REAL-WORLD SURGICAL TREATMENT OF THORACIC CANCER IN THE ERA OF PRECISION MEDICINE

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REAL-WORLD SURGICAL TREATMENT OF THORACIC CANCER IN THE ERA OF PRECISION MEDICINE

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Editorial: Real-world surgical treatment of thoracic cancer in the era of precision medicine

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KEYWORDS

thoracic cancer, surgery, real-world evidence, evidence-based medicine, prognosis

Editorial on the Research Topic
Real-world surgical treatment of thoracic cancer in the era of precision medicine

Surgical resection has been the first choice for treatment of early-stage thoracic cancer, mainly including lung and esophageal malignancies. Nowadays, the advent of the era of precision medicine, has highlighted the significant roles of evidence-based practice, not only applicable for surgical procedures, but also for perioperative management (1). In this section of "Frontiers in Surgery", several studies were included which might facilitate the perfection of real-world surgical treatment.

Conventionally, lobectomy and systematic lymphadenectomy is the standard of care for the management of early-stage non-small cell lung cancer (NSCLC) (2, 3). However, numerous factors might exert impacts on the prognosis of patients with stage IA NSCLC receiving lobectomy, such as tumor pathological type and extent of lymph node dissection. Previously, Long et al. (2021) proposed that the order of vascular processing in lobectomy might become a prognostic factor that should not be ignored. More specifically, although there was no significant difference in recurrence rate between the vein-first group and the artery-first group, the vein-first group had better overall survival (OS) and disease-free survival (DFS), especially in the squamous cell carcinoma (LUSC) subgroup and the stage I-II subgroup. Similarly, in the study by Wei et al. (4), the vein-first group exhibited significantly better outcomes than the artery-first group for 5-year OS (73.6% vs 57.6%; $P = 0.002$), DFS (63.6% vs 48.4%; $P = 0.001$), and lung cancer-specific survival (LCSS) (76.4% vs 59.9%; $P = 0.002$). In the context of pulmonary function reserved as an important indicator, sublobar resection, including segmentectomy and wedge resection, has captured increasing attention in recent years which has shown non-inferiority to lobectomy for patients with stage T1a-bN0M0 NSCLC (5, 6). In our section, Hao et al. (2021) suggested that tumor size should be taken as a critical factor for surgical decision-making. In their study, segmentectomy was associated with better OS in patients with NSCLC ≥10 mm and ≤20 mm than wedge resection. Nonetheless, segmentectomy did not exhibit advantages in survival compared with

wedge resection in patients with NSCLC ≤10 mm. In addition, it was observed that small-sized (≤20 mm) LUSC was associated with worse OS but not LCSS compared with lung adenocarcinoma. In other word, their findings indicated that surgical procedures and intraoperative manipulation should be personalized based on histology and tumor size.

For patients on whom intentional lobectomy are performed, video-assisted thoracic surgery (VATS) and robotic-assisted surgery (RAS) are two prevalent surgical approaches which are increasingly being paid attention to by virtue of the advantages of perioperative recovery (7). Gallina et al. (2021) pointed out that compared with open surgery, VATS and RAS could effectively reduce the incidence of postoperative complications, while the lymph nodes could be effectively dissected as well. They also found that the percentage of mediastinal lymph node metastasis and the number of lymph nodes dissected in the RAS group were significantly higher than those in the VATS group. More interestingly, the ratio of the number of dissected lymph nodes to the number of metastatic lymph nodes was significantly lower in the VATS group and thoracotomy group compared with the RAS group. The limitation of surgical field and operation space of VATS might account for such a phenomenon. Notably, the aforementioned limitations of VATS did not convert to survival disadvantages, while RAS might bring additional financial burdens to patients (8). In a word, although RAS have been more and more popular and exhibiting advantages in intraoperative manipulation and postoperative recovery, VATS has remained irreplaceable in chest surgery nowadays. More studies should be launched to investigate the pros and cons of RAS.

With accumulating evidences, the advantages of VATS are not only reflected in improving survival expectations of tumor patients (9), but also in having a favorable impact on the postoperative recovery of patients. In our section, Aeschbacher et al. (2021) reported that blood loss >100 ml ($P = 0.029$, HR 2.70) and open surgery ($P = 0.032$, HR 2.37) are independent risk factors for surgical site infections (SSI). SSI occurred much more frequently in open surgery than in VATS approach, and SSI was positively associated with significantly longer hospital stay (10). Undeniably, thoracotomy is currently preferred in the case of intraoperative complications or emergent events with extremely low probabilities, including major vascular injury, calcified lymph nodes around the hilum and dense adhesions. In other word, the studies in our section consistently highlighted the predominant role of VATS in lung cancer surgery.

Hitherto, the treatment of advanced-stage NSCLC patients with distant metastasis has been complex and highly personalized. Previous studies have indicated that systemic chemotherapy or targeted therapy instead of surgery should be recommended for NSCLC patients with malignant pleural dissemination (PD) (11). Sawabata et al. (12) even suggested that tumor resection brought no obvious benefit to postoperative survival of patients who have developed PD. However, Fan et al. (2021) observed that patients who underwent surgical resection of primary tumors had longer progression-free survival (PFS) (19.0 vs. 10.0 months, $P < 0.0001$) and OS (48.0 vs. 33.0 months, $P < 0.0001$) than patients who underwent pleural biopsy alone, suggesting that NSCLC patients with pleural metastasis could still benefit from surgical resection of primary tumors. In addition, postoperative targeted therapy and tumor <3 cm were also favorable prognostic factors, and the survival rate of patients receiving targeted therapy was significantly higher than those without (13). In a large cohort analysis of lung cancer patients with brain metastases, He et al. (2021) proposed that patients who received brain therapy before surgery for primary lung tumors might have a better prognosis, irrespective of the treatment modality on the metastasis site. Furthermore, patients who received brain surgery plus radiotherapy followed by primary lung tumor resection had the best survival expectation. The aforementioned studies indeed shed light on the potential therapeutic scheme of NSCLC patients with M1 disease.

In addition, our section also included some reports on surgical techniques Chen et al. (2021). For instance, reconstruction of the right gastroepiploic vessel may solve the awkward situation of injury of the right gastroepiploic artery and vein during the esophagectomy. Chen et al. (2021) highlighted two key technical points as key resolutions: (1) Immediate reconstruction of the right gastroepiploic artery (RGEA) and right gastroepiploic vein (RGEV) and long-term maintenance of the blood flow effectively; (2) Effective tension reduction of gastric conduit anastomosis and vascular anastomosis.

In a word, this section is intended to be the beginning of a small step towards precision medicine in the field of thoracic cancer, which needs further real-world evidences as stepping stones.

Author contributions

YC: concept and review GW: draft the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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High Expression of Tumor Abnormal Protein Preoperatively Predicts Poor Prognosis of Patients With Esophageal Squamous Cell Carcinoma

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Background: Esophageal squamous cell carcinoma (ESCC) acts as a fatal malignant tumor among human beings and is marked by late-stage diagnosis, frequent recurrence, metastasis, and therapy resistance. Tumor abnormal protein (TAP) remarkably affects cancer development and progression of human cancers. TAP has been shown to be a biomarker for gastric and lung cancer progression. Nevertheless, the clinical value exhibited by TAP for ESCC has not been well-explained in the current literature.

Methods: The present study included 183 ESCC cases who received surgical resection and 183 cases who had normal physical checkup from March 2013 to January 2015 at the People's Hospital of Chizhou, and used the TAP detection agent for evaluating the TAP relative level.

Results: As found, ESCC patients presented an obviously higher TAP expression relative to cases who had normal physical checkup. Moreover, TAP expression was significantly downregulated after surgery. Furthermore, the TAP expression was correlated with gender, smoking, pathologic differentiation, and pN stage, but not with age, tumor location, surgical type, pT stage, and vascular invasion. High expression of TAP was significantly correlated with poorer overall survival (OS) rate in ESCC patients. TAP was an independent prognostic predictor in ESCC patients, based on the multivariate survival analysis.

Conclusion: The study reveals how TAP upregulation promotes ESCC malignant progression, and concludes that TAP acts as the therapeutic target and potential biomarker specific to ESCC.

Keywords: tumor abnormal protein, TAP, esophageal squamous cell carcinoma, prognosis, poor

INTRODUCTION

Up to now, esophageal cancer ranks seventh among all common cancer types and ranks sixth among all the causes that lead to cancer-related deaths all over the world. Its 5-year survival rate is <20% (1). Esophageal squamous cell carcinoma (ESCC) is a prevalent type of esophageal cancer (occupying over 90%) worldwide, with a high incidence in Asia, South America, and East Africa (2). Despite the oncology development as well as multidisciplinary treatment, its recurrence and mortality remain high. One important reason is that most ESCC patients present with advanced stage at the time of diagnosis. Therefore, there is a critical need to find effective pathways by which to predict tumor genesis and development. Recently, various proteins have been found to be closely correlated with the occurrence and progression of ESCC. However, new molecules which possess diagnostic value for clinical application are still needed to be discovered. USSR scholars Kostyantin, A. and Galakhin identified the tumor abnormal protein (TAP), and many literatures revealed that TAP was closely associated with the progression and occurrence of numerous cancers (3, 4). In the process of metabolism, cancer cells are capable of emitting complicated abnormal glycoproteins as well as calcium-histone proteins which constitute TAP (5). In essence, TAP results from the glycosylation changes regarding cancer cells. It indirectly reflects the cell cancerization number and degree. Once these substances reach a given volume, they will enter into the blood and, in a larger number, remain in the peripheral blood. During the early detection stage of cancer, an increase in TAP expression is considered as a significant indicator. Thus, it is necessary to further investigate the biological action related to TAP. TAP is produced by gene (oncogene and tumor suppressor gene) mutation in cells. Besides, upregulated TAP promotes tumor growth. In various tumor types, like breast, ovarian, colon, endometrial, stomach, lung cancers, etc., the upregulation of TAP is seen (6). In addition, TAP remarkably affects tumor development, progression, and metastasis, making it a significant indicator of tumor prognosis. However, the role of TAP in the tumorigenesis and progression of ESCC is not yet clear and warrants elucidation.

The study aims at evaluating the TAP expression of ESCC patients compared with cases who had normal physical checkup. In addition, we also analyze the correlation between the TAP expression and the baseline characteristics of ESCC patients, including age, sex, smoking, tumor location, surgical type, pathologic differentiation, pT stage, pN stage, vascular invasion, and overall survival.

MATERIALS AND METHODS

Patient and Sample Collection

The study has obtained the approval of the Ethical Committee of People's Hospital of Chizhou in Anhui Province, China, as well as received all of the participants' written informed consent forms. Experimental implementation was in accordance with the Declaration of Helsinki. Healthy patients were included as the control group. ESCC patients and cases who had normal physical checkup were also included in the study, and blood samples were collected from those who received surgical resection at the People's Hospital of Chizhou during March 2013 and January 2015. The included ESCC patients were those who did not receive radiotherapy and/or chemotherapy prior to the study. The ESCC results were evaluated histopathologically (eighth edition of the TNM Classification for Esophageal Cancer). All 183 ESCC patients' follow-up data were collected as well as retained. OS refers to the period from the time of diagnosis to the date of death or the last known date of life. **Table 1** summarizes all the baseline characteristics.

TAP Detection

Detection Methods

Fasting blood (2 ml) was collected from the patient's fingertips in the morning. Blood smear with uniform thickness was prepared and then allowed to dry at room temperature for 10 min. Coagulants were added to the blood smear and the particles were condensed after 1.5–2 h. All blood samples were examined with the TAP reagent (Biosharp Biotech, Hefei, China), and then we searched and measured the condensed particulate matter by the TAP detection image analyzer. The TAP results of patients with esophageal cancer were examined on admission and on the first day after surgery. Routine tests were performed on the physical examination group.

Determination of TAP Detection Results

TAP in the blood reacted with the reagent for generating a crystal-like condensation product, thereby proving its existence. As shown in **Figure 1**, TAP negative: condensate area is $\leq$121 μm^2; TAP weakly positive or critical type: condensate area is 121–225 μm^2; and TAP positive: the condensate area was observed as follows—the group with a high expression exhibited a condensation particle area $\geq$225 μm^2, and the group with a low expression exhibited a condensation particle area <225 μm^2.

Statistical Analysis

Experiments were repeated for no <3 times. All statistical data were in the form of the mean ± standard error of the mean (SEM). The SPSS 23.0 software package (SPSS, Chicago, IL, USA) was applied for statistical analysis. The TAP expression levels were classified as low expression (the condensation particle area was <225 μm^2) or high expression (the condensation particle area was $\geq$225 μm^2). Independent-samples *t*-test was applied to compare two groups in terms of the TAP expression. The chi-square test was employed to evaluate the correlation of TAP expression with ESCC baseline parameters. The Kaplan–Meier method together with the log-rank test was adopted for checking and comparing the prognosis. Finally, analytical tools of univariate and multivariate analyses were employed to reveal the factors that can independently predict the prognosis of ESCC patients. $P < 0.05$ is considered exhibiting statistical significance.

RESULTS

TAP Upregulation in ESCC Tissues

In this study, we compared the expression of TAP in 183 cases of ESCC tissues before surgery and cases who had normal physical

TABLE 1 | Clinical association of TAP expression with baseline variables of esophageal squamous cell carcinoma (ESCC) patients.

Variable	Number	TAP	*P*-value	
		Low expression	High expression	
Age				0.069
≤65	102	68	34	
>65	81	43	38	
Sex				**0.001**
Male	97	48	49	
Female	86	63	23	
Smoking				**0.000**
No	62	21	41	
Yes	121	90	31	
Tumor location				0.987
Lower	65	37	28	
Middle	104	68	36	
Upper	8	14	6	
Surgical type				0.258
Sweet esophagectomy	65	37	28	
Ivor-Lewis esophagectomy	44	25	19	
Mckeown esophagectomy	74	49	25	
Pathologic differentiation				**0.001**
Well	31	19	7	
Moderate	98	67	31	
Poor	54	25	34	
pT stage				
T1	20	16	4	0.418
T2	69	38	31	
T3	82	50	32	
T4	12	7	5	
pN stage				**0.001**
N0	104	72	32	
N1	54	30	24	
N2	25	9	16	
Vascular invasion				0.844
No	159	96	63	
Yes	24	15	9	

Bold values indicate P < 0.05.

checkup. The results showed that TAP was significantly increased in ESCC tissues compared with cases who had normal physical checkup (**Figure 2A**). We further examined its expression in ESCC patients after surgery. As shown in **Figure 2B**, the results indicated that the expression level of TAP was decreased in ESCC patients after surgery. Therefore, TAP is upregulated in ESCC tissues.

TAP Expression Is Correlated With the Patient's Sex, Smoking, Pathologic Differentiation, and pN Stage of ESCC

The mean value was taken as a standard to classify ESCC blood samples into two groups as mentioned above. **Table 1** reveals that high TAP expression is closely associated with baseline factors like sex, smoking, pathologic differentiation, and pN stage of ESCC, while it is not affected by patient's age, tumor location, surgical type, pT stage, or vascular invasion. Taken together, the increase in TAP expression promotes the growth of ESCC. The association of TAP expression with ESCC baseline characteristics was evaluated to better explain the function possessed by TAP in ESCC. The TAP expression levels in ESCC tissues were categorized as two groups as mentioned above. As indicated in **Table 1**, high TAP expression was significantly correlated with sex, smoking, pathologic differentiation, and pN stage, whereas we did not find a correlation between TAP expression and age, tumor location, surgical type, pT stage, or vascular invasion. Taken together, the increase in TAP expression promotes the malignant progression of ESCC. The baseline data characteristics of the control group are shown in **Table 2**, including gender, age, and smoking.

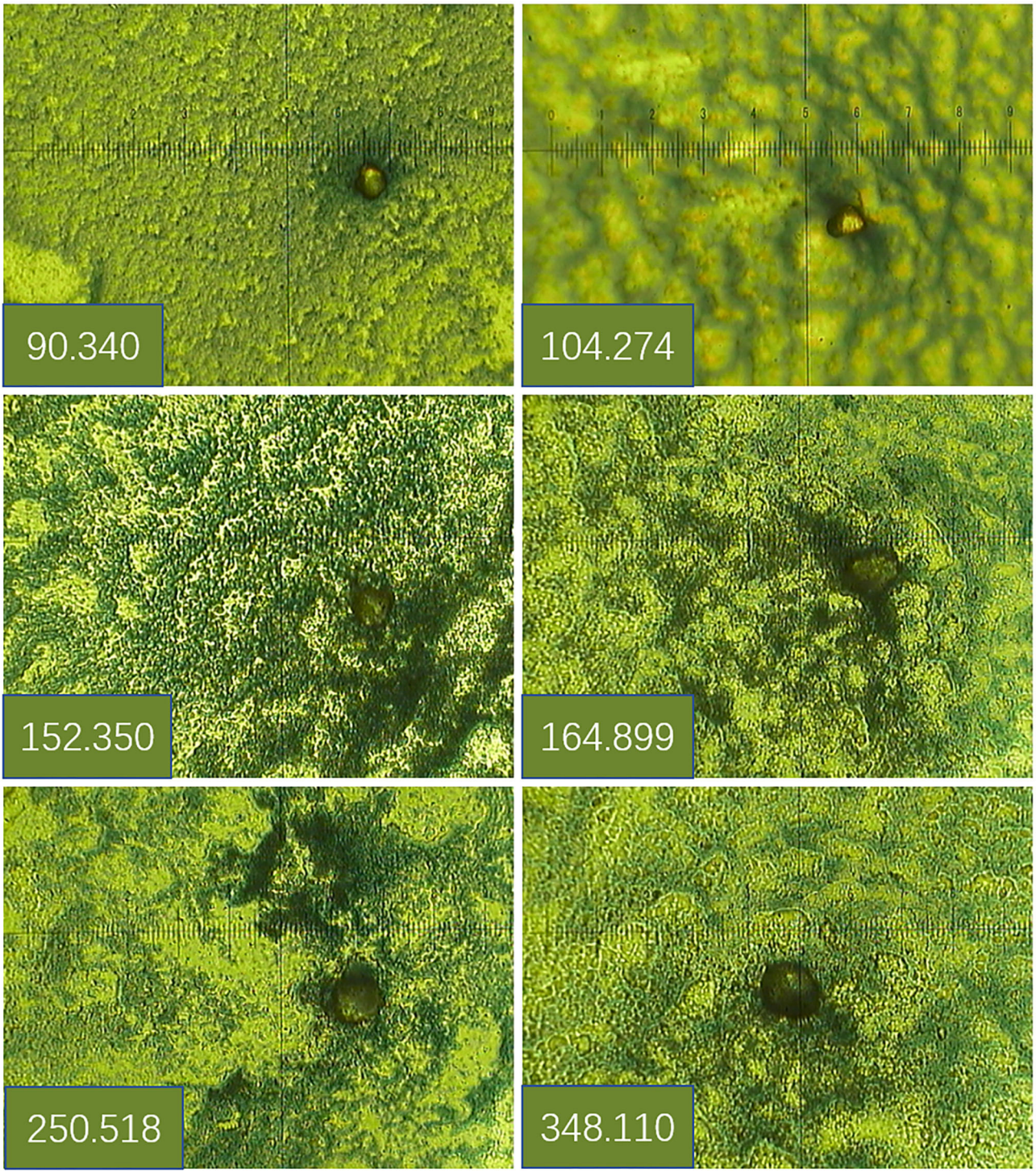

FIGURE 1 | Determination of tumor abnormal protein (TAP) detection results.

For ESCC Patients, High TAP Expression Indicates Poor Prognosis

The study deeply analyzed as well as evaluated the correlation between TAP expression and the survival time of ESCC patients, finding that high TAP expression led to weaker prognosis relative to low TAP expression (**Figure 3A**). After subgroup analysis, it was found that patients with higher post-operative than pre-operative levels had better prognosis than patients

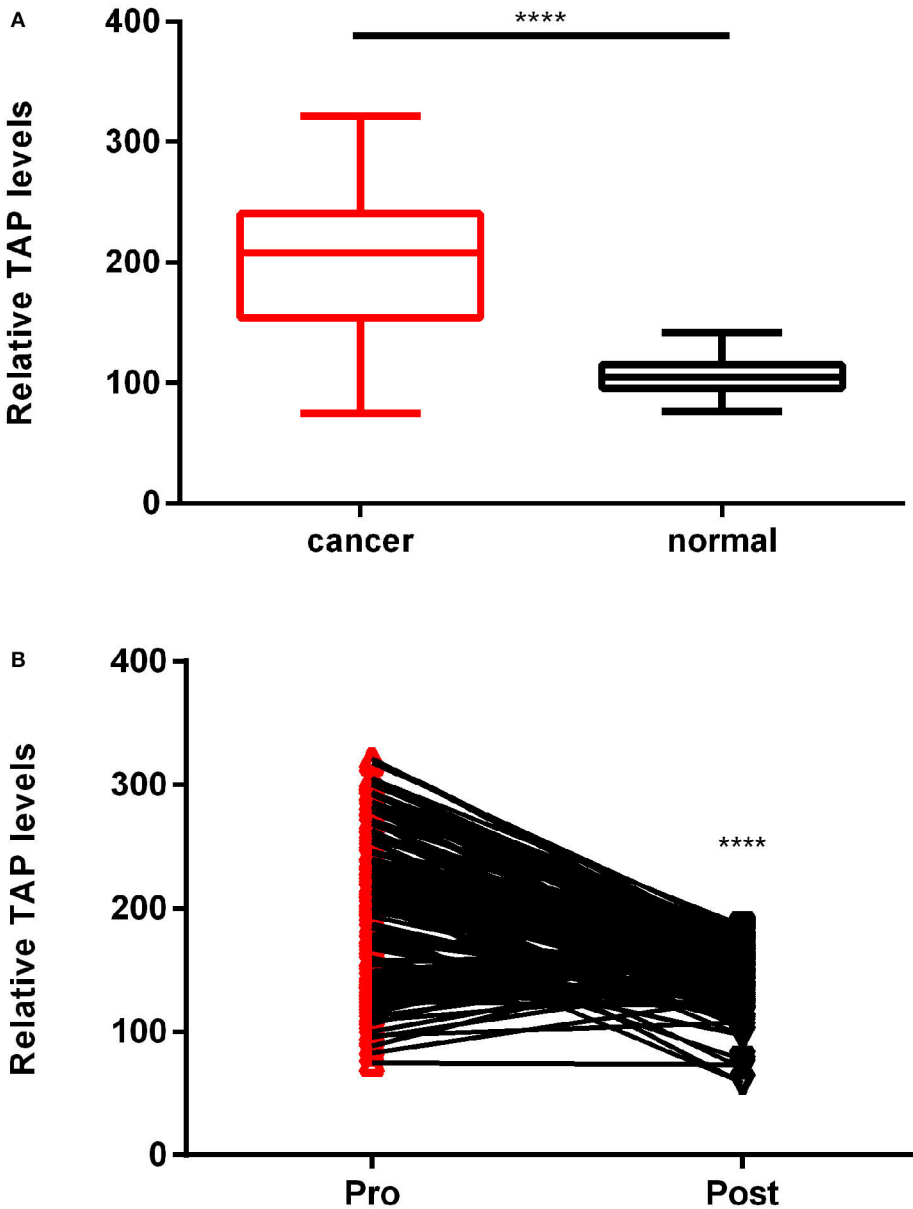

FIGURE 2 | TAP relative expression in esophageal squamous cell carcinoma (ESCC) patients and cases who had normal physical checkup. **(A)** The TAP detection reagent was employed to measure the TAP expression in 183 ESCC and healthy blood samples. **(B)** A line links the pre-operation point to the post-operation point with a downward trend, demonstrating TAP downregulation in ESCC patients following surgery (****$p < 0.0001$).

TABLE 2 | Baseline demographic data for the control group.

Variable	Number	TAP (mean ± SD)	*P*-value
Age			0.424
≤65	170	104.979 ± 13.155	
>65	13	108.015 ± 13.337	
Sex			0.838
Male	107	105.026 ± 13.469	
Female	76	105.432 ± 12.782	
Smoking			0.739
No	102	104.0981 ± 13.42264	
Yes	81	106.5760 ± 12.75596	

with lower post-operative levels (**Figure 3B**). The analytical tools of univariate and multivariate Cox proportional hazards assisted in studying independent factors that predicted survival in ESCC patients. As revealed by univariate analysis data, the overall survival in ESCC patients was significantly correlated with TAP expression, pathologic differentiation, pT stage, and pN stage (**Table 3**). In addition, TAP expression is also an independent prognostic factor for ESCC patients (**Table 4**), whereas pathologic differentiation and pN stage were not independent prognostic factors affecting the overall survival of ESCC patients (**Table 4**). Therefore, our data suggests

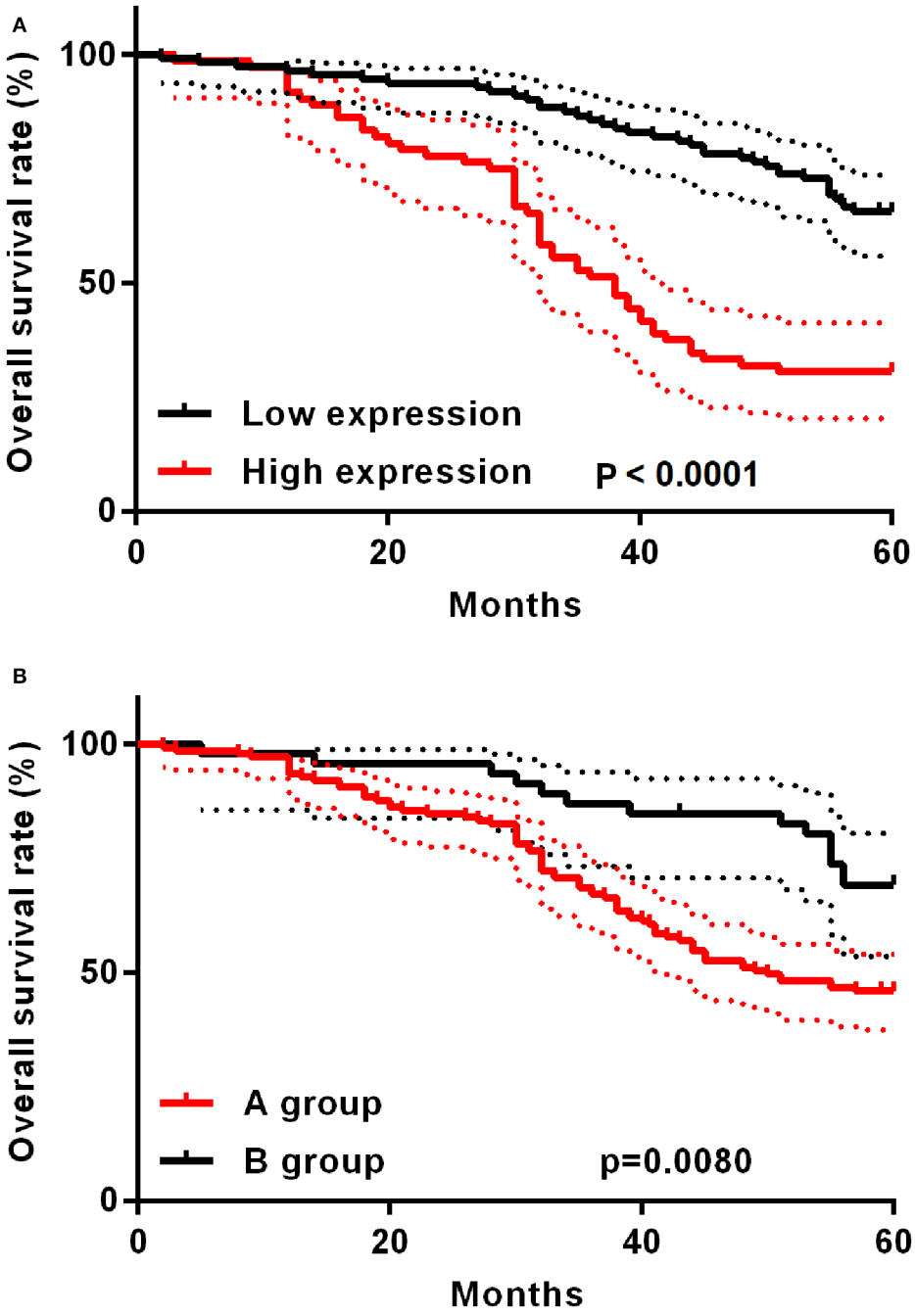

FIGURE 3 | Kaplan–Meier post-operative survival curve specific to ESCC patients with TAP expression. **(A)** For ESCC patients whose TAP expression is high ($n = 72$), the survival time is shorter relative to those whose TAP expression is low ($n = 111$). **(B)** The A group prognosis is worse than the B group. A group: post-operative TAP/pre-operative TAP ratio <1; B group: post-operative TAP/pre-operative TAP ratio >1.

that high expression of TAP can predict poor prognosis in ESCC patients.

DISCUSSION

Studies performed recently have proven that TAP remarkably affects cancer development and progression and regulates cell growth in terms of proliferation and apoptosis (7–9). Gastric carcinoma patients presented an obvious TAP upregulation relative to healthy participants. Besides, patients whose TAP expression was high showed an obvious progression-free survival (PFS) (10). TAP expression in urothelium carcinoma cells of the bladder was detected and examined based on the symptoms and clinical signs (11). TAP detection exhibited a stronger specificity

TABLE 3 | Univariate analysis on ESCC prognostic factors.

Variable	HR(95% CI)	*p*-value
TAP expression (Low/High)	3.051 (2.017–4.615)	**0.000**
Age (≤65/>65)	0.762 (0.505–1.151)	0.197
Sex (Male/Female)	0.844 (0.562–1.267)	0.413
Smoking (Yes/No)	1.493 (0.986–2.260)	0.058
Tumor location (Lower/middle/upper)	1.074 (0.757–1.524)	0.688
Surgical type (Sweet/Ivor-Lewis/Mckeown)	1.018 (0.803–1.289)	0.885
Pathologic differentiation (Well/moderate/poor)	1.436 (1.042–1.980)	**0.027**
pT stage (T1/T2/T3/T4)	1.414 (1.079–1.854)	**0.012**
pN stage (N0/N1/N2)	1.431 (1.088–1.882)	**0.010**
Vascular invasion (No/Yes)	1.349 (0.776–2.347)	0.288

Bold values indicate P < 0.05.

TABLE 4 | Multivariate analysis on ESCC-independent prognostic factors.

Variable	HR(95% CI)	*p*-value
TAP expression (Low/high)	3.055 (1.964–4.751)	**0.000**
Pathologic differentiation (Well/moderate/poor)	1.066 (0.766–1.484)	0.705
pT stage (T1/T2/T3/T4)	1.532 (1.160–2.022)	**0.003**
pN stage (N0/N1/N2)	1.197 (0.898–1.594)	0.219

Bold values indicate P < 0.05.

and sensitivity for colorectal cancer (CRC) patients. Meanwhile, TAP detection also served to independently indicate CRC growth during chemotherapy and clinical monitoring process (12). The unique function possessed by specific TAP shall be essentially figured out to promote the advancement of diagnosis and therapy regarding cancers.

The study adopted 183 peripheral blood samples from ESCC patients while assessing TAP expression. As revealed by TAP detection data, TAP was remarkably upregulated in ESCC tissues compared with cases who had normal physical checkup. Besides, its expression levels were also decreased in ESCC patients after surgery. Therefore, TAP may be involved in the development of ESCC. Besides, according to a thorough analysis, the high expression of TAP was significantly correlated with the patient's sex, smoking, pathologic differentiation, and pN stage of ESCC, but there was no correlation between TAP expression and age, tumor location, surgical type, pT stage, or vascular invasion of ESCC. Because high invasion and metastasis of the tumor are often responsible for poor prognosis in cancer patients, we hypothesized that TAP might affect the prognosis of ESCC patients. To prove the hypothesis, we analyzed the correlation between the TAP expression and the overall survival of ESCC patients. As confirmed, ESCC patients whose TAP expression was high exhibited a weaker prognosis, relative to those whose TAP expression was low. Also, TAP expression was an independent prognostic factor in ESCC patients. Subgroup analysis found that patients with a higher post-operative level than a pre-operative level had better outcomes than patients with a lower post-operative level. The causes were analyzed: (1) Patients with elevated post-operative expression were all patients with low pre-operative expression. (2) Patients with high pre-operative expression had vigorous tumor metabolism and the TAP secreted into the peripheral blood had reached the peak. (3) In patients with low pre-operative expression, the secreted TAP did not reach the peak, and the tumor activity increased after surgical stimulation, leading to an increase in post-operative TAP.

Furthermore, breast cancer patients presented a higher level of TAP expression relative to patients who had a benign diagnosis ($P < 0.001$). There was no correlation between TAP and tumor size, estrogen and progesterone receptors, and her-2 expression, as well as pathological degree (13). By contrast, TAP could be remarkably affected by the patient's age, lymph node metastasis, and TNM stage (13). Based on recent findings, TAP could be utilized to diagnose lung cancer as well as evaluate lung cancer progression (14). TAP detection could assist in sensitively identifying malignant tumor-related aberrant sugar chains in the digestive tract. Hence, it was possible to obtain many tumor-related signals. TAP could be detected in malignant tumors in subclinical stage (15–17). Previous studies verified that TAP detection was achieved 2 years earlier than the discovery of clinical signs and related symptoms as well as malignant lumps (18). It was suggested to further study the exact function and mechanism regarding TAP in regulating ESCC cell proliferation, migration, and invasion, which exhibited an increasing significance as TAP-positive patients showed a greater need for therapeutic interventions as well as for the prevention and treatment of cancers (19, 20).

In addition to ESCC, TAP was also obviously expressed in stomach cancer, colorectal cancer, thyroid cancer, and bladder cancer, as well as lung cancer (9–12, 21, 22). The results of the study generally reviewed the role played by TAP in the development as well as the progression of tumor.

To sum up, TAP expression is dramatically upregulated and downregulated in ESCC blood before and after surgery, respectively. Moreover, TAP expression obviously relates to patient's sex, smoking, pathologic differentiation, and pN stage. Besides, the increase in TAP expression can better predict the weaker ESCC prognosis. Taken together, the study aims at expounding how TAP expression promotes ESCC malignant progression as well as serves as a biomarker for ESCC prognosis. However, this study has some limitations: The lack of benign esophageal tumors as a suitable control group reduces the scientific nature of TAP assessment, and the small sample size objectively reduces the scientific significance of TAP in the diagnosis of esophageal squamous cell carcinoma. These problems need to be further explored in subsequent studies.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study has obtained the approval of the Ethical Committee of ChiZhou People's Hospital in Anhui Province, China, as well as received all participants' written informed consents.

AUTHOR CONTRIBUTIONS

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

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Choice of Treatment for Patients With Non–small-cell Lung Cancer >5 cm Between Surgery Alone and Surgery Plus Adjuvant Radiotherapy

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Background: According to the lung cancer staging project, T2b (>5–7 cm) and T3 (>7 cm) non-small cell lung cancers (NSCLC) should be reclassified into T3 and T4 groups. The objective of this study was to evaluate the effect of surgery alone or surgery plus adjuvant radiation (SART) on survival of node-negative patients with NSCLC >5 cm.

Methods: We identified 4557 N0 patients with NSCLC >5 cm in the Surveillance, Epidemiology, and End Results database from 2004 to 2014. Overall survival (OS) and cancer–specific survival (CSS) were compared among patients who underwent surgery alone and SART. The proportional hazards model was applied to evaluate multiple prognostic factors.

Results: 1,042 and 525 patients who underwent surgery alone and SART, respectively were enrolled after propensity-score matching. OS and CSS favored surgery alone rather than SART. Multivariate analysis showed that the number of lymph nodes examined more than six was associated with better OS and CSS for NSCLC >5 cm, especially in patients treated with surgery alone. Lobectomy should be recommended as the primary option for NSCLC >5 to 7 cm, whereas its superiority was not significant over sublobectomy for NSCLC >7 cm.

Conclusion: Surgery alone should be recommended as the first choice for patients with NSCLC >5 cm. The number of examined lymph nodes should be more than six in patients with NSCLC >5 cm, especially for those who undergo surgery alone. For patients with NSCLC >7 cm who could not tolerate lobectomy, sublobectomy might be an alternative surgical procedure.

Keywords: NSCLC, surgery, postoperative radiotherapy, node-negative, T-stage

INTRODUCTION

Lung cancer is the leading cause of cancer death and the second most prevalent cancer in both men and women in the United States (1), with ∼222,500 estimated new cases in 2017 (1). Non-small cell lung cancer (NSCLC) constitute the most common type of lung cancer (2). Surgery with or without chemotherapy has been adopted as the main treatment offered for curative

intent among patients presenting with early-stage disease, and multimodality consultation has become particularly important for curative-intent treatment of locally advanced NSCLC (3) (stage II-III disease).

The optimal treatment strategy for large pulmonary tumors remains uncertain. The International Association for the Study of Lung Cancer (IASLC) proposed a significant change on T descriptor in the eighth edition of the TNM classification for lung cancer in 2015 (4), in which tumors >5 cm to less than or equal to 7 cm were reclassified as T3, and those greater than 7cm as T4 (4). The proposal has been adopted in the 8th edition of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) staging system. Notably, stage IIB disease includes T3 tumors > 5 cm with no lymph node extension (T3N0), while stage IIIA includes T4 tumors >7 cm without lymph node involvement (T4N0). However, there has not yet been specific study focusing on the optimal treatment modality for patients with NSCLC > 5 to 7 cm and > 7 cm based on the latest TNM staging system.

Surgery plus adjuvant radiotherapy has been considered an important treatment for locally advanced lung cancer (5). However, postoperative radiotherapy (PORT) was routinely not recommended for patients with pathologic stage N0 or N1 disease, at least when using older radiation techniques (3, 6). In addition, the Nation Comprehensive Cancer Network (NCCN) clinical practice guidelines on NSCLC has recommended a minimum number of six nodes removed during surgical resection, three from N1 and three from N2 stations (3). Due to the uncertainty in surgical practice, the resected nodes may not achieve the required number. Since large tumor size is considered as a risk factor of mediastinal lymph nodes involvement even in early clinical stage lung cancer (7, 8), insufficient mediastinal lymph nodes evaluation may lead to a false-negative N descriptor. The consequent imprecise staging can probably misguide the therapeutic strategies, especially PORT, and lead to higher risk of recurrence and metastasis (9, 10). However, the value of PORT for node-negative large tumors has been frequently buried among plenty of studies on the impact of adjuvant therapy for the various stages of disease. With the rapid advance in radiation techniques in the past two decades, the role of PORT should be reevaluated.

The purpose of this study was to evaluate the effect of postoperative radiotherapy on long-term survival of patients with node-negative solitary large NSCLC within a large national database.

MATERIALS AND METHODS

Patients Collection

This study was based on the SEER-18 registry databases, which currently covers ∼28% of the United States population and routinely collects data on demographics, tumor sites, stage at diagnosis, first course of treatment, and follow-up of vital status. We identified the patients diagnosed with lung cancer based on the value of primary site variable (C34.0-34.9). Non-small cell lung cancer (NSCLC) patients was identified using the ICD-O-3 codes, histologic subgroups were defined as squamous cell carcinomas (8050-8052, 8070-8078), adenocarcinomas (8140-8147, 8250-8255, 8260, 8310, 8430, 8480, 8481, 8571-8575) and other types such as large cell carcinoma (8012-8013). The eligible criteria included: (1) diagnosed between 2004 and 2014 and lung was the first primary site, (2) age older than 18 years, (3) underwent surgery to the primary site and with a survival time ≥ 3 months, (4) CS tumor size 2004+ >5 cm and pathological stage T2b-3, N0, and M0 (according to the 7th edition of the AJCC staging manual), (5) cases with death certificate or autopsy were excluded. Types of primary surgery included sublobar resection, lobectomy, and pneumonectomy.

Statistical Analysis

The variables in our analysis included age at diagnosis, gender, race, marital status, characteristics of tumor (location, size, histologic grade and type) and treatment to the primary site (surgical type, sequence of radiation, number of lymph nodes examined) and months of survival and vital status. Patients were divided into two groups: (1) surgery group; (2) surgery plus adjuvant radiotherapy (SART) group, depending on whether they received PORT or not. In order to minimize selection bias under the analytic settings with observational data, we performed a propensity score matching (PSM) analysis between patients with and without PORT based on age, race, and marital status, characteristics of tumor and surgery types. Due to the significantly different number of patients in two groups, a one-to-two matching was conducted based on the nearest neighbor method. Student's *t*-test was employed for continuous data, and we evaluated categorical variables using the Chi-square test of Fisher's exact test. A log-rank test was used to compare Kaplan-Meier survival curves. We defined the Overall survival (OS) as the time from the date of initial treatment to the date of death or the last day of follow-up. Cancer-specific survival (CSS) was measured from the data of initial treatment to death from NSCLC. For multivariate analyses in the matched population, we used the Cox proportional hazards model adjusting all the variables included in the study with p-value <0.2 in the univariate analyses. Two-sided p-value < 0.05 was considered as statistically significant. Hazard ratios with 95% confidence intervals were employed to quantify the strength of the association between predictors and survival. All analyses were performed with the IBM SPSS Statistics 22.0 (IBM, NY, United States), and images of statistics were produced using GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA).

RESULTS

General Information

Overall, the study cohort composed of 4,557 patients, of whom 526 patients (5.6%) underwent SART, as compared with 4,031 patients who underwent surgery alone (**Table 1**). The median follow-up time for the entire cohort was 29 (mean 39.6,

Abbreviations: NSCLC, non-small cell lung cancer; OS, overall survival; CSS, cancer–specific survival; IASLC, the International Association for the Study of Lung Cancer; AJCC, the American Joint Committee on Cancer; UICC, the Union for International Cancer Control; PORT, postoperative radiotherapy; NCCN, the Nation Comprehensive Cancer Network; SART, surgery plus adjuvant radiotherapy; PSM, propensity score matching.

TABLE 1 | Characteristics of patients in the entire cohort.

Characteristics	Before PSM			After PSM		
	Surgery group (n = 4031)	SART group (n = 526)	*P*	Surgery group (n = 1042)	SART group (n = 526)	*P*
Gender (%)			0.850			0.549
Men	2419 (60.0)	318 (60.5)		612 (58.7)	317 (60.4)	
Women	1612 (40.0)	208 (39.5)		430 (41.3)	208 (39.6)	
Age, year			<0.001			0.564
Mean ± SD	67.4 ± 10.1	64.90 ± 10.4		65.3 ± 10.6	64.9 ± 10.4	
Median(range)	68 (20–94)	66 (31-92)		66 (29-90)	66 (31-92)	
Ethnicity (%)			0.186			0.904
Caucasian	3390 (84.1)	438 (83.3)		858 (82.3)	437 (83.2)	
African	398 (9.9)	63 (12.0)		131 (12.6)	63 (12.0)	
Others	243 (6.0)	25 (4.8)		53 (5.1)	25 (4.8)	
Marital status (%)			0.539			
Married	2394 (59.4)	320 (60.8)		623 (59.8)	319 (60.8)	0.752
Unmarried	1637 (40.6)	206 (39.2)		419 (40.2)	206 (39.2)	
Histology type (%)			<0.001			
Squamous cell carcinoma	1633 (40.5)	252 (47.9)		499 (47.9)	251 (47.8)	0.994
Adenocarcinoma	1668 (41.4)	171 (32.5)		341 (32.7)	171 (32.6)	
Others	730 (18.1)	103 (19.6)		202 (19.4)	103 (19.6)	
Pathological grade (%)			<0.001			0.858
Well differentiated	456 (11.3)	28 (5.3)		63 (6.0)	28 (5.3)	
Moderately differentiated	1370 (34.0)	148 (28.1)		276 (26.5)	148 (28.2)	
Poorly differentiated/Undifferentiated	1962 (48.7)	313 (59.5)		631 (60.6)	312 (59.4)	
Tumor size (cm)			0.162			0.827
5-7 cm	2588 (64.2)	321 (61.0)		631 (60.6)	321 (61.1)	
>7 cm	1443 (35.8)	205 (39.0)		411 (39.4)	204 (38.9)	
Location (%)			0.765			0.549
Left	1620 (40.2)	207 (39.4)		426 (40.9)	206 (39.2)	
Right	2408 (59.7)	319 (60.6)		616 (59.1)	319 (60.8)	
Lobe distribution (%)			<0.001			0.895
Upper lobe	2080 (51.6)	361 (68.6)		709 (68)	361 (68.8)	
Middle Lobe	148 (3.7)	12 (2.3)		29 (2.8)	12 (2.3)	
Lower lobe	1603 (39.8)	121 (23.0)		236 (22.6)	121 (23)	
Types of resection (%)			<0.001			0.775
Sublobar resection	197 (4.9)	53 (10.1)		105 (10.1)	52 (9.9)	
Lobectomy	3464 (85.9)	442 (84.0)		866 (63.1)	442 (84.2)	
Pneumonectomy	370 (9.2)	31 (5.9)		71 (6.8)	31 (5.9)	
Number of nodes examined			<0.001			0.668
<6	1467 (36.4)	252 (47.9)		486 (46.6)	251 (47.8)	
≥6	2564 (63.6)	274 (52.1)		556 (53.4)	274 (52.2)	

PSM, propensity-scored matching; SART, surgery plus adjuvant radiotherapy.

range: 3–131). The mean age of the whole cohort was 67.1 years old (median, 68; range, 20–94 years old). Most patients were white in both groups (84.1 and 83.3%, respectively). Squamous cell carcinoma was the predominant histology type in the entire cohort, followed by adenocarcinoma. Notably, there were significant differences in patients' age, histology type, pathological grade, lobe distribution, and types of resection in both groups.

To eliminate selection biases caused by such confounding factors, a 1:2 PSM was conducted between the SART group and surgery group. 1,042 and 525 cases in surgery group and SART group were finally matched for analysis (**Table 1**). There was no significant difference in any patient characteristics between two groups after matching. Multivariate regression analysis identified gender, age, histology type, differentiation grade, tumor size, SART, and number of examined lymph

nodes as risk factors for OS. These risk factors were also found to significantly impact CSS except for histology type (**Supplementary Table 1**).

Comparison of Treatment Modality

Notably, the majority of patients underwent surgery alone in the entire PSM cohort (**Table 1**). Lobectomy predominated in the types of resection in both groups (**Table 1**). As shown in **Figure 1**, patients in the surgery group had significantly better OS ($p < 0.001$) and CSS ($p < 0.001$) than those in SART group. In other word, surgery alone remained the primary option in the treatment of patients with NSCLC larger than 5 cm without lymph nodes involvement.

Since insufficient examined lymph nodes can result in a false-negative N stage, the prognosis of patients in two groups was compared to investigate whether PORT can benefit patients with solitary large tumors, based on the stratification of the number of dissected lymph nodes. The cut-off value was set as six according to the NCCN guidelines (3). As shown in **Figure 2**, the prognosis of patients in surgery group was better than that in the other group ($p < 0.001$), irrespective of the number of examined lymph nodes. Moreover, in surgery group, patients with more lymph nodes examined showed better prognosis than those with nodes examined less than six ($p < 0.001$) (**Supplementary Table 2**). In contrast, more examined lymph nodes provided no remarkably additional survival benefit for patients in SART group but only a trend of prolonged OS ($p = 0.052$) and CSS ($p = 0.115$) (**Supplementary Table 2**). Therefore, PORT should not be recommended for node-negative NSCLC patients with tumor size > 5 cm.

Furthermore, a Cox proportional hazards regression model was applied to further study the potential risk factors in subgroups of NSCLC > 5 to 7 cm and > 7 cm (**Table 2**). In either subgroups, SART was associated with significantly decreased OS and CSS (OS with NSCLC > 5 to 7 cm: HR, 1.896; 95% CI: 1.573 to 2.285; $p < 0.001$; CSS with NSCLC > 5 to 7 cm: HR, 2.172; 95% CI: 1.755 to 2.689; $p < 0.001$; OS with NSCLC > 7 cm: HR, 1.635; 95% CI: 1.288 to 2.075; $p < 0.001$; CSS with NSCLC > 7 cm: HR, 1.751; 95% CI: 1.351 to 2.269; $p < 0.001$). Interestingly, number of lymph nodes dissected less than six was found to have a significantly adverse impact on OS (HR, 1.398; 95% CI: 1.162 to 1.68; $p < 0.001$) and CSS (HR, 1.462; 95% CI:1.18 to 1.811; $p = 0.001$) in patients with NSCLC > 5 to 7 cm, compared with more examined lymph nodes. Similar results for OS (HR, 0.748; 95% CI: 0.591 to 0.946; $p = 0.015$) and CSS (HR, 0.762; 95% CI: 0.589 to 0.986; $p = 0.038$) were observed in patients with NSCLC > 7 cm (**Table 2**).

Since the preferred role of surgery alone has been proved, the surgical procedures were compared to assess the optimal one in patients treated with surgery alone. Another Cox proportional hazards regression model was applied to confirm the impact on prognosis of different types of resection (**Table 3**). In patients with NSCLC > 5 to 7 cm, lobectomy and pneumonectomy, compared with sublobectomy, was associated with increased OS (OS with lobectomy vs. sublobectomy: HR, 0.596; 95% CI: 0.433 to 0.82; $p = 0.002$; OS with pneumonectomy vs. sublobectomy: HR, 1.023; 95% CI: 0.566 to 1.847; $p = 0.093$) and CSS (CSS with lobectomy vs. sublobectomy: HR, 0.525; 95% CI: 0.36 to 0.766; $p = 0.001$; CSS with pneumonectomy vs. sublobectomy: HR, 0.867; 95% CI: 0.427 to 1.759; $p = 0.692$). Meanwhile, lobectomy was associated with increased OS (HR, 0.583; 95% CI: 0.348 to 0.976, $p = 0.040$) and equal CSS (HR, 0.606; 95% CI: 0.325 to 1.131, $p = 0.116$) in patients with NSCLC > 5 to 7 cm. Therefore, lobectomy should be attempted as the optimal type of resection for patients with NSCLC > 5 to 7 cm. In terms of NSCLC > 7 cm, neither lobectomy nor pneumonectomy was associated with increased OS (OS with lobectomy vs. sublobectomy: HR, 0.842; 95% CI: 0.521 to 1.36; $p = 0.482$; OS with pneumonectomy vs. sublobectomy: HR, 0.921; 95% CI: 0.476 to 1.784; $p = 0.807$) and CSS (CSS with lobectomy vs. sublobectomy: HR, 0.922; 95% CI: 0.532 to 1.598; $p = 0.773$; CSS with pneumonectomy vs. sublobectomy: HR, 0.891; 95%

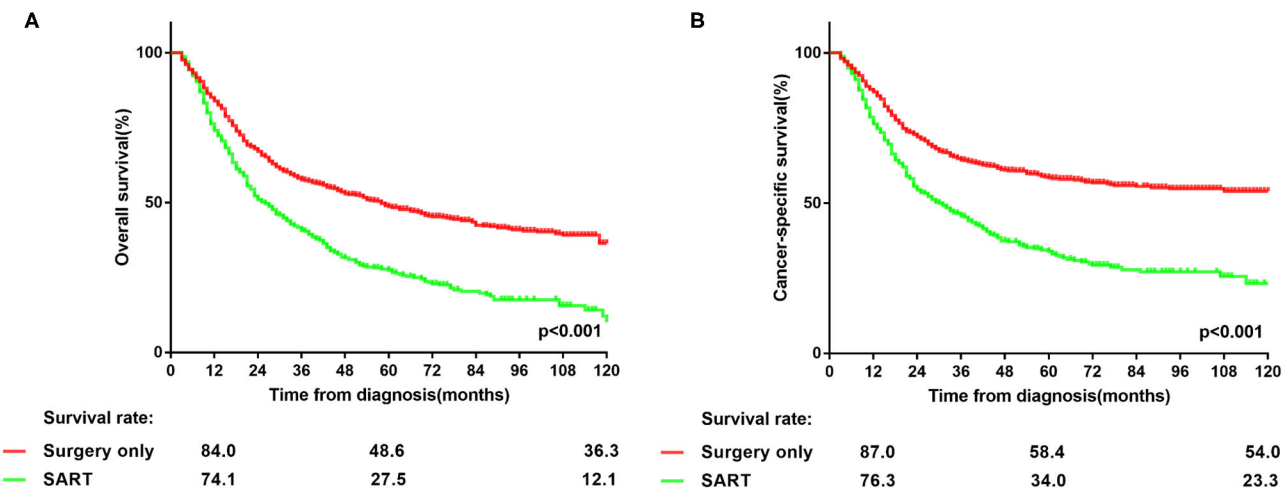

FIGURE 1 | (A,B) Overall and lung cancer-specific survivals in patients with NSCLC >5 cm who underwent surgery alone or surgery plus adjuvant radiotherapy.

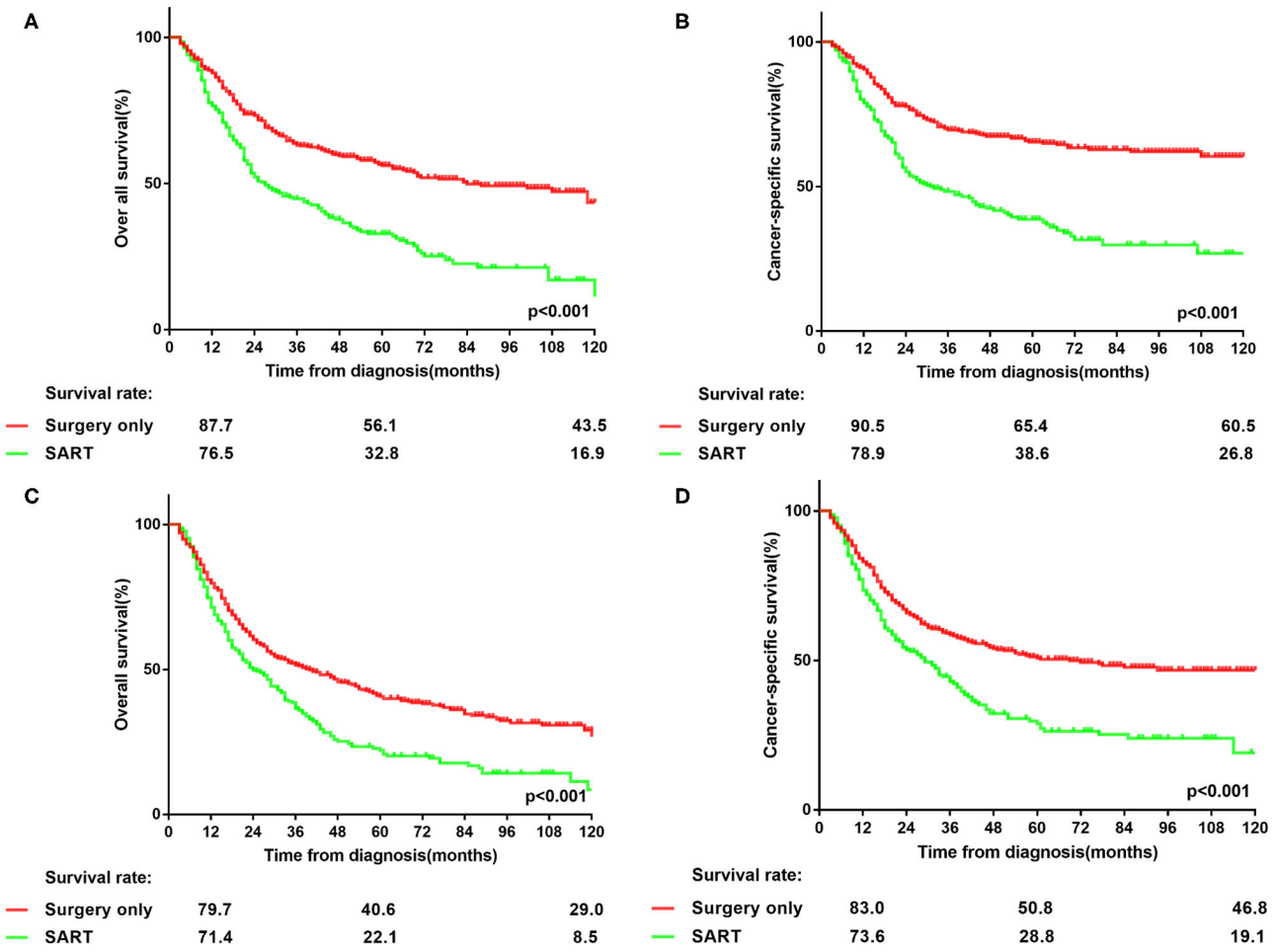

FIGURE 2 | Stratification of overall survival and lung cancer-specific survival in patients with node-negative NSCLC >5 cm at the cut point of the number of harvested lymph nodes who underwent surgery or surgery plus adjuvant radiotherapy. **(A,B)** overall survival and lung cancer-specific survival in patients with node-negative NSCLC > 5 cm who had more than 6 lymph nodes dissected. **(C,D)** overall survival and lung cancer-specific survival in patients with node-negative NSCLC > 5 cm who had <6 lymph nodes examined.

CI: 0.411 to 1.931; $p = 0.77$) compared with sublobectomy. Thus sublobectomy might be considered as an alternative to lobectomy for patients with NSCLC > 7 cm who cannot tolerate lobectomy. In addition, for patients who underwent only surgery, multivariate regression analysis identified age and number of examined lymph nodes as significant prognostic factors (**Table 3**).

DISCUSSION

Despite the increasing detection rate of early-stage NSCLC present as small pulmonary nodules, locally advanced NSCLC remain a complicated and thorny problem in clinical practice. For very large tumors, most clinicians would consider that the optimal treatment modality is still undefined. Part of the confusion arises from the reclassification of T2b tumors > 5 cm to T3 tumors and subsequent changes to stage groupings involving T3 tumors > 5 cm from stage IIA to IIB if node-negative (4, 11). Complete resection is still considered the optimal treatment for locally advanced disease with or without adjuvant chemotherapy to reduce the risk of distant recurrence (3, 12). Furthermore, treatment of stage IIIA disease including T4N0 may include determination of resectability as part of a multidisciplinary consultation (3).

Radiotherapy has been defined a role before or after surgery for locally advanced NSCLC (3), especially for microscopic residual disease (13). However, the latest NCCN guidelines has also pointed out that PORT is not recommended for patients with pathologic stage N0-1 disease at least when using older radiation techniques (3, 6), because it has been associated with increased mortality. Although the cited clinical evidence ranked the highest level, the source itself was a meta-analysis published in 2005. However, the radiotherapy

TABLE 2 | Cox proportional hazards regression model for overall survival and lung cancer–specific survival in patients with non–small-cell lung cancer > 5 to 7 cm and > 7 cm.

	No. (%) of Patients by NSCLC Size and Survival Type in the matched group							
	> 5 to 7 cm				> 7 cm			
	Overall Survival		Cancer Specific Survival		Overall Survival		Cancer Specific Survival	
Variable	**Hazard Ratio (95%CI)**	***P***	**Hazard Ratio (95%CI)**	***P***	**Hazard Ratio (95%CI)**	***P***	**Hazard Ratio (95%CI)**	***P***
Gender		0.269		0.903		0.003		0.009
Men	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Women	0.9 (0.746 to 1.085)		1.014 (0.817 to 1.257)		0.680 (0.527 to 0.879)		0.686 (0.518 to 0.909)	
Age(y)	1.025 (1.016 to 1.034)	0	1.016 (1.006 to 1.026)	0.002	1.029 (1.017 to 1.043)	0	1.022 (1.008 to 1.036)	0.002
Ethnicity	-		-		-		-	
Caucasian								
African								
Other								
Marital status	-		-			0.022		0.218
Married					1.00 (reference)		1.00 (reference)	
Unmarried					1.324 (1.042 to 1.683)		1.18 (0.906 to 1.537)	
Histology type		0.121		0.554		0.57		0.191
SCC	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
ADC	0.83 (0.668 to 1.031)		0.928 (0.725 to 1.187)		0.939 (0.706 to 1.25)		1.009 (0.736 to 1.382)	
Others	1.073 (0.841 to 1.37)		1.1 (0.826 to 1.464)		1.132 (0.821 to 1.561)		1.344 (0.958 to 1.885)	
Grade		0.492		0.239		0.099		0.108
Well differentiated	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Moderately differentiated	1.314 (0.839 to 2.058)		1.584 (0.914 to 2.745)		1.57 (0.833 to 2.959)		1.556 (0.757 to 3.197)	
Poorly differentiated / Undifferentiated	1.264 (0.82 to 1.95)		1.57 (0.922 to 2.673)		1.853 (0.995 to 3.453)		1.905 (0.943 to 3.849)	
Location		0.006		0.005		0.199		0.073
Left	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Right	0.774 (0.644 to 0.931)		0.736 (0.595 to 0.91)		1.171 (0.92 to 1.49)		1.276 (0.978 to 1.665)	
Lobe	-		-			0.64		0.084
Upper					1.00 (reference)		1.00 (reference)	
Middle					1.292 (0.593 to 2.815)		1.821 (0.792 to 4.188)	
Lower					1.115 (0.843 to 1.475)		1.33 (0.985 to 1.795)	
Sequence of radiation		0		0		0		0
Surgery Alone	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
SART	1.896 (1.573 to 2.285)		2.172 (1.755 to 2.689)		1.635 (1.288 to 2.075)		1.751 (1.351 to 2.269)	
Number of LN		0		0.001		0.015		0.038
<6	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
≥6	0.699 (0.582 to 0.84)		0.674 (0.544 to 0.834)		0.748 (0.591 to 0.946)		0.762 (0.589 to 0.986)	

SCC, squamous cell carcinoma; ADC, adenocarcinoma; SART, surgery plus adjuvant radiotherapy; LN, lymph nodes.

planning underwent major changes during the past decades (14). The radiation techniques has also stridden forward from the era of two- dimension (2D) to three-dimension (3D) with 3D-conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT) (14, 15), stereotactic body radiation therapy (SBRT) and the latest proton radiotherapy widely applied within 2004-2014. Therefore, whether the updated radiation techniques can additionally benefit postoperative patients awaits a definite answer. Hitherto, there have been neither radiotherapists nor surgeons focusing on the role of PORT with the new generation of radiation techniques for N0 advanced-stage disease. In our study, it has been well demonstrated that the survival advantages favor surgery alone rather than SART for NSCLC > 5 cm to 7 cm and > 7 cm. The results further validated the prior role of surgery for treating large pulmonary malignancy without nodal involvement.

TABLE 3 | Cox proportional hazards regression model for overall survival and lung cancer–specific survival in patients with non–small-cell lung cancer > 5 to 7 cm and > 7 cm who underwent surgery alone.

	No. (%) of Patients by NSCLC Size and Survival Type in the matched group							
	> 5 to 7 cm				> 7 cm			
	Overall Survival		Cancer-Specific Survival		Overall Survival		Cancer-Specific Survival	
Variable	**Hazard Ratio (95%CI)**	***P***	**Hazard Ratio (95%CI)**	***P***	**Hazard Ratio (95%CI)**	***P***	**Hazard Ratio (95%CI)**	***P***
Gender		0.022		0.257		0.014		0.066
Men	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Women	0.756 (0.596 to 0.961)		0.847 (0.636 to 1.129)		0.675 (0.493 to 0.925)		0.722 (0.51 to 1.022)	
Age(y)	1.031 (1.02 to 1.044)	0	1.018 (1.004 to 1.032)	0.012	1.028 (1.014 to 1.043)	0	1.018 (1.002 to 1.033)	0.026
Ethnicity	-		-		-		-	
Caucasian								
African								
Other								
Marital status	-		-			0.026		0.183
Married					1.00 (reference)		1.00 (reference)	
Unmarried					1.399 (1.041 to 1.879)		1.251 (0.9 to 1.738)	
Histology type	-		-			0.536		0.395
SCC					1.00 (reference)		1.00 (reference)	
ADC					0.847 (0.594 to 1.206)		0.859 (0.577 to 1.279)	
Others					1.047 (0.718 to 1.525)		1.168 (0.778 to 1.754)	
Grade	-		-		-		-	
Well differentiated								
Moderately differentiated								
Poorly differentiated / Undifferentiated								
Location	-		-			0.77		0.593
Left					1.00 (reference)		1.00 (reference)	
Right					1.046 (0.773 to 1.417)		1.096 (0.783 to 1.535)	
Lobe	-		-			0.519		0.422
Upper					1.00 (reference)		1.00 (reference)	
Middle					1.632 (0.696 to 3.827)		1.856 (0.73 to 4.717)	
Lower					0.988 (0.705 to 1.384)		1.068 (0.741 to 1.539)	
Number of LN examined		0.003		0.009		0.026		0.02
<6	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
≥6	0.698 (0.550 to 0.886)		0.677 (0.506 to 0.906)		0.716 (0.533 to 0.961)		0.678 (0.489 to 0.941)	
Surgery type		0.001		0.001		0.755		0.949
Wedge resection	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Lobectomy	0.596 (0.433 to 0.82)		0.525 (0.36 to 0.766)		0.842 (0.521 to 1.36)		0.922 (0.532 to 1.598)	
Pneumonectomy	1.023 (0.566 to 1.847)		0.867 (0.427 to 1.759)		0.921 (0.476 to 1.784)		0.891 (0.411 to 1.931)	

SCC, squamous cell carcinoma; ADC, adenocarcinoma; LN, lymph nodes.

A larger tumor size indicated potentially higher risk of occult lymph nodes metastasis (16–18) and micrometastasis (19, 20) in clinical N0 disease. Recent researches also indicated the residual malignant cells in lymph nodes plays a role in recurrence and distant metastasis (21, 22). Therefore, it is a reasonable assumption that PORT might benefit postoperative patients to some extent. However, evidence from our study conflicts with that logic and suggests the undoubted position of complete surgical resection. Another retrospective study published in 2006 using the SEER database drew a similar conclusion that PORT is associated with a decrease in survival in patients with N1 and N0 nodal disease. Additionally, due to the recommendation proposed by the AJCC, UICC, and IASLC that at least six nodes should be removed during surgical resection (three from N1 and

three from N2 stations), great interest has been raised about whether there could be any difference in the prognosis of patients with NSCLC > 5 to 7 cm and NSCLC > 7 cm based on the suggested number of examined lymph nodes. Our data revealed that the superiority of examining more than six lymph nodes extends to both subgroups. Although more examined lymph nodes led to non-significant improvement on the prognosis of patients who underwent SART, it could be possibly attributed to the local control on residual lymph nodes by PORT. Actually, the long-term survival benefit of more examined lymph nodes on patients has already been reported by Liang et al. (10), who recommended 16 lymph nodes as the cut point for evaluating the quality of lymph nodes examination or prognostic stratification postoperatively for patients with declared node-negative disease. Therefore, our data kept consistent with their findings and supported the value of a thorough lymph nodes examination in NSCLC > 5 cm.

Tumor size has been recognized as a significant prognostic factor of survival outcomes, particularly in patients with early-stage NSCLC (4, 12). Morgensztern et al. (23) previously demonstrated that tumor size is an independent predictor of overall and lung cancer-specific survival in patients with locally advanced disease as well. In our study, tumor size was also associated with a higher risk of decreased OS and CSS upon multivariate analysis. Nowadays, lobectomy has been recommended as the standard surgical procedure for operable NSCLC (3, 24), especially for tumors larger than 2 cm (25–27). Based on our data, lobectomy should be considered as the first choice for NSCLC > 5 to 7 cm which was congruent with the current guidelines. However, lobectomy may be not suitable for NSCLC > 7 cm, at least not superior over sublobectomy in our study. It seemed that for patients who could not tolerate lobectomy with NSCLC > 7 cm, sublobectomy should be recommended as an optimal alternative surgical procedure. In fact, large NSCLC sometimes invade neighboring structures and possibly result in R1 or R2 resections even with lobectomy. Therefore, increasing tumor size could partly account for the non-significant difference in OS and CSS between patients who underwent lobectomy and sublobectomy in patients with NSCLC > 7 cm. A study by Dziedzic et al. (9) identified risk factors for recurrence including tumor size of 5-7 cm and > 7 cm, which partially supported our results. However, both sublobar resection and pneumonectomy were proved to associate with local and distant recurrence (9) which conflicted our data. The disparity may be attributed to the evaluation of appropriate surgical procedures based on stratification of tumor size in our study. To be cautious, we believe that high-quality evidence from ongoing randomized controlled trials are needed to verify our results.

We must acknowledge some limitations of this study. First, potential biases were inevitable because of the retrospective nature of this study. Though some advanced statistical methods were applied to balance the covariates among the arms, there were still some latent biases that could not be adjusted. For example, there was no information on anatomical location and pulmonary function which can affect the types of resection. Furthermore, the information absence of resection margin also poses an insurmountable obstacle for our study, since R1 and R2 resection often led to subsequent PORT and probably resulted in a worse prognosis. Meanwhile, there were potential biases on the prognostic impact of the number of examined lymph nodes because of the lack of definite lymph nodes stations and whether en-bloc resection was performed. In the SEER database there is no ability to discern which patients with tumors > 5 cm received adjuvant chemotherapy, therefore either group invariably included this subset of patients. Notably, information regarding the administration of chemotherapy, either as neoadjuvant or adjuvant therapy, is unavailable in the SEER database as well. Therefore, we could not comprehensively analyze the influence of neoadjuvant chemotherapy alone or adjuvant chemotherapy when used concurrently with radiotherapy on long-term survival of patients with NSCLC > 5 cm. Additionally, no information regarding radiation techniques, including total dose, fraction size, and beam energy, was available, and therefore was not accounted in our analysis. Variations in adjuvant chemotherapy and radiotherapy regimens are likely to be confounded in our study population and may have influenced the lack of significant PORT benefit on survival over pulmonary resection alone.

In conclusion, surgery alone should be recommended as the first choice for patients with NSCLC > 5 cm. The number of examined lymph nodes should be more than six in patients with NSCLC > 5 cm, especially for those who undergo surgery alone. For patients with NSCLC > 7 cm who could not tolerate lobectomy, sublobectomy might be an optimal alternative surgical procedure.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/seerstat/.

ETHICS STATEMENT

The SEER database is available to the public and all patient identities are protected. Our study was therefore exempted from institutional review board at our hospital.

AUTHOR CONTRIBUTIONS

BW, YZ, MJ, and JW are lead authors who participated in data collection, manuscript drafting, table/figure creation, and manuscript revision. BW and YZ aided in data collection. JW and RW is the corresponding author who initially developed the concept and drafted and revised the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.649802/full#supplementary-material

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ORIGINAL RESEARCH
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Simultaneous Vascular Reconstruction and Cervical Anastomosis in McKeown Esophagectomy

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A stomach was considered ineligible to be an ideal conduit conventionally if its right gastroepiploic artery (RGEA) were injured. However, both sufficient blood flow and good venous return are crucial to the success of reconstruction. And there lacks robust evidence regarding the surgical techniques of reconstructing RGEA and right gastroepiploic vein (RGEV) and performing cervical anastomosis with gastric conduit simultaneously. Herein, we summarized the key surgical techniques for simultaneous vascular reconstruction and gastric conduit anastomosis in McKeown esophagectomy.

Keywords: right gastroepiploic artery, right gastroepiploic vein, vascular reconstruction, gastric conduit, McKeown esophagectomy

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INTRODUCTION

McKeown esophagectomy is the primary surgical procedure for esophageal malignancies. As RGEA is the primary source of blood supply of the gastric conduit (1), the unavailability of RGEA disallows the stomach as an ideal substitute for esophagus. Instead, surgeons have to replace the esophagus with colon or jejunum (2, 3). In addition to the intactness of RGEA, unimpeded venous return in RGEV should be highlighted as well. Notably, in recent years, there have been rare reports on the exploration of intraoperative reconstruction of RGEA and RGEV. Moreover, the key surgical techniques during the vascular reconstruction and cervical anastomosis with gastric conduit has not been fully revealed in McKeown esophagectomy. In the past decade, a total of 843 patients received esophagectomy in our department, among whom 3 (0.36%) underwent vascular reconstruction in McKeown esophagectomy. All the three patients had good prognosis. One elderly patient with emphysema suffered from mild anastomotic leakage and respiratory failure after operation. The anastomotic leakage was cured after 2 weeks of conservative treatment (**Figure 1A**). In the present study, we summarized the surgical procedures for simultaneous reconstruction of RGEA and RGEV as well as gastric conduit anastomosis in McKeown esophagectomy based on our previous practice.

SURGICAL TECHNIQUES

Vascular Reconstruction and Assessment of Blood Flow

A midline incision was made in the epigastrium to ensure adequate relaxation of the gastric tissues and immediate exploration of the injured vessels. If the vascular deficit is small, the soft tissues around the vascular stumps should be fully dissociated, and then the tension of the vascular stumps should be accurately assessed. Once acceptable tension was identified at the vascular stumps, the injured vessels could be reconstructed via direct anastomosis promptly.

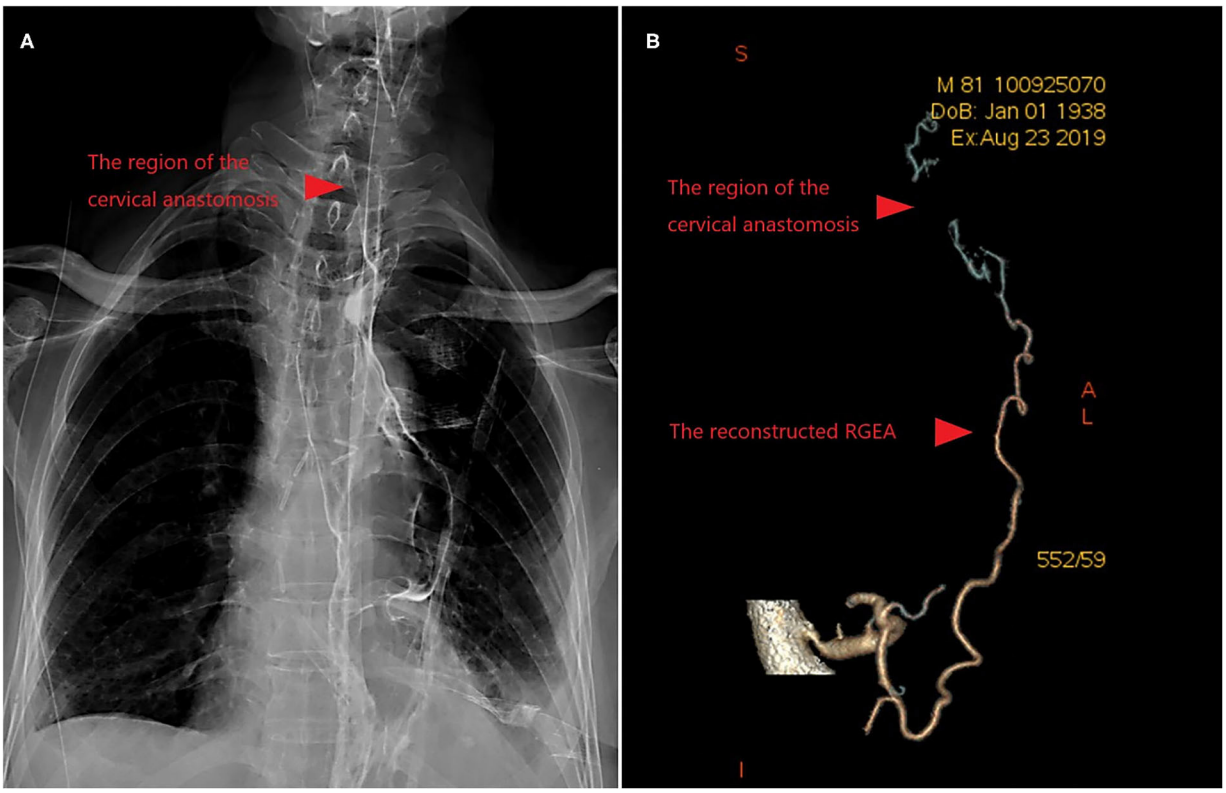

FIGURE 1 | (A) Upper Gastrointestinal Contrast showed that there was no anastomosis leakage after 2 weeks of conservative treatment. **(B)** The postoperative assessment of blood supply was good revealed by Contrast-Enhanced CT.

The principles for vascular anastomosis: (1) Both arteries and veins should be anastomosed by vein-first surgical technique; (2) The vessel stumps should be trimmed into an oblique section, after which continuous suture could be performed from the posterior wall of the vessel stumps using a 7-0 polypropylene thread (**Figures 2A,B**); (3) No additional suture on the stumps unless obvious bleeding after reperfusion; (4) Sufficient drainage in the abdominal cavity.

The blood flow after anastomosis could be accurately assessed intraoperatively with coronary blood flow measuring instrument. Once poor blood flow was found, the vascular reconstruction must be abandoned. Postoperative assessment of blood supply was performed by contrast-enhanced CT (**Figure 1B**) or angiography.

Maintenance of Blood Sufficiency Intra- and Postoperatively

Once the blood perfusion of the anastomosed vessels was disturbed, it will greatly increase the risk of anastomotic leakage. Surgeons should pay attention to preventing thrombosis. Intra-operative anticoagulation therapy should be implemented with diluted heparin (5000 U/single dose), post-operative anticoagulation therapy with low molecular weight heparin (4000 AxaIU/qd), and followed by aspirin (100 mg/qd) for 1 year (**Supplementary Table 1**).

During the early postoperative period, sufficient blood capacity should be maintained to achieve appropriate blood pressure. Drugs that constrict peripheral blood vessels should be used with caution, so as to ensure adequate perfusion to the reconstructed RGEA.

Ensure Adequate Anastomotic Tension of the Vessels and the Gastric Conduit

Minimized tension of vascular anastomosis and gastric conduit anastomosis as follows may be effective to avoid postoperative complications, such as esophageal anastomotic fistula and vascular anastomosis hemorrhage.

Before anastomosis, the tissues around the vascular stump should be fully freed to reduce the tension of the vascular stumps. To extend the length of the gastric conduit and to reduce the tension of esophageal anastomosis, the fundus of stomach should not be clipped during the gastric conduit construction until cervical anastomosis was completed (**Figure 2C**), while the adhesions surrounding the gastric conduit should be dissected sufficiently and cautiously.

After the operation, the gastric tube was placed in the lowest position of the gastric conduit to avoid gastric fluid retention. Enteral nutrition support via jejunostomy was recommended to avoid the physical stimulates from the nutrient tube. Those

Abbreviations: RGEA, right gastroepiploic artery; RGEV, right gastroepiploic vein.

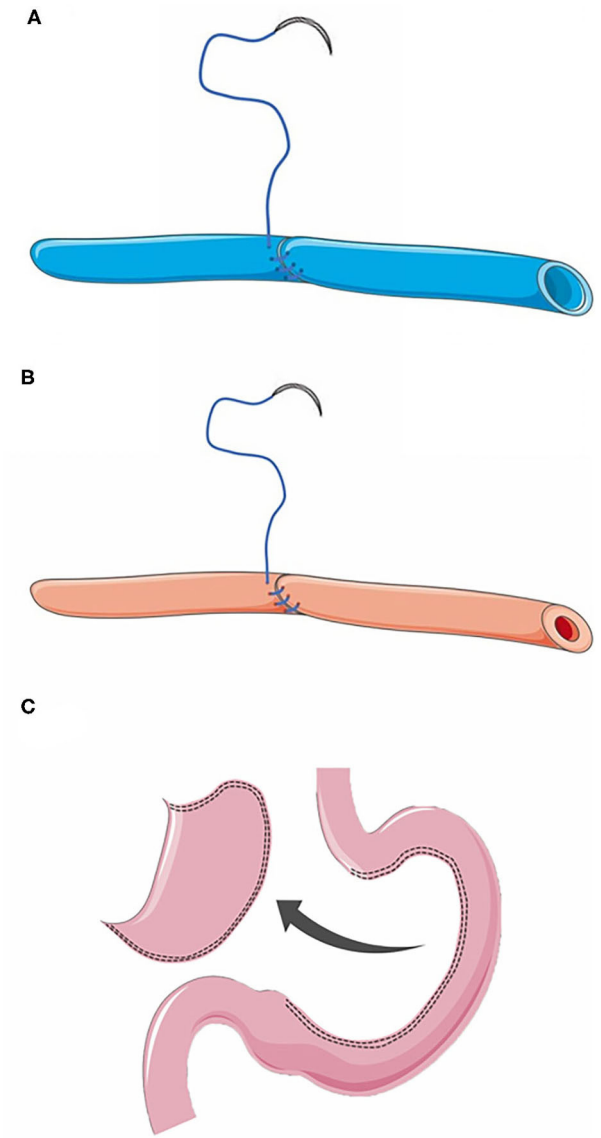

FIGURE 2 | (A) Anastomosis of the right gastroepiploic vein. **(B)** Anastomosis of the right gastroepiploic artery. **(C)** Preparation of a gastric conduit without resection of gastric fundus during the gastric conduit construction until cervical anastomosis was completed.

strategies can eliminate excessive internal tension in the gastric conduit, especially in the pylorus, so as to avoid the local expansion of gastric conduit which may increase the tension of vascular anastomosis.

DISCUSSION

Hitherto, there have been no convincing reports that revealed the feasibility and safety to reconstruct RGEA and RGEV and to perform cervical anastomosis using gastric conduit simultaneously. Given that a previous study introduced the cases on whom RGEA reconstruction was performed in Ivor-Lewis esophagectomy (1), the present study provided a novel perspective for thoracic surgeons who might intraoperatively injured the RGEA in the McKeown esophagectomy. In the present study, 2 patients received reconstruction of RGEA and RGEV in the vein-first order, as both the RGEA and RGEV were injury during the operation. While, another patient received reconstruction of RGEA, as only the RGEA was injury during the operation. The vascular reconstruction and cervical anastomosis using gastric conduit were performed simultaneously in all patients without severe postoperative complication. And no patient died in 6 months after surgery.

Previous Treatment for RGEA and RGEV Disuse

In addition to cancerous involvement, anatomical variations (**Figure 3**) or previous damages on the vessel, the main causes of injuries on the RGEA and RGEV are severe tissue adhesion (2, 3). Once the vessels were severed during the operation, surgeons used to perform gastrectomy and esophageal reconstruction with a long colon or jejunum segment, which may cause greater risk of complications (2). Therefore, it is of great clinical significance to ensure effective vascular reconstruction.

The Key Surgical Techniques

Based on the literature review and clinical experience, we would like to underscore 2 points of the surgical techniques in McKeown esophagectomy, in which reconstruction of RGEA and RGEV and cervical anastomosis using gastric conduit were performed simultaneously: (1) Immediate reconstruction of the RGEA and RGEV and long-term maintenance of the blood flow effectively. (2) Effective tension reduction of gastric conduit anastomosis and vascular anastomosis.

The short-term ischemia reperfusion process can help the gastric conduit adapt to the transient hypoxia environment, which may lower the risk of postoperative anastomotic leakage (4). However, the venous injury may cause severe gastric conduit congestion and even microcirculation thrombosis, which can seriously affect the healing of the anastomosis and impede the blood reperfusion after vascular reconstruction, resulting in postoperative anastomotic fistula possibly. Therefore, we recommend a vein-first principle of vascular anastomosis.

In terms of the anticoagulation therapy after vascular construction, we suggest that anticoagulation therapy should be administered intraoperatively as no previous reports available. Since the average inner diameter of the proximal end of RGEA is similar to that of the coronary artery, we referred to the anticoagulation guideline for coronary artery bypass graft surgery (5).

There are several inherent limitations in the present study. First, the number of patients who underwent vascular reconstruction and cervical anastomosis in McKeown esophagectomy was limited. Second, whether RGEA reconstruction alone could be an alternative to both RGEA and RGEV reconstruction should arouse more attention.

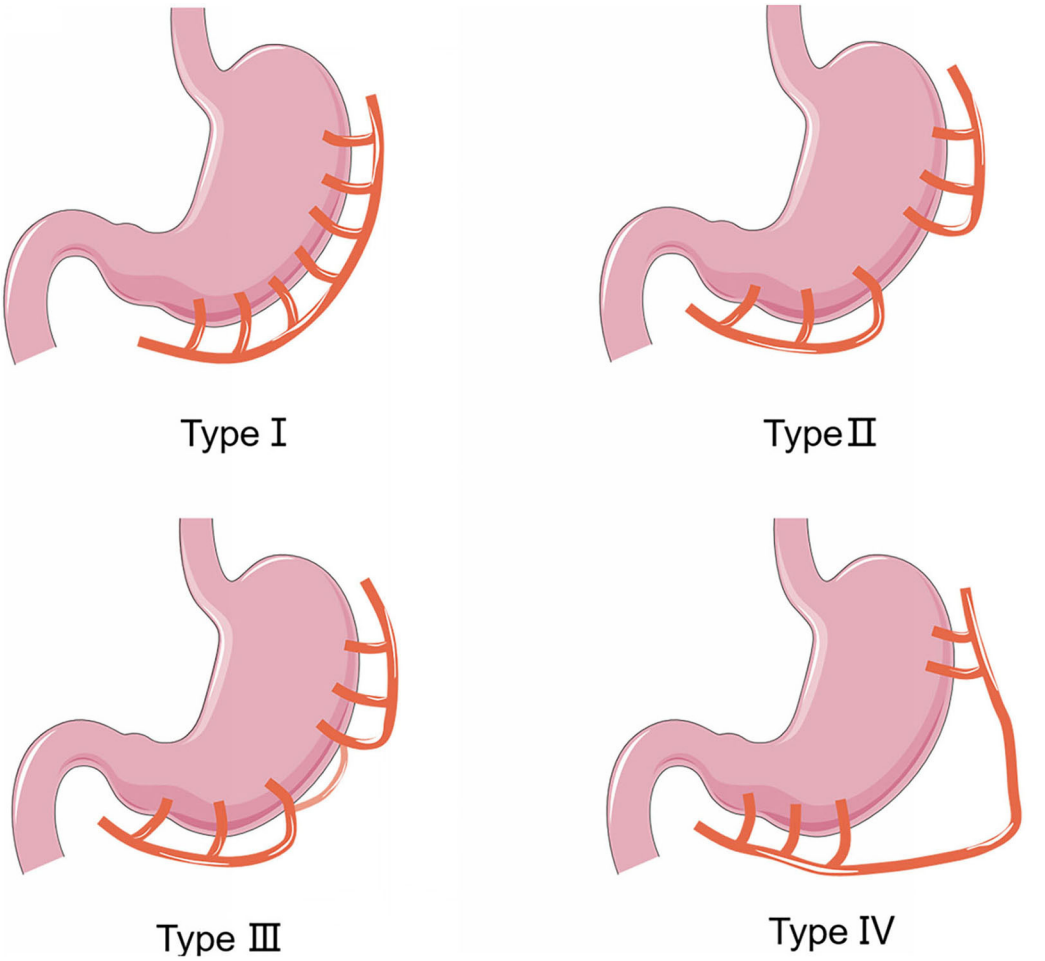

FIGURE 3 | Four types of anatomic variations of the right gastroepiploic artery.

It is recommended to reconstruct the RGEA and RGEV immediately in the vein-first order, after which the simultaneous cervical anastomosis is feasible and reliable in McKeown esophagectomy.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The ethics committee of the Second Affiliated Hospital of Soochow University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC, JZ, and DC: manuscript writing/editing and data analysis. LC and JZ: data collection. YS and WY: protocol/project development and manuscript writing/editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.646811/full#supplementary-material

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ORIGINAL RESEARCH
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Surgical Resection of Primary Tumors Provides Survival Benefits for Lung Cancer Patients With Unexpected Pleural Dissemination

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Background: Surgery is not generally recommended for non-small cell lung cancer (NSCLC) patients with malignant pleural dissemination (PD). However, in some cases, PD is found unexpectedly during surgery. There is no consensus on whether surgical intervention can provide survival benefit for them. We investigated the role of surgery in NSCLC patients with unexpected PD by a cohort study.

Methods: Clinical data of consecutive patients who intended to undergo radical surgery for NSCLC between January 2010 and December 2015 at Shanghai Chest Hospital and Huadong Hospital were collected from a lung cancer database. Patients diagnosed with unexpected malignant pleural nodules intraoperatively were enrolled in this retrospective study.

Results: A total of 181 NSCLC patients were diagnosed with unexpected malignant PD intraoperatively and confirmed with postoperatively histological examinations. Out of these, 80 (44.2%) patients received pleural nodule biopsies alone, and 101 (55.8%) received primary tumor resection (47 with sublobar resection and 54 with lobectomy). The median progression-free survival and overall survival for all patients were 13 and 41 months respectively. Patients in the resection group had significantly better progression-free survival (19.0 vs. 10.0 months, $P < 0.0001$) and overall survival (48.0 vs. 33.0 months, $P < 0.0001$) than patients in the biopsy group. In the resection group, there was no statistical difference between patients with sublobar resection and lobectomy ($P = 0.34$). Univariate and multivariate analyses identified primary tumor resection, targeted adjuvant therapy, and tumor size (≤ 3 cm) as independent prognostic factors.

Conclusions: NSCLC patients with unexpected intraoperative PD potentially benefited from surgical resection of the primary tumor and multidisciplinary targeted therapy, particularly when tumor size did not exceed 3 cm. Our data demonstrated that the resection type was not associated with survival differences, which remains to be defined with a larger sample size.

Keywords: non-small cell lung cancer, malignant pleural nodule, surgery, epidermal growth factor receptor, survival

INTRODUCTION

About 4.5–7.5% of patients with non-small cell lung cancer (NSCLC) are confirmed with pleural dissemination (PD) at diagnosis (1, 2). NSCLC with PD is typically staged as M1a in the 7th and 8th tumor, node, and metastasis (TNM) classification because NSCLC patients with PD had a generally poor prognosis (3–5). The median overall survival (OS) and 5-year survival rate were 8 months and <2%, respectively (2).

Because NSCLC with PD are classified as M1a stage, thus, systemic chemotherapy or targeted therapy, rather than surgical resection, is recommended as standard care for patients at initial diagnosis (6). However, sometimes PD is found unexpectedly during operation. In this case, it is difficult for surgeons to determine whether to proceed the resection of the primary tumors or not, given that, on one hand, there is a lack of evidence of surgical role in unexpected PD cases due to the low incidence of unexpected PD cases, and, on the other hand, there is no technical difficulty with surgical excision of primary and metastatic pleural lesions. Furthermore, with the rapid development of targeted drugs, multidisciplinary treatment including surgery may improve the survival of PD patients bearing a sensitive mutation. But relevant studies focusing on targeted therapy are limited.

In recent years, it was reported that surgical resection showed prognosis benefits for NSCLC with malignant PD (1, 7–13). Several studies focused on patients with PD showed good survival after tumor resection, but without statistical difference or control group (1, 14–17). Besides, some studies included patients with pleural effusion >100 ml in the cohort, which could be found preoperatively and was a sign for metastasis, leading to a potential bias for survival analysis. (7, 16, 18, 19). Li et al. (12) and Ren et al. (7) reported that surgical resection was the significant prognostic factor of patients with unexpected PD, but the sample size was small (43–83 cases), which reduced the level of evidence. On the contrary, a study by Sawabata indicated that tumor resection was not beneficial for the survival (19). Still, the role of surgery in NSCLC with PD remains controversial.

Given the limited evidence concerning the role of surgical resection in NSCLC patients with unexpected PD detected during surgery, we conducted a retrospective study with larger sample size to analyze the clinical characteristics, pathological features, positive mutations and prognosis of patients who intended to undergo surgery and were unexpectedly found to have intraoperative malignant pleural nodules (MPN).

Abbreviations: ALK, anaplastic lymphoma kinase; CI, confidence interval; CT, computed tomography; EGFR, epidermal growth factor receptor; HR, hazard ratio; MPN, malignant pleural nodules; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; OS, median overall survival; PD, pleural dissemination; PET, positron emission tomography; PFS, progression-free survival; PS, performance status; TKI, tyrosine kinase inhibitor; VATS, video-assisted thoracoscopic surgery.

MATERIALS AND METHODS

Patients Demographics

Clinical data of 21,591 consecutive patients who intended to undergo radical surgery for NSCLC between January 2010 and December 2015 at Shanghai Chest Hospital and Huadong Hospital were collected. The patients with unexpected PD, Eastern Cooperative Oncology Group performance status (PS) of 0 to 1 were enrolled in this study. Unexpected PD is defined as (1) preoperative assessments did not detect PD or distant metastasis; (2) no malignant pleural effusion was found preoperatively; (3) PD was only accidentally identified during operations; (4) postoperative pathology confirmed the tumor dissemination to pleural. PD could be separated into localized MPN (several local nodules which could be resected by limited resection) or diffused MPN (uncountable nodules distributed over the parietal pleura).

Clinical characteristics of the patients and respective tumors were abstracted from the electronic medical records by professional staff. NSCLC staging was performed according to the 8th TNM classification (5). Given that the pathological information is incomplete in a considerable number of patients, for example, patients receiving biopsy only or undergoing resection but without systemic lymph node dissection, thus the concept of the best stage instead of the pathological stage was used, which was based on the pathological stage if available, otherwise, the clinical stage would be used instead. Meanwhile, considering the inaccuracy of the stage information, it was excluded in the analysis of prognostic factors. This study was approved by the committees for ethical review of research at Shanghai Chest Hospital and Huadong Hospital, and informed consent was not required because of the retrospective nature of it.

Clinical Assessments

All patients underwent thorough preoperative evaluations preoperatively, including physical examination, routine laboratory tests, serum tumor markers (carcinoembryonic antigen, cancer antigen 125, neuron-specific enolase, cyfra21-1, squamous cell carcinoma antigen), chest computed tomography (CT), respiratory function test, echocardiography, and electrocardiogram. Distant or extrathoracic metastasis was excluded by brain magnetic resonance imaging (MRI), abdominal CT or sonography, and bone scanning. Positron emission tomography (PET) was applied if applicable.

Operations

Posterolateral thoracotomy or video-assisted thoracoscopic surgery (VATS) was performed by surgeons according to the patient's conditions. When pleural nodule was found during the initial exploration, a frozen section biopsy of the pleural was taken to confirm the pleural metastasis. Then different types of surgical resections were chosen by surgeons based on their experience, beliefs, and conditions of patients. These included pleural nodules biopsy, primary tumor resection (wedge resection, segmentectomy, or lobectomy) with or without systemic lymphadenectomy, lymph node sampling, pleurectomy, or pleural nodule resection or electrocautery.

Follow-Up

All patients were instructed to receive 4–6 cycles of adjuvant platinum-based chemotherapies or first-line targeted therapies if they harbored sensitive mutations for medications. Radiotherapies were performed for local progression or distant metastasis, according to the radiation oncologists. Adjuvant therapies were prescribed within 1 month postoperatively.

The follow-up visit was scheduled as the National Comprehensive Cancer Network (NCCN) guidelines (6). All patients were evaluated by a chest CT scan and abdominal sonography. Additionally, brain MRI and bone scintigraphy were regularly performed according to the physicians when necessary. When patients suffered disease progression, subsequent chemotherapy, or targeted therapy was recommended based on the suggestions by oncologists.

OS and progression-free survival (PFS) were regarded as the primary endpoints of the study. OS was recorded from the date of surgery to the date of death or the last follow-up visit. PFS was measured from the date of surgery until the date of the first documented progression or the last follow-up. The closing date of the follow-up for this study was January 31, 2018. Information was obtained from patients through phone calls and outpatient re-visit records.

Statistical Analysis

Measurement data were assessed to compare different patient groups by the chi-square test and Fisher exact probability test for categorical variables and two-tailed Student's *t*-test for continuous variables. And continuous variables were summarized as median and range. Categorical variables were expressed by the median and percentage. Survival curves were obtained using Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analysis use the Cox proportional hazards regression with the test level $\alpha = 0.05$. The proportional hazard assumption was examined and met by plotting the survival curve with Kaplan-Meier method. Significant variables in univariate analysis (defined as $P < 0.15$) would be included in multivariate analysis. Other clinically relevant factors like sex, age, and smoking history were also included in the Cox proportional-hazards model (20). A *P*-value of < 0.05 was considered statistically significant. All analyses were conducted using SPSS 22.0 software (IBM Corporation, Chicago, Illinois, USA) and R software (version 3.6.3).

RESULTS

Patients Clinicopathological Characteristics

Two hundred seventeen (1.0%) of 21,591 cases were found to have a PD. After the exclusion of 36 patients not meeting the inclusion criteria, a total of 181 patients (98/54.1% men, 83/45.9% women) diagnosed with unexpected malignant PD through intraoperatively or postoperatively histological examinations were enrolled in the present study. The median age of them was 59 years ranging 30–75 years. The characteristics of patients and tumors were summarized in **Table 1**. The median follow-up duration was 36 months (range, 4–90 months). Thirteen (7.2%) patients were lost to follow-up. Therefore, 168 patients were included in the survival analysis. Thirty-nine of 181 (21.5%) patients received PET, and no evidence for PD was found preoperatively.

Surgery

Of the 181 patients, 100 (55.2%) patients underwent VATS procedure, and 81 (44.8%) had thoracotomy. Eighty (44.2%) received pleural nodule biopsy alone (biopsy group), and 101 (55.8%) underwent additional primary tumor resection (resection group). In the resection group, 47 (46.5%) cases received sublobar resection (segmentectomy in 7 cases and wedge resection in 40 cases), and 54 (53.5%) cases had lobectomy. Systemic lymphadenectomy and lymph node sampling were performed in 45 and 26 cases, respectively. Additionally, 43 (23.8%) patients were detected with localized MPN intraoperatively, while 138 (76.2%) had diffused MPN (**Table 2**). No severe intraoperative and postoperative complications occurred. There was no postoperative mortality in neither group.

Pathology

Pathologic types of these patients included adenocarcinoma (155; 85.6%), squamous cell carcinoma (13; 7.2%), adenosquamous cell carcinoma (5; 2.8%), large cell carcinoma (3; 1.6%), and others (5; 2.8%). Adenocarcinoma was the predominant pathological type in both the biopsy and resection groups. The patients with the T2 or N2 stage were in the majority, accounting for 44.2 and 36.5%, respectively (**Table 2**). Additionally, sensitive mutations were examined for targeted therapies after surgery, and positive results were found which included epidermal growth factor receptor (EGFR) mutations in 65 of 115 (56.5%) cases (38 with a deletion in exon 19, 27 with a point mutation at codon 858 in exon 21, and 1 with an insertion mutation in exon 20), and anaplastic lymphoma kinase (ALK) rearrangement in 12 of 63 (19.0%) cases.

Adjuvant Therapies

One hundred and thirty nine (82.7%) patients undertook platinum-based chemotherapies as first-line treatment, of which three patients received sequential EGFR-TKIs. Twenty-seven patients undertook targeted therapy as first-line treatment with EGFR-TKIs, including gefitinib (Iressa), erlotinib (Tarceva), and icotinib (Conmana) and anaplastic lymphoma kinase tyrosine kinase inhibitor (ALK-TKI) (crizotinib, Xalkori). After disease recurrence was detected, second-line chemotherapies or targeted therapies were prescribed. In total, 99 of 160 (61.9%) patients received TKIs postoperatively (**Table 1**). Particularly, those EGFR-mutant patients harboring EGFR substitution of threonine 790 with methionine (T790M) received osimertinib (AZD9291) after drug resistance of former EGFR-TKIs in 15 cases. Radiotherapy was administered in 56 patients for local control or metastasis.

Survival

The median PFS and median OS were 13 months and 41 months, respectively. The 3- and 5-year PFS and survival rate for all patients were 13.1%, 5.7%, and 56.0%, 28.7%, respectively.

TABLE 1 | Baseline clinical features of pleural biopsy group and primary tumor resection group.

Variables	Total (n = 181) (count, %)	Biopsy group (n = 80) (count, %)	Resection group (n = 101) (count, %)	P-value
Age (years, median, range)	59, 30–75	60, 35–75	57.5, 30–75	0.39
Gender				0.34
Male	98 (54.1)	40 (50)	58 (57.4)	
Female	83 (45.9)	40 (50)	43 (42.6)	
Location				0.77
Right	110 (60.8)	48 (60.0)	62 (61.4)	
Left	71 (39.2)	32 (40.0)	39 (38.6)	
Smoking history				0.89
Yes	62 (34.3)	27 (33.8)	35 (34.7)	
No	119 (65.7)	53 (66.2)	66 (65.3)	
Performance status				0.31
0	141 (77.9)	59 (73.8)	82 (81.2)	
1	40 (22.1)	21 (26.2)	19 (18.8)	
Tumor location types				0.189
Central	29 (16.0)	16 (20.0)	13 (12.9)	
Peripheral	152 (84.0)	64 (80.0)	88 (87.1)	
Chemotherapy				0.58
Yes	163 (90.1)	73 (91.2)	90 (89.1)	
No	18 (9.9)	7 (8.8)	11 (10.9)	
Targeted therapy				0.11
Yes	99 (54.7)	38 (47.5)	61 (60.4)	
No	61 (33.7)	29 (36.3)	32 (31.7)	
Unknown	21 (11.6)	13 (16.2)	8 (7.9)	
EGFR mutation				0.35
Yes	65 (35.9)	21 (26.2)	44 (43.6)	
No	50 (27.6)	20 (25.0)	30 (29.7)	
Unknown	66 (36.5)	39 (48.8)	27 (26.7)	
Radiotherapy				0.15
Yes	56 (30.9)	22 (27.5)	34 (33.7)	
No	88 (48.6)	36 (45.0)	52 (51.5)	
Unknown	37 (20.4)	22 (27.5)	15 (14.8)	

EGFR, epidermal growth factor receptor.

Clinicopathological Characteristics and Survival Comparison of Patients in the Biopsy and Resection Group

There is no significant difference concerning the baseline characteristics of patients (**Table 1**). However, the resection group has significantly smaller tumor size (median 3.0 vs. 3.75 cm; $P = 0.004$) and less cases with diffused MPN (67/66.3% vs. 71/88.8%; $P < 0.001$) than those in the biopsy group. Additionally, in the resection group, the operation duration (median 91.5 vs. 61 min; $P < 0.001$) and postoperative hospital stay (median 6 vs. 4.5 days; $P = 0.008$) were significantly longer, and there were more cases of bleeding during the operation (37/36.6% vs. 12/15.0%; $P = 0.002$) (**Tables 1**, **2**).

In comparison, patients in the resection group had significant better PFS [19.0 (95% CI: 14.7–23.3) vs. 10.0 (95% CI: 8.0–12.0) months; $P < 0.0001$] and OS [48.0 (95% CI: 41.5–54.5) vs. 33.0 (95% CI: 25.0–41.0) months; $P < 0.0001$] than those in the biopsy group (**Figures 1A,B**). The 3- and 5-year PFS rate of the resection group were higher than the biopsy group (20.8% and 10.8% vs. 3.2% and 0%, respectively). Similar results were seen for OS (67.8% and 37.7% vs. 41.0% and 18.2%, respectively). Additionally, subgroup analysis showed that surgical resection still benefited survival significantly (47.0 vs. 19.0 months, $P < 0.0001$) in patients who did not receive targeted therapies.

The Role of Surgical Resection, Status of MPN, and Adjuvant Therapies

In the resection group, the 5-year survival rate and OS of patients who underwent sublobar resection were 45.6% and 51.0 months (95% CI 33.6–68.4), respectively, while those of patients underwent lobectomy were 29.1% and 48.0 months (95% CI 39.9–56.1). There was no statistical difference in these different types of surgical resection ($P = 0.34$), although the survival of patients with sublobar resection tended to be better.

TABLE 2 | Operative and pathological findings of pleural biopsy group and primary tumor resection group.

Variables	Total ($n = 181$) (count, %)	Biopsy group ($n = 80$) (count, %)	Resection group ($n = 101$) (count, %)	*P*-value
Surgery method				**<0.001***
Biopsy alone		80 (100.0)	0 (0)	
Sublobar resection		0 (0)	47 (46.5)	
Wedge resection		0 (0)	40	
Segmentectomy		0 (0)	7	
Lobectomy		0 (0)	54 (53.5)	
Surgical approach				0.06
VATS	100 (55.2)	51 (63.8)	49 (48.5)	
Thoracotomy	81 (44.8)	29 (36.2)	52 (51.5)	
Lymph node resection				**<0.001***
No	110 (60.8)	69 (86.3)	41 (40.6)	
Lymph node sampling	26 (14.4)	11 (13.7)	15 (14.8)	
Lymphadenectomy	45 (24.8)	0 (0)	45 (44.6)	
Operation duration (minutes, median, range)	75, 15–230	61, 25–149	91.5, 15–230	**<0.001***
Operative bleeding (ml)				**0.002***
≤100	132 (72.9)	68 (85.0)	64 (63.4)	
>100	49 (27.1)	12 (15.0)	37 (36.6)	
Postoperative hospitalization (days, median, range)	5, 1–22	4.5, 1–22	6, 1–15	**0.008***
Pathological type				0.13
Adenocarcinoma	155 (85.6)	65 (81.3)	90 (89.1)	
Others	26 (14.4)	15 (18.7)	11 (10.9)	
Tumor size (cm, median, range)	3.2, 0.7–9.0	3.75, 1.2–8.0	3.0, 0.7–9.0	**0.004***
Malignant pleural nodule				**<0.001***
Localized	43 (23.8)	9 (11.2)	34 (33.7)	
Diffused	138 (76.2)	71 (88.8)	67 (66.3)	
Best T stage				0.112
T1	13 (7.2)	3 (3.7)	10 (9.9)	
T2	80 (44.2)	27 (33.7)	53 (52.5)	
T3	33 (18.2)	17 (21.3)	16 (15.8)	
T4	39 (21.6)	18 (22.5)	21 (20.8)	
Tx	16 (8.8)	15 (18.8)	1 (1.0)	
Best N stage				**<0.001***
N0	50 (27.6)	8 (10.0)	42 (41.6)	
N1	26 (14.4)	13 (16.3)	13 (12.9)	
N2	66 (36.5)	29 (36.3)	37 (36.6)	
N3	8 (4.4)	7 (8.7)	1 (1.0)	
Nx	31 (17.1)	23 (28.7)	8 (7.9)	

*VATS, video-assisted thoracoscopic surgery. *The bold values represented the statistically significant values.*

A similar result was observed for PFS (sublobar resection vs. lobectomy, 20.0 vs. 15.0 months; $P = 0.425$) (**Figures 1C,D**). Notably, Patients underwent lobectomy had a significantly larger tumor size ($P < 0.001$) and less diffused MPN (48% vs. 84.1%, $P < 0.001$), and more patients with lobectomy underwent thoracotomy (76% vs. 25%, $P < 0.001$) and lymph node resection (96% vs. 18.2%, $P < 0.001$) than patients with sublobar resection. Patients with resection of the primary tumor, either sublobar resection or lobectomy, had better survival than patients undergoing biopsy alone ($P < 0.001$ and $P = 0.003$, respectively). Additionally, in the resection group, no statistical difference was observed regarding the OS of patients with systemic lymphadenectomy, lymph node sampling and no lymph node resection ($P = 0.380$).

With regard to the surgical approaches, patients underwent VATS showed significantly better prognosis than patients underwent thoracotomy (median OS, 47.0 vs. 37.0 months; $P = 0.043$). Subgroup analysis demonstrated a similar result in the resection group (median OS, 68.0 vs. 40.0 months; $P = 0.006$; median PFS, 20.0 vs. 16.0 months; $P = 0.029$) (**Figures 1E–H**), while no survival difference was observed in the biopsy group (median OS, 33.0 vs. 27.0 months; $P = 0.484$).

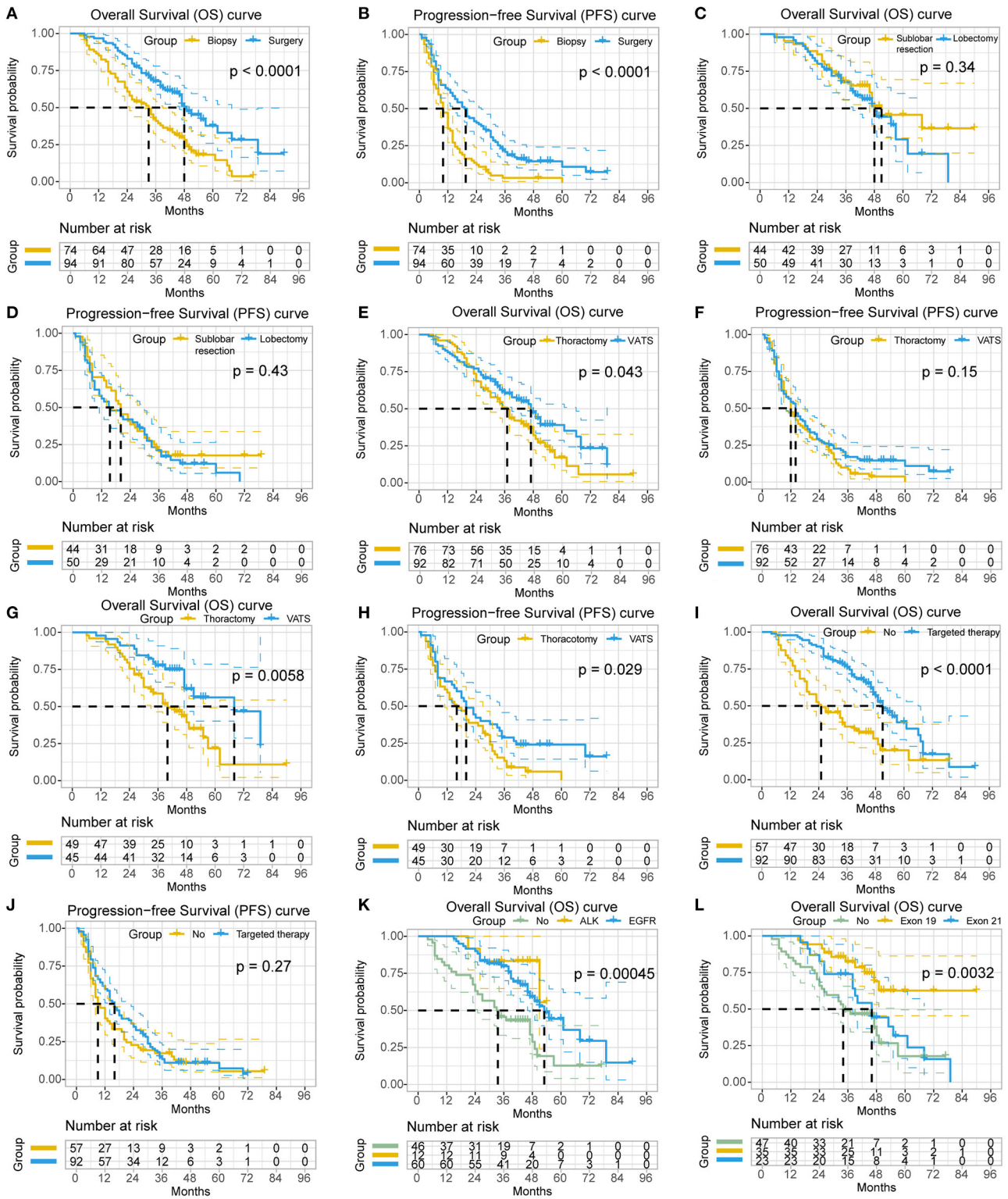

FIGURE 1 | The survival analyses of the clinicopathological characteristics in non-small cell lung cancer (NSCLC) patients with unexpected pleural dissemination (PD). **(A,B)** Comparison of postoperative overall survival (OS) and progression-free survival (PFS) of NSCLC patients with unexpected PD in primary tumor resection group and biopsy alone group. **(C,D)** Comparison of OS and PFS of NSCLC patients with unexpected PD in sublobar resection group and lobectomy group. **(E,F)** Comparison of OS and PFS of NSCLC patients with unexpected PD in video-assisted thoracic surgery (VATS) group and thoracotomy group. **(G,H)** Subgroup analysis of OS and PFS of NSCLC patients with unexpected PD in resection group with or without VATS. **(I,J)** Comparison of OS and PFS of NSCLC patients with

(Continued)

FIGURE 1 | unexpected PD receiving targeted therapy or not. **(K)** Comparison of OS of NSCLC patients with unexpected PD having anaplastic lymphoma kinase (ALK) rearrangement, epidermal growth factor receptor (EGFR) mutation, or not. **(L)** Comparison of OS of NSCLC patients with unexpected PD having different subtypes of EGFR mutation.

No significant survival benefit was observed concerning the amount of MPN in patients within groups (localized vs. diffused, median OS, 46.0 vs. 39.0 months; $P = 1.0$) or subgroups (biopsy group, $P = 0.667$; resection group, $P = 0.082$).

Patients who received targeted therapies had significantly better survival than those not (median OS, 51.0 vs. 25.0 months; $P < 0.0001$) (**Figures 1I,J**), as well as patients with positive EGFR mutations (median OS, 53.0 vs. 34.0 months; $P = 0.005$). Subgroup analysis also showed a better survival for patients with targeted therapies (median OS, biopsy group, 49.0 vs. 19.0 months, $P < 0.001$; resection group, 55.0 vs. 47.0 months, $P = 0.034$). Additionally, the patients with ALK rearrangement had no survival difference with patients with EGFR mutation [mean OS, 48.1 (95% CI: 41.7–54.5) vs. 55.7 (95% CI: 48.1–63.2) months; $P = 0.367$], but they both had significantly longer survival than patients without mutation [mean OS, 36.2 (95% CI: 29.2–43.3) months; $P = 0.011$ or $P = 0.001$, respectively] (**Figure 1K**). As for the subtypes of EGFR mutation, patients with a deletion in exon 19 had significantly better survival than patients with a point mutation in exon 21 [mean OS, 69.7 (95% CI: 59.2–80.1) vs. 47.4 (95% CI: 38.5–56.3) months; $P = 0.024$] (**Figure 1L**).

Risk Factors for Prognosis

Univariate (**Table 3**) and multivariate (**Figure 2**) analyses indicated that primary tumor resection [hazard ratio (HR) 0.52, 95% CI 0.31–0.87, $P = 0.012$], adjuvant targeted therapy (HR 0.40, 95% CI 0.25–0.65, $P < 0.001$), and tumor size $\leq$3 cm (HR 0.44, 95% CI 0.25–0.76, $P = 0.004$) were associated with increased OS, while primary tumor resection (HR 0.52, 95% CI 0.34–0.80, $P = 0.003$) and tumor size $\leq$3 cm (HR 0.57, 95% CI 0.37–0.86, $P = 0.008$) were associated with increased PFS among patients with unexpected PD. Additionally, subgroup analysis in resection group demonstrated that resection type was not associated with better survival by Cox regression model (HR 1.323, 95% CI 0.743–2.357, $P = 0.342$).

DISCUSSION

According to the criteria of 7th and 8th lung cancer TNM staging (4, 5), NSCLC with PD is classified as stage IV (M1a), due to which patients with PD are not recommended for the surgical invention. However, in the clinic, surgeons are sometimes faced with the unexpected PD detected during surgery, which is unidentifiable in preoperative examinations, or suspected pleural nodules, which could not be verified due to the lack of histological evidence. Under these circumstances, surgeons have to decide to stop surgery or go on. Recently, emerging evidence have shown that primary tumor resection could provide survival benefits for NSCLC with malignant PD (1, 7–12, 21, 22), which promoted the re-evaluation of the surgical roles in this type of disease, particularly with the rapid development of VATS with less postoperative pain, shorter hospital stays, and fewer complications (23). However, some of the studies have the limitation of small sample size, patient selection bias (containing patients with pleural effusion, contralateral nodules, or no pathological confirmation of PD), or lack of control group (1, 7, 12, 14–19). Taken together, more studies are needed to investigate the value of surgical treatment for patients with unexpected intraoperative PD (13).

According to the previous studies, the OS, 3- and 5-year survival rate of NSCLC patients with PD were 15–52 months, 25.2–69.2% and 16.0–42.7%, respectively (1, 7–9, 11, 17, 21, 22, 24). Furthermore, the OS, 3- and 5-year survival rate were 20–64 months, 45.8–82.9%, and 31.4–42.7% for patients with primary tumor resection, while 7–35 months, 11.8–41.7%, and 0–19.5% for patients with biopsy alone. Our results were similar to these favorable clinical outcomes. Even the outcomes of the biopsy group in this study were better than the previous clinical data (5-year survival rate, 2%; median OS, 9.5–11.5 months), which supports the opinion that unexpected intraoperative PD may belong to a relatively earlier stage than clinical diagnosed PD (5, 6, 10, 25).

PD represents a wide range of disease states from a single metastasis nodule to diffused pleural nodules involving in pericardium and diaphragm with a large amount of pleural effusion. The tumor burden of these states is different. On the one hand, with the application of high-resolution CT and PET, most PD cases could be diagnosed before surgery. So those unexpected intraoperative PD cases were in the relatively early stage of M1a. Ren et al. pointed out the same thesis as well (7). On the other hand, according to the NCCN guidelines for oligometastatic NSCLC (M1b), surgical resection of primary lesion and metastasis can be beneficial for these patients (6). Theoretically, the tumor burden of PD (M1a) is less than M1b, hence the surgery may also be of advantage to the unexpected PD patient's survival. In this study, the results did show a survival benefit for unexpected PD patients from surgery with a median OS of 41 months. Consistent with our outcomes, a Japanese study of 313 NSCLC patients with PD demonstrated that patients underwent macroscopic complete resection had better survival than patients with exploratory thoracotomy (11). Also, Shen et al. (10) reported a retrospective study of patients with stage M1a NSCLC, in which the patients who underwent primary tumor resection had a significantly better OS than patients accepted no surgery or only metastatic tumor resection ($P < 0.001$).

Another possible reason for the favorable results is related to adjuvant therapies, especially targeted therapy. In our study, the majority of patients (166 of 168, 98.8%) underwent postoperative adjuvant therapies. The significantly better survival was observed in patients who received postoperative targeted therapy than those who did not, which suggests that NSCLC patients with unexpected PD can benefit from mutation tests and targeted therapies (11). In the context of the rapid development of anti-tumor drugs, it may be possible

TABLE 3 | Univariate analysis of prognostic factors.

Variables	Progression-free survival		Overall survival	
	Hazard ratio (95%CI)	*P*-value	Hazard ratio (95%CI)	*P* value
Age				
>59 y vs. ≤59 y	1.099 (0.799–1.513)	0.561	1.599 (1.091–2.344)	**0.015***
Gender				
Female vs. Male	0.894 (0.650–1.230)	0.493	0.873 (0.596–1.277)	0.482
Smoking history				
Yes vs. No	1.086 (0.779–1.513)	0.626	1.079 (0.731–1.592)	0.702
Performance status				
1 vs. 0	1.730 (1.190–2.513)	**0.004***	2.028 (1.316–3.115)	**0.001***
Adjuvant chemotherapy				
Yes vs. No	2.242 (1.212–4.149)	**0.008***	2.028 (0.889–4.630)	0.086
Adjuvant targeted therapy				
Yes vs. No	0.827 (0.583–1.174)	0.287	0.416 (0.274–0.632)	**<0.001***
Primary tumor resection				
Surgery vs. Biopsy	0.478 (0.343–0.665)	**<0.001***	0.458 (0.312–0.672)	**<0.001***
Surgical approaches				
VATS vs. Thoracotomy	0.794 (0.576–1.094)	0.159	0.678 (0.463–0.993)	**0.046***
Tumor size				
≤3 cm vs. >3 cm	0.536 (0.380–0.758)	**<0.001***	0.462 (0.301–0.709)	**<0.001***
Malignant pleural nodule				
Localized vs. diffused	0.824 (0.554–1.227)	0.340	0.886 (0.621–1.510)	0.968

*CI, confidential interval; VATS, video-assisted thoracoscopic surgery. *The bold values represented the statistically significant values.*

to be more active in surgical treatment when encountering unexpected PD.

As for the types of surgical resections, no statistical difference in survival between sublobar resection and lobectomy was observed, similar results were found in some previous studies (7, 8, 10, 12, 17, 24). Notably, the heterogeneity between subgroups of lobectomy and sublobar resection may influence the conclusion, making it difficult to determine which was the best type of resection. Okamoto and Ohta both found that patients received pneumonectomy had a significantly worse survival than patients with limited resection (1, 15). However, a study conducted by Iida et al. showed an opposite view that the survival for patients with macroscopic complete resection was statistically better than patients with macroscopic incomplete resection ($P = 0.009$) and exploratory thoracotomy ($P < 0.001$) (11). Moreover, no statistical difference in survival was observed between patients who underwent systemic lymphadenectomy and not ($P = 0.29$) in our study. The study by Ren et al. also indicated that neither systemic lymphadenectomy nor pleurectomy made difference in survival significantly (7). In summary, more evidences are required to clarify the optimum resection type in these patients, although surgical intervention seems more like a cytoreductive surgery in the PD cases. Sublobar resection by video-assisted thoracoscopic surgery may be a proper choice for the less invasiveness.

Our data demonstrated that patients underwent VATS had a significant better survival, compared with those underwent thoracotomy. However, the multivariate analysis did not support this result. Therefore, the survival difference may be caused by potential bias. Although with the advances of minimally invasive surgery, including robotic-assisted thoracoscopic surgery, better surgical outcomes may improve the patients' quality of life. Additionally, the extent of pleural diffusion is a complex variable, which is difficult to analyze due to the ambiguous definition and limited sample size, and may have a potential influence on the prognosis. Li et al. defined diffused pleural nodules as more than three pleural nodules, and their results showed diffused MPN had no survival difference with localized MPN (11, 12). In our study, there was no significant survival difference between localized MPN and diffused MPN among all patients or in the

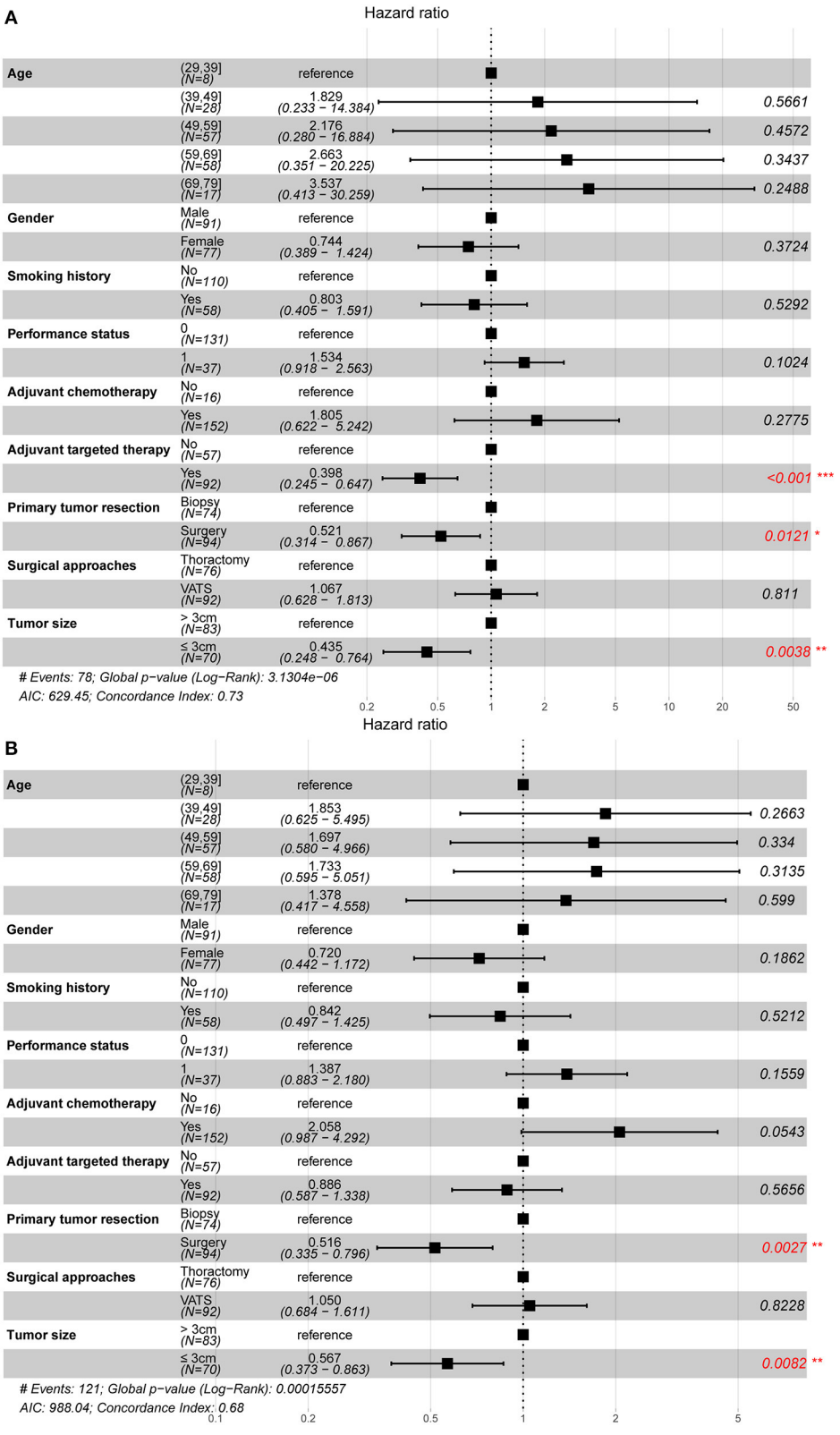

FIGURE 2 | Prognostic factors of non-small cell lung cancer patients with unexpected pleural dissemination after surgery. **(A)** The forest plot of multivariate Cox regression analysis for overall survival. **(B)** The forest plot of multivariate Cox regression analysis for progression-free survival. VATS, video-assisted thoracic surgery. *statistically significant.

resection group, although the biopsy group had more patients with diffused MPN. This indicated that patients with less MPN tended to be selected for resection. It needs more research to clarify the prognosis influence of the MPN.

In this study, univariate and multivariate analyses demonstrated that primary tumor resection, targeted adjuvant therapy, and tumor size $\leq$3 cm were independent predictors of survival in NSCLC patients with unexpected PD. These may suggest that surgeons select unexpected PD patients with small tumor size for resection and perform sensitive mutation detection for targeted therapy, routinely. The previous studies have reported similar prognosis factors to ours (7, 12, 21, 26). However, the time span of this study was relatively short and recent (6 years from 2010) compared with other studies (1, 16, 17, 19, 24), and no patient was lack of pathological confirmation for malignant PD, unlike other studies (16, 19). Besides, the sample size of this study was relatively larger than previous studies, as well as longer follow-up time (1, 7, 12, 14, 15, 22). Additionally, several studies reported that N0 stage was the independent prognostic factor for survival, which, however, has potential bias, given that many patients did not have completely pathological N status (1, 26). Therefore, the N stage was not included in our model.

The major limitation of our study was its retrospective nature. Additionally, there were some potential differences between the two groups, such as the number of pleural nodules and the pathological N stage, leading to the selection bias because there is no consensus on how to choose patients with unexpected PD who can benefit surgical resections. Third, limited resection and no systemic lymphadenectomy could not provide enough information for final pathological staging. Large sample multi-center studies should be conducted in the future to verify the efficacy of surgical procedures in NSCLC patients with PD.

CONCLUSION

NSCLC patients with unexpected PD diagnosed intraoperatively potentially benefited from surgical resection of the primary tumor and multidisciplinary therapies. Patients with targeted adjuvant therapy and primary tumor size $\leq$3 cm had a better prognosis. Our data demonstrated that the resection type was not associated with survival differences, which, however, may be influenced by the heterogeneity of the resection group. Further studies on whether the type of surgical resections (sublobar resection vs. lobectomy) affects the survival remain to be determined.

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 Committee for Ethical Review of Research at Shanghai Chest Hospital and Huadong Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LF: methodology, software, and writing—original draft. HY: conceptualization and software. KH: data curation. YZ: visualization and investigation. WG: formal analysis. RS: writing—reviewing and editing. FY: validation, writing—reviewing, and editing. HZ: supervision, resources, writing—reviewing, and editing. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Surgical Site Infections Are Associated With Higher Blood Loss and Open Access in General Thoracic Practice

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Background: Surgical site infections (SSIs) are the most costly and second most frequent healthcare-associated infections in the Western world. They are responsible for higher postoperative mortality and morbidity rates and longer hospital stays. The aim of this study is to analyze which factors are associated with SSI in a modern general thoracic practice.

Methods: Data were collected from our department's quality database. Consecutive patients operated between January 2014 and December 2018 were included in this retrospective study.

Results: A total of 2430 procedures were included. SSIs were reported in 37 cases (1.5%). The majority of operations were video-assisted (64.6%). We observed a shift toward video-assisted thoracic surgery in the subgroup of anatomical resections during the study period (2014: 26.7%, 2018: 69.3%). The multivariate regression analysis showed that blood loss >100 ml ($p = 0.029$, HR 2.70) and open surgery ($p = 0.032$, HR 2.37) are independent risk factors for SSI. The latter was higher in open surgery than in video-assisted thoracic procedures ($p < 0.001$). In the subgroup of anatomical resection, we found the same correlation ($p = 0.043$). SSIs are also associated with significantly longer mean hospital stays (17.7 vs. 7.8 days, $p < 0.001$).

Conclusion: As SSIs represent higher postoperative morbidity and costs, efforts should be made to maintain their rate as low as possible. In terms of prevention of SSIs, video-assisted thoracic surgery should be favored over open surgery whenever possible.

Keywords: surgical site infection, minimal invasive surgery, video-assisted thoracic surgery, thoracic surgery, complication

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INTRODUCTION

Surgical site infections (SSIs) are the second most frequent healthcare-associated infections in the United States and Europe (1). The overall incidence of SSI in general surgery was reported to be between 1.9 and 5.4% (2–4). Higher SSI rates can be found after colectomies (18.4%) (5). In thoracic surgery, there are some studies reporting SSI occurrence ranging from 0.3 to 6.1%,

but no study looks specifically for factors associated with this burden in a recent period and in a fully implemented minimal invasive practice (6–11).

In the United States, SSIs represent the most costly healthcare-associated infection. They cause higher postoperative mortality, morbidity, and longer hospital stays (12). It is estimated that 55% of SSIs are preventable with the implementation of official recommendations (13, 14).

SSIs are defined by the United States Centers for Disease Control and Prevention (CDC) as "an infection that occurs after surgery in the part of the body where the surgery took place" (15). Superficial SSIs involve only the skin and subcutaneous tissue while deep SSIs affect tissues under the skin like muscle, fascia, adjacent organs/space opened, or manipulated during the operation or foreign body (15–18).

Many risk factors for SSI have been identified in general surgery, such as advanced age, previous radiation, previous skin and soft-tissue infection, high level of serum glucose, obesity, smoking, immunosuppression, malnutrition, malignant disease, hospitalization during the preoperative period, ongoing infection, blood transfusion, and longer operating time (13).

After a progressive introduction during the last three decades, video-assisted thoracic surgery (VATS) is commonly used. VATS in simple thoracic procedures such as pleural biopsy or pleurodesis is relatively easy to perform. VATS in more complex procedures such as lobectomy or segmentectomy can be a real challenge due to a longer learning curve. This results in longer operating times and higher intraoperative complication rates during that learning period (6). Its use in oncological procedures was a controversial subject until proven otherwise (8, 19–22). With experience, operation durations tend to be lower with less intraoperative complications (8, 19, 20). Recent studies report fewer postoperative complications, shorter hospital stay, and shorter chest tube duration without compromising oncological outcomes in VATS (8, 19, 23). Only two studies specifically analyze the risk factors for SSI in thoracic surgery in relation to open or minimally invasive surgery (10, 24). However, they are not able to demonstrate open surgery as a risk factor for SSI in comparison with minimal invasive surgery and they cover a long period of time before the implementation of VATS surgery for anatomical lung resections. Since VATS is now a well-established technique and is regularly performed with the development of expertise, we believe its positive influence on SSI rates in thoracic surgery can be better recognized.

Our study aims to assess the SSI rate over a 5-year period in a general thoracic "real-life" practice and to determine associated risk factors for SSI. During the same period, we implemented our VATS program for anatomical lung resection giving the possibility to measure its effect on this particular complication.

MATERIALS AND METHODS

Patient Inclusion Criteria

Data were collected from the department quality database, which uses the tool of the Association for Quality Assurance in Surgery (AQC). Data are routinely entered prospectively into the database by a trained study nurse. Consecutive patients who underwent a thoracic operation between January 2014 and December 2018 at the Department of Thoracic Surgery of our university tertiary reference center were included. Tracheostomy, bronchoscopy, operation for vascular access, debridement of SSI, or reoperation for post-operative complication within 30 days after thoracic surgery was excluded. Patients <18 years of age were also excluded. This study was approved by the local ethic committee (Project-ID 2020-00850); each patient gave written consent for the use of his/her medical data during hospitalization.

Patient Characteristics

The following clinicopathological variables were recorded: age, sex, BMI, ASA score, comorbidity, previous chemotherapy, or radiotherapy and chronic steroid use.

Patients' demographics includes also the following criteria: malignant and benign pathology of the main bronchus/trachea, of the mediastinum, primary lung malignancy, malignant pathology of the pleura, other malignant pathology, empyema, pneumothorax, pleural effusion and hemothorax, musculoskeletal pathology (unstable rib fracture, pectus excavatum/carinatum), complication after medical treatment or extra-thoracic surgery, and other benign pathology.

Subgroups were made according to operation type: simple thoracoscopy (biopsy, wedge resection, and pleurodesis), decortication and pleurectomy, lobectomy, segmentectomy, pneumonectomy, thymectomy, sympathectomy, mediastinum operation, and other.

For each operation, access type (open, VATS, and conversion) was specified, and whether it was elective or not. Operating time was reported in minutes, and estimated blood loss was reported in milliliters. A cutoff for blood loss was made at 100 ml, as literature reports higher cardiopulmonary complications in VATS surgery with blood loss above 100 ml (25).

Intraoperative complications were reported in four subgroups: vascular lesion, other organ lesions, operation interruption, and other intraoperative complications. Postoperative complications after the surgical procedure were classified according to the Clavien–Dindo classification (26). Clavien–Dindo grade ≥3b was considered a severe postoperative complication. Postoperative complications were divided into the following subgroups: respiratory complication (pneumonia, atelectasis, respiratory insufficiency, pneumothorax, and persistent air leakage, i.e., >5 days), cardiovascular complication, SSI, postoperative bleeding, and persistence of chest tube secretion (>200 ml/24 h for >7 days), bronchial stump insufficiency, hemothorax, chylothorax, empyema, and other complications. More than one complication can be reported per operation. Pneumonia, empyema, and bronchial stump insufficiency were not included in SSI but reported separately.

SSI Definition

SSI was defined according to the abovementioned CDC definition (16). An SSI was diagnosed with the presence of redness, tenderness, heat, localized swelling, fever, purulent discharge, spontaneous wound dehiscence, and/or microorganism isolated form the wound fluid or tissue. The SSI was diagnosed through the attending surgeon.

Surgical Procedure

In our clinic, VATS is performed using a two- or three-port access. For anatomical lung resections, we modified our approach to a uniportal VATS technique, consisting of a 3- to 5-cm incision length, in November 2014. No rib spreader was used for multiport VATS and soft wound protectors were used in uniportal VATS. Standard patient preparation for surgery includes disinfection with povidone-iodine solution (Betaseptic®). Prophylactic antibiotics were routinely administrated 30–45 min prior to skin incision with cefuroxime 1.5 g as standard dosage (or Clindamycin in case of β-lactam allergy). If an antibiotic treatment was already initiated, it was repeated prior to the incision in place of the standard prophylaxis. Antibiotics were adapted to the clinical situation, like the use of broader spectrum in case of empyema for example. For low infection risk surgery such as simple biopsy, the surgeon remains autonomous to decide whether a prophylaxis is needed or not. The skin was closed by means of a continuous intracutaneous suture with Monocryl®4–0.

During hospital stay, each patient was monitored for peri- and postoperative complications including SSI. A clinical nurse contacted each patient 7–10 days after hospital discharge by telephone to inquire about his/her general well-being and presence of any wound infection or discharge. Routine outpatient visits were performed 2–4 weeks after surgery.

Endpoints

The endpoint of our study was to determine the risk factors associated with SSI. Since we initiated our uniportal VATS program during the study period, we also analyzed what effect the minimal invasive approach had on SSI, especially in anatomical lung resections.

Statistical Analysis

Baseline characteristics are presented as medians (IQR) for continuous variables or frequencies for categorical variables. Aiming to identify factors associated with SSI, the following clinicopathological variables were analyzed using a univariate logistic regression model: previous chemotherapy or radiotherapy, chronic use of a corticosteroid, diabetes mellitus, comorbidity, ASA status, blood loss, access type, BMI, and log-transformed operation time in order to have it normally distributed. The maximal number of variable included in the multivariate analysis will be determined according to the incidence of SSI rate (according to the "one in ten rule"). In the subsequent multivariate analysis, the factors with significant p-value in univariate analysis were entered in a logistic regression model to identify predictors for SSI. Fisher's exact test was used to compare the overall number of SSIs by type of operation. Mann–Whitney U test and Kruskal–Wallis test were used to compare continuous variables and Fisher's exact test for categorical variables for comparing VATS vs. conversion vs. open surgery group. p-values < 0.05 were considered statistically significant. Analyses were done using Stata 15 (Stata, RRID:SCR_012763).

TABLE 1 | Clinicopathological characteristics of 2,430 patients undergoing a thoracic surgery.

Variable	All *n* (%) or median (IQR) *N* = 2,430
Age	62.0 (49.0; 71.0)
Female	847 (34.9)
BMI (kg/m^2)	24.5 (21.6; 27.8)
ASA score	
<3	838 (34.5)
≥3	1,577 (64.9)
Unknown	15 (0.6)
Risks factors, comorbidity	
Cardiovascular disease	462 (19.0)
Pulmonary disease	610 (25.1)
Neurological/psychiatric disease	189 (7.8)
Kidney disease	197 (8.1)
Liver disease	68 (2.8)
Diabetes mellitus	227 (9.3)
Oncological disease	1,170 (48.1)
No comorbidity	688 (28.3)
Previous chemotherapy	254 (10.5)
Previous radiotherapy	128 (5.3)
Chronic steroid use	65 (2.7)
Main diagnosis	
Main bronchus, trachea pathology (malignant/benign)	7 (0.3)/1 (0.04)
Primary lung malignancy (NSCLC)	690 (28.4)
Mediastinum pathology (malignant/benign)	31 (1.3)/56 (2.3)
Malignant pleural pathology (mesothelioma)	104 (4.4)
Malignant pathology other	329 (13.5)
Benign pathology other	493 (20.3)
Empyema	208 (8.6)
Pneumothorax	147 (6.0)
Pleural effusion/hemothorax	83 (3.4)/31 (1.3)
Operation on the musculoskeletal apparatus	188 (7.7)
Postoperative complication	62 (2.6)

ASA, american society of anesthesiologists; BMI, body mass index; NSCLC, non-small cell lung carcinoma.

RESULTS

Patient Characteristics

For the reviewed period, 2,671 patients were operated at our department. Due to the abovementioned exclusion criteria, 241 procedures were excluded, leaving 2,430 patients/operations fulfilling the inclusion criteria (2014: 431 patients, 2015: 454, 2016: 476, 2017: 509, 2018: 560). Clinicopathological characteristics are summarized in **Table 1**.

Perioperative Outcome

Elective surgery was mainly performed (93.4%). Antibiotics were administrated prior to the incision or were already prescribed as a therapy in 97.1% of the cases. The median operation time was 85 min. In 24.2% of operations, blood loss was

TABLE 2 | Perioperative characteristics of 2,430 patients undergoing a thoracic surgery.

Variable	All *n* (%) or median (IQR) *N* = 2,430
Operation type	
Thoracoscopy	689 (28.4)
Decortication, pleurectomy	195 (8.0)
Lobectomy	363 (14.9)
Segmentectomy	285 (11.7)
Pneumonectomy	52 (2.1)
Thymectomy	70 (2.9)
Sympathectomy	57 (2.3)
Operation on the mediastinum	186 (7.7)
Other	533 (21.9)
Access type	
Open	683 (28.1)
Video-assisted-thoracoscopy	1,569 (64.6)
Conversion	50 (2.1)
Unknown	128 (5.3)
Antibiotic prophylaxis	
Prophylaxis prior to incision or therapeutic	2,359 (97.1)
Prophylaxis after incision	28 (1.2)
No antibiotics	37 (1.5)
Unknown	6 (0.2)
Elective operation	2,269 (93.4)
Operation time (min)	85.0 (50.0; 138.0)
Blood loss >100 ml	589 (24.2)
Hospitalization duration (days)	6.0 (4.0; 9.0)
Intraoperative complications	104 (4.3)
Vascular lesion	18 (0.7)
Lesion of other organ	6 (0.2)
Operation Interruption	6 (0.2)
Other	76 (3.1)
Postoperative complications (all Clavien–Dindo Grad)	954 (39.3)
Respiratory complication	121 (5.0)
Pneumothorax, persistent air leak	98 (4.0)
Cardiovascular complication	59 (2.4)
Surgical site infection	37 (1.5)
Bleeding	33 (1.4)
Decubitus	16 (0.7)
Persistence of drain secretion	10 (0.4)
Bronchial stump insufficiency	9 (0.4)
Hemothorax/chylothorax/empyema	5 (0.2)/6 (0.2)/8 (0.3)
Other	857 (35.2)
Clavien–Dindo classification ≥3b	108 (4.4)
Postoperative mortality (Grad 5)	17 (0.7)

>100 ml. Median hospitalization time was 6 days. For 104 (4.3%) operations, an intraoperative complication was reported. The global postoperative complication rate was 39.3% ($n = 954$), and there were 4.4% ($n = 108$) complications with a Clavien–Dindo grade ≥3b. Postoperative mortality was 0.7% (**Table 2**).

TABLE 3 | Analysis of factors associated with surgical site infection in 2,430 patients undergoing thoracic surgery.

Variable	UV		MV	
	HR (95% CI)	*p*-value	HR (95%-CI)	*p*-value
Previous radio- or chemotherapy	0.86 (0.30–2.44)	0.775		
Chronic steroid use	1.01 (0.14–7.49)	0.992		
Diabetes mellitus	1.53 (0.59–3.96)	0.384		
Comorbidity	2.06 (0.86–4.96)	0.101		
ASA score ≥3	2.30 (1.01–5.26)	**0.048**	1.54 (0.65–3.66)	0.328
Blood loss >100ml	4.21 (2.11–8.40)	**<0.001**	2.70 (1.11–6.55)	**0.029**
VATS	Ref.		Ref.	
Open	4.17 (2.10–8.28)	**<0.001**	2.37 (1.08–5.24)	**0.032**
Conversion	2.44 (0.31–19.05)	0.394		
BMI	1.00 (0.93–1.07)	0.985		
OP Time (min)	1.82 (1.10–3.01)	**0.02**	0.99 (0.53–1.82)	0.968

ASA, american society of anesthesiologists; BMI, body mass index; CI, confidence interval; MV, multivariate logistic regression analysis; HR, Hazard ratio; UV, univariate logistic regression analysis; VATS, video-assisted thoracic surgery.

SSI

SSIs were reported in 37 cases (1.5%). For the logistic regression analysis, patients with unknown access type were excluded (128 patients). Univariate logistic regression analysis showed that ASA score ≥3, blood loss >100 ml, open surgery, and longer operation time were associated with higher SSI rate. For the access type, the open subgroup and the conversion subgroup were compared individually to the VATS subgroup. In the multivariate logistic regression analysis, blood loss >100 ml [$p = 0.029$, HR 2.70 CI (1.11–6.55)] and open surgery [$p = 0.032$, HR 2.37 CI (1.08–5.24)] were independent risk factors for SSI (**Table 3**). Conversion was not a risk factor for SSI. The only SSI occurring after a conversion was in a patient with severe comorbidities operated for an empyema.

The difference in SSI rate between open procedure and VATS was statistically significant [3.4 vs. 0.8% ($p < 0.001$)]. The difference was also significant in the anatomical resection group [2.3 vs. 0.2% ($p = 0.043$)] (**Figure 1**).

In the empyema subgroup (208 cases), the majority of cases were operated with a minimal invasive technique [VATS = 141 (67.8%) including 12 conversions vs. open = 59 (28.4%) and 8 missing data (3.8%)]. In this subgroup, 10 (4.8%) SSIs occurred (VATS = 3, open = 6, missing = 1).

SSIs were associated with longer hospital stays for all operations (6 vs. 14 days, $p < 0.001$) and for anatomical resections (7 vs. 17 days, $p < 0.001$) (**Table 4**). When SSIs were diagnosed, the mean hospital stay was 9.9 days longer for all thoracic operations and 14.5 days longer in anatomical resection. Persistent air leak was present in one patient with SSI, and even after exclusion of this patient, the length of stay was longer in the SSI subgroup (median 13.5 days). In the anatomical resection subgroup, the Number Needed to Treat using the VATS technique to prevent one SSI was 47.6.

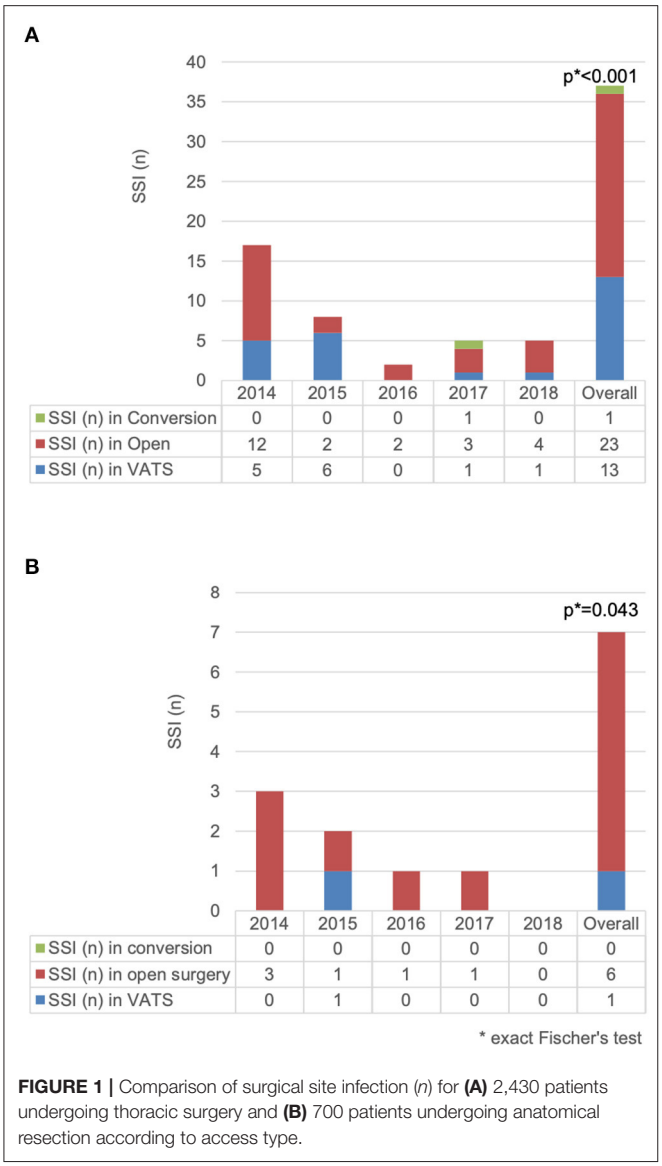

FIGURE 1 | Comparison of surgical site infection (*n*) for **(A)** 2,430 patients undergoing thoracic surgery and **(B)** 700 patients undergoing anatomical resection according to access type.

TABLE 4 | Comparison of hospitalization duration for 2,430 patients undergoing thoracic operation and for 700 patients undergoing anatomical resection according to SSI.

Thoracic operation	*N* = 2,430	Hospitalization duration (days) median (IQR)/mean	*p*-value**
Without SSI	2,201	6 (4.0; 9.0)/7.8	**<0.001**
With SSI	37	14 (8.5; 21.0)/17.7	
Missing data	192		
Anatomical resection	*N* = 700		
Without SSI	693	7 (5.0; 9.5)/8.21	**<0.001**
With SSI	7	17 (16.0; 37.0)/22.71	

IQR, interquartile range; SSI, surgical site infection.
***Mann–Whitney U test.*

Open vs. VATS

The majority of operations were performed using a video-assisted approach (64.6%) with a conversion rate of 3.1% (50/1619). The proportion of VATS increased over the years, from 51.5% (n = 222) in 2014 to 67% (n = 375) in 2018. This is mainly due to the implementation of our VATS program for anatomical lung resections. The rate of conversions ranged from 1.8% (6/336) to 6.0% (20/335), with the highest rate in 2015 and the lowest rate in 2016 and 2018 (**Figure 2A**).

In the cohort undergoing an anatomical lung resection, 58.6% (n = 410) of procedures were done by VATS. In this subgroup, VATS surgery strongly increased over the years [26.7% (n = 24) to 69.3% (n = 115)] as it was progressively introduced at our department as a standard procedure. During the first 2 years (2014 and 2015), the conversion rate was higher [17.2% (5/29) and 10.8% (7/65), respectively], reflecting the learning curve in VATS anatomic resections (2016: 0%; 2017: 4.2%; 2018: 2.5%) (**Figure 2B**).

Table 5 shows the comparison of clinicopathological data between VATS (conversion included) and the open thoracic surgery group. Except for previous chemotherapy and operation indication, there was no statistical difference. However, the outcome differs with a lower intraoperative ($p < 0.001$) and postoperative morbidity ($p < 0.001$). Blood loss and operation time were also lower in the VATS group.

DISCUSSION

Our study describes the SSI rate at our thoracic surgical department between 2014 and 2018. Open surgery and blood loss >100 ml were found to be independent risk factors for SSI in the multivariate analysis.

The overall SSI rate was 1.5%, which reflects current literature rates mentioned above (6–11). There is no consensus on criteria for the diagnosis of SSI (1, 4, 18). Up to 41 SSI definitions are reported in the literature. Only five were reported as standardized definitions: CDC-1988, CDC-1992, SISG (Surgical Infection Study Group), NPS (National Prevalence Survey), and PHLS (Public Health Laboratory Service) (1, 17, 27). This variety of SSI definitions can result in over-/underreporting of SSI rates (27).

We did not consider empyema and pneumonia as SSI, since both can be present in other situations (e.g., in case of bronchial stump insufficiency or atelectasis). Most studies reporting SSI in thoracic surgery did the same. As an exception, the second study of Imperatori et al. on the subject in 2017 includes pneumonia and empyema in SSI. This was not the case in their previous study in 2006 (9, 24).

Current WHO recommendations for the prevention of SSI are reported in "Global Guidelines for the Prevention of Surgical Site Infection" (1). Except for antimicrobial-coated sutures, our clinic puts effort into following the current recommendations for the prevention of SSI in a standardized way. Our strong adherence to current WHO recommendations probably played a role in the low SSI rate reported in our study.

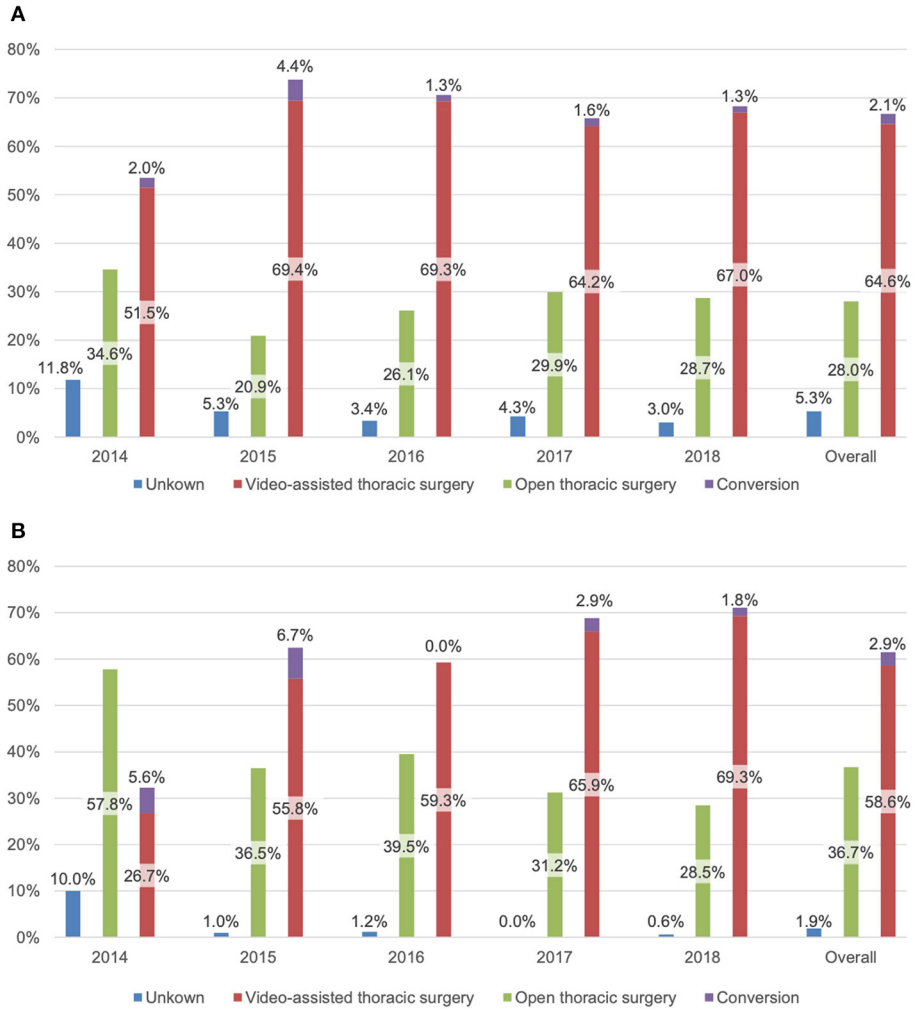

FIGURE 2 | Access type (%) for **(A)** 2,430 patients undergoing thoracic surgery and **(B)** 700 patients undergoing anatomical resection.

We observed a good adherence to protocols for the administration of antibiotic prophylaxis (or the ongoing antibiotic treatment) in 97.1% of the cases. Antibiotic given after the incision (1.2%) can occur when collection of samples for microbial determination is required prior to the administration of antibiotics.

In colorectal surgery, the superiority of laparoscopic surgery has been demonstrated as well as its association with lower SSI rates (28). There are little data determining the influence of VATS on SSI rate especially for anatomical lung resection. Imperatori et al. reported a SSI incidence of 3.2% in 988 thoracic surgical procedures during the years 1996–2005. SSI rate was lower in wedge resections by VATS than in open surgery (5.5 vs. 17.9%, $p < 0.001$), but all anatomical resections were performed by an open approach (9). In his second study from 2006 to 2015, the multivariate analysis did not identify open surgery as a risk factor for SSI in comparison with VATS (24). Only 36 of the 512 anatomical resections were performed with VATS. Cvijanović et al. reported a SSI rate of 6.1% in thoracic surgery in 3,370 patients over a 12-year period (VATS: 2.14%, Open 7.1%), but the result was not significant in a multivariate analysis aiming to identify SSI risk factor and only 30 of the 1,319 anatomical resections were performed by VATS (10). In all these studies, the compared groups were rather heterogeneous, and although the study of Cvijanović et al. is one of the largest studies investigating this matter in thoracic surgery so far, the long study period includes a lot of changes in patient treatment (used disinfectant, preoperative antibiotics, surgical technique, etc.). Three studies based on large state or society databases mention SSI rate but not as one of their main endpoints. Falcoz et al. reported a significantly lower SSI rate in VATS lobectomy (0.2%) vs. open (0.7%, $p = 0.0218$) for primary non-small cell lung cancer in a propensity-matched analysis (21). Two other studies did not confirm the advantage of VATS lobectomy concerning the SSI rate (6, 23).

High blood loss is often a marker of longer and more difficult operations with probable need for transfusion and is associated with more complications, especially of cardiopulmonary origin,

TABLE 5 | Comparison of clinicopathological characteristics of 700 patients undergoing anatomical resection (VATS = 410, Open = 257, Conversion = 20, Missing data = 13) according to access type.

Variable	VATS *n* (%) or median (IQR) *N* = 410	Conversion *n* (%) or median (IQR) *N* = 20	Open surgery *n* (%) or median (IQR) *N* = 257	*p*-value*
Age	66 (59.0; 72.0)	64.5 (58.0; 69.75)	64 (57.0; 71.0)	0.063
Men	264 (64.4)	13 (65)	160 (62.3)	0.568
BMI	24.5 (21.70; 28.15)	24.2 (22.03; 28.2)	24.8 (21.9; 28.4)	0.551
ASA score ≥3	321 (78.3)	17 (85%)	212 (82.5)	0.237
Comorbidity				
Cardiovascular disease	104 (25.4)	4 (20%)	62 (24.1)	0.785
Pulmonary disease	138 (33.7)	6 (30)	95 (37.0)	0.364
Neuro/psych. disease	29 (7.1)	2 (10)	27 (10.5)	0.156
Kidney disease	34 (8.3)	0 (0)	18 (7.0)	0.766
Liver disease	14 (3.4)	0 (0)	7 (2.7)	0.821
Diabetes mellitus	35 (8.5)	1 (5)	29 (11.3)	0.226
Oncological disease	310 (75.6)	17 (85)	202 (78.6)	0.344
No comorbidity	34 (8.3)	1 (5)	20 (7.8)	0.886
Previous chemotherapy	41 (10.0)	3 (15)	51 (19.8)	**0.001**
Previous radiotherapy	31 (7.5)	3 (15)	21 (8.2)	0.886
Chronic steroid use	7 (1.7)	0 (0)	9 (3.5)	0.124
Operation indication				**0.001**
Oncological	348 (84.9)	20 (100)	238 (92.6)	
Benign	54 (13.2)	0 (0)	12 (4.7)	
Infectious	8 (2.0)	0 (0)	7 (2.7)	
Elective operation	409 (99.8)	20 (100)	253 (98.4)	0.068
Operation time (min)	122 (98.0; 152.0)	180 (139.5; 218.75)	174 (136.25; 224.75)	**<0.001**
Blood loss >100 ml	110 (26.8)	12 (60)	168 (65.4)	**<0.001**
Hospitalization duration (days)	6 (5.00; 8.00)	8 (6.25; 13.75)	9 (8.00; 12.00)	**<0.001**
Clavien–Dindo ≥3b	20 (4.9)	2 (10)	30 (11.7)	**0.003**
Postoperative mortality	1 (0.2)	0 (0)	4 (1.6)	0.068
Intraoperative complications	7 (1.7)	7 (35)	25 (9.7)	**0.001**
Postoperative complications	182 (44.4)	9 (45)	170 (66.1)	**<0.001**
Surgical site infection	1 (0.2)	0 (0)	6 (2.3)	**0.013**

ASA, American society of anesthesiologists; BMI, body mass index; IQR, interquartile range VATS, video-assisted thoracic surgery.
**Fisher's exact test for categorical variables, Kruskal–Wallis test for continuous variables.*

as well as shorter survival and immunity impairment (19, 25). Mean blood loss is reported to be lower in VATS surgery and could therefore indirectly influence the SSI rate in VATS operations (13, 19, 22). In our study, however, a blood loss >100 ml was an independent risk factor for SSI in the multivariate analysis.

In current literature, intraoperative complications tend to be identical or higher in VATS than in open surgery (6, 23). The length of hospital stay, overall hospitalization costs, and postoperative complication seem similar or even better for VATS (6, 8, 20). The implementation of the VATS program at our department in the initial study period showed typical characteristics of the learning curve with a conversion rate falling from 4.4% to 1.3–1.6%. Intraoperative and postoperative complications were lower in VATS along the whole period. Cvijanovic et al. as well as our study showed that conversion is not associated with a higher SSI rate ($p = 0.733$) (10). It seems therefore reasonable to attempt a minimally invasive operation even when the risk of conversion is high.

As SSIs represent longer hospital stay, rehospitalization, reoperation, and specific care, it is associated with higher costs. Cost burden associated with SSI in Europe is estimated at 1.47–19.1 billion Euro with 7–14 days of extended hospital stay (4, 29). Our study reports a longer hospital stay in the SSI subgroup. However, other postoperative complications were also more frequent in this subgroup. Therefore, the extended hospitalization can also be explained with a complication cascade including SSI and not solely resulting from an SSI occurrence.

Our study presents the limitation of being retrospective, and the comparison of VATS and open surgery groups for anatomical resection has an inherent bias. There were more preoperative chemotherapies (10.2 vs. 19%) and indication for operation was more often oncological in the open group (92.6 vs. 84.9%). Patient requiring neoadjuvant chemotherapy often have larger

tumors and positive mediastinal lymph nodes and, consequently, open surgery was preferred, especially during the learning phase. However, it is important to notice that the rate of patients operated for infectious diseases (suspicion of malignancy for nodules of organizing pneumonitis) were similar in the open and VATS subgroups (2.7% resp. 2.0%). Interestingly, the 20 cases necessitating a conversion had no SSI. During the learning phase, complex anatomical resection was performed with an open access and could be responsible for a higher rate of intraoperative complications and blood loss. However, this can also be the case for the VATS subgroup where operations performed during the learning phase were included.

We deliberately included cases of empyema in our study for a real-life global overview on the causes of SSI. The majority of those cases were operated with a minimally invasive technique and cannot be an explanation for the global lower SSI rate in the VATS subgroup. Nevertheless, our study is one of the largest study to investigate the matter of SSI in general thoracic surgery practice and especially includes the most homogeneous patients and standardized procedures so far.

CONCLUSION

SSI is associated with open approach and higher blood loss in a general thoracic surgery practice. They are also correlated to higher postoperative morbidity and longer hospital stay, leading to higher overall costs, and attempts should be made to prevent them. From the two risk factors identified, only the minimal invasive approach can be influenced by the surgeon, and since conversion does not seem to harm the patient, we advocate a primary VATS approach whenever possible.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Cantonal Ethics Committee of Bern. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PA, JAL, and GJK: conception and design. T-LN, PD, and JAL: administrative support. T-LN, PD, GJK, and JAL: provision of study materials or patients. PA and JAL: collection and assembly of data and data analysis and interpretation. All authors contributed to the article and approved the submitted version.

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Nodal Upstaging Evaluation After Robotic-Assisted Lobectomy for Early-Stage Non-small Cell Lung Cancer Compared to Video-Assisted Thoracic Surgery and Thoracotomy: A Retrospective Single Center Analysis

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Introduction: The standard surgical procedures for patients with early-stage NSCLC is lobectomy-associated radical lymphadenectomy performed by using the thoracotomy approach. In the last few years, minimally invasive techniques have increasingly strengthened their role in lung cancer treatment, especially in the early stage of the disease. Although the lobectomy technique has been accepted, controversy still surrounds lymph node dissection. In our study, we analyze the rate of upstaging early non-small cell lung cancer patients who underwent radical surgical treatment using the robotic and the VATS techniques compared to the standard thoracotomy approach.

Methods and Materials: We retrospectively reviewed patients who underwent a lobectomy and radical lymphadenectomy at our Institute between 2010 and 2019. We selected 505 patients who met the inclusion criteria of the study: 237 patients underwent robotic surgery, 158 patients had thoracotomy, and 110 patients were treated with VATS. We analyzed the demographic features between the groups as well as the nodal upstaging rate after pathological examination, the number of dissected lymph nodes and the ratio of dissected lymph nodes to metastatic lymph nodes of the three groups.

Results: The patients of the three groups were homogenous with respect to age, sex, and histology. The postoperative major morbidity rate was significantly higher in the thoracotomy group, and hospital stay was significantly longer. The percentage of the mediastinal nodal upstaging rate and the number of dissected lymph nodes was significantly higher in the robotic group compared with the VATS group. The ratio of dissected lymph nodes to metastatic lymph nodes was significantly lower compared with the VATS group and the thoracotomy group.

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Discussion: The prognostic impact of the R(un) status is still highly debated. A surgical approach that allows better results in terms of resection has still not been defined. Our results show that robotic surgery is a safe and feasible approach especially regarding the accuracy of mediastinal lymphadenectomy. These findings can lead to defining a more precise pathological stage of the disease and, if necessary, to more accurate postoperative treatment.

Keywords: NSCLC, robotic thoracic surgery (RATS), mediastinal lymphadenectomy, VATS, thoracic oncology

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) represents 80% of all lung cancers (1). Despite recent advances made in therapy, patients with NSCLC still present an estimated 5-year overall survival rate <25% for all stages (2). Current prognostic factors for this tumor include TNM staging, tumor size, and node positivity, as well as histological grade and histological subtypes; however, there is a need to improve the reliability of these with other indicators (3). Novel diagnostic surgical procedures improved the preoperative staging for patients with suspected NSCLC (4). Despite the accuracy of endoscopic procedures in finding pathological lymph nodes, a high number of postoperative pathological upstaging is still detected (5). In the last few decades, the surgical treatment of NSCLC has evolved toward an increasing use of minimally invasive techniques, at first with video-assisted thoracoscopic surgery (VATS) and more recently with robotics (6). Standard radical surgical treatment for early-stage NSCLC is lobectomy associated with radical lymphadenectomy (7, 8). Despite the fact that the open thoracotomy technique is considered the gold standard, minimally invasive lobectomy has been associated with improved perioperative and comparable long-term outcomes (9). However, controversy remains regarding lymph node assessment. Lymph node dissection is a crucial component in the surgical treatment of NSCLC. Survival in lung cancer after surgery depends on the number of pathological nodes (pN); thus, lymph node upstaging can be considered a surrogate for surgical quality of the procedure. Although previous studies have shown that VATS can yield an adequate lymphadenectomy, other studies have observed that nodal upstaging with VATS was significantly less common. A perceived benefit of robotic surgery is its ease of use for lymph node dissection. Thus, an accurate histopathological evaluation of the hilum-mediastinal lymph nodes seems to be more feasible. In this study, we evaluated patients with early-stage NSCLC who underwent pulmonary resection and radical lymphadenectomy with robotic technology compared to other surgical techniques. In 2012, we started a minimally invasive thoracic surgery program, first with the introduction of VATS and in 2016 with the launch of robotic surgery. We evaluated the nodal upstaging rate of VATS and robotic surgery compared with the gold standard, the thoracotomy approach. As a secondary aim, we retrospectively evaluated the value of the ratio of positive lymph nodes compared to removed lymph nodes.

METHODS AND MATERIALS

Study Design

The study was designed as a single-center and retrospective case-matched analysis (VATS vs. thoracotomy vs. Robotic-Assisted Thoracic Surgery, RATS) in patients presenting with early stage NSCLC with clinical N0 who underwent curative surgery. Data for the analysis were retrieved from our lobectomy database. Up until 2012, our standard surgical technique for the treatment of early stage NSCLC was thoracotomy. From 2012, we started the VATS lobectomy program, first using the tri-portal or bi-portal approach and from 2014 the uni-portal technique. From 2016, we started the RATS lobectomy program using the Robotic Da Vinci technology, first with the Si model, then with the Xi model.

The general inclusion criteria for this study were patients diagnosed with NSCLC at stages I–II with clinical N0 disease undergoing anatomical lobectomy plus systematic lymph node dissection. The completeness of the lymphadenectomy has been evaluated in accordance with the IASLC definition regarding complete lymph node dissection of both N1 and N2 stations (10). Patients with clinical stages III–IV were excluded, and clinical N1 confirmed with endoscopic procedures, patients with SCLC, sublobar resections, and wedge resections were also excluded. Patients who had undergone preoperative chemotherapy or radiotherapy were excluded. Bi-lobectomy or pneumonectomy patients were not included in the study.

From January 2010 to December 2019, we performed a total of 1,352 lobectomies at our Institutes. In all, 505 patients were selected for our study in accordance with the inclusion criteria of this study. And 237 patients underwent robotic surgery, 158 patients underwent posterolateral thoracotomy, and 110 patients were treated with bi-portal or uni-portal VATS.

Preoperative Staging

Preoperative investigations included thoracic and upper abdominal computed tomography (CT) and F18-fluorodeoxyglucose positron emission tomography (FDG-PET) used to establish the absence of multiple pulmonary lesions and the absence of hepatic, adrenal, or brain metastases, and also to evaluate hilar and mediastinal lymph node status. Bone scintigraphy was performed if clinically indicated (11). At the preoperative stage, lymph nodes were considered negative when the CT scan showed a short-axis < 1 cm and/or when the standardized uptake value was <3 in the PET scan, in accordance with the guidelines of nuclear medicine physicians. In the event of nodes > 1 cm and SUV in PET scan < 3, an endobronchial

ultrasound transbronchial fine needle aspiration (EBUS-TBNA), an endoscopic ultrasound fine needle aspiration (EUS-FNA), mediastinoscopy, or VATS was performed to exclude malignancy (12). Before the operations were carried out, all patients had signed an informed consent to undergo a lobectomy. All patients who underwent VATS or RATS procedures were informed about the possibility of switching to thoracotomy in the case of unexpected technical problems during surgery. Before performing surgery, all patient cases were discussed in multidisciplinary meetings consisting of thoracic surgeons, oncologists, pathologists, radiotherapists, and pneumologists.

Surgical Technique

All the procedures were performed by surgeons with demonstrated proof of experience with performing this technique. The posterolateral thoracotomy requires the patient to be positioned in the lateral decubitus. The incision started along the inframammary crease and extended below the tip of the scapula. It was then extended superiorly between the spine and the edge of the scapula, a short distance away. If necessary, the trapezius was also divided. The serratus anterior and latissimus dorsi muscles were identified and could be retracted. The intercostal muscles were then divided along the superior border of the ribs, and the thoracic cavity was accessed.

The VATS approach was performed with a 3-cm anterolateral non rib-spreading utility incision in the fifth intercostal space, splitting the serratus anterior along its muscle fibers. In the case of a bi-portal approach another additional 12-mm port, in the seventh intercostal space on the middle axillary line for using a 10-mm access, 30° camera was added (13).

Robotic surgery was performed by first using the Si da Vinci robot and after adopting the Xi version. The Si da Vinci robot is positioned at the head of the patient. The Xi da Vinci robot is positioned at the back of the patient. We always proceed performing a 3-cm utility incision at the 5th intercostal space anteriorly of the latissimus dorsi. The wound is usually protected with a soft tissue retractor. We then performed the other three operative ports under direct view guidance usually at the 8th or 9th intercostal space. We then started docking the robot. We always use a 30-degree stereoscopic robotic camera. Under direct view, the bed-assistant started to introduce the operative robotics arms.

The lobectomy technique, by thoracotomy, VATS, or RATS, was similar. The pulmonary vein, pulmonary artery, and lobar bronchus were individually isolated and divided with a vascular three-line stapler. A parenchymal stapler was also used for dividing incomplete fissures. In the VATS or robotic approach, the lobe was retrieved with an endoscopic bag.

The lymph node dissection was considered complete, when at least three mediastinal (N2) lymph node stations, always including station 7, were dissected, in addition to the intrapulmonary/hilar (N1) lymph nodes from station 10 and 11 (14).

Histopathological Examination

All specimens were formalin fixed, paraffin-embedded, and stained with hematoxylin and eosin. Tumors were evaluated by an experienced pathologist and graded according to the World Health Organization classification for NSCLC (15). Pleural invasion, lymphatic involvement, and vascular involvement were determined by hematoxylin and eosin staining. In each histological examination the number of resected lymph nodes has been indicated.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences for Windows (SPSS® 23.0, Chicago, IL, USA). Non-parametric tests were used for comparisons, and data were expressed as the median (standard deviation). The significance threshold was $p < 0.05$.

RESULTS

In **Table 1**, all the demographic and surgical features were reported. The three groups were homogenous in terms of age, gender, tumor dimension, preoperative staging and histology. Median age was 66.5 ± 8.8 years. In total, 282 patients were male while 222 were female. All patients after preoperative staging were in stage I or II according to the 8th TNM classification without lymph node disease (cN0). No differences between groups were reported in terms of preoperative clinical stages (I, Ib, IIa, IIb). The three groups were homogeneous with respect to the type of lobectomies performed ($p = 0.3$).

Median hospital stay was 6.28 ± 1.9 days but the VATS and RATS groups showed to have shorter hospital stay compared with the open group. The postoperative major morbidity rate until 30 days after surgery was significantly higher in the thoracotomy group compared to the VATS group and the robotic group (23, 14.5% vs. 6, 5.4% vs. 13, 5.5%; $p = 0.04$). No deaths occurred during the 30 days.

The histopathological yield showed that in all groups the most frequent histological type was adenocarcinoma. The histological examination confirmed pN0 disease in 399 patients. A total of 48 patients presented with pN1 disease while 58 patients presented with pN2 (**Table 2**). The distribution of the dissected lymph node stations are reported in **Figure 1**. Stations 7, 10, and 11 were always dissected according to the IASLC guidelines. There were no differences between groups in terms of number of lymph node stations resected.

In **Table 3**, the nodal upstaging rate is reported. The percentage of nodal upstaging in patients from the three groups was similar, although in the robotic group, a higher percentage of patients compared to the VATS group presented an upstaging from pN0 to pN2, with a statistically significant difference (25, 15.9% vs. 26, 11.0% vs. 7, 6.4%; $p = 0.04$). No patient with neuroendocrine tumors (39 typical and 9 atypical carcinoids) presented a nodal upstaging after surgery in the three groups. No differences between groups were reported in case of an upstaging from pN0 to pN1.

The results of the number of dissected lymph nodes and the lymph nodes ratio are summarized in **Table 4**. The number of the total lymph nodes resected was significantly higher in the robotic and thoracotomy group than the VATS group (13, 3–41 vs. 15, 3–44 vs. 9, 3–25; $p = 0.0001$). Even though the number of hilar

TABLE 1 | Demographic and surgical features in the Robotic, VATS, and Thoracotomy groups.

	Open ($n = 158$)	VATS ($n = 110$)	RATS ($n = 237$)	All Patients ($n = 505$)	*P*-value
Age (years)	68.9 ± 7.8	64 ± 5.3	65.2 ± 6.3	66.5 ± 8.8	0.5
Gender (M/F)	94/64	63/47	134/103	282/222	0.4
Side (R/L)	91/67	73/37	113/124	228/274	0.4
Lobectomy (*n*, %)					0.3
RUL	50 (31.5)	38 (34.5)	55 (23.2)	142 (28.5)	
ML	2 (1.5)	10 (9.6)	14 (5.9)	26 (5.4)	
RLL	39 (24.8)	24 (21.8)	43 (18.2)	106 (21.0)	
LUL	35 (22.5)	22 (20.5)	77 (32.5)	134 (26.5)	
LLL	31 (19.7)	15 (13.6)	48 (20.2)	94 (18.6)	
T Dimension (mm)	2.9 ± 1.8	2.6 ± 1.0	2.7 ± 1.6	2.7 ± 1.2	0.2
Hospital stay (days)	7.12 ± 3.4	5.2 ± 1.2	5.7 ± 1.1	6.28 ± 1.9	0.04
Preoperative stage (*n*, %)					0.3
Ia	75 (47.5)	59 (55.5)	102 (43.0)	237 (46.9)	
Ib	43 (27.2)	29 (26.4)	73 (30.8)	146 (28.9)	
IIa	25 (15.8)	12 (10.8)	49 (20.7)	86 (17.1)	
IIb	15 (9.5)	8 (7.3)	13 (5.5)	36 (7.1)	
Post-operative complications (*n,* %)	23 (14.5)	6 (5.4)	13 (5.5)	63 (12.5)	0.03

TABLE 2 | Histopathological and staging features in the Robotic, VATS, and Thoracotomy groups.

	Open ($n = 158$)	VATS ($n = 110$)	RATS ($n = 237$)	All Patients ($n = 505$)	*P*-value
Histology (*n*, %)					0.5
Adenocarcinoma	114 (72.1)	78 (70.9)	187 (78.9)	379 (75.0)	
Squamous cell carcinoma	23 (14.6)	19 (17.3)	36 (15.2)	78 (15.4)	
Neuroendocrine tumors	21 (13.3)	13 (11.8)	14 (5.9)	48 (9.6)	
pT (*n*, %)					0.3
1a	35 (22.2)	12 (10.9)	22 (9.3)	69 (13.7)	
1b	26 (16.5)	23 (20.9)	65 (27.4)	114 (22.6)	
1c	1 (0.6)	20 (18.2)	25 (10.5)	46 (9.1)	
2a	57 (36.1)	38 (34.5)	94 (39.7)	189 (37.4)	
2b	26 (16.5)	6 (5.5)	20 (8.4)	52 (10.3)	
3	12 (7.6)	9 (8.2)	11 (4.6)	22 (4.3)	
pN (*n*, %)					0.1
N0	118 (74.7)	95 (86.4)	187 (78.9)	399 (79.0)	
N1	15 (9.5)	8 (7.3)	24 (10.1)	48 (9.5)	
N2	25 (15.8)	7 (6.4)	26 (11.0)	58 (11.5)	

lymph nodes did not present any differences between groups, the number of resected lymph nodes in the mediastinal stations was significantly higher in the robotic group than the VATS group. The robotic surgery group showed a significantly lower value of lymph nodes ratio compared to the VATS (9.09, 4–67 vs. 18.55, 4–50; $p = 0.0001$) and the open surgery groups (9.09, 4–67 vs. 16.67, 2–100; $p = 0.0001$).

DISCUSSION

The standard surgical treatment for early-stage NSCLC is lobectomy and radical hilum mediastinal lymphadenectomy (16). The concept of the resection status analysis in early-stage NSCLC is still under great debate where the "IASLC Lung Cancer Staging Project" analysis emphasizes the need for improving pathologic nodal staging. Our group has contributed to the new staging project (17) by evaluating the relevance of nodal dissection with respect to the R status. Survival of lung cancer after surgery depends on the number of pathological nodes; therefore, an adequate surgical lymph node dissection should be the first aim during surgery (18). Survival following surgery for node-negative non-small cell lung cancer is associated with the number of lymph nodes dissected and analyzed (19). Higher numbers of resected lymph nodes provide more complete staging and reduce

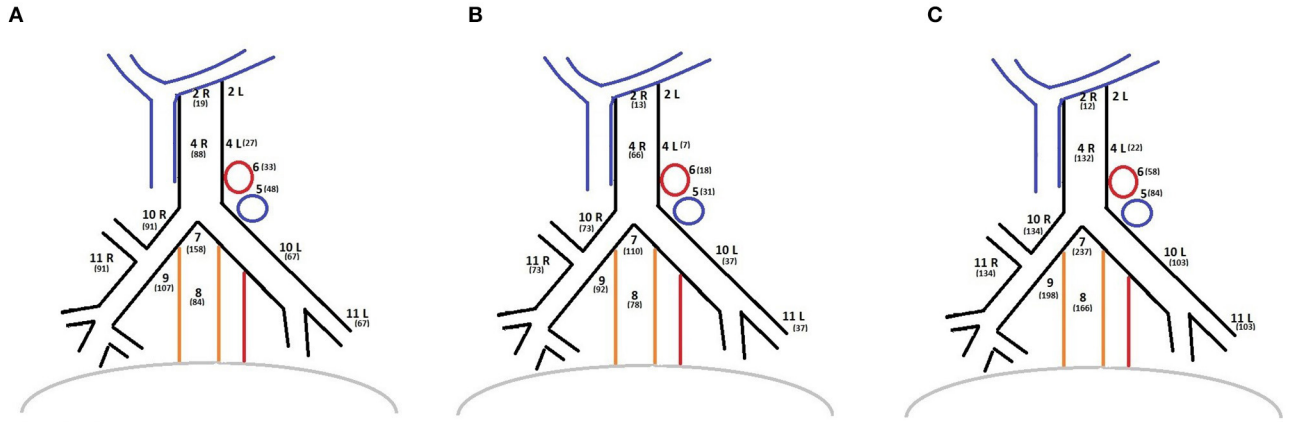

FIGURE 1 | (A) Lymph nodes stations distribution of OPEN group. **(B)** Lymph nodes stations distribution of VATS group. **(C)** Lymph nodes stations distribution of ROBOTIC group.

TABLE 3 | Nodal upstaging in the Robotic, VATS, and Thoracotomy groups.

	Open ($n = 158$)	VATS ($n = 110$)	RATS ($n = 237$)	All patients ($n = 505$)	*P*-value
Nodal upstaging (%)	40 (25.3)	15 (13.6)	50 (21.1)	105 (20.8)	$p = 0.1$
Hilar upstaging (%)	15 (9.6)	8 (7.3)	24 (10.1)	47 (9.3)	$p = 0.2$
Mediastinal upstaging (%)	25 (15.9)	7 (6.4)	26 (11.0)	58 (11.5)	$p = 0.04$

TABLE 4 | Lymph nodes features in the Robotic, VATS, and Thoracotomy groups.

	Open ($n = 158$)	VATS ($n = 110$)	RATS ($n = 237$)	All patients ($n = 505$)	*P*-value
Lymph nodes resected	13 ± 11.6	9 ± 5.7	15 ± 7.01	13 ± 8.2	0.0001
Hilar Lymph nodes resected	5 ± 3.1	3 ± 2.2	4 ± 2.0	4 ± 4.2	0.5
Mediastinal Lymph nodes resected	10 ± 8.2	7 ± 3.4	11 ± 9.6	12 ± 8.1	0.0001
Lymph nodes ratio (metastatic/resected)	16.7 ± 2.1	18.7 ± 1.7	9.1 ± 1.5	12.5 ± 2.1	0.001

the likelihood of missing metastatic lymph nodes (20). Although the preoperative staging technique has greatly improved, the number of metastatic lymph nodes that remain hidden is still significant. Therefore, lymph node upstaging after surgery could represent a quality indicator of treatment (21).

Up until two decades ago, the only surgical technique for treating NSCLC was thoracotomy but in the last few years minimally invasive techniques have significantly improved. The first minimally invasive technique adopted was video-assisted thoracoscopic surgery (VATS), demonstrating excellent morbidity and mortality outcomes (22). Short-term results of VATS compared with thoracotomy are well-documented: fewer complication rates, less postoperative pain, and shorter hospital stays (23). The long-term efficacy of VATS in comparison with the thoracotomy approach for lung cancer surgery is uncertain. In the last few years some authors showed the results of nodal upstaging in VATS procedures compared with thoracotomy, considered the gold standard (24). One of the most important comparative studies between VATS and open lobectomy and lymphadenectomy was performed by Licht et al., who evaluated the pathological results of 1,513 lobectomies for stage I NSCLC. The results showed that the VATS group reported a lower upstaging rate compared with the open group, but no differences in overall survival were found (25). On the other hand, Boffa et al. reported a similar nodal upstaging rate between the VATS and the open groups in a cohort of 11,500 patients from the Society of Thoracic Surgeons database (26). What the two studies have in common are the results concerning the number of mediastinal lymph nodes. VATS procedures showed a lower rate of resected lymph nodes, probably due to the more challenging dissection for a limited angle of maneuverability of thoracoscopic instruments.

The robotic approach represents a technological evolution of the VATS procedure (27). This leads to some technical advantages related to a better view of the operative field (3D instead of 2D), a simpler use of the instruments, more precise movements, and many possibilities deriving from the wide angle

of maneuverability of the instruments, which is even superior to that of the human hand (28, 29). The first experience of upstaging analysis in patients with clinical stage I NSCLC, who underwent robotic segmentectomies or lobectomies, was reported by Wilson. In his multiple institutional study, upstaging was observed in 10.9% of cases, especially in those patients with larger lung tumors (30). In a single-center retrospective study, Zirafa et al. compared the upstaging rate of robotic lobectomy with the gold standard thoracotomy lobectomy showing a similar upstaging rate of robotic lobectomy but a higher upstaging rate evaluating the N2 disease in the robotic group (31). This result demonstrated that the robotic mediastinal lymph node dissection can be carried out safely, leading to better pathological staging of the disease.

Kneuertz et al., in a multicentric retrospective analysis that compared the three approaches (VATS, RATS, and open surgery), included the patients with clinical N0/N1 who had undergone lobectomy for NSCLC. Unlike in our study, the authors selected patients who had undergone radical or sampling lymphadenectomy. The overall rate of lymph node upstaging was highest with open lobectomy (21.8%), followed by robotic (16.2%), and VATS (12.3%) ($p = 0.03$) while no significant differences were seen in mediastinal N2 upstaging between groups (32).

In our study we compared minimally invasive techniques, such as robotic surgery and VATS, with open surgery. We evaluated the rate of nodal upstaging in a cohort of patients with cN0 disease who had undergone lobectomy and radical lymphadenectomy according to the IASLC definition with these three techniques. Then we evaluated the number of dissected lymph nodes and the ratio between metastatic lymph nodes and all the dissected lymph nodes. The results showed that robotic surgery can well replicate the dissection of the lymph nodes performed in open surgery. Nodal upstaging from No to N1 was similar in all the groups. The hilar lymph nodes (stations 10 and 11) should commonly be dissected in order to clear the view of the vascular or bronchial structures that must be closed to perform a lobectomy. Therefore, regardless of the surgical technique, an adequate number of hilar lymph nodes were always dissected. The nodal upstaging rate from N0 to N2 showed that the robotic surgery presented a significantly greater rate compared with the VATS approach. These results are probably due to the greater difficulties encountered in comfortably reaching all mediastinal areas with thoracoscopic instruments compared with the robotic technology. With robotic surgery, the three operative arms allow an excellent view of the anatomical limitations also of small surgical areas such as the mediastinal lymph node stations. The use of 3D imaging allows us to achieve better exposure of the anatomical structures that should be preserved during dissection. Station 4R can be accurately dissected discovering the trachea, preserving the vagus nerve, and respecting the limits of the superior vena cava and the azygos vein. Station 5 can be resected, avoiding the lesions of the laryngeal nerve. Station 7 can be explored by dissecting all the tissues up to the contralateral principal bronchus. We believe that by using robotic technology these steps can be performed safely and standardized more easily. Mediastinal lymph node dissection can cause bleeding and in cases of deep surgical sites, hemostasis can prove to be challenging. The accuracy of the robotic three arms allows a feasible search for the source of bleeding, and the use of bipolar forceps hemostasis can be easily carried out.

The analysis of the number of dissected lymph nodes and the lymph nodes ratio confirmed that robotic surgery enables us to perform a more accurate resection of all the mediastinal lymph node stations compared with the VATS approach. To obtain a more truthful pathological staging of the clinical early stage, non-small cell lung cancer allows setting a faster and more accurate postoperative oncological treatment in the event of positive lymph nodes. We believe that robotic surgery permits a more precise dissection than the VATS approach; therefore, patients who underwent a robotic lobectomy presented a higher rate of nodal upstaging.

This is one of the first studies to compare the three surgical techniques used for the treatment of early-stage NSCLC. Our study has some obvious limitations. Because of the retrospective and non-randomized nature of the analysis, it cannot be claimed with certainty that robotic surgery is the best approach compared with VATS for the mediastinal lymph nodes dissection. However, without prospective studies reported in the literature, we analyzed retrospectively our single center experience with the three approaches that showed a higher mediastinal nodal upstaging rate in the robotic group. The selection of the carcinoid tumors can be considered a limit of this retrospective study. Indeed, the PET-FDG has a poor sensitivity to detect the lymph nodes metastases and the nodal upstaging rate can be higher in comparison with the other histological types (33, 34). The patients with carcinoids presented preoperative contrast-enhanced CT scans without enlarged lymph nodes and after surgery no patient presented a nodal upstaging. Therefore, we think that the inclusion of these patients does not invalidate our results.

Other studies should be conducted to validate the oncological results of minimally invasive lymphadenectomy, but we believe that by using the robotic technique, a higher number of lymph nodes can be removed, and accurate pathological staging could bring better oncological outcomes. These findings place thoracic robotic surgery as a valid alternative to the open approach and support it as the gold standard for the surgical treatment for NSCLC.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of our Ethics Committee. The protocol was reviewed and approved by the Comitato Etico Centrale

IRCCS Lazio Found. Bietti. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

FG designed the manuscript and drafted it. FG, EMel, DF, EMer, DM, SC, and FLC participated in the designing and drafting up of the manuscript. FC and FF critically revised it. PV, MM, SV, and SB coordinated the manuscript. All the authors contributed to the work during the years by their clinical or experimental activity, contributed to the article, and approved the submitted version.

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SYSTEMATIC REVIEW
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Effects of Vessel Interruption Sequence During Lobectomy for Non-small Cell Lung Cancer: A Systematic Review and Meta-Analysis

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Background: For lobectomy in non-small cell lung cancer (NSCLC), whether interrupting the pulmonary vein first (Vein-first) achieves better perioperative and survival outcomes than interrupting the pulmonary artery first (Artery-first) remains controversial. We conducted this meta-analysis to compare outcomes between the two groups to facilitate better surgical decision-making.

Methods: Web of Science, EMBASE, Cochrane Library, Ovid MEDLINE, PubMed, ScienceDirect, and Scopus were searched for eligible studies comparing Vein-first and Artery-first procedures. The primary endpoints were survival indicators [overall survival (OS), disease-free survival (DFS), and lung cancer-specific survival (LCSS)]. Secondary endpoints included intraoperative indicators, hospitalization, and follow-up indicators.

Results: After screening 2,505 studies, 8 studies involving 1,714 patients (Vein-First group: 881 patients; Artery-first group: 833 patients) were included. The vein-first group achieved better OS [HR (hazard ratio): 1.46, 95% confidence interval (CI): 1.12–1.91, $p = 0.005$], DFS (HR: 1.60, 95% CI: 1.23–2.08, $p < 0.001$), and LCSS (HR: 1.64, 95% CI: 1.16–2.31, $p = 0.005$). The survival rates of OS at 2–5 years, DFS at 1–5 years, and LCSS at 3–5 years were also higher in the Vein-First group. Subgroup analyses suggested that the advantages of survival in the Vein-First group were primarily embodied in the subgroups of squamous cell carcinoma (SCC) and earlier pathological TNM stage (I–II). Operative time, intraoperative blood loss, total complications, and total recurrences were comparable between the two groups.

Conclusions: The Vein-first sequence is the suitable choice of vessel interruption sequence during lobectomy for NSCLC with better survival and similar perioperative outcomes, especially for stage I–II SCC.

Keywords: vessel interruption sequence, non-small cell lung cancer, meta-analysis, lobectomy, systematic review

INTRODUCTION

In the past decade, lung cancer was the main cause of cancer-related death worldwide (1, 2). Lobectomy has been used for decades in clinical practice as a classical surgical procedure for stage I–IIIA non-small cell lung cancer (NSCLC) (3). Interruptions of the pulmonary artery (PA) and pulmonary vein (PV) are the essential procedures for lobectomy. However, the choice of which blood vessel to interrupt first is an easily neglected problem in practice (4).

The effects of the interruption sequence of PA and PV has been a long-debated issue, and currently, no guidelines have been confirmed (5, 6). Wei et al. compared 86 patients in a randomized clinical trial (RCT) and suggested that ligation of the effluent veins first reduced tumor cell dissemination and improved survival outcomes (7). He et al. and Sumitomo et al. also reported similar results that favored the pulmonary vein first (Vein-first) group, especially for squamous cell carcinoma (SCC) (8, 9). However, several studies showed that the two groups achieved similar long-term survival and postoperative recurrences (10–12). Li et al. suggested that pulmonary vein interruption first increased blood loss without affecting the operative difficulty, tumor recurrence, metastasis, or survival (13).

To clarify this controversy and standardize the surgical process for a better prognosis of patients with NSCLC, we compared the relation of Vein-first and pulmonary artery first (Artery-first) surgical techniques to perioperative and survival outcomes.

MATERIALS AND METHODS

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Supplementary Table 1**) (14).

Search Strategy

Web of Science, EMBASE, Cochrane Library, Ovid MEDLINE, PubMed, ScienceDirect, and Scopus databases were systematically searched from inception to December 6, 2020, for studies analyzing the effects of vessel interruption sequence during thoracoscopic lobectomy for NSCLC. The following MeSH terms were used: "vein", "artery," and "lung cancer." The references of the retrieved literature (including meta-analyses and abstracts), bibliographies and gray literatures were also searched for further eligible articles. The detailed retrieval strategies are shown in **Supplementary Table 2**.

Abbreviations: NSCLC, non-small cell lung cancer; Vein-first, interrupting pulmonary vein first; Artery-first, interrupting pulmonary artery first; OS, overall survival; DFS, disease-free survival; LCSS, lung cancer-specific survival; OSR, overall survival rate; DFSR, disease-free survival rate; LCSSR, lung cancer-specific survival rate; HR, hazard ratio; SCC, squamous cell carcinoma; PA, pulmonary artery; PV, pulmonary vein; RCT, randomized clinical trial; SCC, squamous cell carcinoma; PRISMA, preferred reporting items for systematic reviews and meta-analyses; CTCs, circulating tumor cells; NOS, Newcastle-Ottawa scale; GRADE, grading of recommendations assessment, development, and evaluation; MD, difference in means; RR, risk ratio; CI, confidence interval; CT, cohort study; TNM, tumor node metastasis.

Selection Criteria

Inclusion criteria:

(1) Population: patients with NSCLC who underwent lobectomy.
(2) Intervention and comparison: Vein-First sequence (the PVs in the hilum of pulmonary lobes were dissected and transected first) vs. Artery-First sequence (all pulmonary arteries were to be completely ligated before venous interruption).
(3) Outcomes: survival, intraoperative outcomes, hospitalization, and follow-up outcomes.
(4) Study design: RCTs or cohort studies.

We excluded pure basic studies, reviews, animal experiments, and articles lacking original data.

Data Extraction

The following data were extracted by two independent investigators (XL and WXZ): the published year, first author, country, study period, participant characteristics (sex, age, comorbidity, and smoking status), tumor characteristics (histology, location, pathological stage), survival [overall survival (OS), disease-free survival (DFS), and lung cancer-specific survival (LCSS)], intraoperative outcomes (operative time, blood loss, and blood transfusion), hospitalization, and follow-up outcomes [postoperative hospital stay, postoperative drainage time, total complications, increment of circulating tumor cells (CTCs), and recurrences]. Any discrepancies between the investigators were resolved by a third author (YML).

Outcome Assessments

In addition to analyzing survival data (OS, PFS, and LCSS), we analyzed the survival rate at 1–5 years (OSR, PFSR, and LCSSR). We also analyzed the subgroup data of OS, DFS, and LCSS according to age, sex, comorbidity, smoking status, tumor location, sequence of vessel ligation, tumor size, N stage, pathological TNM stage, histological type, postoperative adjuvant therapy, use of a stapler, and type of resection.

Quality Assessment for Included Studies

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of cohort studies. The scale included three items: comparability, selection, and outcome. Scores $\geq$6 points indicate medium-high quality (15). A five-point Jadad scale was used to assess the quality of RCTs. The scale included three items: randomization, masking, and accountability of all patients. Scores $\geq$3 points indicate high quality (16).

The Grades of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to assess the evidence level of the results. The system included five items: imprecision, risk of bias, indirectness, inconsistency, and publication bias. Very low, low, moderate, and high were the four levels of evidence (17).

Statistical Analysis

Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA

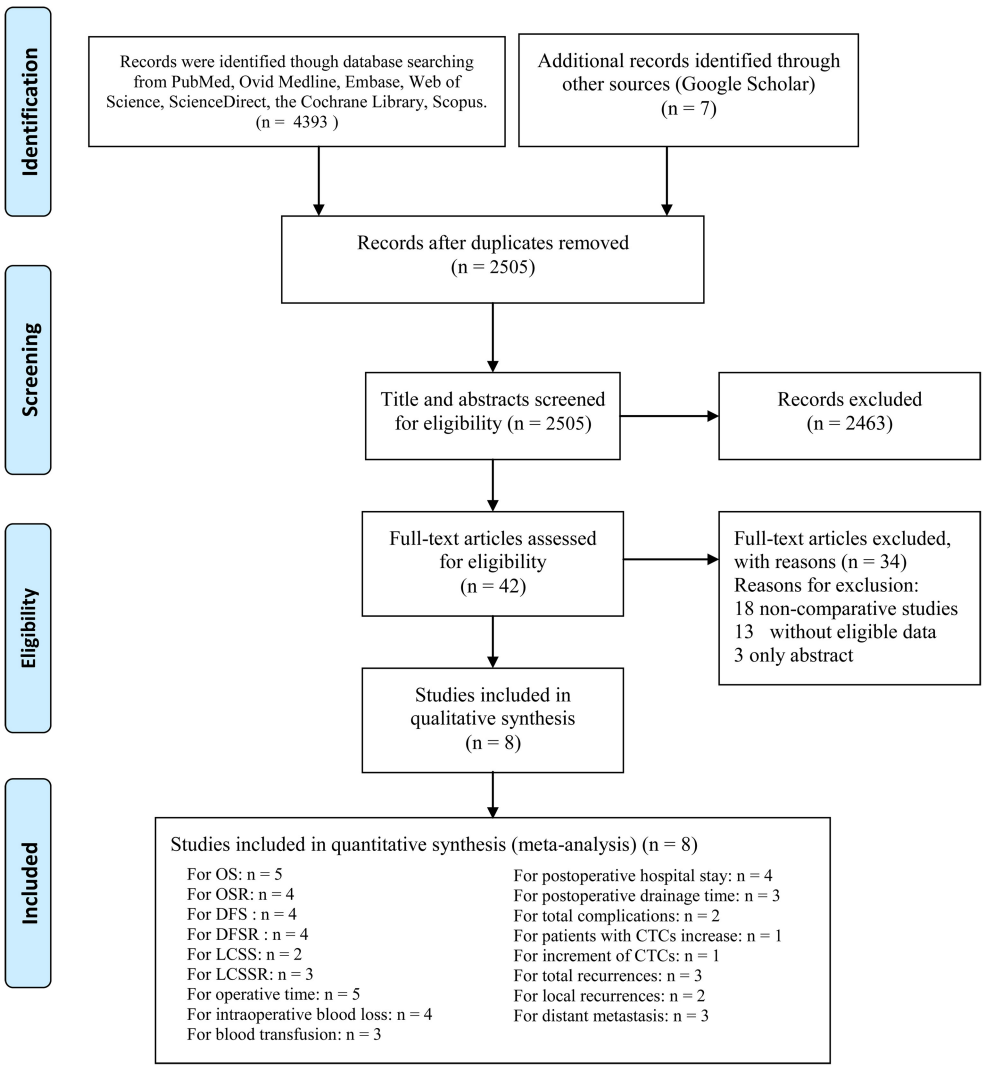

FIGURE 1 | Flow chart of the study selection process.

12.0 (StataCorp, College Station, TX, USA) were used to analyze the pooling data. We used HRs to analyze the survival data (OS, DFS, and LCSS). When the HR > 1, then the results supported the Vein-First group. We used the difference in means (MD) to analyze the continuous variables (operative time, postoperative drainage time, and increment of CTCs). We used the pooled risk ratios (RRs) to analyze the dichotomous variables (OSR, PFSR, LCSSR, blood transfusion, total complications, recurrences, and rate of CTC increase). In the analysis of OSR, PFSR, and LCSSR, the results supported the Vein-First group when the RR > 1. In the analysis of other variables, the results supported the Vein-First group when the RR < 1. The HRs of survival data were extracted directly from the seven studies or the Kaplan-Meier curves according to Tierney's method (18). The I^2 statistic and χ^2-test were used to assess the heterogeneity. The random-effects model was used for significant heterogeneity ($I^2 > 50\%$ or $p < 0.1$). Otherwise, the fixed-effects model was used. Egger's (19) and Begg's tests (20) were used to assess the publication bias. $P = 0.05$ was set as the statistical boundary value, and $p < 0.05$ indicated statistical significance.

RESULTS

Search Results and Quality Assessment of the Included Studies

A total of 2,505 studies were initially searched, and seven papers involving eight studies (Vein-First group: 881 patients; Artery-First group: 833 patients) were included for the final analysis (**Figure 1**) (7–13). Seven (7–9, 11–13) of the eight studies were conducted in Asia, and one (10) study was performed in Europe. Two studies were RCTs, and the other six studies were cohort studies. According to the NOS and Jadad scale, two studies (8, 9) were of

TABLE 1 | Summary of the baseline characteristics of the included studies.

Study		Country	Period (year)	Groups	Patients	Sex (M/F)	Age (Mean, year)	Lesion location (lobes)					Pathological TNM stage[a]								Follow up (months)
								Right			Left		I		II		III		IV		
								Upper	Middle	Lower	Upper	Lower	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB	
2019	Wei (7)-RCT	China	2016–2018	Vein-First	43	25/18	62.1		27			16	22		10		9		2		–
				Artery-First	43	26/17	63.2		28			15	21		10		12		0		
2019	Wei (7)-RT	China	2005–2017	Vein-First	210	113/97	59.7		139			71	137		33		40		0		30
				Artery-First	210	120/90	58.6		126			84	128		30		52		0		
2019	He (8)	China	2012–2013	Vein-First	33	22/11	59.6	18	5	2	8	0	8	6	2	6	10	0	1	0	54.5
				Artery-First	27	19/8	62.2	6	1	10	3	7	1	9	4	5	5	3	0	0	
2018	Sumitomo (9)	Japan	2007–2013	Vein-First	104	51/53	66.1	41	7	20	25	11	65	26	0	5	8	0	0	0	54.9
				Artery-First	83	41/42	66.2	13	6	31	14	19	55	15	3	5	5	0	0	0	
2015	Li (13)	China	2006–2013	Vein-First	174	94/80	62.8	76	27	17	41	13	138	36	0	0	30				
				Artery-First	93	36/57	62.6	12	9	43	3	26	79	14	0	0	26				
2013	Kozak (10)	Poland	1999–2003	Vein-First	170	124/46	60.2	–	–	–	–	–	76	24	39	0	62.4				
				Artery-First	215	143/72	59.8	–	–	–	–	–	105	58	52	0	60.1				
2007	Yellin (11)	Israel	2001–2003	Vein-First	14	8/6	66.6	6	0	3	4	1	–	–	–	–	–	–	–	–	–
				Artery-First	16	9/7	63.1	5	0	4	4	3	–	–	–	–	–	–	–	–	
2003	Refaely (12)	Israel	1992–1998	Vein-First	133	86/47	64.5		85			45	77		21		29		6		22.6
				Artery-First	146	89/57	65.7		78			68	75		29		39		3		

M/F, male/female; TNM, tumor node metastasis.

[a] *Pathological TNM stage: four studies [Wei (7)-RCT, Wei (7)-RT, He (8), and Sumitomo (9)] were according to 8th edition of TNM classification, two studies [Li (13) and Kozak (10)] were according to 7th edition of TNM classification, one studies [Refaely (12)] were according to 6th edition of TNM classification. Data on lung cancer staging are not available in Yellin (11).*

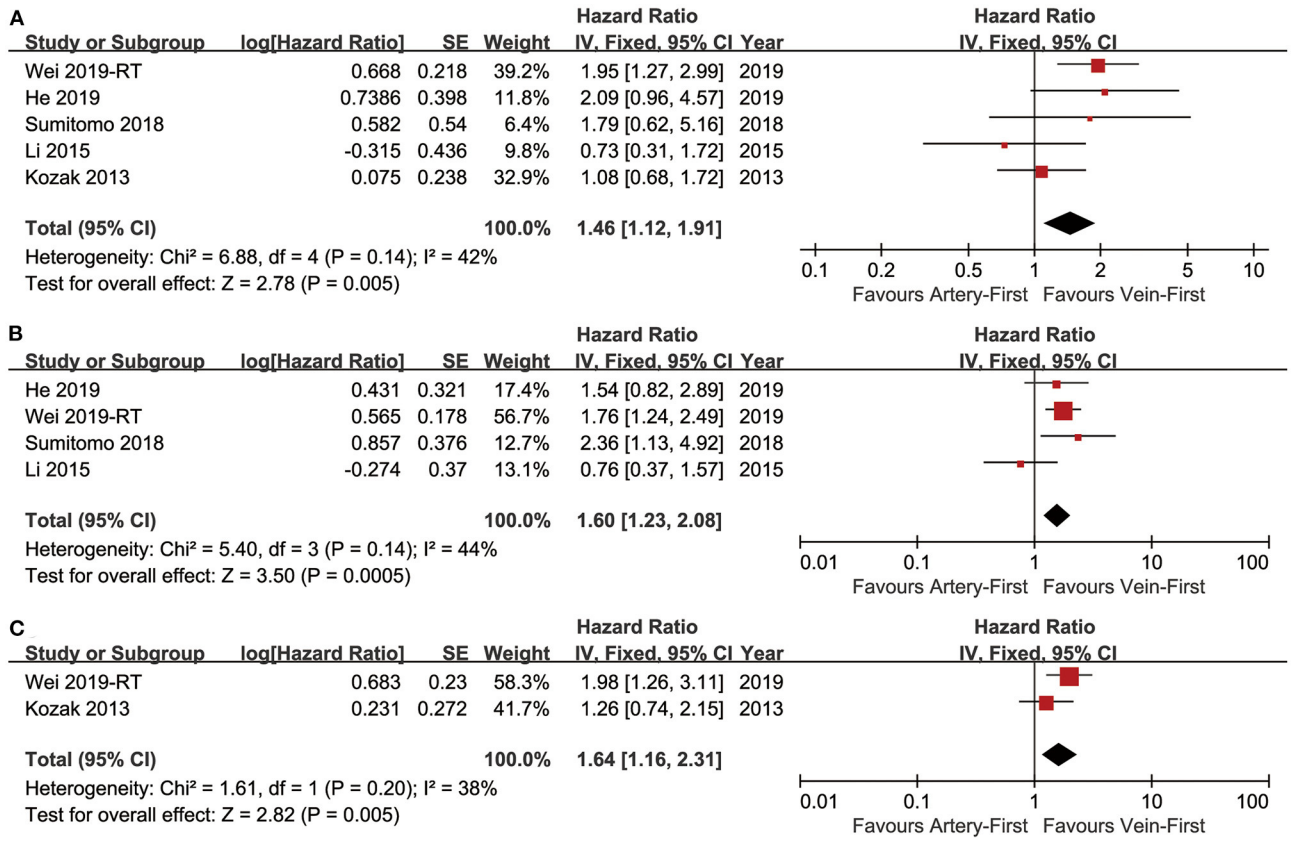

FIGURE 2 | Forest plots of OS **(A)**, DFS **(B)**, and LCSS **(C)** associated with Vein-first vs. Artery-first.

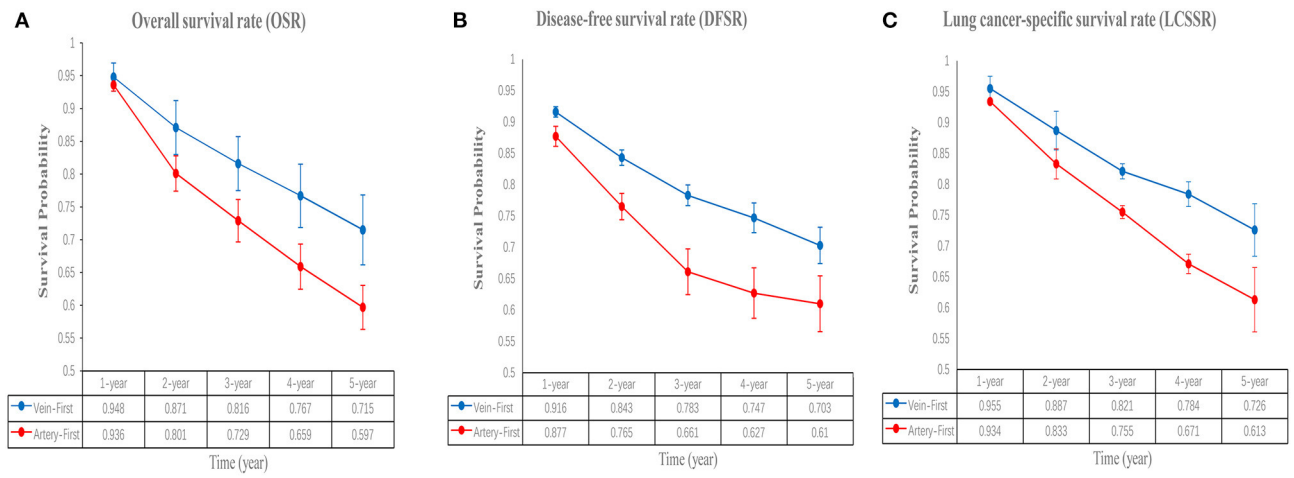

FIGURE 3 | Comparisons of OSR (1–5 years, **A**), DFSR (1–5 years, **B**), and LCSSR (1–5 years, **C**) associated with Vein-first vs. Artery-first according to survival time.

medium quality, and six studies (7, 10–13) were of high quality (**Supplementary Table 3**). The baseline characteristics are listed in **Table 1.** According to the GRADE system, the quality evidence of all results were low to very low (**Supplementary Table 4**).

Survival

Five studies (7–10, 13) compared OS with acceptable heterogeneity (I^2 = 42%). Better OS was found in the Vein-First group [HR: 1.46, 95% confidence interval (CI): 1.12–1.91, p = 0.005, **Figure 2A**]. Subgroup analyses suggested

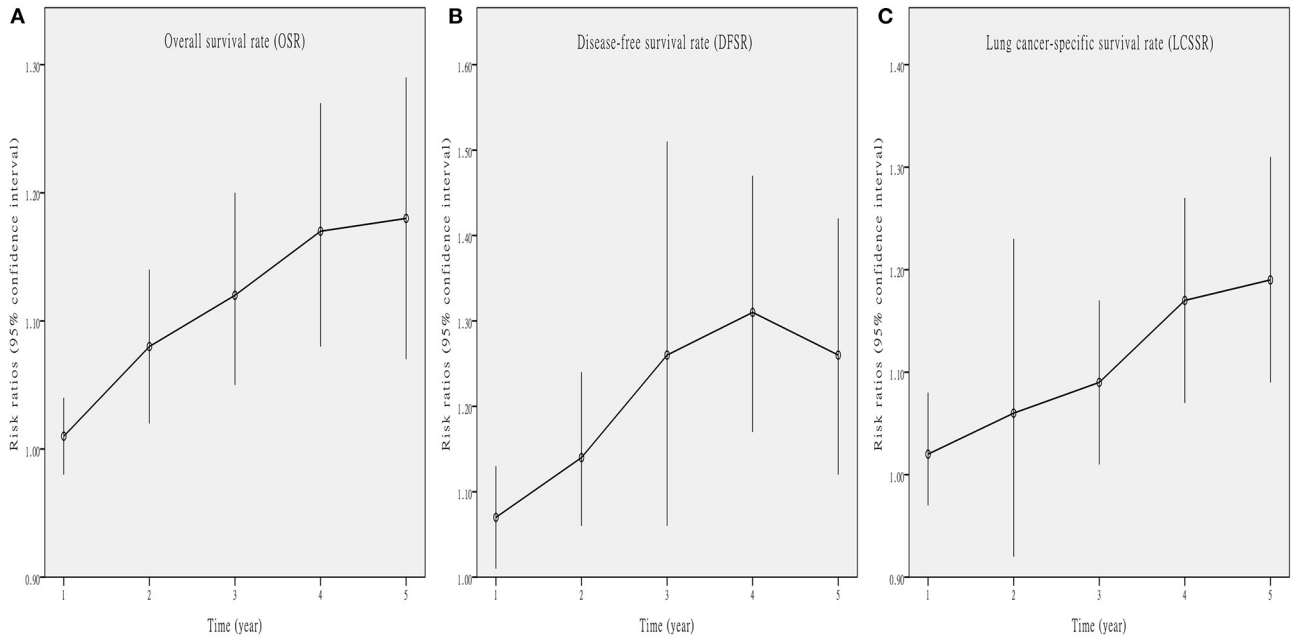

FIGURE 4 | Line charts of OSR (1–5 years, **A**), DFSR (1–5 years, **B**), and LCSSR (1–5 years, **C**) associated with Vein-first vs. Artery-first according to survival time.

that the Vein-First group achieved better OSR-2y (RR: 1.08, 95% CI: 1.02–1.14, $p = 0.007$), OSR-3y (RR: 1.12, 95% CI: 1.05–1.20, $p = 0.001$), OSR-4y (RR: 1.17, 95% CI: 1.08–1.27, $p < 0.001$), and OSR-5y (RR: 1.18, 95% CI: 1.07–1.29, $p < 0.001$) (**Supplementary Figure 1** and **Figure 3A**). The overall survival advantage of the Vein-First group increased over time (**Figure 4A**).

Four studies (7–9, 13) compared DFS with acceptable heterogeneity ($I^2 = 44\%$). Better DFS was found in the Vein-First group (HR: 1.60, 95% CI: 1.23–2.08, $p < 0.001$, **Figure 2B**). Subgroup analyses suggested that the Vein-First group achieved better DFSR-1y (RR: 1.07, 95% CI: 1.01–1.13, $p = 0.01$), DFSR-2y (RR: 1.14, 95% CI: 1.06–1.24, $p = 0.001$), DFSR-3y (RR: 1.26, 95% CI: 1.06–1.51, $p = 0.009$), DFSR-4y (RR: 1.31, 95% CI: 1.17–1.47, $p < 0.001$), and DFSR-5y (RR: 1.26, 95% CI: 1.12–1.42, $p < 0.001$) (**Supplementary Figure 2** and **Figure 3B**). The disease-free survival advantage of the Vein-First group increased over time (**Figure 4B**).

Two studies (7, 13) compared LCSS with acceptable heterogeneity ($I^2 = 38\%$). Better LCSS was found in the Vein-First group (HR: 1.64, 95% CI: 1.16–2.31, $p = 0.005$, **Figure 2C**). Subgroup analyses of LCSSR suggested that the Vein-First group achieved better LCSSR-3y (RR: 1.09, 95% CI: 1.01–1.17, $p = 0.02$), LCSSR-4y (RR: 1.17, 95% CI: 1.07–1.27, $p < 0.001$), and LCSSR-5y (RR: 1.19, 95% CI: 1.09–1.31, $p < 0.001$) (**Supplementary Figure 3** and **Figure 3C**). The lung cancer-specific survival advantage of the Vein-First group increased over time (**Figure 4C**).

Subgroup Analysis of Survival

Based on the included studies, we analyzed the factors that might affect the survival effect of lobectomy for patients with NSCLC. The results suggested that younger age, vein-first sequence, smaller tumor size, earlier N stage, and earlier pathological TNM stage were the favorable factors associated with better survival. No significant differences were found in the subgroup analyses according to sex (female vs. male), comorbidity (no vs. yes), current or former smoking (no vs. yes), tumor location (left lung vs. right lung), histological type (adenocarcinoma vs. non-adenocarcinoma), postoperative adjuvant therapy (no vs. yes), stapler use (no vs. yes), and type of resection (lobectomy vs. pneumonectomy) (**Table 2**).

We evaluated the possible factors that may affect survival of the Vein-first group vs. the Artery-first group for lobectomy. The results suggested that the advantages of survival in the Vein-First group were primarily embodied in the subgroups of SCC and earlier pathological TNM stage (I–II). For stage III NSCLC, no significant survival advantage was found in the Vein-first group, especially in the early published studies (**Table 3**).

Intraoperative Indicators

Operative time (MD: −2.84, 95% CI: −24.70–19.02 min, $p = 0.80$, **Supplementary Figure 4A**), intraoperative blood loss (MD: 2.18, 95% CI: −19.41–23.78 min, $p = 0.84$, **Supplementary Figure 4B**), and blood transfusion (RR: 0.79, 95% CI: 0.41–1.54, $p = 0.49$, **Supplementary Figure 4C**) were similar between the two groups.

Hospitalization and Follow Up Indicators

Postoperative hospital stay (MD: 0.07, 95% CI: −0.32–0.45 days, $p = 0.73$, **Supplementary Figure 5A**), postoperative drainage time (MD: −0.07, 95% CI: −1.26–1.12 days, $p = 0.91$, **Supplementary Figure 5B**), total complications (RR: 1.15, 95% CI: 0.85–1.55, $p = 0.35$, **Supplementary Figure 5C**), total

TABLE 2 | Subgroup analysis of survival (OS, DFS, and LCSS) in NSCLC patients after lobectomy.

Subgroups	No. of studies	Overall survival		No. of studies	Disease-free survival		No. of studies	Lung cancer-specific survival	
		HR (95% CI)	*P*		HR (95% CI)	*P*		HR (95% CI)	*P*
Age, year									
<60 vs. >60	2	1.03 (1.00–1.05)	0.02	1	0.80 (0.57–1.14)	0.22	1	0.96 (0.62–1.49)	0.85
Sex									
Female vs. Male	2	1.20 (0.94–1.54)	0.15	2	1.03 (0.76–1.39)	0.85	1	1.02 (0.67–1.57)	0.92
Comorbidity									
No vs. yes	1	1.05 (0.69–1.61)	0.82	2	0.96 (0.69–1.32)	0.78	1	0.94 (0.60–1.47)	0.77
Current or former smoking									
No vs. yes	1	1.21 (0.81–1.82)	0.35	2	1.19 (0.61–2.35)	0.61	1	1.11 (0.68–1.63)	0.82
Tumor location									
Left lung vs. right lung	1	1.06 (0.70–1.60)	0.79	1	1.08 (0.76–1.53)	0.66	1	1.05 (0.68–1.63)	0.82
Right upper lobe vs. right middle lobe	–	–	–	1	1.08 (0.27–6.74)	0.71	–	–	–
Right upper lobe vs. right lower lobe	–	–	–	1	1.36 (0.84–6.00)	0.11	–	–	–
Right upper lobe vs. left upper lobe	–	–	–	1	2.25 (0.45–4.32)	0.57	–	–	–
Right upper lobe vs. left lower lobe	–	–	–	1	1.54 (0.47–5.04)	0.48	–	–	–
Sequence of vessel ligation									
Vein-first vs. Artery-first	5	1.46 (0.12–1.91)	0.005	4	1.60 (1.23–2.08)	<0.001	1	1.98 (1.26–3.11)	0.003
Tumor size, cm									
<3 vs. ≥3	2	1.53 (1.19–1.97)	0.001	1	1.81 (1.29–2.53)	0.001	1	1.79 (1.17–2.74)	0.008
N stage									
N0 vs. N1-2	1	1.64 (1.25–2.17)	<0.001	–	–	–	–	–	–
Pathological TNM stage									
I vs. II	1	2.23 (1.26–3.96)	0.006	1	1.75 (1.06–2.91)	0.03	1	2.82 (1.55–5.11)	0.001
I vs. III	1	4.02 (2.57–6.30)	<0.001	1	4.18 (2.90–6.00)	<0.001	1	5.07 (3.14–8.18)	<0.001
I vs. II–IIIA	–	–	–	1	4.07 (1.95–8.52)	<0.001	–	–	–
Histological type									
Adenocarcinoma vs. Nonadenocarcinoma	1	1.21 (0.78–1.87)	0.39	2	1.67 (0.56–5.01)	0.36	1	1.18 (0.75–1.87)	0.47
Postoperative adjuvant therapy									
No vs. yes	1	1.00 (0.66–1.50)	0.99	1	1.13 (0.81–1.57)	0.49	1	1.14 (0.75–1.75)	0.54
Stapler use									
No vs. Yes	1	1.04 (0.72–1.51)	0.82	–	–	–	–	–	–
Type of resection									
Lobectomy vs. pneumonectomy	1	1.06 (0.76–1.49)	0.72	–	–	–	–	–	–

OS, overall survival; DFS, disease-free survival; LCSS, lung cancer-specific survival; HR, hazard ratio; CI, confidence interval. When the HR > 1, the results supported the comparison group in front.

recurrences (RR: 0.89, 95% CI: 0.47–1.67, $p = 0.71$), local recurrences (RR: 0.83, 95% CI: 0.33–2.13, $p = 0.70$), and distant metastasis (RR: 0.76, 95% CI: 0.34–1.73, $p = 0.52$) were similar between the two groups (**Supplementary Figure 6**). Only one study (7) analyzed the CTCs and found that a higher rate of CTC increase (RR: 0.46, 95% CI: 0.27–0.79, $p = 0.005$, **Supplementary Figure 7A**), and a greater increase in CTCs was found in the Artery-first group (MD: −1.23, 95% CI: −1.86 to −0.60 Fu/3 ml, $p = 0.0001$, **Supplementary Figure 7B**).

Sensitivity Analysis

Significant heterogeneity was found in the analysis of operative time, intraoperative blood loss, and blood transfusion. Sensitivity analysis showed that removal of each study did not affect the stability or reliability of the results (**Supplementary Figure 8**).

Publication bias

No evidence of publication bias was found in the analysis of OS (**Supplementary Figure 9A**), DFS (**Supplementary Figure 9B**), and operative time (**Supplementary Figure 9C**).

DISCUSSION

With the increase in patients with NSCLC, standardization of the various details of surgical procedures to improve patient outcomes has become a hot research topic. The choice to first interrupt PA or PV during lobectomy is an important and easily neglected problem. Whether the Vein-first procedure can

TABLE 3 | Subgroup analysis of survival (OS, DFS, and LCSS) in the comparison of Vein-first vs. Artery-first for lobectomy.

Subgroups	No. of studies	Overall survival		No. of studies	Disease-free survival		No. of studies	Lung cancer-specific survival	
		HR (95% CI)	*P*		HR (95% CI)	*P*		HR (95% CI)	*P*
Total	5	1.46 (1.12–1.91)	0.005	4	1.60 (1.23–2.08)	<0.001	2	1.64 (0.16–2.31)	0.005
Published year									
Earlier than 2016	2	0.99 (0.65–1.48)	0.94	1	0.76 (0.37–1.57)	0.46	1	1.26 (0.74–2.15)	0.4
2016–2020	3	1.96 (1.38–2.78)	<0.001	3	1.79 (1.35–2.37)	<0.001	1	1.98 (1.26–3.11)	0.003
Country									
China	3	1.69 (1.20–2.38)	0.003	3	1.51 (1.13–2.00)	0.004	1	1.98 (1.26–3.11)	0.003
Japan	1	1.79 (0.62–5.16)	0.28	1	2.36 (1.13–4.92)	0.02	–	–	–
Poland	1	1.08 (0.68–1.72)	0.75	–	–	–	1	1.26 (0.74–2.15)	0.4
Tumor size, cm									
≥3	1	1.94 (0.80–4.70)	0.14	1	1.61 (0.79–3.26)	0.19	–	–	–
Unrestricted	5	1.46 (1.12–1.91)	0.005	4	1.60 (1.23–2.08)	<0.001	–	–	–
Histological type									
Adenocarcinoma	1	1.54 (0.59–4.00)	0.37	1	1.14 (0.52–2.51)	0.75	–	–	–
Squamous cell carcinomas	1	4.00 (0.987–16.14)	0.052	1	3.01 (1.03–8.00)	0.04	–	–	–
Unrestricted (NSCLC)	5	1.46 (1.12–1.91)	0.005	4	1.60 (1.23–2.08)	<0.001	–	–	–
Pathological TNM stage									
I	1	2.06 (1.08–4.03)	0.04	2	1.65 (1.01–2.70)	0.05	1	2.14 (1.00–4.56)	0.05
II	1	3.39 (1.11–10.41)	0.03	1	2.63(1.01–6.86)	0.05	1	3.39 (1.11–10.41)	0.03
III	1	1.04 (0.54–2.00)	0.91	1	1.17 (0.69–2.00)	0.57	1	1.04 (0.54–2.00)	0.91
Unrestricted	5	1.46 (1.12–1.91)	0.005	4	1.60 (1.23–2.08)	<0.001	2	1.64 (0.16–2.31)	0.005
Study design									
RCT	1	1.08 (0.68–1.72)	0.75	4	1.60 (1.23–2.08)	<0.001	1	1.26 (0.74–2.15)	0.4
CT	4	1.70 (1.22–2.35)	0.002	–	–	–	1	1.98 (1.26–3.11)	0.003

OS, overall survival; DFS, disease-free survival; LCSS, lung cancer-specific survival; HR, hazard ratio; CI, confidence interval; NSCLC, non-small cell lung cancer; RCT, randomized controlled trial; CT, cohort study; TNM, Tumor Node Metastasis. When the HR > 1, the results supported the Vein-First group.

achieve better perioperative and survival outcomes compared with the Artery-first procedure is controversial (7–13). This study is the first meta-analysis to compare different vessel interruption sequences during lobectomy for a better clinical decision. The results suggested that the vein-first group had significantly better OS, DFS, and LCSS. The survival rates of OS at 2–5 years, DFS at 1–5 years, and LCSS at 3–5 years were also higher in the Vein-First group. Operative time, intraoperative blood loss, postoperative drainage time, total complications, and total recurrences were similar between the two groups.

Better survival was the greatest advantage for the Vein-first procedure compared to the Artery-first procedure. Similar results were also confirmed by Wei et al. (7). He et al. reported that the survival advantages of the Vein-first group were more significant for patients with SCC (8). The advantages of survival (OS, DFS, and LCSS) in the Vein-First group increased with the prolonged survival time. Two reasons might explain this advantage: (1) Once the effluent vein is blocked, tumor cells are less likely to enter the blood stream. Wei et al. reported that higher rates of incremental change in CTCs were observed in the Artery-first group (26/40 vs. 12/38, $P = 0.003$) (7). Higher expression levels of cancer-related indicators (CK19 mRNA, LUNX mRNA, pin1 mRNA, CD44v6, and CK19 genes) were also found in the Artery-first group after surgery than in the Vein-first group (21–23). (2) For most lung cancer surgeries, single-direction lobectomy with pulmonary vein ligation first may simplify the operational procedure, which decreases repeated grasping and manipulation of the tumor-bearing lobe during surgery (7). The expression levels of CD44v6 and CK19 were higher in the Artery-first group in the late period during surgery (22). Subgroup analyses suggested that the advantages of survival in the Vein-First group were primarily embodied in the subgroups of SCC and earlier pathological TNM stage (I–II). Similar survival outcomes between the two groups were reported by Li et al. (13) and Kozak et al. (10). Two reasons might explain this discrepancy: (1) A favorable trend had been found, but there was no statistical difference due to the small sample size in a single study (10). (2) The proportion of patients with stage I lung cancer was higher in Artery-first group (13). However, although efforts should be made to interrupt the pulmonary vein first for better oncologic results, tumor size and location may dictate an artery-first technique to ensure patient safety.

The main reason why some thoracic surgeons chose to interrupt the PA first is to reduce the risk of bleeding and loss of intravascular volume during surgery. However, the meta-analysis suggested that intraoperative blood loss and blood transfusion were similar between the two groups. Miller et al. reported that

the PA blood flow of the lobe ceased almost immediately with the interruption of the PV (24). Wei et al. suggested that interrupting the PV first would not decrease unnecessary blood loss during surgery (7). Postoperative hospital stay, postoperative drainage time, and total complications were also similar between the two groups. For the follow-up of postoperative recurrence, we only found a trend favoring the Vein-first group without a significant difference, especially for distant metastasis. Sumitomo et al. reported that interrupting the PA first could significantly increase the risk of total recurrences and distant metastasis, which was consistent with our DFS data (HR: 1.60, 95% CI: 1.23–2.08, $p < 0.001$) (9). A significant increase in CTC count in drainage PV after surgical manipulation might be a reasonable explanation for the advantage of the Vein-first group (25). Taken together, interrupting the PV first may significantly decrease the risk of postoperative recurrence without increasing surgical risk.

However, several limitations must be mentioned. First, all of the included studies were published in English, which might introduce a language bias. Second, only two of the eight studies were RCTs, which decreased the quality of the data. Third, only 1,714 patients were included, which might reduce the credibility of the results. Fourth, seven of the eight studies were conducted in Asia. The results of our analysis might not be applicable to patients in other regions. Fifth, the follow-up time and surgical procedures were different between the included studies, which might increase the heterogeneity between studies. Sixth, the editions of TNM classification for pathological stage were different between the studies, which might affect the subgroup analyses according to the TNM classification.

CONCLUSION

In summary, the Vein-first procedure appears to be the suitable choice of vessel interruption sequence during lobectomy for NSCLC with better survival (OS, DFS, and LCSS) and similar perioperative outcomes, especially for stage I–II SCC. The advantages of survival in the Vein-First group increased with prolonged survival. Due to the above limitations, the results must be confirmed in additional large sample RCTs. In complex lobectomy for NSCLC at special sites (e.g., tumor encroaching on the pulmonary vein), the sequence of vessel interruption must be determined according to the actual situation.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

YL had full access to all of the data in the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drafting of the manuscript: XL, BW, and GL. Critical revision of the manuscript for important intellectual content: XL, BW, GL, DY, JP and YL. Statistical analysis: XL, GL, and YL. Supervision: WZ, XL, and YL. All authors. Concept and design, acquisition, analysis, or interpretation of data. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.694005/full#supplementary-material

Supplementary Figure 1 | Comparisons of OSR (1–5 years) associated with Vein-first vs. Artery-first according to survival time.

Supplementary Figure 2 | Comparisons of DFSR (1–5 years) associated with Vein-first vs. Artery-first according to survival time.

Supplementary Figure 3 | Comparisons of LCSSR (1–5 years) associated with Vein-first vs. Artery-first according to survival time.

Supplementary Figure 4 | Forest plots of intraoperative indicators: operative time **(A)**, intraoperative blood loss **(B)**, and blood transfusion **(C)**.

Supplementary Figure 5 | Forest plots of hospitalization indicators: postoperative hospital stay **(A)**, postoperative drainage time **(B)**, and total complications **(C)**.

Supplementary Figure 6 | Forest plots of follow up indicators: total recurrences **(A)**, local recurrences **(B)**, and distant metastasis **(C)**.

Supplementary Figure 7 | Forest plots of CTCs after lobectomy: CTCs increase **(A)** and increment of CTCs **(B)**.

Supplementary Figure 8 | Sensitivity analysis of operative time **(A)**, intraoperative blood loss **(B)**, and blood transfusion **(C)**.

Supplementary Figure 9 | Publication bias of OS **(A)**, DFS **(B)**, and operative time **(C)**.

Supplementary Table 1 | PRISMA 2009 Checklist.

Supplementary Table 2 | Search strategy.

Supplementary Table 3 | Methodological quality assessments of the included studies.

Supplementary Table 4 | GRADE quality assessment by therapeutic strategy and study design for the outcomes.

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A Comparative Analysis of the Gene Expression Profiles of Small Cell Esophageal Carcinoma, Small Cell Lung Cancer, and Esophageal Adeno/Squamous Carcinoma

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Purpose/objectives: Primary small cell esophageal carcinoma (SCEC) is a rare malignancy without an established treatment strategy. This study investigated the gene expression profile of SCEC and compared it with the expression profiles of small cell lung cancer (SCLC) and esophageal adeno/squamous carcinoma (EAC/ESCC).

Materials/methods: All patients with SCEC, SCLC, and EAC/ESCC in the Surveillance, Epidemiology, and End Results (SEER) database 1973–2014 were included. Overall survival (OS) and prognostic analysis were conducted. *De novo* expression array analysis was performed on three pairs of frozen primary SCEC tissues and the corresponding normal samples from the institutional tissue bank using the Affymetrix HG U133 plus 2.0 Array. These data were complemented with public domain expression data sets from the Gene Expression Omnibus (GEO) repository using the same working platforms, which included primary SCLC, EAC/ESCC, and normal lung/esophagus specimens (series GSE30219 and GSE26886). After individual normalization, the primary tumors were submitted to statistical analysis (GeneSpring GX 13.0) to identify the differentially expressed genes (DEGs) relative to their paired normal tissues. Enrichments of genes categorized by function and gene interactions were analyzed by DAVID 6.8 and STRING 11.0, respectively.

Results: The clinical outcomes of the patients with SCEC were significantly more worse than those with EAC/ESCC and SCLC in the SEER database. SCEC had more DEGs in common with SCLC than EAC/ESCC [829 vs. 450; false discovery rate (FDR) <0.01; and fold change ≥ 2], leading to a stronger correlation between SCEC and SCLC (Pearson's correlation coefficient was 0.60 for SCEC vs. SCLC, 0.51 or 0.45 for SCEC vs. ESCC or EAC, and the coefficient was 0.73 for ESCC vs. EAC). Similar findings were obtained by principal component analysis (PCA) using all DEGs retrieved from these four groups. Functional annotation showed that a higher proportion of pathways and biological processes were common between SCEC and SCLC and were associated with the cell cycle (mitosis), DNA replication, telomere maintenance, DNA repair, and P53

and RB pathways (Benjamini $p < 0.05$). Compared with EAC/ESCC, SCEC shared more co-upregulated DEGs coding for the aforementioned common pathways with SCLC (584 vs. 155). In addition, SCEC and SCLC were found to have possessed overlapping gene-interactive networks, with centromere protein F (*CENPF)*, never in mitosis gene A-related kinase 2 **(***NEK2)*, kinesin family member 11 (*KIF11)*, thymopoietin (*TMPO)*, and forkhead box protein M1 (*FOXM1)* as common skeletons centered by gene regulatory network (*NUF2)*.

Conclusions: This study is the first attempt to examine the genomic signatures of SCEC at the transcriptomic level and compare the expression profiles between SCEC, SCLC, and EAC/ESCC. Our preliminary data indicate that SCEC and SCLC display notably similar patterns of gene expression for mitosis and DNA repair. Further validation studies are warranted.

Keywords: small cell esophageal carcinoma, small cell lung cancer, esophageal squamous carcinoma, gene expression profile, esophageal adenocarcinoma

INTRODUCTION

Small cell carcinoma (SCC) is a highly aggressive malignancy that predominantly arises in the lung. Primary small cell esophageal carcinoma (SCEC) is the most common extrapulmonary SCC (∼2%), with a reported incidence rate of 0.05–3.1% among all esophageal neoplasms (1–3). Due to a lack of prospective clinical trials or cell line experimental data, a consensus on treatment strategies for patients with SCEC has not been reached (4, 5). Previous studies have indicated similarities in pathology and clinical manifestations between SCEC and small cell lung cancer (SCLC), and patients with SCEC are staged and treated following the well-established therapeutic strategies for SCLC (4, 6) However, patients with SCEC have a significantly worse prognosis than those with esophageal adeno/squamous carcinoma (EAC/ESCC) and SCLC. Generally, patients with SCEC die within 2 years of diagnosis and experience a median survival of only 8–13 months. Chemotherapy is initially effective for SCEC, but most patients suffer a rapid recurrence and respond inadequately to second-line chemotherapy. More effective and precise therapeutic strategies for SCEC are urgently needed (7–9).

The lung and esophagus arise from the anterior foregut endoderm in the thorax, and they share common properties during development (10, 11). Theoretically, on one hand, SCCs in the lung and esophagus may be more similar than those occurring in other organs. On the other hand, the tissue of origin of a tumor is just as important as the mutations that drive it. The tissue of origin is an important determinant of how a tumor meets its metabolic needs (12). Thus, it seems essential to analyze the molecular characteristics of SCEC and identify the differences between SCLC and EAC/ESCC.

Although the genetic landscape of SCLC and EAC/ESCC has been extensively studied, little is known about SCEC (13–15). Gene expression profiling can investigate altered cellular mechanisms, thus improving our understanding of various diseases and enabling the development of novel therapeutic targets (16). SCEC, SCLC, and EAC/ESCC are highly aggressive cancers, but their detailed differences on the transcriptional levels are currently unknown. To the best of our knowledge, comparative analyses of gene expression profiles of these malignancies have not been reported so far, which is the starting point of this study.

In this study, we compared the overall survival (OS) data of SCEC, SCLC, and EAC/ESCC from the Surveillance, Epidemiology, and End Results (SEER) database. Then, genes with significantly altered expression in SCEC were screened and identified. We compared the gene expression profile of SCEC with the known data of SCLC and EAC/ESCC to highlight biomolecular markers with potential clinical significance. Finally, quantitative reverse transcription (qRT)-PCR analysis was performed to confirm the differential expression of 10 of these genes.

MATERIALS AND METHODS

Patient Collection

This study utilized the SEER-18 registry databases, which currently cover 28% of the population of the United States. SEER routinely collects demographic, tumor site, stage at diagnosis, the first course of treatment, and follow-up of vital status data. We retrieved data from 1973 to 2014 using SEER 8.3.5 software and searched for all cases of SCEC using the ICD-O-3 codes 8041, 8043, and the primary site codes C150-159. In addition, patients who were diagnosed with other subtypes of esophageal neoplasms during the same period were also identified according to the corresponding ICD-O-3 codes (adenocarcinoma: 8050, 8140-8147, 8160-8162, 8180-8221, 8250-8507, 8514, 8520-8551, 8560, 8570-8574, 8576, and 8940-8941; squamous cell carcinoma: 8070-8078, 8083, and 8084). Patients with SCLC were identified using the primary site codes C340-349 and the ICD-O-3 codes 8041 and 8043. Patients were deemed eligible if they were ≥18 years old, had more than 1 month of follow-up time, and the first primary tumor.

TABLE 1 | Basic characteristics of SCEC, ESCC, EAC, and SCLC in the SEER database.

Stratified by histology type	level	SCEC	ESCC	EAC	SCLC	*p*-value
n		468	13,100	16,573	33,627	
Race (%)	White	361 (77.1)	8,160 (62.3)	15,785 (95.2)	29,537 (87.8)	<0.001
	Black	78 (16.7)	3,642 (27.8)	386 (2.3)	2,875 (8.5)	
	Others	29 (6.2)	1,298 (9.9)	402 (2.4)	1,215 (3.6)	
Sex (%)	Male	282 (60.3)	8,816 (67.3)	14,515 (87.6)	18,635 (55.4)	<0.001
	Female	186 (39.7)	4,284 (32.7)	2,058 (12.4)	14,992 (44.6)	
Year at diagnosis (%)	1973–1982	43 (9.2)	1,622 (12.4)	271 (1.6)	5,399 (16.1)	<0.001
	1983–1992	67 (14.3)	2,204 (16.8)	997 (6.0)	8,470 (25.2)	
	1993–2002	115 (24.6)	4,608 (35.2)	4,003 (24.2)	9,160 (27.2)	
	2003–2014	243 (51.9)	4,666 (35.6)	11,302 (68.2)	10,598 (31.5)	
Stage (%)	Localized	81 (17.3)	4,040 (30.8)	4,078 (24.6)	1,916 (5.7)	<0.001
	Regional	78 (16.7)	5,133 (39.2)	6,362 (38.4)	6,830 (20.3)	
	Distant	240 (51.3)	3,927 (30.0)	6,133 (37.0)	14,157 (42.1)	
	Unstage	69 (14.7)	0 (0.0)	0 (0.0)	10,724 (31.9)	
Age at diagnosis [mean (SD)]		68.35 (11.97)	65.06 (11.01)	64.15 (11.60)	64.66 (9.94)	<0.001
Marital status (%)	Married	250 (53.4)	6,489 (49.5)	10,787 (65.1)	19,657 (58.5)	<0.001
	Unmarried	197 (42.1)	6,114 (46.7)	5,232 (31.6)	12,907 (38.4)	
	Unknown	21 (4.5)	497 (3.8)	554 (3.3)	1,063 (3.2)	

SEER, Surveillance, Epidemiology, and End Results; SCEC, small cell esophageal carcinoma; ESCC, esophageal squamous carcinoma; EAC, esophageal adenocarcinoma; SCLC, small cell lung cancer; SD, standard deviation.

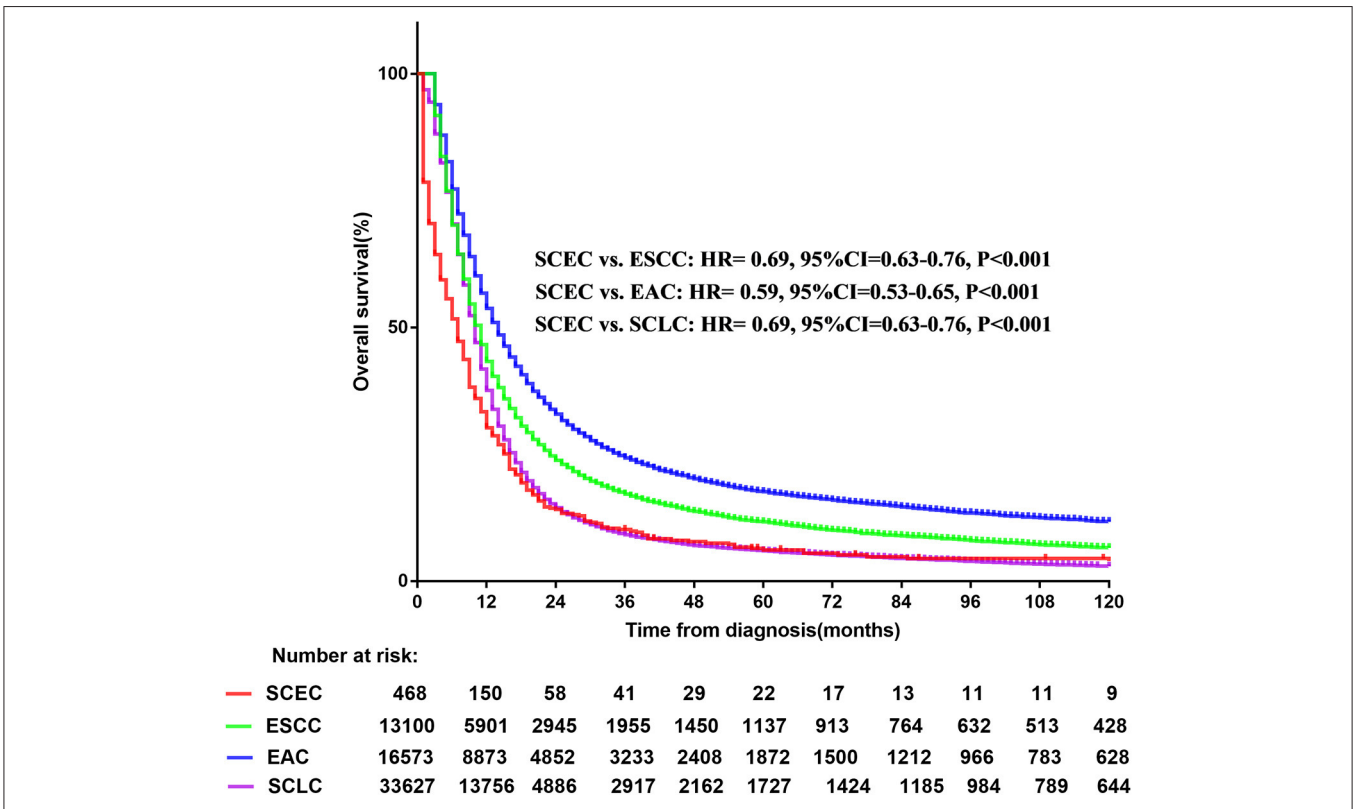

FIGURE 1 | Overall survival comparison for SCEC, ESCC, EAC, and SCLC patients. SCEC, Small cell esophageal cancer; ESCC, esophageal squamous cell cancer; EAC, esophageal adenocarcinoma; SCLC, small cell lung cancer; HR, hazard ratio; CI, confidence interval.

Statistical Analysis

Our analysis included age at diagnosis, sex, race, SEER summary stage, marital status, months of survival, and vital status. A log-rank test was conducted to compare the Kaplan–Meier survival curves. Overall survival (OS) was measured from the date of the initial treatment to the date of death or the last day of follow-up. Multivariate analyses with the Cox proportional hazards model were performed to evaluate the covariate effect on OS. Hazard ratios with 95% CIs were employed to quantify the strength of the association between the predictors and survival. A two-tailed p-value of <0.05 was considered statistically significant. All statistical calculations using were performed R software version 3.4.2 (Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org).

Tissues and Total RNA Preparation

A total of three SCEC tissues and matched adjacent non-cancerous tissues were dissected from the surgical specimens and reviewed by at least two independent expert pathologists, and the diagnosis of SCEC was confirmed by H & E staining and immunohistochemistry (IHC) for synaptophysin, chromogranin A, neuro-specific enolase (NSE), neural cell adhesion molecule (CD56), and antigen KI-67 (Ki67). Any sample with squamous or adenocarcinoma differentiation was excluded. These tumor samples were pathologically assessed to have a purity of at least 60% and minimal necrosis. Additionally, by pathological assessment adjacent non-tumorigenic tissue was confirmed to be free of tumor contaminants. The selected patients did not receive any anticancer therapy before surgery and had not been diagnosed with any other cancer. Ethics approval for this study

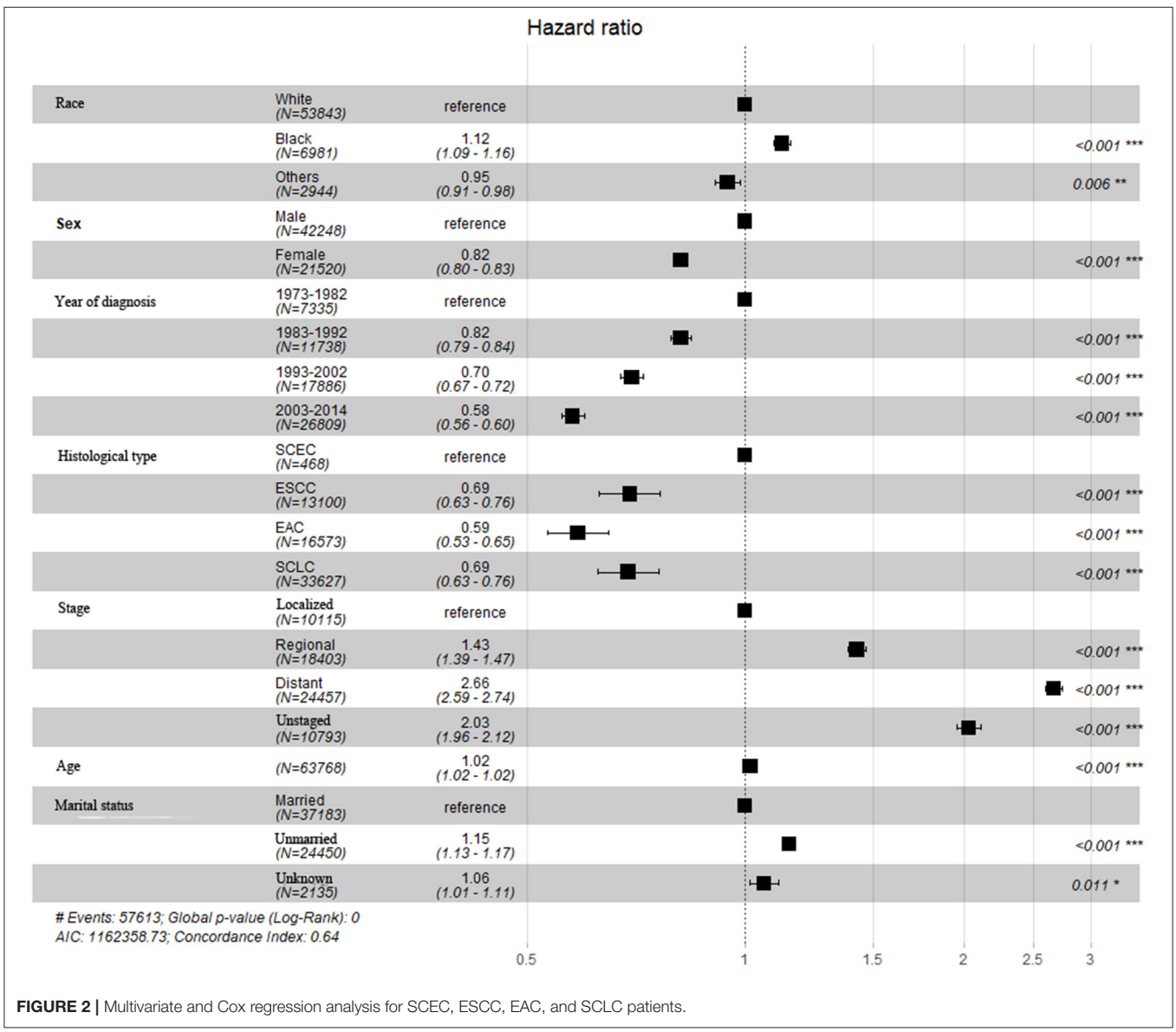

FIGURE 2 | Multivariate and Cox regression analysis for SCEC, ESCC, EAC, and SCLC patients.

was granted by the Human Research Ethics Committee of Fudan University Shanghai Cancer Center (FUSCC), and informed consent was obtained from all patients. Two of the patients were women, and the patients had a median age of 59 years (range from 56 to 67). The primary location of all of the tumors was the middle thoracic region of the esophagus and was stage III (TNM staging system of the American Joint Committee on Cancer, 6th edition) or limited stage (Veteran's Administration Lung Cancer Study Group, VALSG). All of the patients were deceased at the last follow-up.

Total RNA was extracted from the SCEC and matched adjacent non-cancerous tissues with TRIzol reagent (Life Technologies, Carlsbad, CA, USA) according to the instructions of the manufacturer. The concentration and purity of the RNA in each sample were determined by measuring the absorbance at 260 and 280 nm. RNA integrity was confirmed by electrophoresis on 1% agarose gels. Only RNA samples with a renewable identification number (RIN) > 7.5 were applied in later microarray and quantitative reverse transcription (qRT) -PCR experiments.

Gene Expression Microarray and Interactive Analysis

The generation of cDNA and cRNA, hybridization with Affymetrix HG U133 Plus 2.0 Array (Affymetrix, Santa Clara, CA), scanning, and microarray gene expression data analyses were performed as previously described (4). These data were complemented with public domain expression data sets from the GEO repository using the same platforms, which included primary SCLC, primary EAC/ESCC, and normal lung/esophagus specimens (series GSE30219 and GSE26886). The quality control of the samples was assessed by boxplots and principal component analysis (PCA) (**Supplementary Figure 1**). A pairwise comparison was performed by direct comparison of differentially expressed genes (DEGs) filtered from the above four paired groups (SCEC, SCLC, EAC, and ESCC), starting from the raw data (CEL files), after individual normalization within each

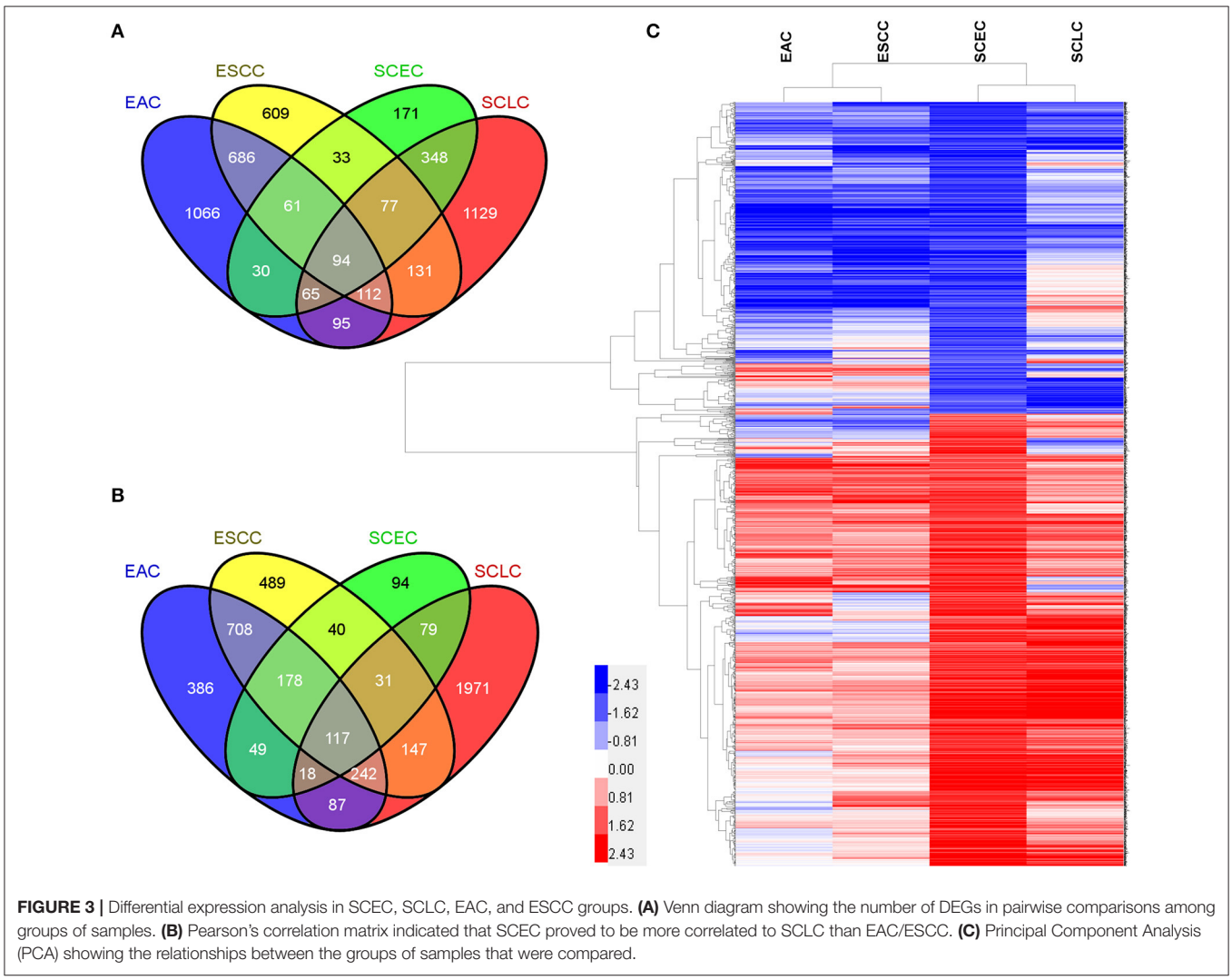

FIGURE 3 | Differential expression analysis in SCEC, SCLC, EAC, and ESCC groups. **(A)** Venn diagram showing the number of DEGs in pairwise comparisons among groups of samples. **(B)** Pearson's correlation matrix indicated that SCEC proved to be more correlated to SCLC than EAC/ESCC. **(C)** Principal Component Analysis (PCA) showing the relationships between the groups of samples that were compared.

paired group and applying the same analytical approach using GeneSpring GX 13.0 software. The DEGs were analyzed through moderated *t*-test analysis with Benjamini–Hochberg multiple testing correction using the following parameters: fold change (FC) ≥2 and false discovery rate (FDR) cutoff <0.01. The DEGs were visualized in a volcano plot (**Supplementary Figure 2**). Gene enrichments with functional annotation and gene interaction networks were analyzed by DAVID 6.8 and STRING 11.0, respectively.

Validation of Microarray by qRT-PCR

Ten genes differentially expressed in SCEC compared wit h matched adjacent non-cancerous tissues identified in the microarray experiment were selected for validation by qRT-PCR. Total RNA extraction, cDNA synthesis, and quantification of gene expression levels were performed on a 7,500 Fast Real-Time PCR cycler (Applied Biosystems, Foster City, CA) with SYBR Green reagents (Takara Bio Inc, Shiga, Japan). as previously described (4). Primers were designed and synthesized by BioTNT Co. (Shanghai, China), and their sequences are listed in **Supplementary Table 1**. β-actin was used as an endogenous control. PCR reactions of each sample were conducted in triplicate. The relative expression of the target genes was calculated by $2^{-\Delta\Delta Ct}$.

RESULTS

SEER Data of SCEC as Compared to SCLC and EAC/ESCC

Surveillance, Epidemiology, and End Results data of SCEC as compared to SCLC and EAC/ESCC.

A total of 63,768 patients diagnosed from 1973 to 2014 were identified from the SEER database. Among them, patients with SCLC accounted for the largest proportion (33,627, 52.7%), followed by EAC (16,573, 26.0%), ESCC (13,100, 20.5%), and SCEC (468, 0.7%). The baseline characteristics are summarized in **Table 1**. Kaplan–Meier analyses and log-rank testing were conducted to compare the OS among these specific histological types, and the results are shown in **Figure 1**. Regarding OS, the 5-year survival for patients with SCEC was 6.1%, similar to that of patients with SCLC (5.9%). Patients with EAC (5-year OS: 17.6%) and ESCC (5-year OS: 11.6%) had a better prognosis than those with the other two types. To further refine the analysis on the prognostic value of histological types, we utilized Cox models

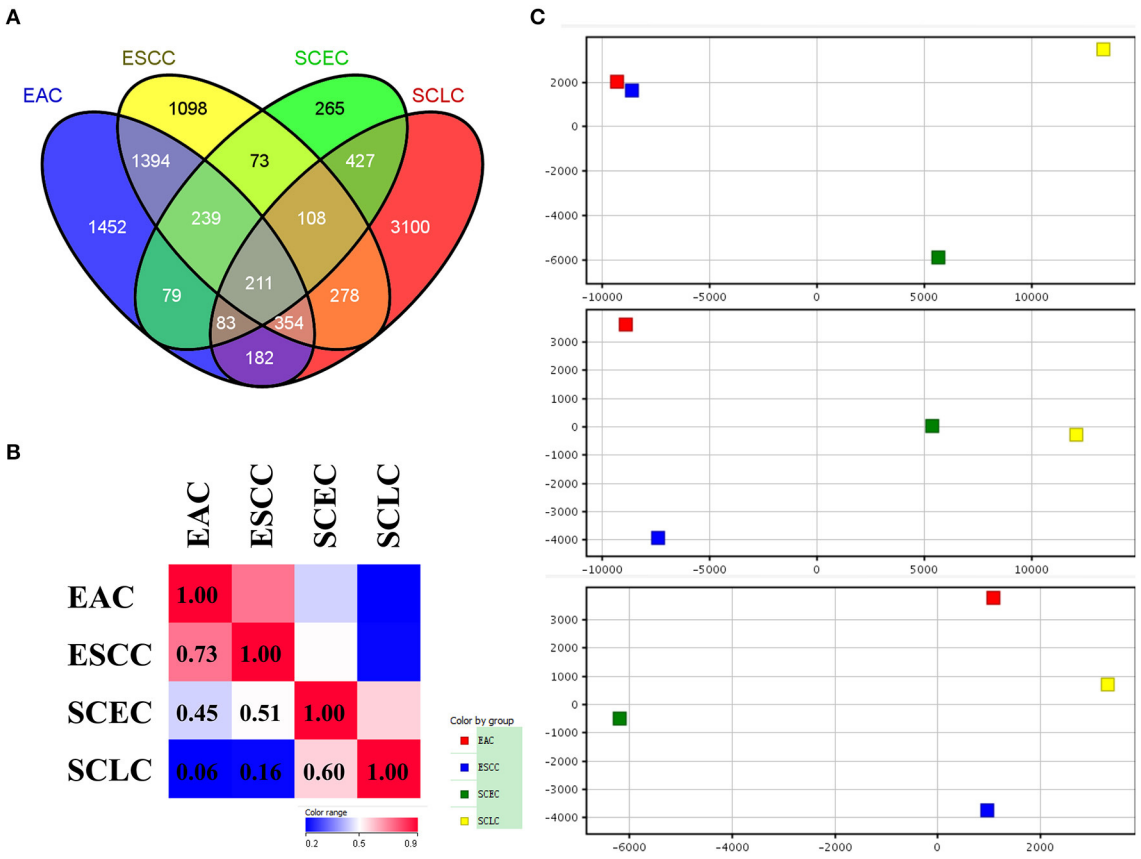

FIGURE 4 | Differential expression analysis in SCEC, SCLC, EAC, and ESCC groups divided by up-regulated and down-regulated genes. **(A,B)** Venn diagram showing SCEC shared more co-up regulated DEGs with SCLC compared with EAC/ESCC. **(C)** Hierarchical clustering of SCEC, SCLC, EAC, and ESCC groups. The color scale represents the level of expression from low (blue) to high (red).

TABLE 2 | DAVID annotation of DEGs in SCEC group.

Database	Name	Count[a]	Benjamini *p*-value
KEGG	**DNA replication[b]**	19	8.88E-10
	Cell cycle	33	8.61E-09
	P53 signaling pathway	19	4.80E-05
	Progesterone-mediated oocyte maturation	18	0.00457
	Base excision repair	11	0.00419
	Oocyte meiosis	20	0.00790
REACTOME	**Cell cycle, mitotic**	100	3.47E-36
	DNA replication	29	7.19E-08
	DNA repair	22	0.00173
	Cell cycle checkpoints	23	0.00184
	Telomere maintenance	14	0.00713
PANTHER	**P53 pathway**	22	0.0456
GO BP (TOP10)	**M phase**	99	3.91E-28
	M phase of mitotic cell cycle	78	1.97E-26
	Mitosis	77	2.12E-26
	DNA replication	61	2.41E-18
	DNA metabolic process	98	2.54E-13
	Mitotic sister chromatid segregation	18	1.73E-07
	Spindle organization	20	1.55E-07
	Cell cycle checkpoint	27	2.09E-06
	Regulation of cell cycle process	28	6.97E-05
	DNA repair	50	7.34E-05
GO MF	**Pyrophosphatase activity**	91	0.00138
	Adenyl ribonucleotide binding	152	0.00573
	Guanyl ribonucleotide binding	44	0.0486

[a] *Threshold values: count ≥10 and Benjamini p-value <0.01.*
[b] *The biological processes or pathways in common between SCEC and SCLC were in bold.*
GO, gene ontology; BP, biological process; MF,molecular function.

to predict OS incorporating age at diagnosis, sex, ethnicity, year of diagnosis, SEER summary stage, and marital status and found that the prognosis of patients with SCEC was significantly inferior to that of the other three histological types ($p < 0.001$, **Figure 2**).

Gene Expression Profile of SCEC Compared to SCLC and EAC/ESCC

A total of 1,485 DEGs in SCEC vs. adjacent non-cancerous tissues with 879 upregulated genes and 606 downregulated genes were identified in a previous study; these were enriched for overexpression of proliferation-associated and neuroendocrine-associated genes (4). Pathway analysis showed enrichment of DNA replication, cell cycle, mitosis, telomere maintenance, DNA repair, and p53 and RB pathways by the database for annotation, visualization, and integrated discovery (DAVID) annotation (count ≥10 and Benjamini *p*-value <0.01).

The expression data demonstrated that SCEC had more DEGs in common with SCLC than EAC/ESCC (829 vs. 450; FDR<0.01; and FC ≥2; **Figure 3**), leading to a stronger correlation between SCEC and SCLC (Pearson's correlation coefficient was 0.60 for SCEC vs. SCLC, 0.51 or 0.45 for SCEC vs. ESCC or EAC, and 0.73 for ESCC vs. EAC). Similar findings were obtained by PCA using all DEGs retrieved from these four groups (**Figure 4**). Functional annotation showed that a higher proportion of biological processes or pathways were shared in common between SCEC and SCLC and were associated with the cell cycle, mitosis, DNA replication, telomere maintenance, DNA repair, and p53 and RB pathways (count ≥10 and Benjamini *p*-value <0.05; **Table 2** and **Supplementary Tables 2–4**). Compared with EAC/ESCC, SCEC shared more co-upregulated DEGs coding for the aforementioned common pathways with SCLC (584 vs. 155; **Figure 3**). Hierarchical clustering of SCEC, SCLC, and EAC/ESCC according to gene ontology (GO) annotation is shown in **Supplementary Figure 3**. In addition, SCEC and SCLC possessed overlapping gene-interactive network with *CENPF*, *NEK2*, *KIF11*, *TMPO*, and *FOXM1* as common skeletons centered by *NUF2* (**Supplementary Figure 4**). The genes involved in the SCEC-regulated network were related to cell cycle, mitosis, cell cycle checkpoint, spindle organization, microtubule binding, cytoskeletal protein binding, and other biological processes (**Supplementary Tables 6**, **7**).

Validation of Microarray Results by qRT-PCR

Genes of interest identified by microarray were validated by qRT-PCR. The genes assayed were neuroendocrine-associated genes (*INSM1*, *ASCL1*, *NRCAM*, and *SNAP25*), one gene centered in the gene regulatory network (*NUF2*), and five possibly cancer-associated genes (*PTP4A3*, *RFC4*, *REST*, *APEH*, and *FBLN2*). The microarray and the qRT-PCR results demonstrated that *INSM1*, *ASCL1*, *NRCAM*, *SNAP25*, *NUF2*, *PTP4A3,* and *RFC4* were significantly upregulated while *REST*, *APEH*, and *FBLN2* were downregulated (**Figure 5**).

DISCUSSION

Small cell carcinoma is a high-grade neoplasm characterized by markers of neuroendocrine differentiation and aggressive histological features (high mitotic rate, extensive necrosis, and nuclear atypia), which confers a poor clinical prognosis (5, 17, 18). The majority of SCCs originate within the lung followed by the esophagus (3, 19–21). SCEC is a very rare disease with a tendency to metastasize early through lymph and blood circulation, and many recommendations about the treatment approach to SCEC are extrapolated from research on SCLC. Treatments for SCEC include surgical resection, chemotherapy, radiotherapy, and combinations of these treatments. First-line systemic chemotherapy with a platinum agent (cisplatin or carboplatin) and etoposide is recommended for most patients; however, response durations are often short, and long-time survivors are rare (22–24). Therefore, SCLC treatments are not sufficient or optimal for patients with SCEC. In addition, SCC originating in different organs may be distinct, as suggested in the literature study (20).

This study compared the survival data in the SEER database. Kaplan–Meier analysis showed that patients with SCEC had the worse OS, which was closer to SCLC and far worse than patients with EAC/ESCC. The multivariate

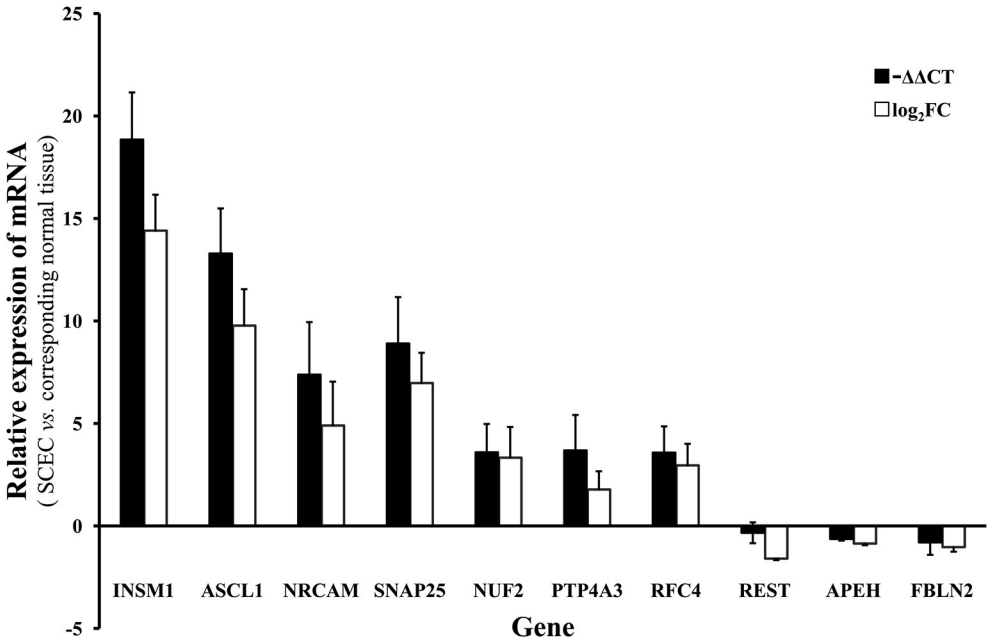

FIGURE 5 | The mRNA level of of *INSM1, ASCL1, NRCAM, SNAP25, NUF2, PTP4A3, RFC4, REST, APEH*, and *FBLN2* in SCEC. Expression levels in SCEC were compared with the corresponding normal tissues. The *X* axis display gene symbols and the *Y* axis shows gene expression log ratios from microarray or qRT-PCR. Bars: standard error (SE).

analysis demonstrated that SCC was associated with a poor prognosis compared with pathological subtypes of squamous cell carcinoma or adenocarcinoma. Previous limited retrospective studies have suggested that SCEC is more malignant than other types of esophageal cancers (5). This study is in accordance with the literature study and is the first real-world study comparing the prognosis among SCEC with SCLC and EAC/ESCC using data from a large dataset.

The histogenesis of SCEC is controversial, and no definite conclusions have been made. It is assumed that SCEC may arise from amine precursor uptake and decarboxylation (APUD) cells or multipotent reserve cells (25, 26). SCEC and SCLC share several histological features, which support the theory that SCC arises from APUD cells. Observations of heterogeneous carcinoma components, including EAC/ESCC or mucoepidermoid carcinoma and ESCC *in situ*, provide evidence of derivation from multipotent reserve cells (27). It is interesting to elucidate the relationship of SCEC with SCLC and EAC/ESCC.

Genome sequencing studies have revealed several potential driver events in two other major subtypes of esophageal carcinoma and showed that they have distinct molecular characteristics, indicating the heterogeneity of esophageal carcinomas (13). A recently published SCEC landscape revealed the characteristics of the SCEC mutation spectrum and copy number variation spectrum, indicating that SCEC is highly distinct and may have a special genetic background (7). To date, detailed whole genetic studies of this disease at the mRNA level have been sparse.

In this study, we performed gene expression profiling of three patients with SCEC compared with matched adjacent non-cancerous tissues by microarray analysis. This study found that phosphatase and tensin homolog *(PTEN)*-, retinoblastoma protein (*RB)*-, and wingless and int-1 (*WNT)*-related gene sets and neuroendocrine- and proliferation-associated genes were significantly upregulated, while notch homolog 1 (*NOTCH)*-related gene sets were downregulated in SCEC, as previously described (4). Combined with the genomic aberrance of SCEC as reported previously (4, 7), the aforementioned gene sets and pathways might contribute to tumorigenesis and the development of SCEC, and these results were also in line with a recent publication (21).

Furthermore, we compared the gene expression profiles of SCEC between SCLC and EAC/ESCC. Our data demonstrated that there are more gene expression similarities between SCEC and SCLC than there are between SCEC and EAC/ESCC. We observed that DEGs in SCEC were significantly enriched in the cell cycle, mitosis, DNA replication, telomere maintenance, DNA repair, and p53 and RB pathways, which is highly concordant with those in SCLC. In addition, SCEC and SCLC display notably similar patterns of gene-interactive networks with *CENPF*, *NEK2*, *KIF11*, *TMPO*, and *FOXM1* as common skeletons centered by *NUF2*. In terms of the gene expression profile, the characteristics of SCEC are unique but more closely resembled SCLC than EAC/ESCC, as they share similar signaling pathways and gene-interactive networks. This similarity of expression profiles between SCEC and SCLC is consistent with the poor prognosis of SCC, since SCEC and SCLC are both highly aggressive.

With the deepening research studies into tumor biology, SCLC has entered the era of precision medicine (28). SCEC still remains outside the realm of precision medicine, where

chemotherapy is the bedrock of treatment. Without biomarkers predictive of efficacy and toxicity and in the absence of precise identification of optimal treatment strategies, the prognosis of patients with SCEC is dismal. In addition, as our data suggested in the study, SCEC is a highly heterogeneous disease; however, its heterogeneous biology is poorly understood. Our attempt is only the first step, which has enabled a more comprehensive understanding of the transcriptomic landscape of SCEC.

A large-scale study is needed because our study had many limitations, such as a small number of samples and difficulty examining the protein level of interesting DEGs from microarrays. Only a small proportion of SCEC are resectable; inevitably, small numbers of samples are available. SCEC is a rare and deadly cancer. Although, we only examined insufficient cases, this study has added to the knowledge of SCEC at the transcriptomic level and highlights the potential useful genes and pathways for more precise diagnosis and treatment. Further, investigations based on the large-scale collection of samples are needed.

CONCLUSIONS

This study is the first to examine the genomic signatures of SCEC from a gene expression perspective with comparison to SCLC and EAC/ESCC. SCEC has an extremely poor prognosis compared with SCLC and EAC/ESCC. Our preliminary data indicated that SCEC is a distinct disease and should be treated individually and precisely. Further, validation studies are warranted.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

Conception and design: DL, ZZ, and MF. Collection and assembly of data: JW, BW, and JC. Data analysis and interpretation: DL, JW, and XX. All authors contributed to manuscript writing, final approval of manuscript, and accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

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Upfront Brain Treatments Followed by Lung Surgery Improves Survival for Stage IV Non-small Cell Lung Cancer Patients With Brain Metastases: A Large Cohort Analysis

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Background: Current treatment guidelines for stage IV non-small cell lung cancer (NSCLC) with brain metastases recommend brain treatments, including surgical resection and radiotherapy (RT), in addition to resection of the primary lung tumor. Here, we investigate the less-studied impact of treatment sequence on the overall survival.

Methods: The National Cancer Database was queried for NSCLC patients with brain metastases who underwent surgical resection of the primary lung tumor ($n = 776$). Kaplan-Meier survival curves with log-rank test and propensity score stratified Cox regression with Wald test were used to evaluate the associations between various treatment plans and overall survival (OS).

Results: Compared to patients who did not receive any brain treatment (median OS = 6.05 months), significantly better survival was observed for those who received brain surgery plus RT (median OS = 26.25 months, $p < 0.0001$) and for those who received brain RT alone (median OS = 14.49 months, $p < 0.001$). Patients who received one upfront brain treatment (surgery or RT) before lung surgery were associated with better survival than those who received lung surgery first ($p < 0.05$). The best survival outcome (median OS 27.1 months) was associated with the sequence of brain surgery plus postoperative brain RT followed by lung surgery.

Conclusions: This study shows the value of performing upfront brain treatments followed by primary lung tumor resection for NSCLC patients with brain metastases, especially the procedure of brain surgery plus postoperative brain RT followed by lung surgery.

Keywords: brain metastases, National Cancer Database, treatment sequencing, surgery, non-small cell lung cancer

INTRODUCTION

Lung cancer is one of the most frequent sources of brain metastases (1). For non-small cell lung cancer (NSCLC), about 7–10% patients present with brain metastases at the time of diagnosis, and 20–40% of patients will develop brain metastases during their illness (2). The incidence of brain metastases is increasing with the improved availability of diagnostic imaging technology (1). Presence of brain metastases indicates stage IV NSCLC, for which the 5-year survival rate is only 5.5% (3). Patients with metastatic NSCLC are generally candidates for systemic therapy, including chemotherapy, targeted therapy, and immunotherapy (4). However, the efficacy of chemotherapy in treating brain metastases is largely limited due to the blood-brain barrier (5). On the other hand, the potential benefit of brain-local treatments, such as surgical resection and radiation therapy (RT), has been established for appropriately selected cases of stage IV NSCLC with brain metastases.

According to the National Comprehensive Cancer Network (NCCN) guidelines, stage IV NSCLC patients with limited oligometastatic disease (e.g., a single brain or adrenal metastasis) and otherwise limited-stage disease in the chest may benefit from aggressive local treatments to both the primary lung cancer and metastatic sites. Aggressive local treatment may include surgical resection and definitive RT to each site, and may be preceded or followed by chemotherapy (6). For resectable single brain metastasis, high level evidence supports category 1 recommendations for either surgical resection or stereotactic radiosurgery (SRS), followed by whole brain RT (WBRT), whereas SRS alone or following surgical resection is also a reasonable option (6–8). For single adrenal metastasis, it is only a category 2B recommendation for adrenalectomy or definitive RT (6). For solitary metastasis in organs other than the brain and adrenal glands, surgical resection to the metastatic site is still under debate.

For patients with synchronous NSCLC and brain metastases, survival benefit from resection of the primary lung tumor has been demonstrated over the past decades (9–11). Although recommended for its potential benefits, surgical intervention to the brain metastases remains a disputable option, as reflected by the frequent revisions to the guidelines (12–15). In practice, management for such a severe disease stage should be based on multidisciplinary planning. There is limited research on prognosis associated with different brain treatment options by which clinicians can plan the therapy precisely. Previously published therapeutic outcomes related to this scenario were largely based on retrospective single institution studies of highly selected cases. In the real-world clinical settings, the decision of using brain surgery in a stage IV NSCLC case is largely influenced by personal opinions and/or institutional experiences. In the present study, a total of 776 patients were carefully selected from 43,024 cases of synchronous NSCLC and brain metastases in the National Cancer Database (NCDB), generating a relatively homogenous cohort of patients who (1) had brain metastases at the diagnosis of stage IV NSCLC and (2) eventually underwent surgical resection of the primary lung tumor. Survival outcomes associated with the timing of brain-local treatments (surgery and RT) relative to lung surgery were analyzed to investigate the potentially optimal treatment plan not yet specified in the NCCN guidelines.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board at University of Texas Southwestern Medical Center (STU 072016-028).

Cohort Selection and Variable Definitions

De-identified data for patients with stage IV NSCLC and brain metastases were obtained from the National Cancer Database (NCDB). The overall cohort selection procedure is summarized in **Figure 1**. Variables describing metastases, staging, the type and timing of treatments were used for patient selection and grouping (**Supplementary Table 1**). Specifically, histologic types of NSCLC were selected based on the 3rd edition of the International Classification of Diseases for Oncology (ICD-O-3), including squamous cell (8051–8052, 8070–8076, 8078, 8083–8084, 8090, 8094, 8120, 8123), adenocarcinoma (8015, 8050, 8140–8141, 8143-8145, 8147, 8190, 8201, 8211, 8250–8255, 8260, 8290, 8310, 8320, 8323, 8333, 8401, 8440, 8470–8471, 8480–8481, 8490, 8503, 8507, 8550, 8570–8572, 8574, 8576), large cell (8012–8014, 8021, 8034, 8082), non-small cell carcinoma (8046), and other specified carcinomas (8003–8004, 8022, 8030, 8031–8033, 8035, 8200, 8240-8241, 8243–8246, 8249, 8430, 8525, 8560, 8562, 8575) (2). The cohort was then confined to patients who had brain metastases and underwent resection of the primary lung tumor. This step effectually excluded all cases from 2004 to 2009, since the collection of brain metastases information in NCDB started in 2010. In this study, treatments of interest were limited to lung surgery, brain surgery, and brain RT. Patients were further excluded if (1) there was missing information on treatment approaches or time intervals; (2) they received only palliative surgery on either lung or brain lesions, or radioactive implants or radioisotopes; (3) they had extracranial metastases or uncertain metastatic involvement; or (4) they had inconsistent M1a staging. The metastasis staging according to the 8th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) lung cancer staging system was derived as previously described (16). Stage M1b is expected for NSCLC patients with brain metastases. Fifteen patients were excluded because they instead had M1a stage and no evidence for brain treatment, which was inconsistent with the condition of brain metastases. In addition, the variable for identifying the anatomic target of regional RT (RAD_TREAT_VOL, **Supplementary Table 1**) only recorded the primary site of RT if more than one region were treated. Therefore, by selecting the cases with brain RT or without any RT, patients who received lung RT were naturally excluded.

Patient Grouping

Variables describing the type and timing of the three treatments (lung surgery, brain surgery, and brain RT) were used for patient grouping (summarized in **Table 1**; see also **Supplementary Figure 1**). In this study, lung was the primary

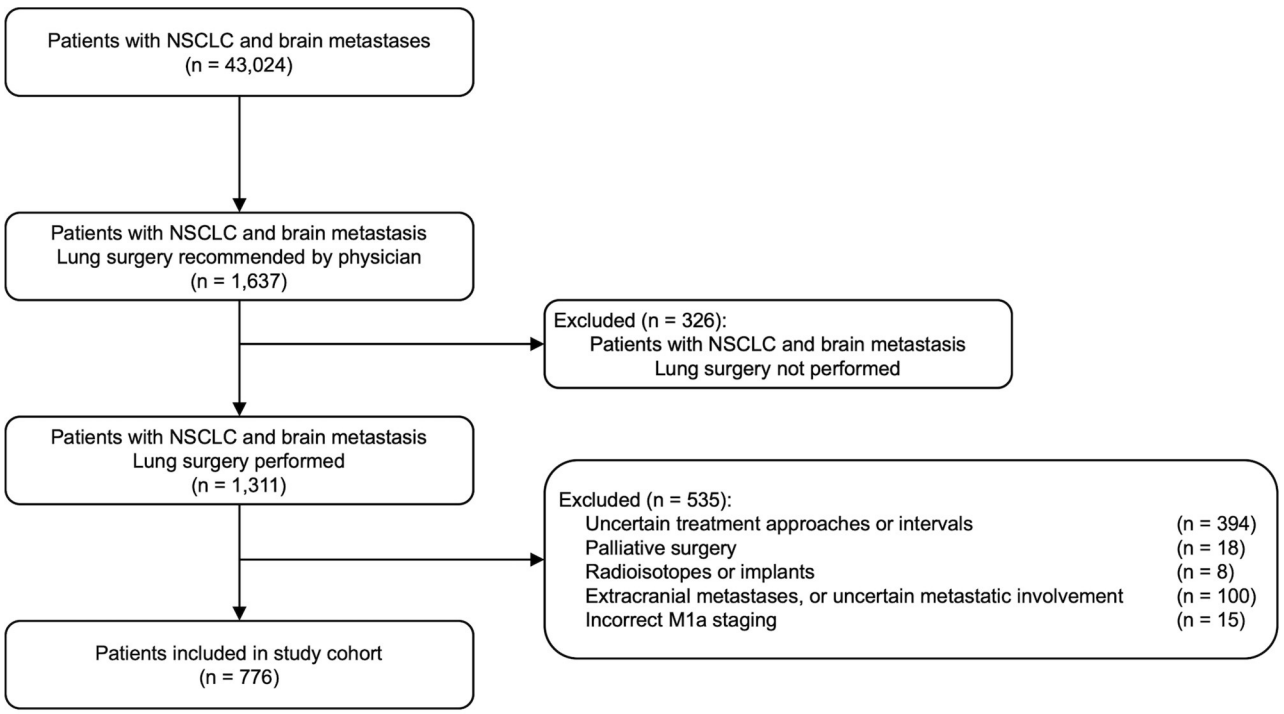

FIGURE 1 | Patient cohort selection.

TABLE 1 | Patient grouping.

Treatment combination		Treatment sequence		
Level I	**Level II**	**Level III**	**Level IV**	**Group size**
Brain surgery	Brain surgery + RT	Upfront brain treatment	1. Brain surgery → Brain RT → Lung surgery	153
			2. Brain surgery → Lung surgery → Brain RT	60
			3. Brain RT → Brain surgery → Lung surgery	3
			4. Brain RT → Lung surgery → Brain surgery	6
		Subsequent brain treatment	5. Lung surgery → Brain surgery + RT	50
	Brain surgery		6. Brain surgery → Lung surgery	2
			7. Lung surgery → Brain surgery	2
No brain surgery	Brain RT	Upfront brain RT	8. Brain RT → Lung surgery	123
		Subsequent brain RT	9. Lung surgery → Brain RT	278
	No brain treatment		10. Lung surgery	99

The symbol "→" denotes "earlier than." The symbol "+" indicates the order of two treatments is not specified.

surgery site and the distant surgery site was confined to the brain. We derived the sequence of treatments using time intervals referenced to the time of diagnosis (**Supplementary Table 1**). One particular group (Group 5, **Table 1**) included patients who received all three treatments, with lung surgery as the first treatment. In this case, the exact order of the subsequent brain treatments (surgery and RT) could not be derived based on the existing variables in NCDB. For this group, the combined brain treatments (without definite order) were denoted as Brain Surgery + RT. Details of group definitions are shown in **Table 1**.

Statistical Analysis

Kaplan-Meier survival curves were generated and compared using log-rank test. A multivariate Cox regression model was used to evaluate the impact of treatments. In addition to the treatment group, we considered age at diagnosis, gender, race, facility volume, pathologic stage, type of surgical resection (sub-lobar vs. lobar) and the receipt of chemotherapy as covariates. Facility volumes were split into high and low groups by the median treatment volume of lung surgery (45 cases per year). Pathologic stage was defined based on pathologic T and N categories. Sublobar resection was

TABLE 2 | Demographic and clinical characteristics of the study cohort.

Characteristic	Brain surgery ($n = 276$)	No brain surgery ($n = 500$)
Age (year)		
≤75	267 (96.74%)	444 (88.8%)
>75	9 (3.26%)	56 (11.2%)
Sex		
Male	144 (52.17%)	250 (50%)
Female	132 (47.83%)	250 (50%)
Race		
White	237 (85.87%)	425 (85%)
Black	30 (10.87%)	50 (10%)
Other	9 (3.26%)	25 (5%)
Income (USD)		
<$38,000	42 (15.22%)	103 (20.6%)
$38,000–$62,999	147 (53.26%)	257 (51.4%)
≥$63,000	84 (30.43%)	136 (27.2%)
Unknown	3 (1.09%)	4 (0.8%)
Insurance type		
None	15 (5.43%)	21 (4.2%)
Private	129 (46.74%)	195 (39%)
Public	130 (47.1%)	278 (55.6%)
Unknown	2 (0.73%)	6 (1.2%)
Facility volume (cases/year)		
≤45	151 (54.7%)	263 (52.6)
>45	125 (45.3%)	237 (47.4%)
Charlson-Deyo score		
0	184 (66.66%)	311 (62.2%)
1	72 (26.09%)	119 (23.8%)
2	20 (7.25%)	70 (14%)
Chemotherapy		
Yes	189 (68.48%)	263 (52.60%)
No	87 (31.52%)	237 (47.40%)
Type of surgical resection		
Sublobar resection	43 (15.58%)	174 (34.8%)
Lobectomy or larger resection	214 (77.54%)	290 (58%)
Unknown	19 (6.88%)	36 (7.2%)
Pathologic T stage		
T1	79 (28.62%)	116 (23.2%)
T2	112 (40.58%)	173 (34.6%)
T3	37 (13.41%)	75 (15%)
T4	12 (4.35%)	24 (4.8%)
Unknown	36 (13.04%)	112 (22.4%)
Pathologic N stage		
N0	154 (55.8%)	189 (37.8%)
N1	40 (14.49%)	68 (13.6%)
N2	31 (11.23%)	72 (14.4%)
N3	0 (0%)	5 (1%)
Unknown	51 (18.48%)	166 (33.2%)

identified as the surgical procedure of the primary site code ranging from 20 to 24. To further eliminate confounding, we employed propensity score stratification so that the distributions of covariates within each stratum were the same for the groups being compared. Propensity scores were estimated by logistic regression as a function of baseline age, gender and Charlson/Deyo Score. Five strata were formed based on quantiles of the estimated propensity scores. In **Figures 3**, **4**, a Tarone-Ware test was used for comparing survival outcomes between treatment groups. The Tarone-Ware test has been shown to have greater power than the standard log-rank test when the proportional hazards assumption does not hold (17). All statistical tests were considered significant as $p < 0.05$. Survival analyses were implemented with R packages "survival" (version 2.43–3) and "survminer" (version 0.4.3) in RStudio (version 3.5.3).

RESULTS

Characteristics of the Study Cohort

In total, 43,024 cases with NSCLC and brain metastases were identified in the NCDB, among which 1,637 cases were recommended for lung surgery by the physician. After excluding those who did not eventually receive lung surgery or did not meet other data quality criteria described above, the finalized study cohort included 776 patients (**Figure 1**). **Table 2** summarizes the characteristics of the study cohort, separated according to whether brain surgery was performed.

Benefit of Brain Treatments

The cohort was first divided according to whether brain surgery was performed (**Table 1**). The patients who received brain surgery had significantly better survival than those who did not (median survival time 26.2 vs. 13.3 months, log-rank test $p < 0.0001$; **Figure 2A**). The survival benefit from brain surgery was also shown by propensity score stratified multivariate Cox regression ($p < 0.0001$), after accounting for the effect of age at diagnosis, gender, race, facility volume, pathologic stage, type of surgical resection and the receipt of chemotherapy.

The Level II grouping in **Table 1** allows for assessing the therapeutic effects of two major brain treatment regimens: brain surgery in conjunction with RT, and brain RT alone. Patients who received only brain surgery in addition to lung surgery ($n = 4$) were not included due to the small sample size. The median survival time gradually increased with the addition of brain treatments: from 6.05 months for the No Brain Treatment group, to 14.49 months for the Brain RT group, and 26.25 months for the Brain Surgery + RT group (three-group log-rank test $p < 0.0001$; **Figure 2B**). All three pair-wise log-rank tests show significant differences in the overall survival within the pair. Multivariate Cox regression showed significant survival benefit for the Brain Surgery + RT group when compared with the Brain RT group ($p < 0.001$) and the No Brain Treatment group ($p < 0.001$), but no significant survival difference between the Brain RT group and No Brain Treatment group ($p = 0.08$).

Benefit of Upfront Brain Treatments

The Level III patient grouping (**Table 1**) was used to study the effect of the timing of brain treatments relative to the resection of primary lung cancer. When brain RT was applied in conjunction with brain surgery, patients receiving either brain surgery or

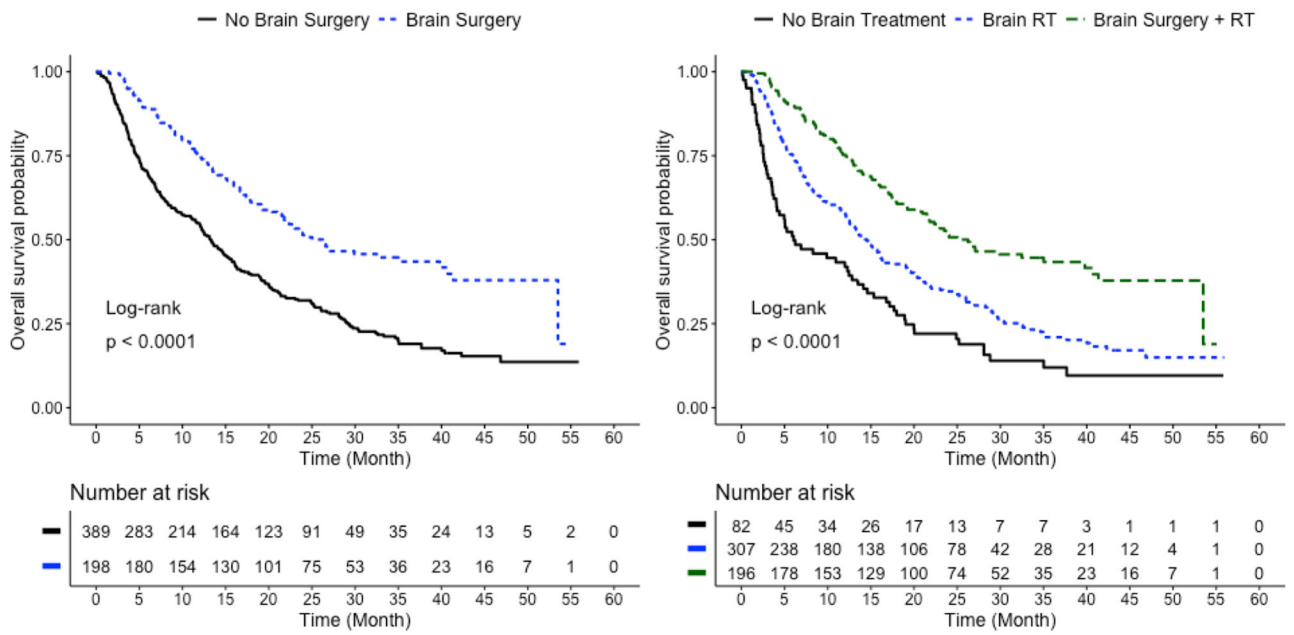

FIGURE 2 | Benefit of brain treatments. **(A)** Survival curves for patients with (blue) and without (black) brain surgery. Median survival time: 26.2 months for Brain Surgery group; 13.3 months for No Brain Surgery group ($p < 0.0001$, log-rank test). **(B)** Survival curves for patients who received, in addition to lung surgery, brain surgery and RT (green), brain RT alone (blue), and no brain treatment (black). Median survival time: 26.25 months for Brain Surgery + RT group; 14.49 months for Brain RT group; 6.05 months for No Brain Treatment group. Three group comparison: log-rank test $p < 0.0001$. Pair-wise log-rank test: $p < 0.0001$ for Brain Surgery + RT vs. Brain RT; $p < 0.0001$ for Brain Surgery + RT vs. No Brain Treatment; $p < 0.001$ for Brain RT vs. No Brain Treatment. Number of patients with available survival data: $n = 198$ in Brain Surgery group; $n = 389$ in No Brain Surgery group; $n = 196$ in Brain Surgery + RT group; $n = 307$ in Brain RT group; $n = 82$ in No Brain Treatment group.

RT as the first treatment (the Upfront Brain Treatment group) had better survival than those receiving lung surgery as the first treatment (median survival time 26.6 vs. 19.2 months; Tarone-Ware test $p < 0.05$; **Figure 3A**). A similar pattern was also observed for patients who only received brain RT in addition to lung surgery: the Upfront Brain RT group had better survival than the Subsequent Brain RT group (median survival time 16.0 vs. 13.4 months; Tarone-Ware test $p < 0.05$; **Figure 3B**).

To further study the sequence of three local treatments, three Level IV groups in **Table 1** were studied: Group 1 (Brain Surgery → Brain RT → Lung Surgery), Group 2 (Brain Surgery → Lung Surgery → Brain RT), and Group 5 (Lung Surgery → Brain Surgery + RT). Patients who received brain RT as the first treatment (Groups 3 and 4; $n = 9$ in total) were excluded due to the small sample size. The group that received upfront brain surgery followed by brain RT and lung surgery (Group 1) had longer median survival time (27.1 months) than the other two groups, respectively (median survival time 19.2 months for both Groups 2 and 5). Significant difference in overall survival (Tarone-Ware test $p < 0.05$) was observed for Group 1 (Brain Surgery → Brain RT → Lung Surgery) vs. Group 5 (Lung Surgery → Brain Surgery + RT) but not in other pair-wise comparisons. When compared with Group 5 (Lung Surgery → Brain Surgery + RT), Group 2 (Brain Surgery → Lung Surgery → Brain RT) had a trend of survival benefit within the first 19 months, although not statistically significant over the whole follow-up period (**Figure 4**). If Groups 1 (Brain Surgery → Brain RT → Lung Surgery) and 2 (Brain Surgery → Lung Surgery → Brain RT) are combined to represent patients receiving brain surgery as the first treatment, they also had better survival compared to Group 5 (median survival time 26.6 vs. 19.2 months; Tarone-Ware test $p < 0.05$).

DISCUSSION

This retrospective study of NCDB data investigates the benefit of brain-local treatments and their optimal timing relative to resection of primary lung tumor for stage IV NSCLC patients with brain metastases. Management strategy for such a severe stage is underdeveloped and still lacks consensus in terms of surgical intervention to the brain. While in most circumstances the treatments at stage IV are palliative and the prognosis is very poor, survival benefit from surgical resection of primary lung tumor and brain metastasectomy has been demonstrated in patients with synchronous NSCLC and brain metastases over the past decades (9–11, 18). These findings suggest that aggressive local treatments, such as surgical resection and definitive RT, can be beneficial to appropriately selected patients, at least those

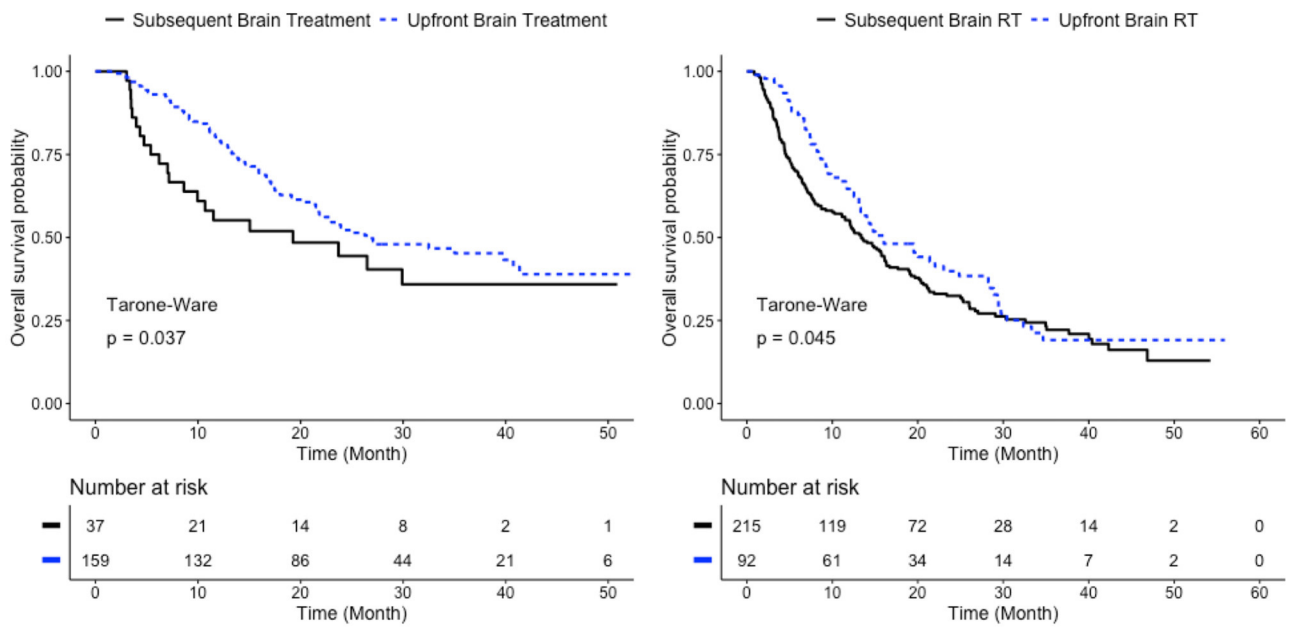

FIGURE 3 | Benefit of upfront brain treatments. **(A)** Survival curves for patients who received all three local treatments with one brain treatment (surgery or RT) as the first treatment (blue) and lung surgery as the first treatment (black). Median survival time: 26.6 months for Upfront Brain Treatment group; 19.2 months for Subsequent Brain Treatment group ($p < 0.05$, Tarone-Ware test). **(B)** Survival curves for patients who received only brain RT and lung surgery (blue: upfront brain RT; black: subsequent brain RT). Median survival time: 16.0 months for Upfront Brain RT group; 13.4 months for Subsequent Brain RT group ($p < 0.05$, Tarone-Ware test). Number of patients with available survival data: $n = 159$ in Upfront Brain Treatment group; $n = 37$ in Subsequent Brain Treatment group; $n = 92$ in Upfront Brain RT group; $n = 215$ in Subsequent Brain RT.

with small primary tumors or without mediastinal nodal disease. According to the NCCN guidelines, patients who have a single brain metastasis and otherwise a stage I or possibly stage II lung cancer may be advised for surgical resection and definitive RT to both the primary lung and metastatic brain sites (6). However, due to limited study under such conditions, clinical practices are largely influenced by individual and/or institutional preferences.

In this study, we focused on the NSCLC patients who had eventually undergone surgical resection of the primary lung cancer, and we investigated the survival outcomes associated with different treatment plans engaging the brain metastases. In a clinical setting, individualized surgical planning is dependent on the number, size, and location of tumors, histological type, and the patient's overall health. Among the 43,024 cases with NSCLC and brain metastases in NCDB, 1,637 patients were recommended for lung surgery by the physician (**Figure 1**). A clear survival benefit was observed for those who eventually received lung surgery ($n = 1{,}002$) compared with those who did not ($n = 262$; median survival time 15.74 vs. 5.62 months; log-rank test $p < 0.0001$; **Supplementary Figure 2**).

In principle, resection of the primary lung lesion should be applied only to patients who have a single brain metastasis and a lung tumor that is otherwise staged at T1-2, N0-1 or T3, N0 (i.e., resectable) (6, 19). Since the NCDB data set lacks detailed information on the brain metastases (e.g., number, size, and location), in order to form a relatively homogeneous cohort regarding brain metastasis, we selected only the patients who eventually received surgical resection to the primary lung site. The fact that these patients were indeed recommended for lung surgery by the physician indicates they should have only a single brain metastasis, assuming the NCCN guidelines were followed (6). Even if considering only solitary brain metastasis, local treatment plans can be different. For a single brain metastasis, NCCN category 1 recommendations include (1) neurosurgical resection followed by WBRT, and (2) SRS followed by WBRT. SRS alone or following neurosurgery are also regarded as reasonable options, essentially giving the same priority for brain surgery plus postoperative RT and definitive RT alone (6–8). However, if the brain lesion is determined unresectable, WBRT and/or SRS can be used (7, 8). Therefore, to further minimize bias in choosing brain surgery, we separated the cohort into three major subcohorts: (1) those who received brain surgery plus RT (SRS and/or WBRT), (2) those who received brain RT (SRS and/or WBRT) without brain surgery, and (3) those who did not receive any brain treatment (**Table 1**, Level II). Clear survival benefits were observed for those who received brain surgery plus RT and those who received RT alone, respectively, compared to those who did not receive any brain treatments (**Figure 2B**). In particular, the synergistic effect of brain surgery and RT is observed as previously reported (7, 20–26). While brain surgery with postoperative WBRT has become the standard of care for solitary brain metastases (7, 20–22), similar local control of brain

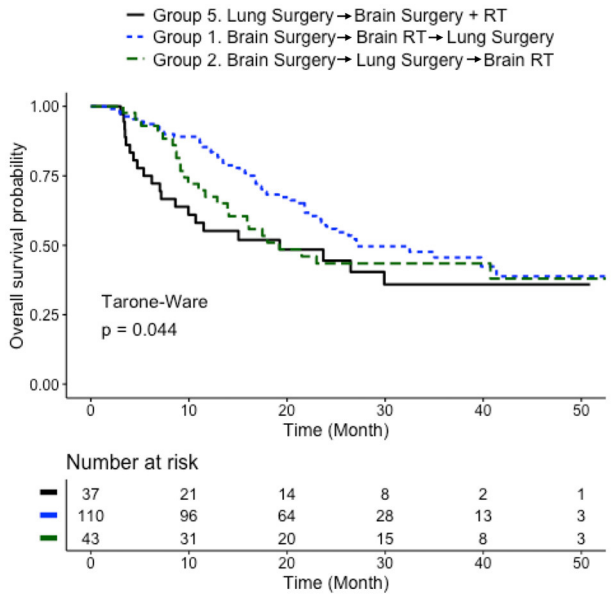

FIGURE 4 | Comparison of sequences of three local treatments. Survival curves for patients who received three local treatments in different sequences (blue: brain surgery followed by brain RT and then lung surgery; green: brain surgery followed by lung surgery and then brain RT; black: lung surgery followed brain multitherapy). Median survival time: 27.1 months for Group 1; 19.2 months for Group 2; 19.2 months for Group 5. Three group comparison: Tarone-Ware test $p < 0.05$. Pair-wise Tarone-Ware test: $p < 0.05$ for Group 1 vs. Group 5; $p = 0.14$ for Group 1 vs. Group 2; $p = 0.33$ for Group 2 vs. Group 5. Number of patients with available survival data: $n = 110$ in Group 1; $n = 43$ in Group 2; $n = 37$ in Group 5.

surgery paired with postoperative SRS has also been recognized recently (23–26). On the other hand, for limited metastases, studies of randomized trials have shown no survival benefit but increased risk of cognitive decline when adding WBRT to SRS (6, 27, 28). Interestingly, in this study only two cases involved combined SRS and WBRT and were merged into the Brain RT subcohort. The investigation of the independent benefit of brain surgery was hindered by the limited number of patients who received only brain surgery in addition to lung surgery ($n = 4$, **Table 1**).

As a key focus of this study, treatment sequences were investigated separately for the "Brain Surgery + RT" subcohort and the "Brain RT" subcohort (**Table 1**, Level II). The precise sequence of treatments was derived by analyzing the treatment time intervals (**Supplementary Figure 1**), a new approach in this subject. For the "Brain Surgery + RT" subcohort, where all three local treatments were performed (brain surgery, brain RT and lung surgery), an upfront brain treatment (either surgery or RT) benefited the overall survival (**Figure 3A**). Similarly for the "Brain RT" subcohort, where only brain RT was used in addition to lung surgery, an upfront brain RT benefited the overall survival (**Figure 3B**). Among the various sequences of three local treatments, brain surgery with postoperative brain RT followed by lung surgery (Group 1) appeared to be the optimal treatment plan, especially when compared with the sequence with upfront lung surgery (**Figure 4**). In fact, Group 1 demonstrated the longest median survival time (27.1 months) among all the groups that were tested. Performing lung surgery after the complete resection of a single brain metastasis has been advised previously (9–11). In a clinical setting, this sequence is preferred likely to observe severe neurological complications, which could render a lung surgery meaningless if it is performed before the brain surgery. Our findings in this study provide further evidence to support such clinical practices. The particular effect of an upfront brain RT in a three-treatment scenario could not be investigated due to the small sample size ($n = 9$, **Table 1**).

Chemotherapy is the cornerstone for the combined surgical treatment of lung cancer with synchronous brain metastases. In principle, aggressive treatment to each site may be preceded or followed by chemotherapy (6, 29). In this study, the receipt of chemotherapy was included with other covariates to avoid selection bias (i.e., patients who had better survival might simply be healthier patients, with unbalanced traits, or attributes).

STRENGTHS AND LIMITATIONS

To our knowledge, this is the first large cohort study of the joint effect of local treatments to both the primary NSCLC and brain metastases. Due to the relative rarity of NSCLC with synchronous brain metastases and the lack of large prospective studies, clinical practices in such case are still largely influenced by the subjective opinions of clinicians and patients. This study analyzed a large cohort of NSCLC patients with brain metastases ($n = 776$) and demonstrates the particular value of performing brain treatments (surgery and/or RT) before resection of the primary lung cancer.

Adjustment for confounders, as conducted herein, may remove part but not all of the selection bias that might be present in this observational study. Since the NCDB data set lacks information about the number, size and location of brain metastases, we selected the study cohort based on the receipt of lung surgery, which should in principle apply only to patients with a single brain metastasis. To compare survival outcomes associated with different treatment sequences, we analyzed the "Brain Surgery + RT" subcohort and the "Brain RT (alone)" subcohort separately, which potentially minimizes the bias in surgical eligibility of the brain metastasis. Although apparent survival difference was observed if directly comparing these two subcohorts (**Figure 2B**), we avoided attributing this difference simply to the involvement of brain surgery, as patients in the Brain RT (no brain surgery) subcohort might have had brain metastasis that was not resectable. In fact, physicians are more likely to recommend brain surgery to patients with fewer, smaller, and/or more accessible brain lesions, which can exist as confounders for survival outcome. Detailed information describing the brain metastases would be desirable.

Furthermore, sample size was small for the groups receiving upfront brain RT in the "Brain Surgery + RT" subcohort (Groups 3 and 4, **Table 1**). This may be explained by the fact that physicians are more likely to strictly follow the NCCN guidelines and perform brain surgery (when feasible) before brain RT. In addition, sample size was small for patients who received brain surgery without RT (Groups 6 and 7, **Table 1**). Performing brain

surgery without RT is not among the recommendations in the NCCN guidelines. RT is a relatively gentle treatment, and both postoperative WBRT and SRS are increasingly recommended to be performed in conjunction with neurosurgery (7, 20–26). This explains why most patients who had received brain surgery ($n = 276$) also had brain RT (Groups 1 through 5; $n = 272$).

CONCLUSION

This study shows the benefit of upfront brain treatments for patients with synchronous NSCLC and brain metastases. For the patients who would eventually receive resection of the primary lung cancer, performing brain treatments (either neurosurgery or definitive RT) before the primary lung surgery yielded improved prognosis. The best overall survival appears to be associated with the procedure sequence of Brain Surgery → Brain RT → Lung Surgery ($n = 153$), with a median survival time of 27.1 months.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.facs.org/Quality-Programs/Cancer/NCDB.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board at University of Texas Southwestern Medical Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XH, DY, and YX designed the study. XH, SY, HL, and RL performed the data analysis. XH, SY, DY, and YX wrote the article. KK and DG provided critical input. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.649531/full#supplementary-material

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The Prognostic Significance of the Histological Types in Patients With Nonsmall Cell Lung Cancer ≤2 cm

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Background: Few studies attempt to investigate the impact of histology on the outcome of nonsmall-cell lung cancer (NSCLC) patients. In this study, we aim to determine whether the type of histology influenced the outcome of stage IA NSCLC patients with tumor size (TS) ≤20 mm.

Methods: The data of the population in our study was collected from the Surveillance, Epidemiology, and End Results (SEER) program, which is supported by the National Cancer Institute of the United States. The primary outcome was overall survival (OS). Cox-regression proportional hazards models were performed to identify prognostic factors for OS. The secondary outcome was lung cancer-specific mortality (LCSM). A competing risk model was used to identify risk factors associated with LCSM.

Results: A total of 4,424 eligible patients (T1a-bN0M0) who received sublobar resection [wedge resection (WR) and segmentectomy] were identified and included in the study for further analysis. For patients with TS ≤ 10 mm, multivariate Cox-regression analyses for OS showed that lung squamous cell carcinoma (LUSC) yielded poorer OS compared with lung adenocarcinoma (LUAD), and no difference was observed between LUSC and LUAD for LCSM in competing risk models. For patients with TS > 10 and ≤20 mm, multivariate analyses revealed that LUSC patients experienced poorer OS compared with that of LUAD; the univariate competing risk analysis indicated SCC pathology predicted an increased risk of death from lung cancer, whereas no difference is observed in the multivariate competing analysis. In addition, segmentectomy was associated with longer OS in patients with >10 and ≤20 mm but not in patients with ≤10 mm compared with WR.

Conclusion: Our study demonstrated that squamous pathology was associated with the worse OS but not LCSM for patients with ≤20 mm compared with adenocarcinoma. Moreover, segmentectomy when compared to wedge resection appears to be associated with a better prognosis in patients with neoplasm >10 mm, but not in the case of nodule ≤10 mm.

Keywords: lung squamous cell carcinoma, lung adenocarcinoma, overall survival, lung cancer-specific mortality, histology

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INTRODUCTION

Lung cancer is the leading cause of cancer-associated mortality for patients and the second most commonly diagnosed cancer in 2020 worldwide (1) and thus has been a huge challenge for public health (2). Currently, surgical resection is the only potentially curative treatment for early-stage nonsmall-cell lung cancer (NSCLC). However, the extent of resection remains debated. Subloar resection is reported to achieve a similar survival to lobectomy in early-stage patients (3, 4), and has been gradually accepted for patients with small tumor size or poor pulmonary reserve (5). NSCLC constitutes about 85% of all lung cancer cases, with adenocarcinoma and squamous cell carcinoma accounting for the most proportion.

Currently, the TNM stage is the major factor that needs to be taken into consideration for clinical decisions, and histological subtype is often ignored in IA stage NSCLC patients. Whether histology should play a role in therapeutic decision-making for IA stage NSCLC patients remains controversial. Some studies pointed out that lung squamous cell carcinoma (LUSC) had a better outcome than lung adenocarcinoma (LUAD) (6, 7), whereas other studies demonstrated LUSC was associated with a worse prognosis (8–10). More and more researchers came to realize that prognostic factors and outcomes were quite different between LUAD and LUSC. Therefore, the difference in prognosis between the two types of lung cancer was needed to be well researched.

In the present study, we collected clinical data from the Surveillance, Epidemiology, and End Results (SEER) database to investigate the prognostic effect of histology on the survival of early-stage NSCLC patients. We performed a population-based study using data from the years ranging from 2004 to 2011 to investigate the impact of histology on postoperative survival of early-stage NSCLC patients.

METHODS

Data Source

The SEER Program is supported by the National Cancer Institute of the United States. It is one of the largest resources of clinical information on cancers. Data from the SEER database has been used in numerous studies to assess the role of prognostic factors in lung cancer (4, 11–14), and this database is recognized as an authoritative source of clinical information, including tumor histology, tumor size, demographics, primary site, pathological stage, survival time, and so on.

Study Population

The inclusion criteria in our study should meet: (a) pathologically confirmed primary T1N0M0 NSCLC, only squamous cell carcinoma (SCC) and adenocarcinoma with tumor size $\leq$2 cm; (b) history of surgery, only wedge resection (WR) and segmentectomy were included; (c) no history of chemotherapy treatment before or after surgery; (d) no record of radiation treatment before or after surgery; (e) age $\geq$50, since LUSC is less likely to occur in patients with an early age; (f) tumor was not located in the main bronchus; (g) active follow-up and follow-up time no less than 3 months.

The study variables in this study included the baseline demographics of the population (gender, age at diagnosis, and race record), the details of tumors (TNM stage, grade, location, size, and histology diagnosis), and surgical procedures (wedge resection and segmentectomy). All patients were divided into two cohorts according to histology (adenocarcinoma and SCC). The histological type of the enrolled cases was identified according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3). The histological types were included as follows: adenocarcinoma (8140–8147, 8244, 8245, 8250–8255, 8260, 8290, 8310, 8320, 8320, 8323, 8330–8332, 8470, 8480–8481, 8550–8551, 8570–8573) and SCC (8052, 8070–8075, 8078,

TABLE 1 | Baseline characteristics.

	AD (n = 3211)	SC (n=1213)	P value
Gender			<0.001
Male	1,233 (38.4%)	599 (49.4%)	
Female	1,978 (61.6%)	614 (59.6%)	
Age (years)			<0.001
50–75	1,627 (50.7%)	513 (42.3%)	
≥76	1,584 (42.3%)	700 (57.7%)	
Race			<0.001*
White	2,827 (88.0%)	1,102 (90.8%)	
Black	233 (7.3%)	85 (7.0%)	
Others	151 (4.7%)	26 (2.1%)	
Grade			<0.001*
Well/moderate	2,290 (71.3%)	678 (55.9%)	
Poor/UD	555 (17.3%)	465 (38.3%)	
Unknown	366 (11.4%)	70 (5.8%)	
Resected LNs			0.039*
0	1,506 (46.9%)	603 (49.7%)	
1–3	778 (24.2%)	299 (24.6%)	
≥4	799 (24.9%)	254 (20.9%)	
Unknown	128 (4.0%)	57 (4.7%)	
Tumor size (mm)			<0.001*
≤10	948 (29.5%)	278 (22.9%)	
11-20	2,263 (70.5%)	1,213 (77.1%)	
Surgical procedure			0.138
Wedge resection	2,620 (81.6%)	1,013 (83.5%)	
Segmental resection	2,176 (18.4%)	200 (16.5%)	
Location			0.023*
Upper	1,901 (59.2%)	776 (64.0%)	
Middle	121 (3.8%)	44 (3.6%)	
Lower	1,147 (35.7%)	383 (31.6%)	
others	42 (1.3%)	10 (0.8%)	
Laterality			0.720
Left	1,434 (44.7%)	549 (45.3%)	
Right	1,777 (55.3%)	664 (54.7%)	

*Indicates that the difference was statistically significant.
UD, undifferentiated; LN, lymph node; AD, adenocarcinoma; SCC, squamous cell carcinoma.

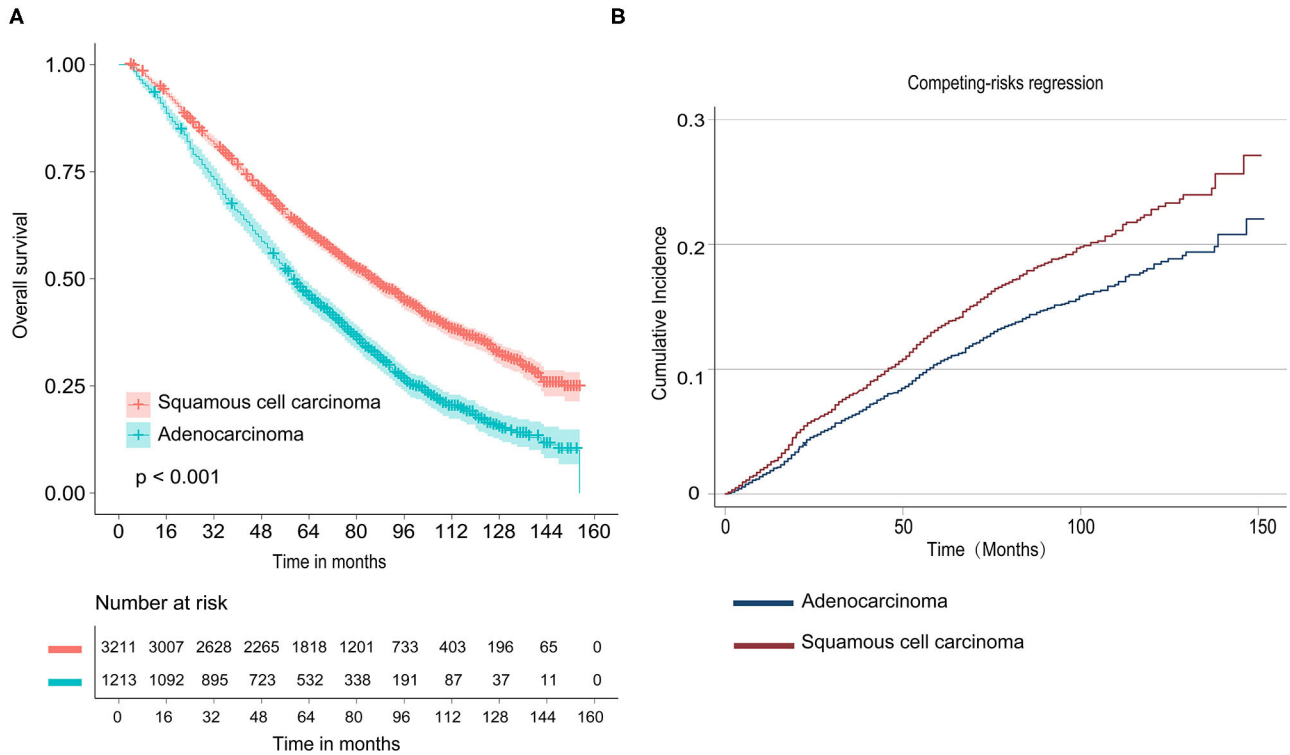

FIGURE 1 | Survival analyses for stage nonsmall-cell lung cancer (NSCLC) patients with tumor size ≤20 mm. **(A)** Kaplan–Meier estimates for overall survival by histological subtype; **(B)** Cumulative incidence for lung cancer-specific mortality by histological subtype.

8083–8084) (15–17). Surgical procedures (SP) were divided into wedge resection (WR) (surgery code: 21) and segmentectomy (surgery code: 22). The grade well/moderate group included grades I and II, and the poor/undifferentiated (UD) included III and IV.

Overall survival and lung cancer-specific mortality (LCSM) are the primary outcomes to be assessed in our study. The length of time from diagnosis to death due to any cause was defined as OS. The length of time from diagnosis to death due to NSCLC was defined as LCSM, and death from causes other than lung cancer was considered a competing risk event. To assess the impact of TS on OS and LCSM, the study populations were further stratified by TS.

Statistical Analysis

The difference in the distributions of continuous data (age, number of resected regional lymph nodes, and TS) was calculated by Wilcoxon tests and categorical variables (gender, location, laterality, histology, and grade) by the Pearson χ^2 tests. The Kaplan–Meier method was used to establish the curves of OS and the difference was evaluated by log-rank tests. All comparisons of OS for all prognostic factors were analyzed by Cox proportional hazards models. A Fine-Gray subdistribution hazard model was performed to identify risk factors associated with LCSM. In the model, death from any other cause, but not lung cancer, was recognized as a competing risk event. It is noted that, only when the univariate analysis indicated a significant difference, multivariate analysis was performed then, and generally, the results of multivariate analyses were more reliable than univariate ones.

A two-sided $P < 0.05$ was considered to indicate a statistical difference in all analyses. All of the hazard ratios (HRs) and its 95% confidence intervals (CIs) in Cox models were calculated using SPSS 22.0 (IBM, Armonk, NY) and all of the subdistribution hazard ratios (HRs) and its 95% confidence intervals (CIs) in Fine-Gray model were analyzed by Stata/SE version 26.0 (Stata Corp. LP, College Station, TX). Survival curves were established by R 4.0.1 (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics of the Population

After selection, a total of 4,424 patients with NSCLC ≤ 20 mm (only LUAD and LUSC) were included, of whom 3,211 patients were pathologically confirmed LUAD and 1,213 confirmed LUSC. Among the population, 1,746 were male and 2,678 were female. The date of the study population spanned from January 1, 2004, to December 31, 2011. There were 2,140 patients aged between 50 and 75 years and 2,284 patients aged 76 years and older. The median follow-up time for the patients with adenocarcinoma was 69 months and that for squamous cell carcinoma (SCC) was 58 months (data was not shown). The detailed descriptions of variables and the correlation between

TABLE 2 | Survival comparisons for NSCLC patients with tumor size ≤20 mm.

	Overall survival						Lung cancer-specific mortality					
	HR[a]	95% CI[a]	*P*[a]	HR[b]	95% CI[b]	*P*[b]	SHR[a]	95% CI [a]	*P*[a]	SHR[b]	95% CI [b]	*P*[b]
Gender												
Male	1			1			1			1		
Female	0.682	0.632–0.736	<0.001*	0.730	0.676–0.789	<0.001*	0.788	0.669–0.929	0.005*	0.837	0.708–0.988	0.035*
Age (years)												
70–75	1			1			1			1		
≥76	1.730	1.601–1.870	<0.001*	1.633	1.509–1.767	<0.001*	1.251	1.062–1.473	0.007*	1.183	1.002–1.396	0.046*
Race												
White	1			1			1					
Black	0.890	0.763–1.038	0.137	0.950	0.814–1.109	0.707	1.073	0.787–1.461	0.655			
Others	0.677	0.544–0.841	<0.001*	0.651	0.523–0.811	<0.001*	0.705	0.447–1.111	0.133			
Location												
Upper	1						1					
Middle	1.075	0.886–1.306	0.463				1.408	0.972–2.039	0.070			
Lower	0.968	0.892–1.050	0.429				0.862	0.719–1.032	0.107			
Others	1.214	0.868–1.696	0.257				1.084	0.499–2.355	0.838			
Laterality												
Left	1						1					
Right	1.004	0.931–1.084	0.911				1.090	0.924–1.286	0.305			
Grade												
Well/moderate	1			1			1			1		
Poor/UD	1.344	1.231–1.467	<0.001*	1.215	1.109–1.331	<0.001*	1.406	1.170–1.690	<0.001*	1.348	1.111–1.636	0.002*
Unknown	0.984	0.863–1.122	0.806	1.065	0.933–1.216	0.352	0.797	0.580–1.096	0.163	0.855	0.621–1.178	0.339
Resected LNs												
0	1			1			1			1		
1–3	0.818	0.745–0.898	<0.001*	0.847	0.770–0.932	0.001*	0.964	0.792–1.174	0.720	0.939	0.769–1.145	0.534
≥4	0.607	0.549–0.671	<0.001*	0.664	0.599–0.736	<0.001*	0.752	0.609–0.929	0.008*	0.756	0.613–0.933	0.009*
Unknown	0.665	0.542–0.816	<0.001*	0.673	0.548–0.827	<0.001*	0.489	0.285–0.839	0.009*	0.473	0.275–0.813	0.007*
Tumor size (mm)												
≤10	1			1			1			1		
11–20	1.234	1.131–1.347	<0.001*	1.176	1.076–1.285	<0.001*	1.545	1.260–1.894	<0.001*	1.486	1.208–1.826	<0.001*
SP												
WR	1			1			1					
Segmentectomy	0.758	0.683–0.841	<0.001*	0.850	0.763–0.946	0.003*	0.930	0.752–1.149	0.503			
Histology												
AD	1			1			1					
SCC	1.600	1.476–1.735	<0.001*	1.367	1.257–1.285	<0.001*	1.274	1.066–1.522	0.007*	1.102	0.911–1.332	0.316

[a]*Univariate analysis,* [b]*multivariate analysis, *indicates that the difference was statistically significant.*
HR, hazard ratio; SHR, subdistribution hazard ratio; UD, undifferentiated; LN, lymph node; AD, adenocarcinoma; SCC, squamous cell carcinoma; WR, wedge resection; LT, lobectomy; SP, surgical procedure.

each variable and histology were presented in **Table 1**. Compared to patients diagnosed with LUAD, LUSC patients were more likely to occur in the male gender, white origin, and upper lobe. In addition, larger TS and advanced tumor grades were significantly associated with LUSC.

Survival Analysis

As shown in **Figure 1A**, Kaplan–Meier survival curves of OS calculated by log-rank revealed that patients who were diagnosed with adenocarcinoma had better OS than SCC ($P < 0.001$). In Cox-regression proportional hazards models, the results showed that LUSC patients experienced shorter OS [multivariate: HR = 1.367, 95% CI (1.257, 1.285), $P < 0.001$] compared with LUAD (**Table 2**). We found that patients who received segmentectomy with TS ≤ 20 mm had better OS [multivariate: HR = 0.850, 95% CI (0.763, 0.946), $P = 0.003$] compared with WR. In this study, we also demonstrated that a larger number of resected lymph nodes and smaller TS were strongly associated with longer OS.

As shown in **Figure 1B** and **Table 2**, univariate competing risk-regression models for LCSM showed that LUSC patients were more likely to die of lung cancer compared with LUAD [SHR = 1.274, 95% CI (1.066, 1.522), $P = 0.007$]. However, the

TABLE 3 | Survival comparisons for patients with TS ≤10 mm.

	Overall survival						Lung cancer–specific mortality					
	HR[a]	95% CI [a]	*P*[a]	HR[b]	95% CI [b]	*P*[b]	SHR[a]	95% CI [a]	*P*[a]	SHR[b]	95% CI [b]	*P*[b]
Gender												
Male	1			1			1					
Female	0.668	0.573–0.779	<0.001*	0.698	0.597–0.815	<0.001*	0.792	0.546–1.149	0.221			
Age (years)												
70–75	1			1			1					
≥76	1.652	1.419–1.924	<0.001*	1.622	1.392–1.892	<0.001*	1.372	0.954–1.972	0.087			
Race												
Caucasian	1						1					
African	0.988	0.736–1.326	0.936				1.048	0.529–2.078	0.891			
Others	0.837	0.552–1.270	0.404				0.831	0.308–2.241	0.715			
Location												
Upper	1						1					
Middle	0.945	0.635–1.405	0.945				1.146	0.504–2.607	0.744			
Lower	0.973	0.829–1.143	0.743				0.566	0.369–0.868	0.009*			
Others	1.179	0.609–2.284	0.625				1.330	0.296–5.981	0.710			
Laterality												
Left	1						1					
Right	1.009	0.866–1.176	0.908				0.924	0.642–1.331	0.674			
Grade												
Well/moderate	1			1			1					
Poor/UD	1.290	1.068–1.557	0.008*	1.156	0.950–1.406	0.147	1.315	0.849–2.036	0.219			
Unknown	0.985	0.788–1.232	0.896	1.100	0.879–1.378	0.405	0.650	0.344–1.228	0.185			
Resected LNs												
0	1			1			1					
1–3	0.940	0.780–1.132	0.512	1.003	0.831–1.210	0.978	0.877	0.559–1.374	0.568			
≥4	0.606	0.492–0.747	<0.001*	0.661	0.533–0.818	<0.001*	0.662	0.405–1.082	0.100			
Unknown	0.627	0.391–1.007	0.053*	0.663	0.412–1.066	0.090	0.412	0.103–1.637	0.208			
SP												
WR	1			1			1					
Segmentectomy	0.730	0.573–0.930	0.011*	0.850	0.663–1.089	0.198	0.819	0.467–1.436	0.487			
Histology												
AD	1			1			1					
SC	1.579	1.334–1.869	<0.001*	1.345	1.126–1.608	0.001*	1.290	0.853–1.951	0.227			

[a] *Univariate analysis,* [b] *Multivariate analysis, *indicates that the difference was statistically significant.*

HR, hazard ratio; SHR, subdistribution hazard ratio; UD, undifferentiated; LN, lymph node; AD, adenocarcinoma; SCC, squamous cell carcinoma; SR, sublobar resection; LT, lobectomy; SP, surgical procedure.

multivariate analyses indicated the difference was not significant [SHR = 1.102, 95% CI (0.911, 1.132), $P = 0.316$]. Moreover, patients who underwent segmentectomy had a similar LCSM [SHR = 0.930, 95% CI (0.752, 1.149), $P = 0.503$] compared with those who underwent WR.

Survival Comparisons Stratified by Tumor Size

To further investigate the impact of histology on survival in different TS, the survival analyses were investigated according to subclassification of TS (TS ≤ 10 mm, and TS > 10 mm and ≤20 mm).

In the subgroup of TS ≤ 10 mm, there was a significant difference in OS [multivariate: HR = 1.345, 95% CI (1.126, 1.608), $P < 0.001$] between LUAD and LUSC (shown in **Table 3**), and the survival curves of histology were shown in **Figure 2A**. In the competing risk model, the difference was not observed in tumor histology and surgical procedures (**Table 3** and **Figure 2B**).

As shown in **Table 4**, in Cox-regression proportional hazard models, SCC predicted worse OS [multivariate: HR = 1.378, 95% CI (1.252, 1.517), $P < 0.001$] in patients with TS >10 mm and ≤20 mm compared with adenocarcinoma. Consistent with the results of Cox-regression analyses, Kaplan–Meier survival curves indicated that SCC was associated with worse OS ($P < 0.001$) (**Figure 2C**). Besides, segmentectomy achieved better OS

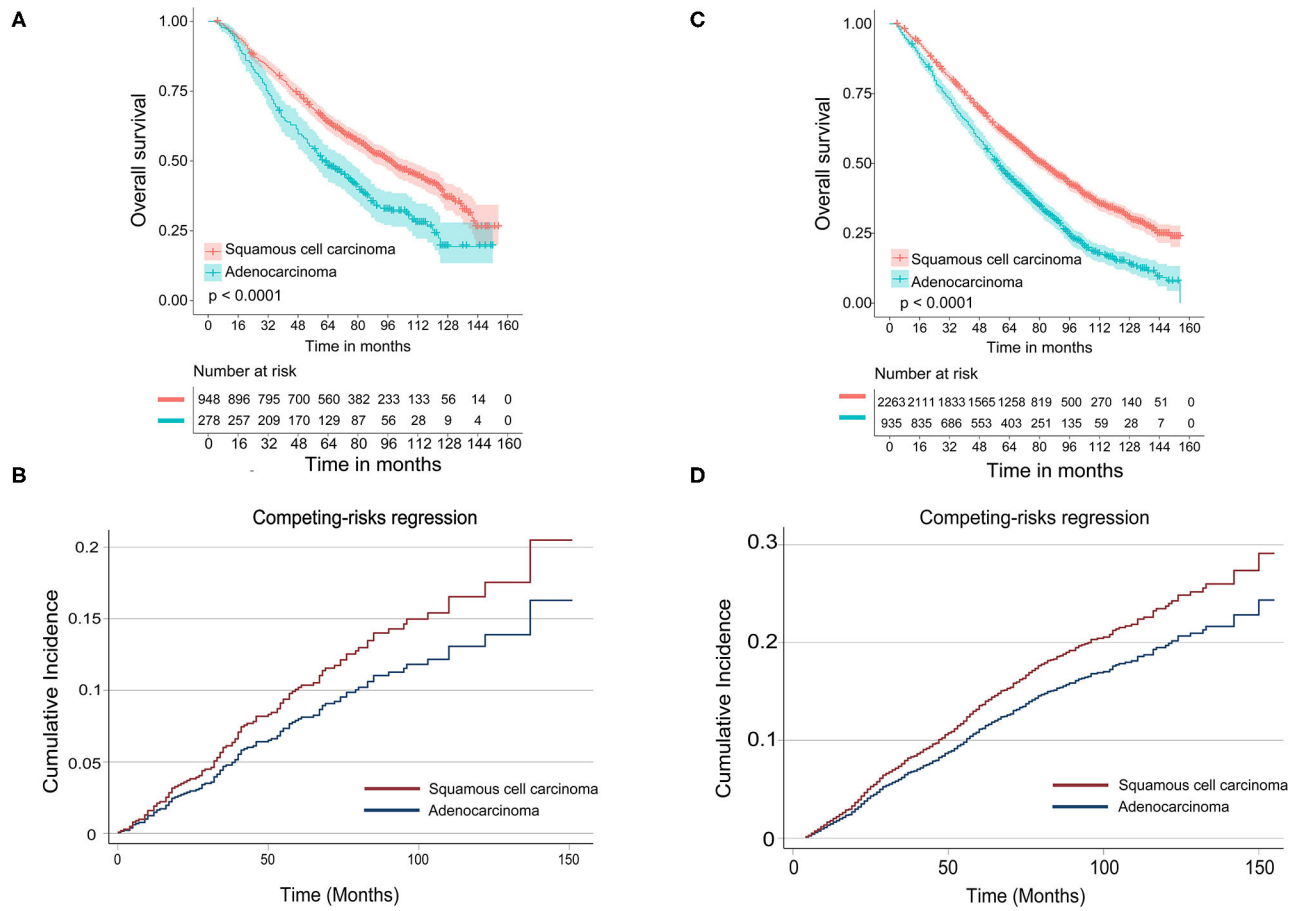

FIGURE 2 | Survival analyses for stage IA NSCLC patients aged 70 and older stratified by tumor size. **(A)** Kaplan–Meier estimates for overall survival by histological subtype of patients with tumor size ≤10 mm; **(B)** cumulative incidence for lung cancer-specific mortality by histological subtype of patients with tumor size ≤10 mm; **(C)** Kaplan–Meier estimates for overall survival by histological subtype of patients with tumor size >10 and ≤20 mm; **(D)** cumulative incidence for lung cancer-specific mortality by histological subtype of patients with tumor size >10 and ≤20 mm.

[multivariate: HR = 0.850, 95% CI (0.775, 0.957), $P = 0.007$] compared with WR. The difference was also observed in gender, age, the number of resected lymph nodes, and tumor grade. SCC pathology predicted an increased risk of death from lung cancer [SHR = 1.233, 95% CI (1.013, 1.502), $P = 0.037$] in univariate competing risks models (**Table 4** and **Figure 2D**); however, the difference was not significant [SHR = 1.123, 95% CI (0914, 1.382), $P = 0.265$] in multivariate analysis.

DISCUSSION

In our study, we investigated the relationship between histology types and prognosis of stage I A1–A2 NSCLC patients who underwent sublobar resection. We found that LUSC patients were at a higher risk of reduction of OS compared with LUAD, whereas the difference was not significant for LCSM. After taking TS into full consideration, the results remained stable. These results suggested that the histological subtype might be an independent prognostic factor for OS but not for LCSM in NSCLC patients with TS ≤ 20 mm.

Although numerous studies have involved the relationship between histology subtypes and the prognosis of stage I A NSCLC patients, they all focused on other prognostic factors, and few studies have deeply investigated the impact of histology on the outcome of NSCLC patients. However, the outcome of LUSC and LUAD had mixed results. Some studies suggested that LUSC was associated with a favorable survival (6, 7, 18, 19), whereas other studies pointed out that LUAD yielded better survival than LUSC (8–10), even though there were also studies showing that there were no differences in survival between the two types of histology (20, 21). In our study, patients with squamous histology had a higher risk of shorter OS than those with adenocarcinoma. Nakamura et al. (9) pointed out that LUSC patients were likely to have a history of smoking, and patients with a smoking habit were more susceptible to cancers other than the respiratory system, chronic obstructive pulmonary diseases, pneumonia, ischemic heart diseases, and cerebrovascular diseases, all of which may lead to shorter OS (9). Since some models have inherent weaknesses, it is important to select a suitable model to analyze clinical data. Considering that conventional Kaplan–Meier and Cox models

TABLE 4 | Survival comparisons for patients with tumor size >10 and ≤20 mm.

	Overall survival						Lung cancer-specific mortality					
	HR[a]	95% CI [a]	P[a]	HR[b]	95% CI [b]	P[b]	SHR[a]	95% CI [a]	P[a]	SHR[b]	95% CI [b]	P[b]
Gender												
Male	1			1			1					
Female	0.696	0.637–0.760	<0.001*	0.742	0.679–0.811	<0.001*	0.806	0.671–0.969	0.022*	0.838	0.696–1.008	0.062
Age (years)												
70–75	1			1			1					
≥76	1.732	1.582–1.896	<0.001*	1.635	1.491–1.792	<0.001*	1.183	0.985–1.421	0.072			
Race												
Caucasian	1			1			1					
African	0.859	0.717–1.029	0.099	0.901	0.751–1.080	0.259	1.083	0.766–1.531	0.651			
Others	0.621	0.481–0.802	0.001*	0.603	0.466–0.780	<0.001*	0.668	0.400–1.114	0.122			
Location												
Upper	1						1					
Middle	1.130	0.905–1.412	0.280				1.508	0.998–2.282	0.051			
Lower	0.971	0.884–1.068	0.545				0.966	0.791–1.179	0.732			
Others	1.229	0.833–1.812	0.299				1.010	0.409–2.499	0.982			
Laterality												
Left	1						1		1.129			
Right	1.004	0.920–1.097	0.923				1.140	0.947–1.373	0.166			
Grade												
Well/moderate	1			1			1			1		
Poor/UD	1.346	1.219–1.487	0.001*	1.236	1.115–1.369	<0.001*	1.405	1.147–1.720	0.001*	1.353	1.094–1.672	0.005*
Unknown	1.021	0.867–1.203	0.802	1.050	0.891–1.238	0.562	0.925	0.641–1.336	0.679	0.880	0.608–1.273	0.500
Resected LNs												
0	1			1			1			1		
1–3	0.767	0.688–0.854	<0.001*	0.798	0.715–0.891	<0.001*	0.958	0.769–1.194	0.706	0.943	0.754–1.793	0.609
≥4	0.596	0.532–0.669	<0.001*	0.660	0.587–0.743	<0.001*	0.756	0.598–0.954	0.019*	0.759	0.601–0.959	0.021*
Unknown	0.655	0.522–0.822	<0.001*	0.674	0.536–0.847	0.001*	0.487	0.271–0.877	0.017*	0.482	0.267–0.870	0.015*
SP												
WR	1			1			1					
Segmentectomy	0.745	0.664–0.837	<0.001*	0.850	0.755–0.957	0.007*	0.912	0.725–1.147	0.434			
Histology												
AD	1			1			1					
SC	1.586	1.447–1.739	<0.001*	1.378	1.252–1.517	<0.001*	1.233	1.013–1.502	0.037*	1.125	0.914–1.382	0.265

[a] *Univariate analysis,* [b] *Multivariate analysis, *indicates that the difference was statistically significant.*

HR, hazard ratio; SHR, subdistribution hazard ratio; UD, undifferentiated; LN, lymph node; AD, adenocarcinoma; SCC, squamous cell carcinoma; WR, wedge resection; SP, surgical procedure.

may overestimate the crude incidence of an outcome of interest, competing risk models were used to analyze lung cancer-specific death. The difference in LCSM between LUSC and LUAD was not observed in this study. We speculate that the reason for shorter OS may be that SCC histology is more likely to occur in patients with older age and they die of other causes. Consistent with our results, previous studies suggested that the two types of lung cancer should be analyzed separately to provide more precise outcomes (8, 22).

We demonstrated that segmentectomy achieved better OS for patients with TS > 10 mm and ≤20 mm, but not TS ≤ 10 mm compared with WR, while as for LCSM, segmentectomy yielded a similar outcome compared with WR. These results suggest that segmentectomy is more suitable for NSCLC with TS >10 mm and ≤20 mm than WR. We also found that the number of lymph nodes examined is an important prognostic factor for OS in NSCLC patients who received sublobar resection. A larger number of resected lymph nodes ("4" vs. "0") was closely associated with longer OS; however, as for LCSM, the difference was significant in patients with TS >10 and ≤20 mm, but not in TS ≤ 10. These results suggested the necessity of examining lymph nodes when an operation was being performed, especially for patients with larger tumor sizes. Recently, a study pointed out that adenocarcinoma and SCC are significantly different in many prognostic factors, such as age, tumor location, smoking status, gender, pathological stage, clinical TNM stage, tumor

differentiation grade, and survival (8). Our study also revealed that older age, male gender, advanced tumor grade, and larger tumor size were associated with worse OS.

Certainly, our study has some limitations. In recent years, with the development of targeted therapies and immunotherapies for lung adenocarcinoma, these patients who received targeted therapy and immunotherapy may undergo a longer survival than those who did not. Lacking relative information, we could not further assess the impacts of different targeted therapies and immunotherapy on OS and LCSM. However, IA stage resectable NSCLC patients were less likely to receive such treatments; Therefore, there is little possibility that our study has been substantially affected. Secondly, because of the nature of the retrospective study, some bias was inevitable. Finally, the information of the exact type of resected lymph nodes and the resection margin was not provided, and we will further investigate the impact of these factors on survival in the future. Our results need to be further validated by a large randomized cohort study in the future.

Taken together, our study demonstrated that SCC histology was an independent prognostic factor for the worse OS, but not for LCSM in NSCLC patients with TS $\leq$ 20 mm who received sublobar resection. Moreover, segmentectomy when compared with WR appears to be associated with a better prognosis in patients with neoplasm $>$10 mm, but not in the case of nodule $\leq$10 mm.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

BH, TF, and JX: study design, manuscript writing, and final approval. LZ, ZL, BL, HM, and RH: data collection and analysis. NL and QG: manuscript revision and final approval. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Targeted Therapy Followed by Salvage Surgery and Adjuvant Therapy: A Promising Therapy for Lung Cancer With Malignant Pleural Effusion From a Case Report

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Introduction: Malignant pleural effusion was encountered in about 8–15% of lung cancer patients at initial cancer diagnosis. The optimal therapeutic strategies for lung cancer with malignant pleural effusion (MPE) remain unclear.

Case Description: In this study, we reported a case of lung cancer with MPE, which was successfully managed with a multidisciplinary therapeutic strategy. The patient initially received gefitinib for 4 months with excellent response and he underwent salvage thoracoscopic lobectomy and systematic lymphadenectomy. Pathological complete response was confirmed for the patient and he discontinued gefitinib but received 4 cycles of adjuvant chemotherapy instead. The patient is still alive without disease progression for 62 months after surgery.

Conclusions: Combining targeted therapy, salvage surgery, and adjuvant therapy may be a promising treatment strategy for lung cancer with MPE harboring oncogene-targeted mutations.

Keywords: lung cancer, malignant pleural effusion, targeted therapy, salvage surgery, adjuvant therapy

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INTRODUCTION

Malignant pleural effusion is commonly encountered in about 8–15% of lung cancer patients at the time of initial cancer diagnosis, which has been categorized as stage IVa disease in the eighth edition of the tumor-node-metastasis staging system (1). The prognosis of lung cancer patients with malignant pleural effusion (MPE) remains dismal with a median overall survival time of 5 months and a 5-year survival rate of 3% (2). Current guidelines recommended non-surgical therapy including local therapy (for example ambulatory small catheter drainage, pleurodesis, and pericardial window) with similar treatment strategies to other stage IV diseases consisting of

systemic therapy and palliative therapy (3). In this study, we reported a case of lung cancer with MPE, which was successfully managed with the combined therapeutic strategy of targeted therapy followed by salvage surgery and adjuvant therapy.

CASE REPORT

In April 2016, a 51-year old male patient complained of consistent cough for 2 months and was admitted to our center for a diagnosis of poorly differentiated lung adenocarcinoma [PCK(+), CK7 (focally +), TTF-1(+), CK18(+), CK5/6(-), P63(scattered +), CK14(-), CDX-2(-), CD56(+), CgA(-), Sgn(-), Ki-67(∼50%)] in the right upper lobe with enlarged ipsilateral mediastinal lymph node and MPE confirmed by cytological examination of the fluid *via* both cell block and smear from the collected sample by thoracentesis, which was not further confirmed by pleural biopsy (cT3N2M1a, IVa) (**Figure 1**). The patient was generally in normal condition but was found to have type two diabetes mellitus with an Eastern Cooperative Oncology Group score of 1. With the primary tumor extracted *via* percutaneous needle biopsy for next-generation sequencing, it was confirmed to have epidermal growth factor receptor (EGFR) gene mutation (exon 21 L858R) and the patient was advised to receive gefitinib (250 mg, QD) for treatment. After taking gefitinib for 4 months, the patient was re-evaluated comprehensively and an excellent radiographic response to gefitinib was found on his chest computed tomography scan (**Figure 2**). Therefore, the patient was discussed in a multidisciplinary meeting in our center, and salvage surgery was recommended for him. In August 2016, after providing signed informed consent, the patient received lobectomy and systematic lymph node dissection under video-assisted thoracoscopic surgery (VATS) successfully and intraoperative findings did not reveal any pleural involvement, which was further confirmed by pleural biopsy. The patient was discharged on postoperative day 5 uneventfully and his postoperative pathological finding revealed no residual tumor neither in the right upper lobe nor in the mediastinal lymph node and pathological complete response to gefitinib was confirmed in the patient (ypT0N0M0) as shown in his pathological report that numerous chronic inflammatory cells, foamy histiocytes, and dense fibrosis were observed and no viable tumor was seen [PCK(-), EMA(-), CK7(-), TTF-1(-), NapsinA(-), CK5/6(-), P63(-), PGM-1 (inflammatory cells+), complete pathologic

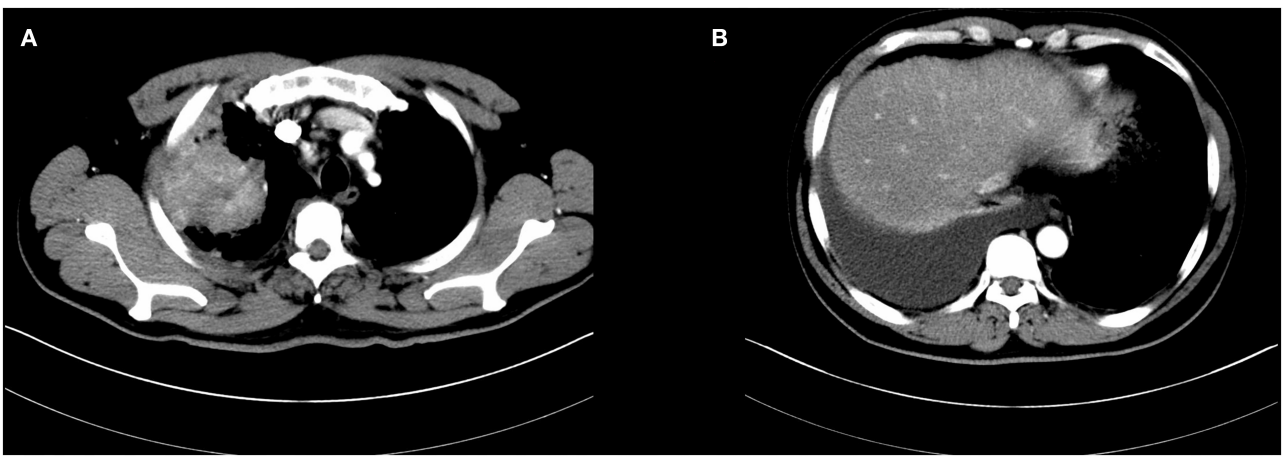

FIGURE 1 | Initial chest computed tomography of the patient revealed a large mass in the right upper lobe with enlarged mediastinal lymph node and malignant pleural effusion **(A,B)**.

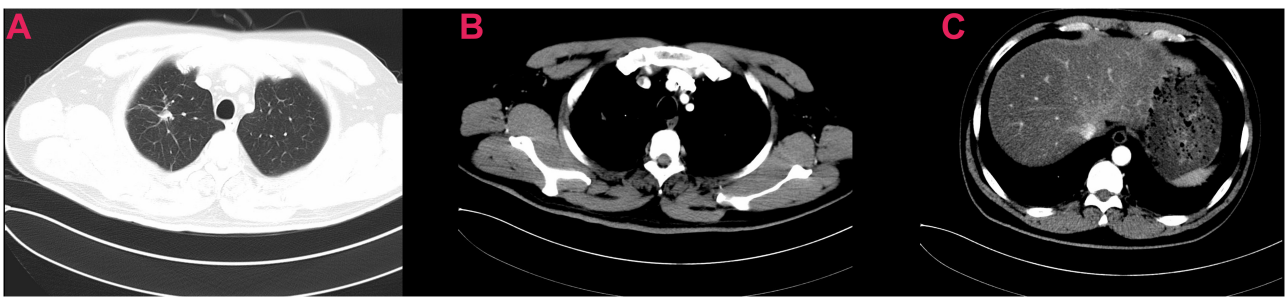

FIGURE 2 | Preoperative chest computed tomography of the patient showing excellent response to neoadjuvant targeted therapy **(A–C)**.

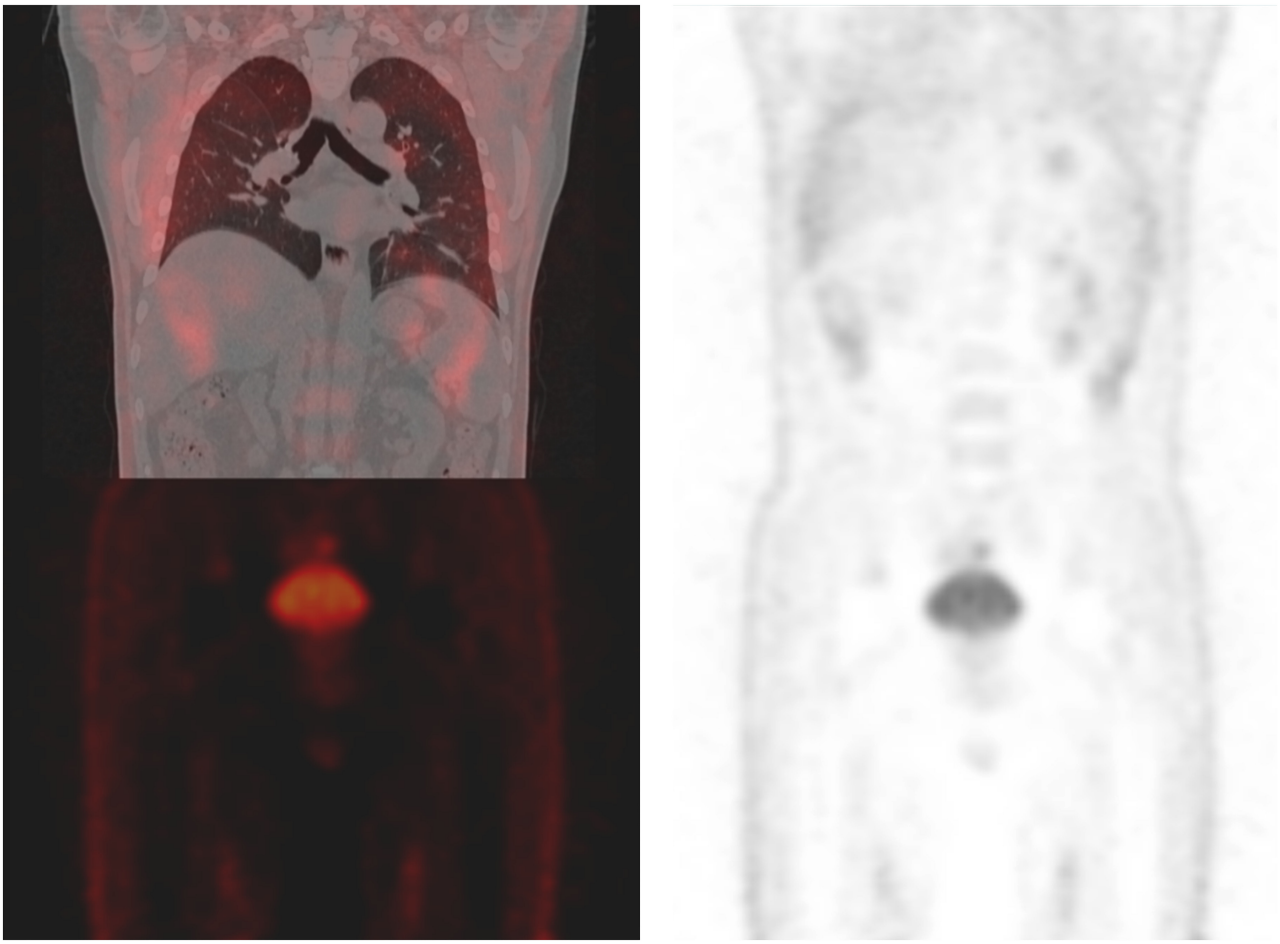

FIGURE 3 | Recent positron emission tomography/computed tomography of the patient shows no sign of recurrence.

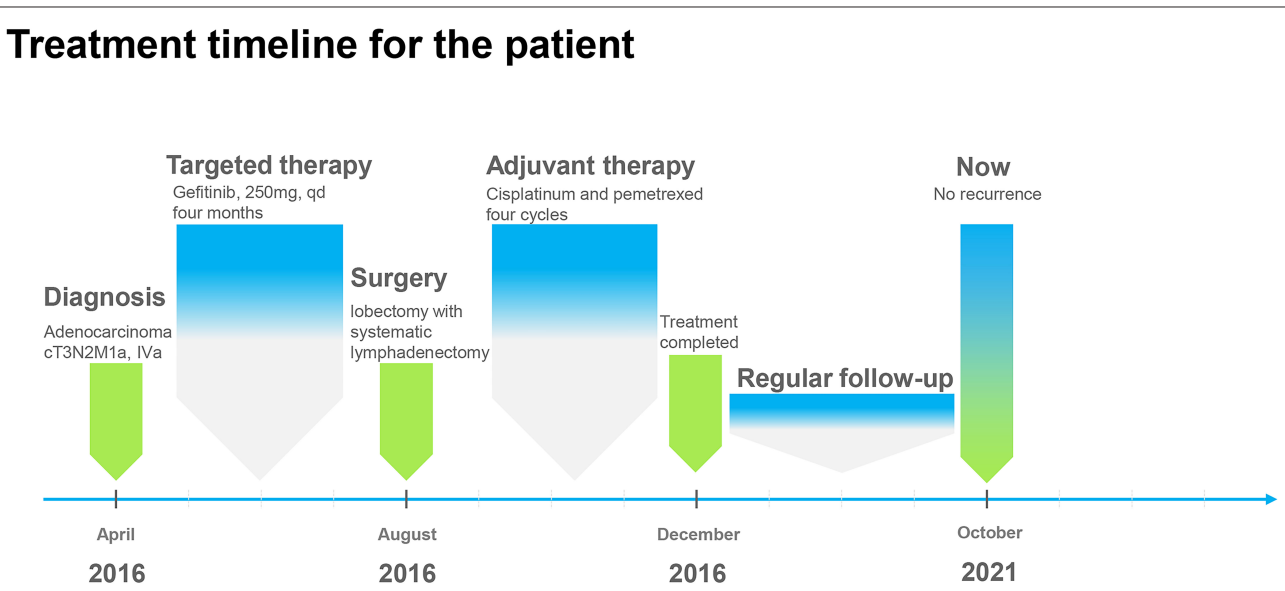

FIGURE 4 | Treatment timeline of the patient in our case.

response]. As usual, after surgery, the patient discontinued gefitinib and underwent four cycles of adjuvant chemotherapy (cisplatinum 40 mg on day 1 to 3 and pemetrexed 800 mg on day 1) instead because chemotherapy was the regular regimen for postoperative adjuvant therapy then and finished his last course of adjuvant chemotherapy in December 2016 with only grade 2 of leukopenia without any drug-related grade 3 to 4 adverse events. Since then, the patient received no additional treatment (such as targeted therapy, chemotherapy, or radiotherapy) and was followed up regularly every 3–4 months with chest and abdominal CT scans and tumor biomarkers and annual positron emission tomography (PET)/CT scan. The patient's recent PET/CT scan (October 2021) still revealed no sign of recurrence (**Figure 3**), and he is still alive without disease for 62 months after surgery (disease-free survival: 62 months). The whole treatment timeline of the patient in our case was summarized in **Figure 4**.

DISCUSSION

Previous studies have shown that surgery could benefit certain carefully selected patients with pleural metastasis and the reported 5-year OS of these patients treated with surgical resection ranged from 16 to 31% (4). Our previous study also indicated that surgical resection of the primary tumor could bring survival benefits for patients with unexpected pleural metastasis found during operation (5). However, it should be noted that patients with MPE yielded significantly worse survival than those without after surgery for pleural metastasis (6), suggesting that MPE may represent diffused pleural dissemination and surgery may be precluded for MPE (7). However, previous studies applied surgery with systemic therapy for treating advanced lung cancer with MPE and found that the long-term outcomes of combined therapy for these patients remain conflicting as some found that surgery with systemic therapy could benefit patients while others found a worse outcome after surgery (8). Therefore, for MPE, induction therapy followed by salvage surgery and subsequent systemic therapy was investigated. However, most of the previous studies applied chemoradiotherapy for induction therapy in patients with MPE and the rate of complete response was extremely low (9, 10). Moreover, the majority of these patients after surgery relapsed during follow-up (9). Therefore, the role of salvage surgery in treating advanced lung cancer with MPE remains further to be elucidated.

Similar to the dilemma encountered in neoadjuvant therapy for stage III lung cancer (11), the optimal induction regimens for lung cancer with MPE remain far from being established. As the promising effects of oncogene-targeted therapy for lung cancer, targeted therapy has already become the first-line therapy for advanced lung cancer harboring sensitizing mutations. Considering that EGFR tyrosine kinase inhibitors (TKIs) could yield a significantly higher response rate than chemoradiotherapy and confer survival benefit over chemoradiotherapy in advanced lung cancer harboring sensitizing mutations (12), in our case, the patient received gefitinib as the initial treatment because of the EGFR gene mutation. Surprisingly, the patient showed

TABLE 1 | Literature review for case reports regarding targeted therapy followed by salvage surgery for treating lung cancer with malignant pleural effusion.

Case	Gender	Age	Histology	Clinical stage	Driver gene	Targeted therapy	Drug duration	Therapeutic response	Postoperative stage	Postoperative treatment	Status	PFS (months)	OS (months)	References
1	Female	65	AD	cTxN2M1a	EGFR, 19del	Erlotinib	5 cycles	SD	NA	Erlotinib	Alive without progression	32	32	(10)
2	Female	63	AD	cTxN2M1a	EGFR, 19del	Afatinib	6 cycles	SD	NA	Afatinib	Alive without progression	28.25	28.25	(10)
3	Female	63	AD	cT2N0M1a	EGFR, 19del	Icotiinib	46 months	PR	pT2bN0M0	Icotinib	NA	NA	44	(15)
4	Male	45	AD	cT2N0M1a	EGFR, 19del	Gefitinib	6 months	PR	pT2aN2M0	Osimertinib	NA	NA	27	(15)
5	Female	56	AD	cT2N2M1a	ALK translocation	Crizotinib	8 months	PR	pT1aN2M0	Crizotinibi	NA	NA	6	(15)
6	Female	59	AD	cT1cN0M1a	EGFR, 19del	Gefitinib	7 months	PR	pT1bN0M0	Gefitinib	Progression of pubic bone metastasis	13	NA	(16)
7	Male	51	AD	cT3N2M1a	EGFR, L858R	Gefitinib	4 months	PR	pT0N0M0	Chemotherapy	Alive without progression	62	62	Our case

PFS, progression-free survival; OS, overall survival; AD, adenocarcinoma; EGFR, epidermal growth factor receptor; SD, stable disease; NA, not available; PR, partial response; ALK, anaplastic lymphoma kinase.

complete response to gefitinib after 4-month treatment. As we all know, the majority of patients receiving the first generation of EGFR-TKIs will progress within 1 year due to resistance mutation (12). Therefore, in our case, salvage surgery was recommended because of the radiographic finding of complete response. Moreover, we have successfully performed VATS lobectomy with systematic lymphadenectomy for the patient. Because of no residual tumor in the right upper lobe and mediastinal lymph node (ypT0N0), the patient only received 4 cycles of adjuvant chemotherapy without postoperative targeted therapy (as discussed by the multidisciplinary team considering that no residual tumor was revealed in the patient) for minimizing postoperative recurrence and was regularly followed up thereafter. And the patient is still alive without any sign of recurrence or metastasis for nearly 62 months. Therefore, this is an interesting case in a stage IVa lung cancer patient, who was managed successfully with a therapeutic combination of targeted therapy, salvage surgery, and adjuvant therapy.

Previously, Kubo et al. (13) reported a total of 7 cases of lung cancer with MPE treated with gefitinib, who responded effectively to gefitinib and chest drainage. However, the time to treatment failure for these patients was about 0.2–19.0 months. Tsai et al. (14) reported a case with stage IV oligometastatic adenocarcinoma of the lung successfully managed with neoadjuvant afatinib (pathological complete response) followed by surgery and adjuvant afatinib as well as radiotherapy for oligometastasis (the third lumbar vertebra) and the patient was alive for 32 months after initial diagnosis. A previous study also confirmed that salvage surgery after targeted therapy could serve as a promising therapeutic option for advanced lung cancer (15). Therefore, targeted therapy may serve as induction therapy for lung cancer with MPE. Arrieta et al. (10) reported two cases of lung cancer patients with malignant pleural effusion but without extra-thoracic disease, who were treated with neoadjuvant targeted therapy followed by salvage surgery and adjuvant targeted therapy. One case was treated with erlotinib and was alive without disease for 32 months while another was treated with afatinib and was alive without disease for 28.25 months. Song et al. (15) reported three cases of lung cancer with malignant pleural effusion treated with targeted therapy followed by salvage surgery and found that the postoperative survival was 6–44 months, proving that salvage surgery after targeted therapy was feasible and promising for treating advanced lung cancer with malignant pleural effusion. Li et al. (16) also reported a case of advanced lung cancer with malignant pleural effusion treated with salvage surgery followed by targeted therapy who finally developed progression of pubic bone metastasis after 13 months after surgery. Here we summarized these similar cases of lung cancer with malignant pleural effusion successfully managed with targeted therapy followed by salvage surgery in **Table 1**. Therefore, taking our case together, we believe that the combination of targeted therapy followed by salvage surgery and adjuvant therapy seems to be a promising therapeutic strategy for lung cancer with MPE harboring oncogene-targeted mutations.

However, several limitations existed in our case report. First, we drew our conclusions based on only one case, which could decrease the evidence level of our conclusions. Second, our case was diagnosed with MPE only confirmed by cytological examination of the fluid without thoracoscopic pleural biopsy, which may lead to false-positive results. Therefore, for such patients, a well-detailed algorithm should be designed to ensure proper patient selection in the future. Moreover, expanding surgical indications for patients with MPE may carry significant risks, such as perioperative morbidity and mortality as well as postoperative recurrence and metastasis, and should be done only after great deliberation and thoughtful consideration of all risks. In our opinion, the salvage surgery may be considered for patients with MPE, whose tumors showed a significant radiographic response (CT or PET/CT) to initial therapy with the disappearance of pleural effusion. However, the widely accepted criteria to decide salvage surgery for patients with MPE remains further to be established. Therefore, our conclusions should be taken with caution and further similar cases are encouraged to add evidence to our conclusions.

CONCLUSION

Lung cancer with MPE has an extremely poor prognosis and targeted therapy followed by salvage surgery and adjuvant therapy seems to be a promising therapeutic strategy for lung cancer with MPE harboring oncogene-targeted mutations.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by West China Hospital, Sichuan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

H-YD and YR collected data and drafted the manuscript. XT, DL, and KW designed the study and revised the manuscript. All authors read and approved the final manuscript.

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