G1	1 (referent)		1 (referent)	
G2	2.58 (1.01–6.63)		0.97 (0.35–2.72)	
G3	8.55 (3.31–22.08)		2.26 (0.77–6.58)	
AJCC stage		0.006		
IA + IB	1 (referent)			
II	3.54 (1.37–9.15)			
IIIA + IIIB	4.60 (1.80–11.80)			
TLR		0.038		0.022
LLR	1 (referent)		1 (referent)	
ELR	1.69 (1.03–2.77)		1.79 (1.09–2.95)	
Adjuvant therapy		0.032		
Yes	1 (referent)			
No	1.72 (1.05–2.82)			
Metastasis after recurrence		<0.001		<0.001
Yes	1 (referent)		1 (referent)	
No	0.09 (0.05–0.15)		0.12 (0.07–0.23)	
Therapy after recurrence		<0.001		0.033
Surgery	1 (referent)		1 (referent)	
No surgery	5.06 (2.87–8.93)		1.94 (1.06–3.57)	

SAR, survival after recurrence; HR, hazard ratio; CI, confidence interval; LLR, late local recurrence; ELR, early local recurrence.

conclusions should be verified in a larger population of STS patients from multiple centers. In addition, the clinicopathological data of some patients, such as data on AJCC stage in 44 patients, and the details of adjuvant therapy, were incomplete owing to the huge spans of time, thus we were unable to provide more information about the effects of the chemotherapy and/or radiotherapy. It seems reasonable that tumors with different subtypes may exhibit different clinical behaviors and altered survivals, and this is a topic that requires further investigation to figure out the relationship between the histologic subtypes and local recurrence.

Despite these limitations, this is the largest study based on a heterogeneous group of patients to demonstrate the prognostic values of TLR in STS of the extremity and abdominothoracic wall, the conclusions postulated remain highly reasonable.

CONCLUSION

Our results showed that local recurrence was significantly associated with a decreased OS in patients with STS of the extremity and abdominothoracic wall, and those with deeply located initial tumor or a higher tumor grade were more likely to experience local recurrence than their counterparts. Surgery after local recurrence could prolong the OS and SAR of the patients as compared to other treatments. Furthermore, ELR after R0 resection indicated a worse prognosis than those with LLR, and TLR can be considered an independent prognostic factor for OS and SAR. If substantiated in a larger, multicenter study, the observations from this pilot study might provide the rationale to develop individualized surveillance programs for the patients at higher risk, providing an earlier diagnosis and better second treatment chance in the case of a recurrence.

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 of Sun Yat-sen University Cancer Center. 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

YL, TG, and DH collected the patients' data. YL and TG did the data analysis. All authors designed the study, and YL, TG, and DH finished the original manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by grants from the National Natural Science Foundation of China (no. 81902736).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.599097/full#supplementary-material

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA: A Cancer J Clin* (2018) 68(1):7–30. doi: 10.3322/caac.21442
2. Kraybill WG, Harris J, Spiro IJ, Ettinger DS, DeLaney TF, Blum RH, et al. Long-term results of a phase 2 study of neoadjuvant chemotherapy and radiotherapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. *Cancer* (2010) 116(19):4613–21. doi: 10.1002/cncr.25350
3. Chowdhary M, Chowdhary A, Sen N, Zaorsky NG, Patel KR, Wang D. Does the addition of chemotherapy to neoadjuvant radiotherapy impact survival in high-risk extremity/trunk soft-tissue sarcoma? *Cancer* (2019) 125(21):3801–9. doi: 10.1002/cncr.32386
4. Hu Q-C, Mei X, Feng Y, Ma J-L, Yang Z-Z, Shao Z-M, et al. Early Local Recurrence Presents Adverse Effect on Outcomes of Primary Breast Sarcoma. *Medicine* (2016) 95(1):e2422. doi: 10.1097/md.0000000000002422
5. Rieken M, Kluth LA, Fajkovic H, Capitanio U, Briganti A, Krabbe LM, et al. Predictors of Cancer-specific Survival After Disease Recurrence in Patients With Renal Cell Carcinoma: The Effect of Time to Recurrence. *Clin Genitourin Cancer* (2018) 16(4):e903–e8. doi: 10.1016/j.clgc.2018.03.003
6. Li H, Jin X, Liu P, Hong W. Time to local recurrence as a predictor of survival in unrecetable gastric cancer patients after radical gastrectomy. *Oncotarget* (2017) 8(51):89203–13. doi: 10.18632/oncotarget.19038
7. Wittekind C, Compton CC, Greene FL, Sobin LH. TNM residual tumor classification revisited. *Cancer* (2002) 94(9):2511–6. doi: 10.1002/cncr.10492.abs
8. Westberg K, Palmer G, Johansson H, Holm T, Martling A. Time to local recurrence as a prognostic factor in patients with rectal cancer. *Eur J Surg Oncol* (2015) 41(5):659–66. doi: 10.1016/j.ejso.2015.01.035
9. Novais EN, Demiralp B, Alderete J, Larson MC, Rose PS, Sim FH. Do surgical margin and local recurrence influence survival in soft tissue sarcomas? *Clin Orthop Relat Res* (2010) 468(11):3003–11. doi: 10.1007/s11999-010-1471-9
10. Cates JMM. AJCC eighth edition for soft tissue sarcoma of the extremities and trunk. *Ann Oncol Off J Eur Soc Med Oncol* (2018) 29(9):2023. doi: 10.1093/annonc/mdy247
11. Neuville A, Chibon F, Coindre JM. Grading of soft tissue sarcomas: from histological to molecular assessment. *Pathology* (2014) 46(2):113–20. doi: 10.1097/PAT.0000000000000048
12. In J, Lee DK. Survival analysis: Part I - analysis of time-to-event. *Korean J Anesthesiol* (2018) 71(3):182–91. doi: 10.4097/kja.d.18.00067
13. Daigeler A, Zmarsly I, Hirsch T, Goertz O, Steinau HU, Lehnhardt M, et al. Long-term outcome after local recurrence of soft tissue sarcoma: a retrospective analysis of factors predictive of survival in 135 patients with locally recurrent soft tissue sarcoma. *Brit J Cancer* (2014) 110(6):1456–64. doi: 10.1038/bjc.2014.21
14. Zaidi MY, Cardona K. Post-operative surveillance in soft tissue sarcoma: using tumorspecific recurrence patterns to direct approach. *Chin Clin Oncol* (2018) 7(4):45. doi: 10.21037/cco.2018.08
15. Gundle KR, Kafchinski L, Gupta S, Griffin AM, Dickson BC, Chung PW, et al. Analysis of Margin Classification Systems for Assessing the Risk of Local Recurrence After Soft Tissue Sarcoma Resection. *J Clin Oncol Off J Am Soc Clin Oncol* (2018) 36(7):704–9. doi: 10.1200/jco.2017.74.6941
16. Ezuddin NS, Pretell-Mazzini J, Yechieli RL, Kerr DA, Wilky BA, Subhawong TK. Local recurrence of soft-tissue sarcoma: issues in imaging surveillance strategy. *Skeletal Radiol* (2018) 47(12):1595–606. doi: 10.1007/s00256-018-2965-x
17. Zhao R, Yu X, Feng Y, Yang Z, Chen X, Wand J, et al. Local recurrence is correlated with decreased overall survival in patients with intermediate high-grade localized primary soft tissue sarcoma of extremity and abdominothoracic wall. *Asia-Pacific J Clin Oncol* (2018) 14(2):e109–e15. doi: 10.1111/ajco.12807
18. Eilber FC, Rosen G, Nelson SD, Selch M, Dorey F, Eckardt J, et al. High-grade extremity soft tissue sarcomas: factors predictive of local recurrence and its effect on morbidity and mortality. *Ann Surg* (2003) 237(2):218–26. doi: 10.1097/01.SLA.0000048448.56448.70
19. Posch F, Leitner L, Bergovec M, Bezan A, Stotz M, Gerger A, et al. Can Multistate Modeling of Local Recurrence, Distant Metastasis, and Death Improve the Prediction of Outcome in Patients With Soft Tissue Sarcomas? *Clin Orthop Relat Res* (2017) 475(5):1427–35. doi: 10.1007/s11999-017-5232-x
20. Gronchi A, Lo Vullo S, Colombo C, Collini P, Stacchiotti S, Mariani L, et al. Extremity soft tissue sarcoma in a series of patients treated at a single institution: local control directly impacts survival. *Ann Surg* (2010) 251 (3):506–11. doi: 10.1097/SLA.0b013e3181cf87fa
21. Fujiwara T, Stevenson J, Parry M, Tsuda Y, Tsoi K, Jeys L. What is an adequate margin for infiltrative soft-tissue sarcomas? *Eur J Surg Oncol* (2020) 46 (2):277–81. doi: 10.1016/j.ejso.2019.10.005
22. Milovancev M, Tuohy JL, Townsend KL, Irvin VL. Influence of surgical margin completeness on risk of local tumour recurrence in canine cutaneous and subcutaneous soft tissue sarcoma: A systematic review and meta-analysis. *Vet Comp Oncol* (2019) 17(3):354–64. doi: 10.1111/vco.12479
23. Sugiura H, Nishida Y, Nakashima H, Yamada Y, Tsukushi S, Yamada K. Surgical procedures and prognostic factors for local recurrence of soft tissue sarcomas. *J Orthop Sci* (2014) 19(1):141–9. doi: 10.1007/s00776-013-0469-z
24. Maretty-Nielsen K, Aggerholm-Pedersen N, Safwat A, Jorgensen PH, Hansen BH, Baerentzen S, et al. Prognostic factors for local recurrence and mortality in adult soft tissue sarcoma of the extremities and trunk wall: a cohort study of 922 consecutive patients. *Acta Orthop* (2014) 85(3):323–32. doi: 10.3109/17453674.2014.908341
25. Cates JMM. AJCC eight edition for soft tissue sarcoma of the Extremities or Trunk: A Cohort Study of the SEER Database. *J Natl Compr Cancer Netw JNCCN* (2018) 16(2):144–52. doi: 10.6004/jnccn.2017.7042
26. Cates JMM. AJCC 8th edition for soft tissue sarcoma of the extremities and trunk. *Ann Oncol* (2018) 29(9):2023. doi: 10.1093/annonc/mdy/247
27. Brennan M, Antonescu C, Moraco N, Singer S. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. *Ann Surg* (2014) 260:416–22. doi: 10.1097/SLA.0000000000000869
28. Maki R, Moraco N, Antonescu C. Toward better soft tissue sarcoma staging: building on American Joint Committee on Cancer staging systems versions 6 and 7. *Ann Surg Oncol* (2013) 20:3377–83. doi: 10.1245/s10434-013-3052-0
29. Brookman-May SD, May M, Shariat SF, Novara G, Zigeuner R, Cindolo L, et al. Time to recurrence is a significant predictor of cancer-specific survival after recurrence in patients with recurrent renal cell carcinoma–results from a comprehensive multi-centre database (CORONA/SATURN-Project). *BJU Int* (2013) 112(7):909–16. doi: 10.1111/bju.12246

30. Robbins JR, Yechieli R, Laser B, Mahan M, Rasool N, Elshaikh MA. Is time to recurrence after hysterectomy predictive of survival in patients with early stage endometrial carcinoma? *Gynecol Oncol* (2012) 127(1):38–42. doi: 10.1016/j.ygyno.2012.06.042
31. Sugiura H, Tsukushi S, Yoshida M, Nishida Y. What Is the Success of Repeat Surgical Treatment of a Local Recurrence After Initial Wide Resection of Soft Tissue Sarcomas? *Clin Orthop Relat Res* (2018) 476(9):1791–800. doi: 10.1007/s11999.0000000000000158
32. Lochan R, French JJ, Manas DM. Surgery for retroperitoneal soft tissue sarcomas: aggressive re-resection of recurrent disease is possible. *Ann R Coll Surg Engl* (2011) 93(1):39–43. doi: 10.1308/003588410x12771863936729

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.