Original Article

Minimally invasive (robotic assisted thoracic surgery and video-assisted thoracic surgery) lobectomy for the treatment of locally advanced non-small cell lung cancer

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Background: Insufficient data exist on the results of minimally invasive surgery (MIS) for locally advanced non-small cell lung cancer (NSCLC) traditionally approached by thoracotomy. The use of telerobotic surgical systems may allow for greater utilization of MIS approaches to locally advanced disease. We will review the existing literature on MIS for locally advanced disease and briefly report on the results of a recent study conducted at our institution.

Methods: We performed a retrospective review of a prospective single institution database to identify patients with clinical stage II and IIIA NSCLC who underwent lobectomy following induction chemotherapy. The patients were classified into two groups (MIS and thoracotomy) and were compared for differences in outcomes and survival.

Results: From January 2002 to December 2013, 428 patients {397 thoracotomy, 31 MIS [17 robotic and 14 video-assisted thoracic surgery (VATS)]} underwent induction chemotherapy followed by lobectomy. The conversion rate in the MIS group was 26% (8/31) The R0 resection rate was similar between the groups (97% for MIS *vs.* 94% for thoracotomy; P=0.71), as was postoperative morbidity (32% for MIS *vs.* 33% for thoracotomy; P=0.99). The median length of hospital stay was shorter in the MIS group (4 *vs.* 5 days; P<0.001). The 3-year overall survival (OS) was 48.3% in the MIS group and 56.6% in the thoracotomy group (P=0.84); the corresponding 3-year DFS were 49.0% and 42.1% (P=0.19).

Conclusions: In appropriately selected patients with NSCLC, MIS approaches to lobectomy following induction therapy are feasible and associated with similar disease-free and OS to those following thoracotomy.

Keywords: Lobectomy; minimally invasive surgery (MIS); thoracotomy; lung cancer surgery

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Introduction

The use of minimally invasive surgery (MIS), including video-assisted thoracic surgery (VATS) (1-6) and robotic lobectomy (7-16) , for the treatment of early-stage non-small cell lung cancer (NSCLC) has increased rapidly. The majority of experience has been in early stage disease, and because of the benefits with respect to hospital stay,

morbidity and cost have made MIS a preferred approach over thoracotomy. However, data regarding MIS for the treatment of locally advanced NSCLC, particularly following induction chemotherapy has been limited.

Recently a limited number of case series have been published on the feasibility of the VATS approach for locally advanced NSCLC (17-20). The main focus of these studies was the feasibility of a minimally invasive approach in carefully selected patients. Only one (17) looked at patients that received induction chemotherapy uniformly, although all four studies included some fraction of patients undergoing preoperative therapy. Three of the studies (17-19) did report some survival data that appeared to be consistent with historical comparisons, although only one (19) overtly compared VATS versus open groups. There are currently no published series of robotic surgery for locally advanced disease.

In our institution all three approaches are utilized to treat patients with locally advanced disease. In order to assess the feasibility and survival associated with these approaches, we compared the outcomes of patients who underwent MIS or open lobectomy for locally advanced disease. We considered true locally advanced disease to be those patients with clinical stage II-III disease who underwent induction chemotherapy.

Methods

Patient selection

This study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center (MSKCC). The study was conducted using data from a prospectively maintained database on surgical treatment of NSCLC, covering patients treated between January 2002 and December 2013 at MSKCC.

All patients included in the analysis fit the following criteria: (I) the disease was histologically defined NSCLC; (II) the disease was clinical stage II or stage IIIa by the seventh American Joint Committee on Cancer (AJCC 7) staging system (21); (III) the patient underwent lobectomy; (IV) the resection was preceded by induction chemotherapy or chemoradiotherapy.

We excluded patients with a history of concurrent malignant disease, patients with other previous primary cancers, and patients who had a lung resection procedure other than lobectomy, such as wedge resection, segmentectomy, bilobectomy, pneumonectomy, and chest wall resection. Operative death was defined as death within 30 days of the operation or any time after the operation if the patient did not leave the hospital alive.

Patients were retrospectively classified into two groups on the basis of the surgical approach: MIS group (VATS and robotic lobectomy) and thoracotomy group. Patients undergoing conversion were analyzed by an intent-to-treat analysis and remained in their original group and were not crossed over.

Surgical procedures

At our institution surgeons approached locally advanced disease by thoracotomy, VATS or robotic techniques. Each surgeon that performed MIS (VATS, robotic) conformed to the Cancer and Leukemia Group B (CALGB) 39802-consensus technique of MIS lobectomy (5). The da Vinci Surgical System (Intuitive Surgical, Mountain View, CA, USA) was used to perform robotic lobectomy with either a 3- or 4-arm approach previously described (14). VATS lobectomy was performed via a 4-cm utility incision at the anterior axillary line, at the fourth or fifth intercostal space, without rib spreading. A port at the eighth or seventh intercostal space, at the posterior axillary line, was used for camera visualization, and a posterior port was used for lung retraction and stapler insertion. Thoracotomy lobectomy was performed through a standard, partial muscle-sparing posterolateral incision. Systematic mediastinal lymph nodal dissection or sampling was performed. Conversion was defined as the use of a rib-spreading thoracotomy at any point after initiation of hilar dissection by an MIS approach.

Statistical analysis

Fisher's exact test and the Wilcoxon rank sum test were used to compare patient and disease characteristics, as well as postoperative outcomes, between patients in the MIS and thoracotomy groups. Since the distribution of sex, smoking status, pulmonary function, clinical stage, and tumor cell differentiation were comparable between the two groups (*Table 1*), we did not perform propensity score matching in further analysis. Overall survival (OS) was calculated from the day of surgery to the time of death. Patients who did not die during the study period were censored at the date they were last confirmed to be alive. Disease-free survival (DFS) was calculated from the day of surgery to the date of cancer recurrence or death from any cause. Patients who did not have a recurrence or who did not die during the study

Table 1 Patient and disease characteristics

Variable	MIS (n=31)	Open (n=397)	P
Age, median (range)	67 [50–83]	65 [34–87]	0.038
Sex, n [%]			0.44
Female	14 [45]	215 [54]	
Male	17 [55]	182 [46]	
Smoking, n [%]			0.13
Current	1 [3]	65 [16]	
Former	27 [87]	290 [73]	
Never	3 [10]	42 [11]	
FEV_1[a], median (range)	91 [54–130]	88 [28–141]	0.21
DLCO[a], median (range)	80 [35–114]	74 [30–128]	0.41
ASA score, n [%]			
2	2 [7]	88 [25]	0.069[b]
3	28 [90]	264 [74]	
4	1 [3]	7 [2]	
Pathologic type, n [%]			0.045[c]
Adenocarcinoma	24 [77]	269 [68]	
Squamous cell	6 [19]	77 [19]	
Large cell	0	23 [6]	
Other[d]	1 [3]	9 [2]	
Unclassified NSCLC	0	19 [5]	
Clinical stage, n [%]			0.075
IIA	8 [26]	60 [15]	
IIB	6 [19]	44 [11]	
IIIA	17 [55]	293 [74]	
Tumor site, n [%]			0.99[e]
RUL	9 [29]	183 [46]	
RML	1 [3]	20 [5]	
RLL	4 [13]	56 [14]	
LUL	11 [35]	105 [26]	
LLL	6 [19]	33 [8]	
Cell differentiation, n [%]			0.38[f]
Well	0	10 [3]	
Moderately	5 [16]	112 [28]	
Poorly/undifferentiated	16 [52]	179 [45]	
Unknown	10 [32]	96 [24]	
Induction therapy, n [%]			0.15
Chemotherapy	30 [97]	345 [87]	
Chemoradiotherapy	1 [3]	52 [13]	

Data are no. [%] of patients, unless otherwise noted. DLCO, diffusing capacity of carbon monoxide; FEV_1, forced expiratory volume in 1 second; ASA, American Society of Anesthesiologists; LLL, left lower lobe; LUL, left upper lobe; MIS, minimally invasive surgery; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe. [a], percentage predicted; [b], cases with unknown ASA score were excluded; [c], large cell, other, and unclassified NSCLC combined; [d], five cases of adenosquamous cell carcinoma, 2 cases of large cell carcinoma combined with small cell carcinoma, 1 case of adenocarcinoma combined with small cell carcinoma, 1 case of squamous cell carcinoma combined with small cell carcinoma, and 1 case of sarcomatoid carcinoma; [e], tumor site was regrouped into left or right lobe; [f], cases with unknown cell differentiation were excluded.

period were censored at the date they were last confirmed to be alive with no evidence of disease. Both endpoints were estimated using the Kaplan-Meier method. Univariate associations between patient, disease, or treatment factors and OS and DFS were analyzed using Cox proportional hazards regression. Multivariate Cox regression models were built using factors with P<0.20 in univariate analyses. A two-sided P value <0.05 was considered to indicate statistical significance. Statistical analyses were performed using the "survival" and "survcomp" packages in R (version 2.11.1; R Development Core Team).

Results

General patient characteristics

In total, 428 patients fit the criteria for inclusion in this study: 31 treated with MIS approaches (17 robotic and 14 VATS) and 397 treated with thoracotomy (*Table 1*). Patients in the MIS group were older than those in the thoracotomy group (P=0.038). Adenocarcinoma was the predominant pathologic type in both groups but was observed more often in the MIS group (P=0.045). The distribution of sex, smoking status, pulmonary function, ASA (American Society of Anesthesiologists) score, clinical stage, and tumor cell differentiation were comparable between the two groups.

Operation-related and postoperative outcomes

Results of the surgical treatment in all patients are seen in *Table 2*. Operative complications, extent of resection, and final pathologic stage were comparable between the two groups. Perioperative mortality was comparable in both groups as well, although there were no deaths in the MIS group. Eight patients were converted to thoracotomy, for various reasons: five for extent of disease, two for severe adhesions, and one for bleeding. More stations of lymph nodes were sampled in the MIS group than in the thoracotomy group, but the difference was not statistically significant (P=0.081). Patients undergoing MIS had a shorter length of hospital stay (P<0.001). A higher proportion of patients in the MIS group underwent adjuvant therapy, primarily radiotherapy (61%) (P<0.001).

Survival comparison

The median follow-up was 40.7 months. Tumor recurrence or death occurred in 258 cases (222 deaths, 36 alive with disease) during follow-up. The median OS was 29.2 months for the MIS group and 45.4 months for the thoracotomy group; the corresponding 3-year OS were 48.3% and 56.6%. The difference between the groups was not statistically significant (P=0.84) (*Figure 1*). The only variable associated with OS on univariate analysis was age: older patients had a higher risk of death (P=0.027) (*Table 3*). In the multivariate analysis, only age was independently associated with OS (P=0.045) whereas clinical stage, forced expiratory volume in 1 second, and surgical approach (P=0.99) were not associated with OS.

The median DFS for the MIS and thoracotomy groups were 27.3 and 23.6 months, respectively; the corresponding 3-year DFS were 49.0% and 42.1%, respectively. The difference between the groups was not statistically significant (P=0.19) (*Figure 2*). No factors were associated with DFS in univariate or multivariate analysis (*Table 4*).

Discussion

Despite the increasing use of MIS in recent years, thoracotomy remains the most common approach for lobectomy in the United States (1-3), and the relative merits of MIS procedures for the treatment of locally advanced NSCLC in particular are unclear. For locally advanced NSCLC with established nodal metastases, multimodality therapy with induction chemotherapy is a feasible and preferred approach (22,23). However, utilization of MIS approaches is increasing, and it is therefore important to establish the role of VATS and robotics in the multimodality treatment of of patients with more advanced disease.

In this study, we compared survival and other outcomes in patients who underwent MIS compared with thoracotomy for lobectomy for NSCLC following induction chemotherapy. Our data showed that OS and DFS were comparable between the two groups, suggesting that in appropriately selected patients with locally advanced NSCLC, MIS approaches are feasible and can result in similar DFS and OS to those following thoracotomy.

Because of quicker in hospital recovery and reduced perioperative morbidity in certain patients compared with thoracotomy (1-6), MIS lobectomy has been used increasingly during the last decade, although no substantive prospective, randomized trials directly comparing the two have every been performed. It is interesting that we observed similar rate of surgical complications between approaches, perhaps due to the similar groups of patients all with locally advanced disease and good performance

Table 2 Operation-related and postoperative outcomes

Variables	MIS (n=31)	Open (n=397)	P
Deaths, n [%]	0	4 [1]	0.99
LOS, days, median (range)	4 [1–14]	5 [1–61]	<0.001
Conversion to open, n [%]	8 [26]	—	—
Sampled LN stations, median (range)	5 [3–7]	4 [1–9]	0.081
Complications, n [%]			
No	21 [68]	265 [67]	0.99
Yes	10 [32]	132 [33]	
Type of complications, n [%]			—
Cardiovascular	2 [6]	42 [11]	
Pulmonary	6 [19]	61 [15]	
Renal failure	0	3 [1]	
Chylothorax	1 [3]	2 [1]	
Hemorrhage	1 [3]	3 [1]	
Recurrent nerve palsy	0	4 [1]	
Wound infection	0	3 [1]	
Others	0	14 [4]	
Resection completeness, n [%]			0.71
R0	30 [97]	372 [94]	
R1/R2[a]	1 [3]	25 [6]	
Pathologic stage, n [%]			0.47[b]
0	2 [6]	29 [7]	
I	12 [39]	101 [25]	
II	5 [16]	90 [23]	
IIIa	11 [35]	170 [43]	
IIIb[c]	0	5 [1]	
IV[d]	1 [3]	2 [1]	
Type of adjuvant therapy, n [%]			<0.001[e]
Chemotherapy	4 [13]	43 [11]	
Chemoradiotherapy	1 [3]	24 [6]	
Radiotherapy	19 [61]	83 [21]	
None	7 [23]	243 [61]	
Unknown	0	4 [1]	

Data are no. [%] of patients, unless otherwise noted. ARDS, acute respiratory distress syndrome; LN, lymph node; LOS, length of hospital stay; MI, myocardial infarction; MIS, minimally invasive surgery. [a], including 6 cases with R2 resection, all in the thoracotomy group; [b], stage IIIa, IIIb, and IV combined; [c], four cases with metastatic lesions in different lobes on the same side of lung; 1 case with T4 invasion; [d], clinical stage IIIa cases at primary diagnosis; after induction therapy, solitary brain metastasis occurred; [e], cases with unknown adjuvant therapy have been excluded.

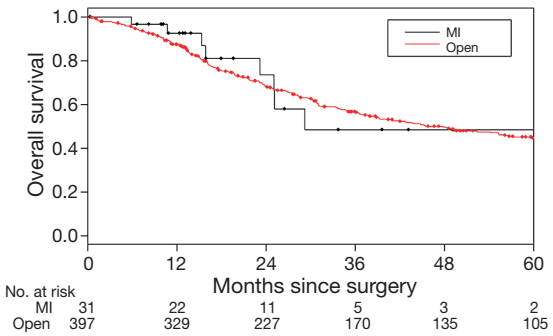

Figure 1 Kaplan-Meier curve for overall survival (P=0.84).

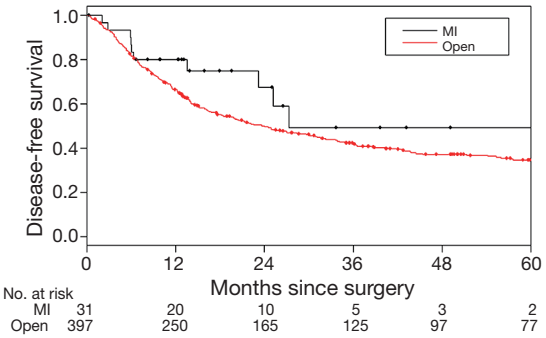

Figure 2 Kaplan-Meier curve for disease-free survival (P=0.19).

Table 3 Prognostic factors for overall survival (univariate analysis)

Variable	HR	95% CI	P
Age (continuous)	1.02	1.002–1.03	0.027
Sex (male *vs.* female)	1.18	0.90–1.53	0.23
Smoking			
Current *vs.* never	0.81	0.48–1.36	0.43
Former *vs.* never	0.79	0.52–1.20	0.27
Clinical stage			
IIB *vs.* IIA	1.49	0.87–2.57	0.15
IIIA *vs.* IIA	1.45	0.97–2.18	0.071
Pathologic type			
Squamous *vs.* adenocarcinoma	1.07	0.75–1.52	0.71
Other *vs.* adenocarcinoma	1.02	0.67–1.55	0.93
Cell differentiation			
Moderately *vs.* well	1.56	0.63–3.87	0.33
Poorly/undifferentiated *vs.* well	1.45	0.59–3.56	0.42
Unknown *vs.* well	0.97	0.38–2.47	0.95
FEV_1 (continuous)	0.99	0.98–1.00	0.17
DLCO (continuous)	1.00	0.99–1.01	0.50
Approach (open *vs.* MIS)	1.07	0.53–2.19	0.84

CI, confidence interval; DLCO, diffusing capacity of carbon monoxide; FEV_1, forced expiratory volume in 1 second; HR, hazard ratio; MIS, minimally invasive surgery.

Table 4 Prognostic factors for disease-free survival (univariate analysis)

Variables	HR	95% CI	P
Age (continuous)	1.01	1.00–1.02	0.15
Sex (male *vs.* female)	1.03	0.81–1.32	0.81
Smoking			
Current *vs.* never	0.75	0.46–1.21	0.24
Former *vs.* never	0.83	0.56–1.22	0.34
Clinical stage			
IIB *vs.* IIA	1.17	0.71–1.93	0.54
IIIA *vs.* IIA	1.29	0.90–1.84	0.17
Pathologic type			
Squamous *vs.* adenocarcinoma	0.92	0.66–1.29	0.30
Other *vs.* adenocarcinoma	1.22	0.84–0.64	0.64
Cell differentiation			
Moderately *vs.* well	1.99	0.81–4.90	0.14
Poorly/undifferentiated *vs.* well	1.59	0.65–3.89	0.31
Unknown *vs.* well	1.14	0.45–2.88	0.78
FEV_1 (continuous)	1.00	0.99–1.00	0.22
DLCO (continuous)	1.00	0.99–1.01	0.55
Approach (open *vs.* MIS)	1.53	0.81–2.88	0.19

CI, confidence interval; DLCO, diffusing capacity of carbon monoxide; FEV_1, forced expiratory volume in 1 second; HR, hazard ratio; MIS, minimally invasive surgery.

status. In addition, even though the only perioperative deaths were in the thoracotomy group (4/397) there was no difference in mortality. Length of hospital stay was shorter for the MIS group than for the thoracotomy group, likely due to shorter chest tube duration. However, due to the retrospective nature of the study we were lacking specific data in this regard, and this is one of the limitations of this study. These findings indicate that, with careful selection of patients, MIS approaches are safe and oncologically sound with potential benefits in hospital recovery.

In patients undergoing complete surgical resection adjuvant chemotherapy has been shown to benefit patients with pathological stage II-III disease (24,25). However, the ability for patients having a traditional thoracotomy to receive adjuvant chemotherapy has been limited. In the ANITA trial of adjuvant chemotherapy only approximately 60% of such

patients were able to complete three cycles of treatment (26). Thus, at our institution even for clinical stage II disease we favor the use of induction therapy prior to surgical resection.

Long-term data on the use of MIS for locally advanced NSCLC are lacking. Hennon and coauthors from Roswell Park reported on 125 consecutive patients whom were evaluated for thoracoscopic lobectomy for advanced NSCLC (19). Eleven patients were excluded for chest wall involvement, and 19 patients had planned thoracotomy. Of the remaining 95 patients, 73 (77%) had successful MIS lobectomy. Only 19% of their patients underwent induction therapy. Like our findings, there were no differences in perioperative morbidity, mortality or survival. However, a higher proportion (37.2% *vs.* 5.2%) of the thoracoscopic group were able to undergo adjuvant therapy.

Huang *et al.* recently reported on 43 patients with NSCLC who were treated with VATS following induction therapy. They found good feasibility, good safety, and an acceptable 3-year OS (17). One patient underwent conversion, and seven patients were reported to have had a "hybrid" procedure for a total conversion rate of 19%. This is consistent with ours and other studies. Unfortunately, this study had only a single arm, and no comparison to standard thoracotomy was performed. Two other studies published recently also found good feasibility and safety for the VATS approach in patients with locally advanced NSCLC; however, most of the patients in these two studies did not receive induction therapy (18,20). Nakanishi and colleagues reported on 76 consecutive patients over a 9-year period, analyzing their results in three different time periods (18). Conversion rate was low (2.6%, 2/76), though the rate of bilobectomy (14.5%) and pneumonectomy (15.8%) were substantial. Gonzalez-Rivas and coauthors reported on 130 patients that had uniportal VATS for treatment of NSCLC (20). Forty-three patients were considered to have locally advanced disease without induction therapy. Complication rates were similar between early stage and advanced stage patients, suggesting VATS is feasible for more advanced disease. Once again pneumonectomy rate was 14%.

Our report has limitations. First, by nature of the disease and retrospective design of the study, there is considerable selection bias which may influence the comparison of outcomes between groups. Indeed, patients who underwent MIS approaches were older and tended to have lower stages of disease. The results should be interpreted as reflective of the current practice at our institution, in the context of careful selection of patients who are eligible for MIS. Definitive conclusions regarding comparisons between the two surgical approaches can be drawn only from randomized studies or larger matched case-control studies. Second, the sample size of the MIS group was small and reflects the experience of one tertiary care center. There were not enough individual VATS or robotic cases to conduct a relevant subgroup analysis to see if there are any advantages of robotics. Future multicenter studies are likely to provide more generalizable results.

In conclusion, our findings suggest that in appropriately selected patients with locally advanced NSCLC MIS approaches to lobectomy (VATS and robotic) following induction therapy are feasible and associated with comparable survival to that following thoracotomy. Additional multicenter studies are warranted to yield greater insight into the feasibility and validity of our findings.

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Footnote

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

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