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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Analysis of unexpected small cell lung cancer following surgery as the primary treatment

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Abstract

Purpose Small cell lung cancer (SCLC) is considered a systemic disease and surgery is generally not recommended to treat it. High heterogeneity within the tumor and preoperative diagnostic capabilities can sometimes fail to identify SCLC correctly, leading to a subset of unexpected SCLC patients that are diagnosed only after pulmonary resections.

Methods We retrospectively reviewed the clinical records of patients who were diagnosed as having SCLC only after surgery between 2008 and 2015 at a single institution.

Results A total of 125 unexpected SCLC patients were identified, including those with pure (p-SCLC; $n=76$, 60.8%) and combined (c-SCLC; $n=49$, 39.2%) SCLC. Highly differential diagnoses were observed between pre- and postoperative tissue examinations. Sixty-nine (55.2%) patients with postoperatively pathological-proven SCLC, including 31 with p-SCLC and 38 with c-SCLC, were diagnosed preoperatively with poorly differentiated carcinoma ($n=23$), squamous carcinoma ($n=14$), adenocarcinoma ($n=10$), malignant cells with necrosis ($n=10$), large cell carcinoma ($n=8$), or carcinoid ($n=4$). Also, inconsistencies between the clinical (c-) and pathological (p-) stages were found in this cohort, which were less common in patients with preoperative PET examination than those without (24.4% vs. 43.8%; $p=0.032$). Multivariable analyses showed that higher p-stage (hazards ratio (HR) = 1.7349, $p=0.0025$), sub-lobar resection (HR = 1.9078, $p=0.0395$), and a lack of prophylactic cranial irradiation treatment (PCI, HR = 0.3873, $p=0.0057$) were unfavorable prognostic factors for overall survival.

Conclusion Non-resection approaches reveal an inadequate diagnosis of SCLC. PET examination facilitates the evaluation of the clinical staging of SCLC. For unexpected SCLC undergoing resection, favorable outcomes can be achieved if radical resection and postoperative PCI are performed.

Keywords Small cell lung carcinoma · Surgery · Diagnosis · Stage · Survival

Introduction

Small cell lung cancer (SCLC) is usually characterized by a large intrathoracic mass at presentation, with a high propensity for early metastasis and a poor prognosis. Therefore, SCLC is considered a systemic disease, and surgery is rarely recommended (Lad et al. 1994). After the diagnosis of SCLC, which is based primarily on cytology and non-resection small biopsies, and the systemic chemotherapy will be given subsequently.

Nevertheless, sometimes SCLC histology can be unexpectedly identified after surgical resections. For some patients with small nodules located peripherally, tumor biopsies are not undertaken in general. Also, for well- or moderately differentiated lung cancers, it is easy for pathologists to make an accurate diagnosis based on non-surgically resected

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small biopsies or cytology specimens. However, for poorly differentiated cancers, the diagnosis is usually tricky, which can result in an inconsistency between the pre- and postoperative diagnosis (Marchevsky and Wick 2015; Kyritsis et al. 2017). In addition, small biopsies or cytology specimens, rather than surgically resected specimens, provide insufficient diagnostic information, especially for tumors with a mixed histology such as adenosquamous lung carcinoma and combined SCLC (Chen et al. 2015; Zhang et al. 2017, 2018). Hence, the diagnosis by a non-surgically-resected sample might not truly reflect the histology of lung cancer. Furthermore, SCLC is associated with a high propensity for early occult micro-metastasis, which is difficult to be detected using routine examinations (Meuwissen et al. 2003). As a result, potential SCLC patients with resectable tumors may undergo surgical resections. In the above cases, patients may have a diagnosis of SCLC made only at the postoperative examination of the resection specimens (Thomas et al. 1993; Song et al. 2015; Iwata et al. 2012).

The role of surgery in the treatment of SCLC is highly controversial, from initially contraindicating the surgical intervention to a current recommendation in a small proportion of SCLC patients with early-stage disease (Song et al. 2015; Iwata et al. 2012). A recent large-cohort study investigating the role of surgery in SCLC patients demonstrated that surgery could provide a significant survival benefit for patients with a broader range of disease stages (I–IIIA; Combs et al. 2015). However, the surgical indications for those SCLC patients were not given.

In the present study, we report a cohort of unexpectedly detected SCLC patients whose histology is not confirmed until after surgery. The clinical characteristics, pathological features, and the prognostic outcomes of these unexpected patients were retrospectively analyzed.

Patients and methods

Patients

Unexpected SCLC cases were defined as patients who were not initially considered to have SCLC but found to have this disease after resection of the tumor. Based on this, a total of 125 (0.7%) patients were identified from a database of 17,548 patients undergoing surgical resection of primary lung cancers in the Department of Thoracic Surgery of Shanghai Chest Hospital (Shanghai, China) between January 2008 and December 2015. During this period, 963 SCLC patients were diagnosed and treated. We excluded patients with confirmed SCLC before resection because, for those patients, neoadjuvant therapy is routinely given before surgery.

Preoperative examination

All these patients had the preoperative examination to evaluate the resectability and exclude distant metastasis, including chest-computed tomography (CT) scan, bronchoscopy, abdominal CT or ultrasonography examination, brain magnetic resonance imaging and whole-body bone scan. Mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is selectively performed in patients with enlargement of the lymph node, and those with suspected lymph node metastasis indicated by positron emission tomography (PET). PET–CT is not routinely performed during this period. SCLC staging was performed according to the 7th TNM classification (Vallieres et al. 2009).

Operations

Posterolateral thoracotomy and video-assisted thoracic surgery (VATS) were the standard surgery incisions performed by surgeons based on the patient's conditions. For small nodules without a definitely preoperative diagnosis, a wedge resection is taken firstly and then with an immediately frozen section examination to confirm the malignancy and histology. Subsequently, different surgical approaches were chosen by surgeons based on the tumor histology and their individuals' experience, patients' conditions and family members' informed consent. Those included primary tumor resection (wedge resection, segmentectomy, standard lobectomy, sleeve lobectomy, bi-lobectomy or pneumonectomy) with systemic lymphadenectomy (standard lobectomy, sleeve lobectomy, bi-lobectomy or pneumonectomy) or lymph node sampling (wedge resection, segmentectomy). Radical resection is defined as complete tumor resection (standard lobectomy, sleeve lobectomy, bi-lobectomy or pneumonectomy) with systemic lymphadenectomy. All patients did not suffer from severe intraoperative and postoperative complications.

Follow-up

All patients were instructed to receive 4–6 cycles of adjuvant SCLC-based chemotherapies. Radiotherapies were performed according to the radiation oncologists. Adjuvant therapies were prescribed within 1 month postoperatively. Information was obtained from patients through phone call or outpatient clinic re-visit records. The patients were scheduled for a first re-visit for evaluation of postoperative recovery at 4 weeks after the operation. Then, a follow-up visit was scheduled every 3 months for tumor evaluation after the first visit, by chest CT scans, brain MRI or CT, abdominal sonography or CT, and serum tumor markers.

Other examinations were performed according to the physicians if it is necessary. The primary end-point of the study was overall survival (OS), which is defined as the interval between the day of surgery and the date of death by any cause or the last follow-up date.

Statistical analysis

Normally distributed continuous variables were presented as the mean ± SD, otherwise as the median and range. Categorical variables were shown as numbers and percentages. Survival was expressed as median with 95% confidence interval (CI). Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. The variables found to be significant on univariate analysis (defined as a probability value of less than 0.15) were included in the multivariate analysis using the Cox proportional-hazards model after backward stepwise Wald elimination. Other clinically relevant factors like sex, age, and smoking history were also included in the Cox proportional-hazards model. All tests were two-sided and a p value < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS software (version 19.0; IBM-SPSS, Inc., Chicago, IL, USA).

Results

Clinical characteristics

The mean age was 61.10 ± 8.50 years. Most of the patients were men (85.6%) and had a smoking history (79.2%). The clinical characteristics of patients included in this study are shown in Table 1.

Pre- and postoperative stage and diagnosis

Thirty-two patients had a preoperative examination of mediastinoscopy ($n = 17$, 13.6%) or EBUS-TBNA ($n = 15$, 12.0%), and 45 (36.0%) had a PET–CT examination. The clinical stages (c-stage) of these unexpected SCLC patients were classified as I ($n = 96$, 76.8%) and II ($n = 29$, 23.2%), respectively. The pathological stages (p-stage) of SCLC patients were classified as I ($n = 45$, 36.0%), II ($n = 45$, 36.0%), and IIIA ($n = 35$, 28.0%), respectively. The staging inconsistency between c- and p-stage was noticed to be less common in SCLC patients undergoing a preoperative PET examination (11/45, 24.4%) than those not (35/80, 43.8%; $p = 0.032$), suggesting that PET examination provides a more accurate stage evaluation of SCLC. This inconsistency was caused by nodal upstaging.

Of the total 125 SCLC patients, there were 76 (60.8%) patients with pure SCLC (p-SCLC) and 49 (39.2%) with combined SCLC (c-SCLC). The eventually diagnosed c-SCLC, based on histopathological analysis of the surgical specimens, showed that large cell neuroendocrine carcinoma ($n = 18$) was the most common mixed component, followed by squamous carcinoma (Sq, $n = 15$), adenocarcinoma (AC, $n = 12$), adenosquamous carcinoma ($n = 3$), and spindle cells ($n = 1$). All patients had a bronchoscopy examination with bronchial brushing. Sixty-nine (55.2%) patients underwent preoperative biopsies. Of those, patients were diagnosed preoperatively with poorly differentiated carcinoma ($n = 23$), Sq ($n = 14$), AC ($n = 10$), malignant cells with necrosis ($n = 10$), and large cell carcinoma ($n = 8$), as well as carcinoid ($n = 4$), based on the cytologic and histologic analysis. Eventually, those patients were diagnosed as SCLC, including those with p-SCLC ($n = 31$) and c-SCLC ($n = 38$) according to the histopathological examination of the resected specimens. These discrepancies indicate a considerable inconsistency between pre- and postoperative diagnosis.

Surgery

Overall, lobectomy was performed in 97 (77.6%) patients. Seventy-eight cases were diagnosed with definitive SCLC by intraoperative frozen section examinations, and 54 of those patients were subsequently performed with lobectomies (46 with standard lobectomy, 4 with sleeve lobectomy, 2 with bi-lobectomy and 2 with pneumonectomy) and 24 with sub-lobar resections (21 with wedge resection and 3 with segmentectomy). The rest 47 cases were intraoperatively diagnosed with poorly differentiated or non-specific lung cancer ($n = 39$), Sq ($n = 4$), AC ($n = 3$), carcinoid ($n = 1$), 43 of those patients then underwent lobectomy and 4 received a following wedge resection. Survival comparisons showed a longer median OS in patients with a lobectomy than patients with a sub-lobar resection (50.0 (38.0–84.0) vs. 26.0 (18.0–65.0) months, hazards ratio (HR) = 0.4801, 95% CI 0.2299–1.0027; $p = 0.0134$; Fig. 1), which indicates that lobectomy is superior as a surgical option in SCLC detected incidentally during the primary surgical intervention.

Adjuvant treatment

None of those patients received neoadjuvant chemotherapy. A total of 119 patients (95.2%) received postoperative adjuvant chemotherapy. Of those, 42 (33.6%) patients received prophylactic cranial irradiation (PCI) therapy, including patients with p-stage I ($n = 4$), stage II ($n = 12$), and stage III ($n = 26$). The presence of PCI was associated with longer OS than those not (yes. vs. no, $p = 0.0098$; Fig. 2).

Table 1 Patients' characteristics and univariate analyses

Characteristics	*n* (%)	Univariate		
		HR (95% CI)	Median OS (95% CI)	*p* value
Sex				0.7129
Male	107 (85.6)	0.8691 (0.3933–1.9206)	50.0 (38.0–84.0)	
Female	18 (14.4)	Ref.	32.0 (23.0–34.0)	
Smoking history				0.3435
Yes	99 (79.2)	1.4086 (0.7351–2.6991)	40.0 (35.0–84.0)	
No	26 (20.8)	Ref.	–[a]	
Age (years)				0.5560
< 60	60 (48.0)	1.0290 (0.5943–1.7815)	44.0 (34.0–65.0)	
≥ 60	65 (52.0)	Ref.	50.0 (32.0–84.0)	
Location				0.0093*
Central	50 (40.0)	2.0478 (1.1722–3.5772)	35.0 (23.0–65.0)	
Peripheral	75 (60.0)	Ref.	–[a]	
Surgical approach				0.0091*
Open	62 (49.6)	2.1371 (1.2343–3.7002)	30.0 (17.0–71.0)	
VATS	63 (50.4)	Ref.	–[a]	
Type of resection				0.0134*
Lobectomy	97 (77.6)	0.4801 (0.2299–1.0027)	50.0 (38.0–84.0)	
Sub-lobar	28 (22.4)	Ref.	32.0 (18.0–65.0)	
Histology				0.6426
p-SCLC	76 (60.8)	1.1420 (0.6495–2.0080)	39.0 (34.0–50.0)	
c-SCLC	49 (39.2)	Ref.	65.0 (25.0–84.0)	
c-stage				0.2799
I	96 (66.5)	0.8525 (0.4568–1.5913)	65.0 (34.0–84.0)	
II	29 (27.5)	Ref.	35.0 (24.0–50.0)	
p-stage				0.0102*
I	45 (36.0)	0.3431 (0.1652–0.7126)	84.0 (40.0–84.0)	
II	45 (36.0)	0.6706 (0.3182–1.4129)	44.0 (31.0–50.0)	
IIIa	35 (28.0)	Ref.	32.0 (22.0–38.0)	
PCI				0.0098*
N0	83 (26.4)	2.3281 (1.3264–4.0865)	35.0 (24.0–65.0)	
Yes	42 (33.6)	Ref.	–[a]	

VATS video-assisted thoracoscopic surgery, *OS* overall survival, *HR* hazards ratio, *CI* confidence interval, *p-SCLC* pure small cell lung cancer, *c-SCLC* combined small cell lung cancer, *Ref.* reference, *c-stage* clinical stage, *p-stage* pathological stage, *PCI* prophylactic cranial irradiation

*Significantly different

[a]Median survival could not be estimated because more than half of the patients in the corresponding subgroup are alive

Survival

There was no treatment-related death in this cohort. The median follow-up period was 24.0 (7.0–92) months. Follow-up was completed for all unexpected SCLC patients. At the end of follow-up, there were 74 (59.2%) surviving patients. Median OS and 5-year OS were 44.0 (24.6–63.4) months and 46.0%, respectively.

Univariate analyses (Table 1) identified, besides the type of resection ($p = 0.0134$) and PCI ($p = 0.0098$), the tumor location (central vs. peripheral, $p = 0.0093$), surgical approach (open vs. VATS, $p = 0.0091$) and pathological stage ($p = 0.0102$) as significant prognostic factors of OS. There was no significant difference between patients with p-SCLC and c-SCLC ($p = 0.6426$).

Multivariable analyses were presented in Table 2. After adjustment for prognosis-related factors, the p-stage (HR = 1.7349, 95% CI 1.2157–2.4758; $p = 0.0025$) was the most significantly influential factor on survival, but the c-stage ($p = 0.150$) was not associated with differential prognosis. Additionally, the presence of PCI treatment after surgery could benefit the SCLC patients significantly (yes vs. no,

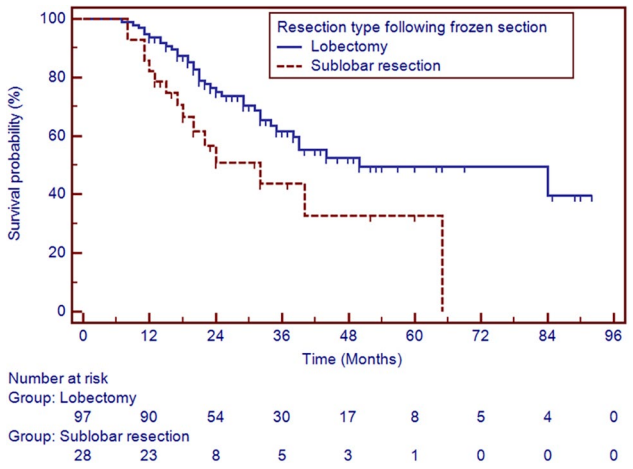

Fig. 1 Survival analysis of small cell lung cancer (SCLC) treated with lobectomy and sub-lobar resection. Survival comparisons showed a longer median overall survival (OS) in patients with a lobectomy than patients with a sub-lobar resection (hazards ratio (HR) = 0.4801, $p = 0.0134$)

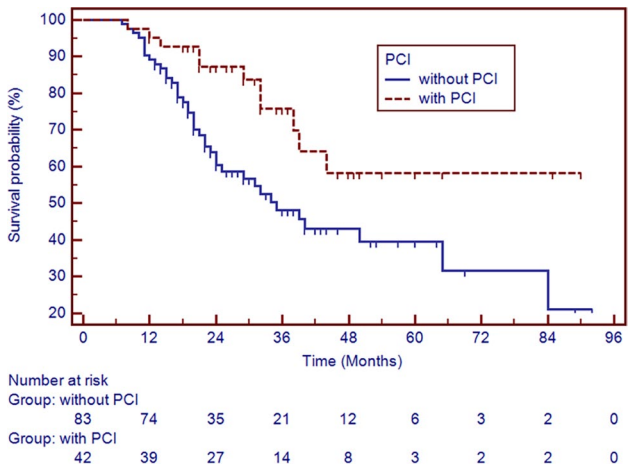

Fig. 2 Survival analysis of small cell lung cancer (SCLC) with and without adjuvant prophylactic cranial irradiation (PCI) treatment. Survival comparisons showed that the lack of PCI treatment was associated with a shorter median overall survival (OS) in unexpected SCLC patients (hazards ratio (HR) = 2.3281, $p = 0.0098$)

HR = 0.3873, 95% CI 0.1984–0.7560; $p = 0.0057$). Sub-lobar resection was associated with a poor survival compared with lobectomy in this cohort (sub-lobar resection vs. lobectomy, HR = 1.9078, 95% CI 1.0347–3.5174; $p = 0.0395$).

Discussion

Small cell lung cancer is distinguished from non-SCLC (NSCLC) by its rapid progress and early development of widespread intrathoracic lymph node and distant metastases.

Table 2 Multivariable analyses

Characteristics	Multivariable		
	HR	95% CI	*p* value
Resection			
Lobectomy		Ref.	0.0395
Sub-lobar	1.9078	1.0347–3.5174	
p-stage	1.7349	1.2157–2.4758	0.0025
PCI			
No		Ref.	
Yes	0.3873	0.1984–0.7560	0.0057

Only the significantly independent factors in the Cox multivariable model were presented

CI confidence interval, *p-stage* pathologic stage, *PCI* prophylactic cranial irradiation, *Ref.* reference

As a result, SCLC is considered a systemic disease and, thus, not suitable for surgical treatment (Lad et al. 1994).

The majority of SCLC cases are diagnosed by non-resection approaches, which, however, have an appreciable inaccuracy to specify the category of lung cancers (Thomas et al. 1993). The accuracy of diagnosis is critical for the subsequently optimal treatment strategy and potentially affects the prognosis of patients. For patients with SCLC, a definitive preoperative diagnosis is more challenging. Studies show that, in some cases, the diagnosis is tricky even for senior pathologists, which may be a result of inherent poor differentiation and heterogeneity within SCLC, inadequate sampling and tissue artifacts (Marchevsky and Wick 2015; Kyritsis et al. 2017; Song et al. 2015).

Furthermore, the presence of NSCLC components within SCLC, that is combined SCLC, also potentially causes a diagnostic challenge preoperatively (Zhang et al. 2017, 2018; Nicholson et al. 2002; Adelstein et al. 1986). In the present study, the most unexpected SCLC cases were preoperatively diagnosed as poorly differentiated, or not-otherwise-specified lung cancer or NSCLC. This inaccuracy in diagnosis was mainly due to the poor differentiation and the combined NSCLC components. Therefore, concerning the precise diagnosis of SCLC, non-resection approaches provide insufficient diagnostic information, whereas surgical resection allows a considerable number of specimens for the diagnosis (Chen et al. 2015; Iwata et al. 2012). Iwata et al. (2012) showed that 25% of SCLC patients could be misdiagnosed pre- or intraoperatively, which also suggested the inadequacy of preoperative non-resection diagnosis. Taken together, these data suggest a diagnostic dilemma for SCLC cases by non-resection approaches, meaning that a considerable number of SCLC cases might have been missed.

SCLC is an aggressive subtype of lung cancer with a high propensity for occult metastasis. Thus some SCLC patients who present with small solitary pulmonary nodule might

suffer from micro-metastasis, which was confirmed by our current study showing a considerable upstaging of p-stage compared to c-stage. Data from The International Association for the Study of Lung Cancer demonstrated that 20% of SCLC patients with c-stage I/II were finally upstaged to p-III due to mediastinal lymph node metastasis (Vallieres et al. 2009). In a more recent study, Thomas et al. (2017) demonstrated that pathological upstaging was common after resection of SCLC, accounting for 25% (117/477) of c-stage I SCLC. Collectively, this implies a high malignancy of SCLC and its micro-metastatic tendency even at a clinically early stage.

More importantly, our study showed that the performance of various imaging modalities affects the c-stage, and the inclusion of PET–CT examination could provide a more accurate evaluation of the early disease stage of SCLC. This is consistent with a study demonstrating that PET–CT has a high sensitivity to detect lymph node metastases for SCLC patients with limited-stage disease (Bradley et al. 2004). Stish et al. (2015) also reported that nodal upstaging happened more frequently in patients staged with CT compared to those staged with PET/CT (1/27 vs. 11/27). In a more recent meta-analysis, PET–CT is demonstrated to be more sensitive than other imaging modalities concerning pretreatment staging of SCLC (Mitchell et al. 2016). PET–CT was not done routinely in this current cohort mainly because of the cost and unavailability at this institute during that period, which might be one of the critical reasons for the upstaging observed in the present study. Further studies are required to investigate the best diagnostic approaches for SCLC (Nobashi et al. 2016; Kwon et al. 2016).

Small cell lung cancer (SCLC) is considered a systemic disease due to its frequent dissemination and rapid progress at the time of diagnosis. The role of surgical resection is controversial, resulting in the inconsistent determination of surgical treatment for SCLC detected by intraoperative frozen sections. Our study demonstrated a favorable survival in the unexpected patients treated with lobectomy compared to those with sub-lobar resections. This provides evidence that a following radical resection should be performed as much as possible if the histology of SCLC is reported in the intraoperative frozen sections. Despite the inherently high malignancy and poor survival of SCLC, more and more studies demonstrate a promising prognosis in patients with early-stage SCLC undergoing resection (Takenaka et al. 2015; Varlotto et al. 2011; Yang et al. 2017a, b; Yu et al. 2010). Furthermore, surgery is recommended in selected SCLC patients as part of the multimodal treatment strategy (Varlotto et al. 2011). However, it is unclear whether patients in the above studies have a diagnosis of SCLC made only based on the postoperative histological examination. In our study, the median and 5-year OS of unexpected SCLC patients were 44.0 (24.6–63.4) months and 46.0%, respectively, which appear to be better than that noted previously (Takenaka et al. 2015; Varlotto et al. 2011; Yu et al. 2010). Our favorable outcomes might be due to the high selection of patients in this cohort and that the extent of nodal metastasis was likely to be minimal and microscopic.

The present study has three main limitations. It was a retrospective analysis, and the patient cohort was small. Also, whether the surgery could provide survival benefit compared to the non-surgical treatment was not studied. Last but not least, the comparison between patients who had the diagnosis of SCLC preoperatively and received surgical resections subsequently, and patients in the current unexpected SCLC cohort, has not been studied, because all patients in the former group receive the neoadjuvant therapy before surgery that could influence the p-stage considerably.

Conclusion

The poor differentiation and tumor heterogeneity within SCLC can influence the preoperatively diagnostic outcomes. This scenario signifies that the optimal treatment for some potentially unresectable SCLCs may not be possible. PET–CT provides a promising role in the evaluation of early disease stage in SCLC patients, which can be used to select the surgical SCLC candidates. Favorable survival outcomes can be achieved in the PCI-treated group based on the univariate and multivariate analyses. Our results also demonstrated improved outcomes in SCLC patients who undergo a radical lobectomy during primary surgical intervention for clinically resectable tumors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study has been examined and approved by the Institutional Ethics Committee of Shanghai Chest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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