Original Article

Intraoperative frozen sections of the regional lymph nodes contribute to surgical decision-making in non-small cell lung cancer patients

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Background: Individualization of pulmonary parenchymal resection and lymphadenectomy in lung cancer patients will likely become more important as surgical innovation. This study explored the utility of intraoperative pathological frozen sections of regional lymph nodes in non-small cell lung cancer (NSCLC) patients.

Methods: Patients with NSCLC underwent intraoperative sampling of N1 station lymph nodes depending on the location of the tumor, any other suspicious lymph nodes were also biopsied. The contribution of frozen-section analysis to surgical decision-making was evaluated.

Results: Of 74 lung cancer patients who underwent intraoperative frozen section analysis of lymph nodes, the positive rate was 18/74 (24.3%). The extents of agreement between preoperative N staging (cN) and intraoperative N staging (sN), cN staging and postoperative N staging (pN), and sN staging and pN staging were 62.2% (46/74), 63.5% (47/74), and 71.6% (53/74), respectively. When frozen section was combined with evaluation of pulmonary function and intrathoracic adhesions, surgical strategies were modified during operations in 18 cases (5 sN-positive, 13 sN-negative). Of these patients, five underwent extensive pulmonary parenchymal resection, and four had conservative lung parenchymal resection. In nine patients, the extent of lymph node dissection (LND) was changed.

Conclusions: Intraoperative frozen section of regional lymph nodes led to 24.3% operative strategies modification in lung cancer. Frozen section analysis may make an important contribution to surgical decision-making in terms of pulmonary parenchymal resection and LND.

Keywords: Lymph node; frozen sections; non-small cell lung cancer (NSCLC)

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Introduction

Lymphatic metastasis is a significant feature of lung cancer, and lymph node dissection (LND) plays a significant role during lung cancer operations. Presently, systematic mediastinal lymph node dissection (SMLND) or sampling is recommended during radical lung cancer operations (1-3). In 2005, the International Association for the Study of Lung Cancer (IASLC) Staging Committee definited SMLND as the dissection and histological examination of intrapulmonary (lobar, interlobar and segmental) and hilar nodes and, at least, three of the mediastinal nodal stations

Table 1 Patient characteristics

Characteristic	N=74 (%)
Sex	
Male	44 (59.5)
Female	30 (40.5)
Age, yrs	
Median (range)	58.7 (36.0–81.0)
Smoking	
Yes	29 (39.2)
No	45 (60.8)
Pathologic type	
Adeno	53 (71.6)
Adeno-squamous	2 (2.7)
Squamous	19 (25.7)
cN status	
cN0	43 (58.1)
cN1	16 (21.6)
cN2	15 (20.3)
sN status	
sN0	50 (67.6)
sN1	12 (16.2)
sN2	12 (16.2)
pN status	
pN0	41 (55.4)
pN1	11 (14.9)
pN2	22 (29.7)
TNM stage	
I	30 (40.5)
II	18 (24.3)
III	23 (31.1)
IV	3 (4.1)

Adeno, adenocarcinoma; squamous, squamous cell carcinoma.

depending on the lobar location of the primary tumor (4). SMLND not only prolongs the survival of non-small cell lung cancer (NSCLC) patients but facilitates accurate staging, in turn allowing appropriate, multidisciplinary, individualized treatment plans to be formulated (1). Some studies had indicated that survival after complete mediastinal lymphadenectomy tends to improve (5-7). However, the extent to which it improves prognosis, and the role played by SMLND compared to mediastinal lymph node sampling (MLS) in patients with resectable NSCLCs, remain controversial. Although patients may been found to have enlarged (and thus suspicious) lymph nodes during an operation, no study has yet explored whether intraoperative examination of frozen lymph node sections influences surgical decision-making in terms of the extent of pulmonary parenchymal resection and that of LND. In this study, we retrospectively analyzed clinical data on 74 lung cancer patients who underwent intraoperative lymph node biopsies to evaluate the clinical utility of frozen section analysis during pulmonary operations.

Methods

From January 2010 to December 2014, a total of 2,057 consecutive patients who underwent radical lung cancer operations in the Guangdong Lung Cancer Institute were initially enrolled. Ultimately, 74 lung cancer patients who had undergone intraoperative analysis of frozen lymph node sections were identified, and divided by tumor location. Overall, 44 patients were male and 30 were female; all were aged 36–81 years (average: 58.7 years); 29 were smokers and 45 were non-smokers; 47 presented with cough, chest pain, or chest tightness; and 27 were diagnosed upon physical examination, although they lacked any symptoms. The general characteristics of the 74 patients are summarized in *Table 1*. All underwent computed tomography (CT) or positron emission tomography (PET) for clinical diagnosis of lung cancer. TNM staging used the 7th classification of the IASLC (8). The lymph nodes of the N1 station were considered to be the ipsilateral hilar, interlobar, and lobar lymph nodes, in line with the 2009 IASLC guidelines (9).

According to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, we defined enlarged lymph nodes as short diameter ≥10 mm preoperatively or we found enlarged lymph nodes in operation based on surgeon's experience. When preoperative CT or PET showed enlarged lymph nodes, mediastinoscopy or EBUS could be used in the lymph nodes of station 2, 4 and 7. While for the hilar and interlobar lymph nodes, mediastinoscopy or EBUS were limited for accurate staging. Thus, when preoperative CT or PET showed enlarged lymph nodes or we found enlarged lymph nodes of N1 station in surgery, which were suspected metastatic nodes. We suggested to conduct frozen sections of the lymph nodes.

Totally, 26 and 48 patients underwent left lung and right lung cancer surgery, respectively. SMLND was defined as follows: complete resection of stations 1–4 and 7–9 of the mediastinal lymph nodes for right lung cancer, and complete resection of stations 5–9 of the mediastinal

Table 2 The extents of agreement between preoperative N staging (cN) and intraoperative N staging (sN)

N staging	Intraoperative N0 (sN0)	Intraoperative N1 (sN1)	Intraoperative N2 (sN2)
Preoperative N0 (cN0)	37 (50.0%)	3 (4.1%)	3 (4.1%)
Preoperative N1 (cN1)	5 (6.8%)	5 (6.8%)	6 (8.1%)
Preoperative N2 (cN2)	8 (10.8%)	4 (5.4%)	3 (4.1%)

lymph nodes for left lung cancer, together with resection of the hilar, lobar, and segmental lymph nodes, and the surrounding adipose tissue (10,11).

Results

Preoperative imaging showed that 30 patients had mediastinal lymph node enlargement; frozen sections revealed metastases in 12 of these patients (40%), including 5 cN1-sN1 patients, 3 cN2-sN2 patients, and 4 cN2-sN1 patients. Eighteen patients had inflamed lymph nodes that lacked metastases. Preoperative imaging showed that 44 patients lacked mediastinal lymph node enlargement; of these, intraoperative analysis of frozen sections of N1 lymph nodes and any suspected metastatic lymph node showed that six patients had metastases (13.6%) (three cN0-sN1 and three cN0-sN2 patients). A significant difference was evident between these two groups (P<0.001); the data are summarized in *Table 2*. Of the 30 patients with enlarged mediastinal lymph nodes in preoperative imaging, 21 (70%) had lymph node metastases in postoperative pathology analyses. Of the 44 patients who lacked enlarged lymph nodes in preoperative imaging, 12 cases (27.3%) were confirmed to have metastases in postoperative pathology analyses. A significant difference was evident between these two groups (P<0.001).

In 18 patients for whom frozen section analysis revealed metastatic lymph nodes, postoperative paraffin pathology showed metastases to other lymph nodes in 17 (94.5%). In the other 56 patients, whose frozen sections revealed no metastatic lymph nodes, 15 (26.8%) had metastases to other lymph nodes upon postoperative pathology. Seven (46.7%) of these lacked metastatic N1 lymph nodes but had metastatic N2 lymph nodes. This was partly attributable to skip transfer and occult lymph node metastasis. In seven (46.7%) cases, the intraoperatively sampled N1 lymph nodes were not metastatic; however, postoperative pathology revealed that other N1 lymph nodes were metastatic. Finally, 1 of the 15 cases (6.7%) had intraoperatively negative N2 lymph nodes; however, postoperative pathology revealed that the N1 lymph nodes were metastatic. A total of 41 patients (73.2%) had no lymph node metastases.

The operative strategies were adjusted intraoperatively in 18 cases when frozen section data were combined with analysis of pulmonary function and intrathoracic adhesions (5 sN-positive, 13 sN-negative cases) (*Figure 1*). The extents of pulmonary parenchymal resection were extended in five patients (one left pneumonectomy with SMLND, one right middle and lower lobectomy with SMLND, and three right upper and middle lobectomies with SMLND). The extents of pulmonary parenchymal resection were reduced in four patients (R2 resection and MLS in one patient with left upper lung cancer, one left lower lobectomy with SMLND, and two pulmonary wedge resections with MLS). In nine cases, the extent of LND was reduced, including three who underwent pulmonary wedge resection, whose lesions were all <2 cm in diameter, and whose hilar and lobar lymph nodes were not metastatic. We did not perform SMLND in five cases with serious pleural adhesions, whose calcified lymph nodes were embedded in vascular tissue, and for whom intraoperative analysis of the hilar, interlobar, and lobar lymph nodes revealed no metastases. We also did not perform SMLND in one M1a-stage case whose mediastinal lymph nodes were widely metastatic. The surgical strategies are summarized in *Table 3*.

Discussion

The optimal resection mode for mediastinal lymph nodes (SMLND or MLS) continues to be controversial (12). In an earlier review, Martini reported that complete SMLND was associated with greater long-term survival (13). Wu *et al.* conducted a large randomized trial of 532 patients with NSCLC of clinical stage I, II, or IIIA, and found that SMLND significantly improved survival compared to MLS (12). The median survival times were 43 and 32 months, respectively (P<0001). Thus, SMLND has been considered the standard of care for lung cancer resection at most academic centers. The American College of Surgery Oncology Group Z0030 Trial found that SMLND did not improve long-term survival in patients with early-stage (T1 or T2, N0 or nonhilar N1) NSCLC, compared to MLS. In patients with tumors of the right lung, lymph

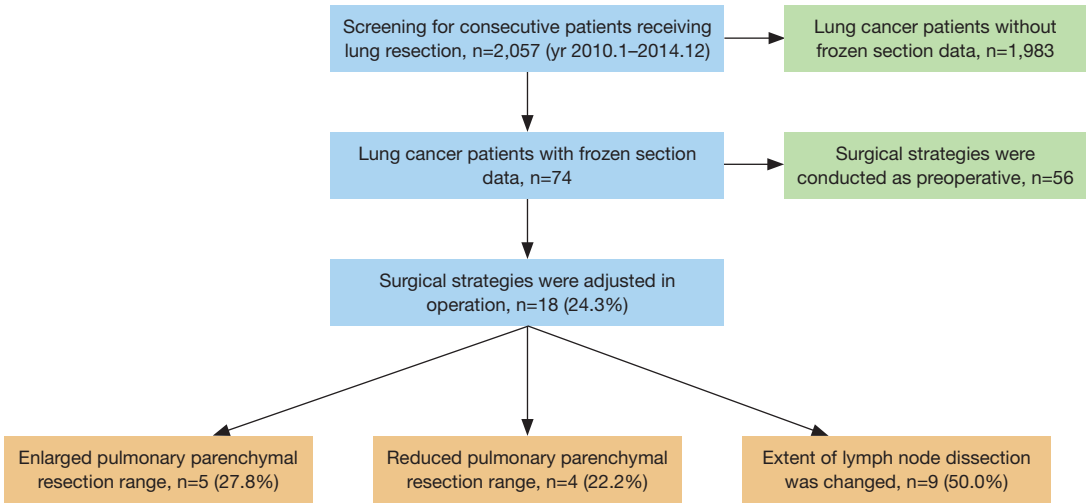

Figure 1 Intraoperative strategies were modified in 18 cases when frozen section combined with pulmonary function and intrathoracic adhesions.

Table 3 Surgical strategies were modified for 18 lung cancer patients when frozen sections were combined with pulmonary function and the extent of intrathoracic adhesions

Surgical strategy	Characteristic
Five patients for whom pulmonary parenchymal resections were extended	
One left pneumonectomy + SMLND	1. A tumor of the left lower lobe (T3) lying close to the upper lobe 2. Interlobar lymph node (+)
One right middle and lower lobectomy + SMLND	1. A tumor of the right lower lobe (T2a) lying close to the middle lobe 2. Interlobar lymph node (+)
Three right upper and middle lobectomies + SMLND	1. A tumor of the right upper lobe (T2a, T2b and T3) lying close to the middle lobe 2. Interlobar lymph node (+)
Four patients for whom pulmonary parenchymal resections were reduced	
One left upper pulmonary R2 resection + MLS	1. A tumor of the left upper lobe (T3) that had metastasized to the chest wall 2. Hilar lymph node (–)
One left lower lobectomy + SMLND	1. A tumor of the left lower lobe (T3) lying close to the upper lobe 2. Interlobar lymph node (–)
Two pulmonary wedge resections + MLS	1. All tumors <3 cm in diameter (T1a and T1b) 2. Hilar and lobar lymph nodes (–)
Nine patients for whom lymph node dissection was reduced	
Three pulmonary wedge resections + MLS	1. All tumors <2 cm in diameter (T1a) 2. Hilar lymph node >0.5 cm in diameter and (–) 3. Other lymph nodes <0.5 cm in diameter
Five lobectomies + MLS	1. Serious pleural adhesions (T1a and T1b) 2. Calcified lymph nodes embedded in vascular tissue 3. Interlobar and hilar lymph nodes (–)
One right upper pulmonary R2 resection + MLS	1. The tumor was in the M1a period (T4) 2. Lymph nodes were widely metastatic (+)

SMLND, systematic mediastinal lymph node dissection; MLS, mediastinal lymph node sampling.

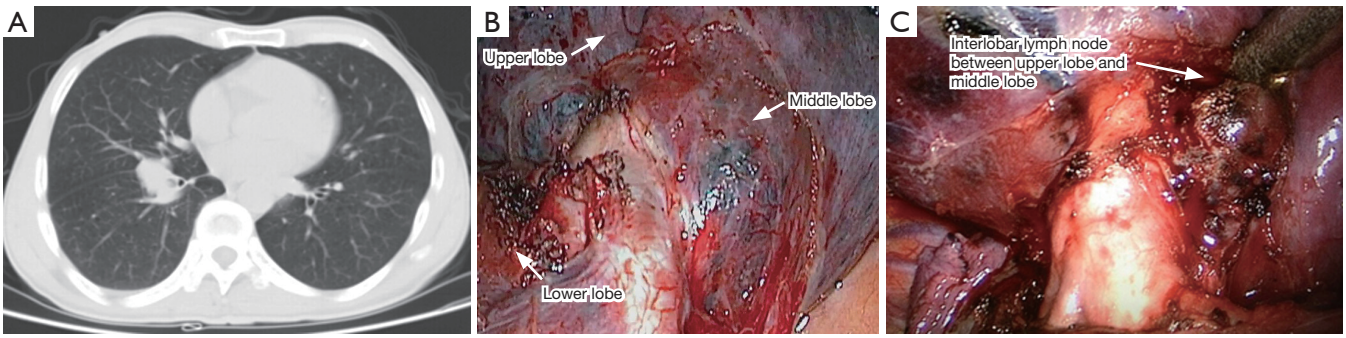

Figure 2 Tumor of right lower lobe, we planned to perform right lower lobectomy at first, turned to the right middle and lower lobectomy for frozen section of interlobar lymph node was positive and extracapsular invasive. (A) Image data before surgery; (B) planned to perform right lower lobectomy at first; (C) interlobar lymph node with extracapsular invasion was positive in frozen section, then a right middle and lower lobectomy was performed.

node stations 2R, 4R, 7, and 10R were sampled. In those with tumors of the left lung, stations 5, 6, 7, and 10L were sampled. Any suspicious lymph nodes were also biopsied. If no sampled lymph node showed any evidence of cancer on frozen-section examination, patients were randomized into SMLND or MLS groups. At a median follow-up time of 6.5 years, no survival benefit was evident in the SMLND group (14). Sugi *et al.* also found no survival difference between SMLND and MLS patients (5-year survival: 81% and 84%, respectively) who had small NSCLCs (<2 cm in diameter) of clinical stage I (15). In our study, 94.5% of patients (17/18) exhibited metastases to other lymph nodes upon postoperative pathology when the frozen sections had revealed metastatic lymph nodes. In the 56 patients for whom frozen section analysis did not reveal any metastatic lymph nodes, only 15 patients (26.8%) had metastases to other lymph nodes confirmed upon postoperative pathology (P<0.001). Thus, if frozen sections are positive, SMLND is necessary. Three patients underwent pulmonary wedge resection and MLS; all lesions were <2 cm in diameter, and the hilar and lobar lymph nodes were free of metastases. SMLND was not performed in five patients with serious pleural adhesions, whose calcified lymph nodes were embedded in vascular tissue, and for whom intraoperative analysis of the hilar, interlobar, and lobar lymph nodes revealed no metastases.

Lobectomy has been considered the gold standard of surgical care for early-stage NSCLC patients, but the extent of parenchymal resection required for local tumor control and the high probability of disease-free survival remains controversial (16-18). Landreneau *et al.* found that, in patients with small peripheral lung cancers (stage I), anatomical segmentectomy appeared to afford comparable local control, and prolonged disease-free and overall survival. The survival outcomes did not differ significantly from those afforded by lobectomy at a mean follow-up time of 5.4 years (19). Matsuguma *et al.* found that, in 96 patients with T1N0M0 adenocarcinoma of the lung, those in whom the proportions of ground-glass opacity (GGO) were >50% developed neither lymphatic invasion nor recurrence, and limited surgical intervention was thus advised (20). Dembitzer reported that no significant survival difference was evident between patients treated with lobectomy, or wedge resection or segmentectomy (W/S), after adjustment for tumor size, regardless of the histological subtype or other negative predictors of prognosis (P=0.770). These results suggest that limited resection may be appropriate to treat small tumors, particularly those <2 cm in diameter (21). A meta-analysis also showed that, among stage I NSCLC patients, those who had undergone intentional W/S had survival rates comparable to those who underwent lobectomy (22). In our study, the extents of pulmonary parenchymal resection of five patients were extended intraoperatively to ensure complete (R0) resection; intraoperative frozen sections of lymph nodes were positive in these patients. For example, a 56 years old man was diagnosed of lung cancer of right lower lobe, we planned to perform right lower lobectomy at first, then turned to the right middle and lower lobectomy for frozen section of interlobar lymph node was positive and extracapsular invasive (*Figure 2*). In addition, based on frozen section data, the extents of pulmonary parenchymal resection of four patients were intraoperatively reduced. Two patients underwent pulmonary wedge resection with MLS; their

lesions were small and peripheral, and the lymph nodes were negative.

In recent years, the concept of selective mediastinal lymphadenectomy has attracted increasing attention. LND is performed by reference to the lobe-specific patterns of nodal metastases. Any suspicious lymph nodes are also resected. Selective mediastinal lymphadenectomy can reduce surgery-induced trauma, particularly in elderly patients and those with comorbidities. The survival rate is acceptable, compared to that of early-stage NSCLC patients after complete mediastinal lymphadenectomy (23). Thus, prospective randomized controlled studies are needed to explore the utility of selective mediastinal lymphadenectomy and analysis of intraoperative frozen sections of mediastinal lymph nodes. Such modifications may reduce complications in lung cancer patients and improve their quality of life.

Conclusions

Intraoperative frozen section of regional lymph nodes led to 24.3% operative strategies modification. Given that the aim is complete tumor resection, the extent of resection of the pulmonary parenchyma may be appropriately expanded or narrowed depending on the frozen section, selective LND can also be performed. Such modifications may afford a better quality of life and greater benefits to patients. Examination of lymph nodes frozen sections may be important in surgical decision-making in terms of the extents of both pulmonary parenchymal resection and dissection. These topics require further prospective study.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by institutional ethics board and written informed consent was obtained from all patients.

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