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Outcome of Limited Resection for Lung Cancer

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Background: Up to now, lobectomy, bilobectomy and pneumonectomy combined with extensive lymph node dissection have been regarded as the standard procedures for non-small cell lung cancer (NSCLC). In high-risk patients, however, limited resection (LR) has been attempted as a salvage procedure, and, recently, indication for LR has been extended to selected cases with early-stage NSCLC. ***Material and Methods:*** Among the 773 patients who underwent surgical procedures for NSCLC in Seoul National University Bundang Hospital from May 2003 to December 2008, 43 patients received LR. Medical records of these patients were retrospectively reviewed. ***Results:*** Mean age at operation was 66.0±12.4 years, and there were 30 males. Twenty-five patients underwent conservative limited resection (CLR) and 18 underwent intentional limited resection (ILR). Indications for CLR were multiple primary lung cancer in 9 (9/25, 36%) and severe concomitant diseases in 5 (5/25, 20%). Of these, 6 patients underwent segmentectomy and 19 received wedge resection. During the follow-up period of 28.0±17.8 months, 15 patient developed recurrent lung cancer. ILR was selectively performed in lesions almost purely composed of ground glass opacity (≥95%), or in small solid lesions (≤2 cm). Of these, 11 patients underwent segmentectomy and 7 underwent wedge resection. During the follow-up period of 31.7±11.6 months, no patient developed recurrence. ***Conclusion:*** Intermediate-term outcome of LR for early-stage lung cancer is comparable to that of standard operation. For the delineation of the indications and appropriate surgical techniques for LR, prospective randomized multi-institutional study may be expedient.

Key words: 1. Lung neoplasm
2. Risk
3. Lung surgery

INTRODUCTION

Ever since the clinical reports in 1950s indicated that lobectomy is superior to pnemonectomy in terms of survival and postoperative complications [1-3], pulmonary lobes have been regarded as the basic units of surgical excision in non-small cell lung cancer (NSCLC). Thus, lobectomy, bi-lobectomy and pneumonectomy in combination with extensive lymph node dissection have long been the standard procedures for NSCLC. In patients with poor lung function or compromised general condition, however, limited resection (LR) of the lung has also been performed as a salvage procedure (i.e. conservative LR or CLR), and, from this experience, indication for LR has been extended to selected cases

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of early-stage NSCLC as a minimally invasive procedure (i.e. intentional LR or ILR). Given the preoperative condition of the patients, the outcome of CLR is presumed to be poor. To the contrary, the outcome of LR for early-stage NSCLC, particularly in cases with low grade malignancy, would well be good, considering less aggressive nature of the cancer, less surgical trauma and minimal excision of normal lung tissue. The exact indication and appropriate surgical technique of LR, however, have remained unclear and arbitrary, because they are mainly based on individual surgeon's preference rather than a scientific algorithm. Thus, by analyzing the preoperative patient characteristics and postoperative outcome of LR in our series, we sought to delineate the subset of patients with NSCLC who would best benefit from this new therapeutic strategy, which may help to postulate a guideline of LR for this disease entity.

MATERIAL AND METHODS

Between May 2003 and December 2008, 773 patients underwent lung resection for NSCLC in our institute, and the extent of the excised lung tissue was smaller than a lobe in 68 patients, including 43 patients with primary lung cancer who constituted study population in this research. There had been no well-established guideline or principle regarding the indication for limited resection (LR) during this time frame, and the employment of LR strategy was at the discretion of individual surgeon's decision. Consent to LR was obtained preoperatively in all patients after fully detailed information regarding LR was provided. For the preoperative diagnostic work-up, all patients underwent chest computerized tomography (CT) scanning, and other diagnostic studies, such as positron emission tomography (PET), bronchoscopy, percutaneous needle aspiration, and mediastinoscopy, were selectively conducted, if indicated. For the prediction of postoperative pulmonary function and determination of operability, pulmonary function test (PFT) was performed in all patients, and other studies, such as treadmill test, echocardiography and myocardial SPECT (Single-Photon Emission Computed Tomography), were selectively done. Surgery was conducted through open thoracotomy or thoracoscopic approach, and the latter was preferred to the former, if possible.

Table 1. Number of patients with lung cancer according to the types of resection

Type of resection	Number of patient (n=773)
Pneumonectomy	49
Bilobectomy	39
Lobectomy	614
Sublobar resection	68
For primary lung cancer	43
For recurred lung cancer	25

Postoperative follow-up in the out-patient department (OPD) was monthly for postoperative 3 months, every 3 months between postoperative 3 months and 3 years, every 4 months between postoperative 3 years and 5 years, and every 6 months from then on. There was no follow-up loss. Studies for postoperative assessment in the OPD, such as simple chest X-ray, chest CT, PET scan, bronchoscopy, PFT, and tumor marker assay, were performed in a timely manner, and more frequently if cancer recurrence was suspected.

RESULTS

The extent of lung resection in the 773 patients with NSCLC is summarized in Table 1. Among the 68 patients who underwent LR, postoperative pathological diagnosis was proven to be primary lung cancer in 43, who constituted study population. Their age were 66.0±12.4 years, and 30 were males. LR was done as a salvage procedure in 25 (conservative LR or CLR group) and was done as a minimally invasive procedure for early-stage lung cancer in 18 (intentional LR or ILR group).

The rationales for CLR are summarized in Table 2. Among the 25 patients with CLR, 10 had surgical risk score, proposed by American society of anesthesiologists (ASA score), of 3 or 4. In the 4 patients who had CLR for poor pulmonary function, their forced expiratory volume in one second was 1.11±0.22 L (53±19% of predicted value). Preoperative clinical staging of the NSCLC was stage I in 20, II to IIIa in 3, IIIb in 1 and IV in 1. Among the 20 patients with preoperative stage I, 7 remained to be stage I postoperatively, 1 changed to stage II due to positive regional lymph node, and, in the remaining 12, precise cancer staging remained un-

Table 2. Reasons of limited resection

Reasons	Number of patients
Conservative limited resection (n=25)	
Double primary lung cancer	9 (36%)
Poor lung function	4 (16%)
Extrapulmonary primary cancer	4 (16%)
Advanced-stage lung cancer	3 (12%)
Severe lung disease	3 (12%)
Severe accompanying disease	2 (8%)
Intentional limited resection (n=18)	
Mixed GGO or solid lesion and small-sized lesion*	9 (50%)
Pure GGO or nearly pure GGO lesion†	8 (44%)
Others‡	1 (5%)

GGO=Ground glass opacity; *=Small size: ≤2 cm; †=Nearly pure GGO lesion: GGO>95% of the lesion; ‡=Tumor size: 2.3 cm and mixed GGO lesion.

certain because extensive lymph node dissection was dispensed with due to the palliative nature of the procedure. Two patients with stage IIIb showed intra-pleural seeding of the cancer (T4N0M0), and received CRL of the primary cancer with intra-pleural hyperthermic perfusion therapy. As to the surgical technique of LR, 6 received segmentectomy and 19 had wedge resection, and resection of the primary tumor was deemed complete (R0 resection) in 22 and incomplete (R1, R2 resection) in 3. Surgical approach was thoracoscopic in 11 (segmentectomy: 1, wedge resection: 10). Lymph node dissection was dispensed with in 14, selectively sampled in 8, and extensively done in 3. Pathological types were adenocarcinoma in 11, squamous cell carcinoma in 11, bronchioloalveolar carcinoma in 2, and larger cell tumor in 1. Postoperative hospital stay was 7.58±4.4 days. Postoperative complications developed in 7, and most of them were not significant except for one case of surgical bleeding which necessitated reoperation. There was no surgical mortality. Late deaths occurred in 12, and 10 were related to cancer recurrence. Follow-up was complete with a mean duration of 28.0±17.8 months, and, during the follow-up, cancer recurrence occurred in 15. Mean expected duration of cancer-free survival was 18.5±16.8 months. Recurrence developed in the same side as the primary lung cancer in 6 (in the same lobe in 4, in the resection margin in 2), in the lymph node in 1, in the chest wall in 2, in the contra-lateral lung in 3, and in the distant location in 3. The primary cancer stage of the 15 patients who developed recurrence was uncertain in 8, stage I in 3, II and IIIa in 3, IIIb in 1 and IV in 1. Ten patients with recurrent lung cancer have died to date, and the remaining 5 patients have received chemotherapy or radiotherapy with partial (n=3) or no remission (n=2).

ILR strategy was selected based on the tumor size, location and the degree of the association of ground glass opacity (GGO), which signifies low-grade malignancy. Among the 18 patients with ILR, 11 had segmentectomy and 7 had wedge resection. The indications for wedge resection were small sized (≤2 cm) pure GGO lesion (n=4), and small (≤2 cm) peripheral mixed GGO-solid lesion (n=3). These criteria for wedge resection, however, were not exclusively applied, for one patient who had 1.6 cm-sized pure GGO lesion received segmentectomy. The indications for segmentectomy were small lesion without GGO lesion, or mixed GGO-solid tumor with solid lesion dominance. PET scan was performed in patients with solid tumor dominance (n=9), and maximal standardized uptake value was 2.13±2.04. Among these nine patients, there were cases with non-visualization of the tumor on PET scan. With respect to surgical approach, both thoracoscopic approach (n=9) and open thoracotomy approach (n=9) were used equally. Postoperative hostpital stay was 6.24±3.49 days, and postoperative follow-up duration was 31.7±11.6 months. On postoperative pathologic examination, five patients showed findings of bronchioloalveolar carcinoma (BAC), and 4 received wedge resection. When Noguchi classification system [4] for adenocarcinoma was applied for five patients with BAC, the number of patients with type A, B and C was 1, 2, and 2, respectively. One patient with BAC who had segmentectomy was proven to have type C lesion. In patients with ILR, there was no difference in postoperative course between wedge resection group and segmentectomy group, except for the hospital stay, which was longer in the latter (Table 3). There was no recurrence of lung cancer during the follow-up period. One patient died of colon cancer 41 months after the lung cancer surgery.

Clinical characteristics of patients with LR according to the rationale for LR (i.e. CLR versus ILR) are summarized in Table 4. There were significant differences in FEV1, tumor size, ASA risk score and the surgical procedure (wedge re-

Table 3. Comparison of tumor characteristics and clinicopathological parameters of the patients with stage Ia NSCLC according to the surgical procedures of intentional limited resection

Variables	Wedge resection	Segmentectomy	p-value
Total number of patients	7	11	
Age (Mean±SD, years)	64.52±11.48	61.05±11.79	0.548
Gender, male : female	4 : 3	6 : 5	1.000
ASA score			
1~2	6	10	0.896
3~4	1	1	
FEV1 (Mean±SD, liter)	2.43±0.43	2.38±0.56	0.833
Tumor size (Mean±SD, cm)	1.20±0.34	1.61±0.77	0.205
Tumor histology			
Adenocarcinoma	3	6	0.486
BAC	4	2	
Squamous cell carcinoma	0	1	
Others	0	2	
Type of approach			
Thoracotomy	2	7	0.335
VATS	5	4	
Number of dissected lymph node (Mean±SD)	2.5±0.7	9.0±5.7	0.151
Complications	0	2	0.497
Postoperative hospital stay (Mean±SD, days)	3.71±0.95	8.00±3.56	0.004
Follow up duration (Mean±SD, months)	29.7±12.4	31.4±12.4	0.781

NSCLC=Non-small cell lung cancer; SD=Standard deviation; ASA=American society of anesthesiologists; FEV1=Forced expiratory volume in 1 second; BAC=Bronchioloalveolar carcinoma; VATS=Video-assisted thoracic surgery.

section versus segmentectomy) between the two groups.

DISCUSSION

Application of LR strategy for NSCLC is still controversial. While Ginsberg and Rubinstein [5] claimed that the outcome of LR for early-stage lung cancer is worse than that of more extensive resection, others asserted that long-term outcome of LR would be better than that of lobectomy because larger amount of normal lung tissue is preserved while the risk of cancer recurrence is comparable to lobectomy [6-11]. This striking discrepancy in outcome interpretation between various clinical researches pertaining to this issue may result from the differences in study population, non-standardized surgical technique, and lack of consensus-based treatment algorithm.

Conservative LR (CLR) has been performed for a various proportion of patients with hardly-operable/hardly-resectable NSCLC, depending on the indication for LR or capability of each program in postoperative care. The rationale for conventional LR centers around improving early survival and quality of life, and preoperative risk analysis should be cautiously focused on precise assessment of risk-benefit relationship on an individual patient basis. Because patients with stage I NSCLC who are indicated for non-surgical treatment due to multiple risk factors are rare, there have been only a few reports on the long-term outcome of CRL in comparison to radiotherapy or chemotherapy [12,13] for this subset. In our study, the overall surgical outcome after CRL was less than optimal with high recurrence rate. This could partly be attributed to advanced disease in 5 patients whose clinical stage was higher than II, and pathologic staging of the patients with clinical stage I could have been changed to a higher grade if they had had extensive lymph node dissection. Furthermore, all patients except for two had solid tumor without ground glass opacity, and their maximal standardized uptake value (MSUV) on PET scan was higher than 3.0, which was the average MSUV of whole population with stage I NSCLC during the same time frame. These findings suggest that patients with preoperatively 'presumed' stage I would have had a high risk

Table 4. Comparison of tumor characteristics and clinicopathological parameters of patients with NSCLC according to the rationales for limited resection

Variables	Conservative	Intentional	p-value
Total number of patients	25	18	
Age (Mean±SD, years)	68.63±12.58	62.40±11.46	0.104
Sex (male : female)	20 : 5	10 : 8	0.105
ASA score			
1~2	15	16	0.046
3~4	10	2	
FEV1 (Mean±SD, liter)	1.98±0.72	2.40±0.49	0.042
Tumor size (Mean±SD, cm)	2.10±1.45	1.45±0.65	0.049
Tumor pathology			
Adenocarcinoma	11	9	0.339
BAC	2	6	
Squamous cell carcinoma	11	1	
Others	1	2	
Types of resection			
Segmentectomy	6	11	0.026
Wedge resection	19	7	
Number of lymph node (Mean±SD)	9.36±8.08	7.92±5.73	0.623
Postoperative hospital stay (Mean±SD, days)	7.58±4.40	6.24±3.49	0.301
Follow up duration (Mean±SD, months)	28.0±17.8	31.7±11.6	0.519
Recurrence	15 (60.0%)	0	
Cancer related death	10 (40.0%)	0	

NSCLC=Non-small cell lung cancer; SD=Standard deviation; ASA=American society of anesthesiologists; FEV1=Forced expiratory volume in 1 second; BAC=Bronchioloalveolar carcinoma.

of recurrence even after conventional resection, and extensive lymph node dissection might have lowered the recurrence rate, at least to some extent. Considering the 6 cases with local recurrence at the resection margin or in the same lobe, some may argue that they would have benefitted from conventional resection in terms of recurrence rate. However, given that 4 of the 6 patients were older than 70 years, 2 had severe associated lung disease, 2 had multiple lung cancer, and one had ASA grade of 3, it is prudent to say that these patients would have poorly tolerated lung resection more extensive than limited resection.

With respect to intentional LR (ILR), indications for performing ILR are less complicated than CLR. As to the size of the primary tumor, Tsubota et al proposed rationale for intentionally performed segmentectomy for NSCLC with small lesion (≤2 cm), and they have accumulated data to substantiate their novel strategy [6-8]. New TNM staging system categorizes small tumor (≤2 cm) as T1a, and this sub-classification is expected to boost the application of ILR for early stage NSCLC [14]. This new strategy, however, may render extensive lymph node dissection even more important, and planned ILR should be converted to conventional resection once lymph node metastasis becomes evident by frozen biopsy. As to the pathologic type of NSCLC, Noguchi et al proposed a histologic classification of adenocarcinoma [4], which has been proven to correlate well with the degree of ground glass opacity on chest CT [15,16]. Based on recent studies from Japan [17,18], patients with pure GGO on chest CT, which is equivalent to Noguchi type A or B, are good candidates for wedge resection, because the malignant potential of this lesion is even lower than that of small peripheral lung cancer. However, the application of ILR for GGO lesions is still controversial, and only a few studies have been undertaken in western countries. Furthermore, there is no consensus on the extent of lung resection for GGO, and some favor wedge resection as a definitive surgery while others perform segmentectomy or lobectomy after pathologic diagnosis is obtained by frozen biopsy from the wedge resection

specimen. The rationales for the former strategy are as follows: 1) The differentiation between Noguchi type A lesion (localized bronchioloalveolar carcinoma, LBAC) and atypical adenomatous hyperplasia (AAH) is difficult by frozen biopsy, 2) Procurement of tumor tissue for frozen biopsy may jeopardize the precise pathologic assessment later on, 3) By some scholars, Noguchi type A or B lesions are classified as carcinoma in situ or stage 0 disease [4], and, therefore, it is sensible to minimize surgical excision for very early stage disease in which intra-lobar spread of the cancer is less likely.

Current practice for NSCLC in Korea is characterized by decreased frequency of pneumonectomy, sleeve lobectomy, or other types of extensive resection, which may be due, at least in part, to the decreased incidence of once-prevailing central-type squamous cell carcinoma. To the contrary, the increasing number of peripheral adenocarcinoma or stage I disease has propelled the less extensive surgery employing thoracoscopic surgery technique. This contemporary trend towards minimally invasive surgery, however, has more to do with minimizing surgical trauma and hospital stay, rather than minimizing the extent of surgery for lung cancer, which may violate the principles for cancer surgery. In a practical sense, segmentectomy or wedge resection as a cancer surgery is a technically more demanding and complicated compared to those for benign lung lesions. In this regard, standard surgical technique of ILR needs to be defined. Furthermore, the consensus-based criteria for ILR in early-stage NSLCL have not established yet. Given that the number of patients with peripheral tumors and GGO lesions, who are potential candidates for ILR, is rapidly growing in Korea, benefits from ILR for this subset should be delineated as soon as possible, by thorough review of the patients who were indicated for ILR. Multi-institutional study may be expedient to this end.

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