

No Adverse Outcomes of Video-Assisted Thoracoscopic Surgery Resection of cT2 Non-Small Cell Lung Cancer during the Learning Curve Period

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Background: Video-assisted thoracoscopic surgery (VATS) anatomic lung resections are gradually becoming the standard surgical approach in early-stage non-small cell lung cancer (NSCLC). The technique is being applied in cases of larger tumors depending on the experience of the surgical team. The objective of this study was to compare early surgical and survival outcomes in patients undergoing anatomic pulmonary resections using VATS and thoracotomy techniques for clinical T2 NSCLC during the adaptation period of the surgical team to the VATS approach. **Methods:** The data of all patients who underwent anatomic pulmonary resection for NSCLC using VATS and open techniques since April 2012 were recorded to create a prospective lung cancer database. Clinical T2 NSCLC patients who underwent VATS anatomic lung resection were identified and compared with cT2 patients who underwent open resection. **Results:** Between April 2012 and August 2014, 269 anatomical resections for NSCLC were performed (80 VATS and 189 thoracotomy). Thirty-four VATS patients who had clinical T2 disease were identified and stage-matched to thoracotomy patients. The average tumor diameter was comparable ($34.2\pm 11.1\times 29.8\pm 10.1$ mm vs. $32.3\pm 9.8\times 32.5\pm 12.2$ mm, $p=0.4$). Major complications were higher in the thoracotomy group ($n=0$ vs. $n=5$, $p=0.053$). There was no 30-day mortality, and the 2-year survival rate was 91% for VATS and 82% for thoracotomy patients ($p=0.4$). **Conclusion:** VATS anatomic resections in clinical T2 NSCLC tumors are safe and have perioperative and pathologic outcomes similar to those of thoracotomy, while remaining within the learning curve.

Key words: 1. Video-assisted thoracic surgery
2. Surgical complications
3. Learning curve
4. Patient safety

Introduction

Video-assisted thoracoscopic surgery (VATS) lobectomy for patients with non-small cell lung cancer (NSCLC) has become more widely adopted because of the reported advantages of faster recovery in comparison to thoracotomy [1,2]. Although there are no

randomized double-blind reports on this issue because of the technical aspects and patient/surgeon preferences, after the publication of large database studies evaluating perioperative outcomes and oncological effectiveness, VATS anatomic lung resections are being established as the standard of care for early-stage NSCLC [3,4]. While the indications for VATS

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anatomic resection are clearer for peripheral T1 NSCLC, clinical T2 tumors pose additional points of concern regarding minimally invasive surgery, such as larger size, visceral pleural invasion, higher incidence of mediastinal lymph node metastasis, up-staging, and technical difficulties [5].

Despite very strong patient preferences and enthusiasm from the surgical community, the widespread adoption of VATS was slower than that of laparoscopic surgery, mostly because of a steeper learning curve. As of 2014, 30% of the anatomic resections in the US have been performed using VATS [6]; however, standardization of the technique and problems with lymph node dissection still remain. Some authors have proposed robotic surgery as an alternative involving a more intuitive process [7], but cost issues and the accessibility of the required equipment have stalled this possibility.

Most of the literature reporting the outcomes and defining the learning curve for the adaptation of VATS anatomic resections concentrates overwhelmingly on T1 tumors and ground-glass lesions. Despite the fact that lung cancer screening has gained importance, resulting in the diagnosis of an increased number of such lesions, a large subset of patients present in later stages [8], and the question of the feasibility of offering these patients minimally invasive surgery in a newly established VATS program is unanswered.

The objective of this study was to determine the perioperative and early survival outcomes of clinical T2 NSCLC patients who underwent anatomic resection via thoracotomy and VATS in a newly established VATS program.

Methods

1) Patients

VATS anatomical resections were routinely performed by a team (an attending surgeon, a senior resident, and 2 operating room nurses) as the first-line approach for all applicable cases (excluding cases with central tumors and cases needing pneumonectomy, chest wall resection, or sleeve resection), irrespective of the clinical stage, at Marmara University Hospital since April 2012. No other exclusion criteria were used for the oncologically resectable patients referred to the VATS team. The at-

tending surgeon of the VATS team had been routinely performing minor VATS operations (VATS lysis of adhesions, pleural biopsy, VATS bullectomy, and VATS sympathectomy) and had completed 20 VATS lobectomies under supervision at another institute.

Patients were staged using computed tomography of the chest, including the adrenal glands, and positron emission tomography (PET) for systemic disease. Magnetic resonance imaging of the brain was added to the preoperative staging if the patient was symptomatic or received neoadjuvant treatment.

Patients with clinical T2 NSCLC in the VATS database (out of 71 anatomic resections) were included in the study, whereas 34 out of the 158 patients who underwent anatomic resections done by the thoracotomy team during the same time were enrolled. All patients met the oncologic criteria for resection after the standard-of-care clinical staging. The timeline was chosen to allow a mean follow-up of at least 18 months.

Invasive mediastinal staging (cervical mediastinoscopy and endobronchial ultrasonography sampling) was performed in patients with PET-positive N2 lymph nodes. If pN2 disease was discovered preoperatively, rendering the patient's stage inoperable, the patient was referred for neoadjuvant treatment and restaged appropriately for surgery after treatment.

Patients who underwent VATS anatomical resections for clinical T2 tumors were identified from the prospectively collected database and compared with those who underwent thoracotomy and anatomical resection.

2) Operative technique

All patients underwent general anesthesia and double-lumen endotracheal intubation. Intraoperative moderate fluid restriction was used (4–6 mL/kg) per institutional protocol. Patients were transferred to the normal surgical floor after arterial blood gas tests. The intensive care unit stay was determined clinically, and no routine protocol was followed. Postoperative pain was controlled with epidural bupivacaine patient-controlled analgesia (PCA) or intravenous morphine PCA if epidural placement was not successful. All patients started oral intake at postoperative hour 6 if there was no contraindication, and maintenance fluids were restricted accordingly. All patients were encouraged to mobilize as maximally tolerated, and

Table 1. Patient demographics and preoperative evaluation

Characteristic	Video-assisted		p-value
	Thoracotomy	thoracoscopic surgery	
Age (yr)	61.0±7.1	61.9±8.9	0.278
Gender			0.549
Male	26 (76)	28 (82)	
Female	8 (24)	6 (18)	
Smoking (pack year)	42.1±27.9	43.4±35.5	0.914
FEV ₁ (L)	2.5±0.7	2.6±0.7	0.502
%FEV ₁	94±25	87±18	
FVC (L)	3.1±0.7	3.4±0.7	
%FVC	99.6±25.7	96.4±14.7	
Comorbidities			1.000
None	16 (47)	16 (47)	
Chronic obstructive pulmonary disease	6 (18)	6 (18)	
Hypertension	15 (44)	10 (29)	
Coronary artery disease	5 (15)	9 (26)	
Diabetes	2 (6)	3 (9)	
Chronic renal failure	1 (3)	1 (3)	
Previous malignancy	3 (9)	2 (6)	

Values are presented as mean±standard deviation or number (%). FEV₁, forced expiratory volume in one second; FVC, forced vital capacity.

chest tubes were pulled out if there was no air leak and the drainage was less than 150 mL per 24 hours.

VATS resection was performed using the anterior biportal and triportal technique, with a non-rib spreading utility incision at the fourth or the fifth intercostal space. Individual vascular and bronchial structures were dissected and divided using appropriate endoscopic staplers. A single chest drain was advanced through the camera port at the seventh or the eighth intercostal space.

Standard posterolateral thoracotomy through the fifth intercostal space was used for open surgery cases. Lobar vessels were hand-tied, and bronchial closure was done using either bronchial staplers or sutures according to the surgeon's preference. All patients underwent lymph node dissection of all routine stations irrespective of the operative approach.

3) Statistical analysis

All anatomic lung resection cases that were done after April 2012 were recorded in a prospective database. Clinical T2 NSCLC patients were selected.

Table 2. Clinical and pathological staging results by operation type

Variable	Video-assisted		p-value
	Thoracotomy	thoracoscopic surgery	
Tumor width (mm)	32.4±9.9	34.2±11.1	0.460
Tumor length (mm)	32.6±12.6	29.9±10.1	0.382
Reason for clinical T2 staging			
Size	23 (68)	24 (71)	
Pleural invasion	7 (20)	10 (29)	
Atelectasis	4 (12)	0	
Clinical N stage			0.490
N0	18 (50)	22 (65)	
N1	4 (12)	4 (12)	
N2	12 (35)	8 (24)	
Operation type			
Right upper lobectomy	13 (38)	10 (29)	
Right lower lobectomy	5 (15)	6 (18)	
Bilobectomy	4 (12)	0	
Left upper lobectomy	6 (18)	10 (29)	
Left lower lobectomy	4 (12)	4 (12)	
Pneumonectomy	1 (3)	0	
Segmentectomy	1 (3)	4 (12)	
Operation time (min)	311±63	278±71	0.04
Pathological T stage			
T1	6	6	
T2	28	24	
T3	0	4	
Pathological N stage			
N0	22	20	
N1	8	11	
N2	4	3	

Values are presented as mean±standard deviation, number (%), or number.

Data regarding the patient demographics, pulmonary function tests, comorbidities, additional treatment modalities, clinical/surgical staging, postoperative course, pathology results, and overall survival were collected.

Statistical analysis was performed using IBM SPSS ver. 20.0 (IBM Corp., Armonk, NY, USA). The chi-square test, Mann-Whitney U-test, and t-test for independent samples were used for the comparison. All p-values < 0.05 were considered to indicate statistical significance. Six patients who converted to thoracotomy because of perioperative complications were kept out of the lymph node count analysis.

The study protocol was reviewed and approved by the institutional review board, and all patients gave

Table 3. Complications and LOS

Variable	Video-assisted thoracoscopic surgery	Thoracotomy	p-value
No. of complications	9	17	0.046
Complication breakdown	Atelectasis (1), atrial fibrillation (1), pneumonia (2), prolonged air leak (5)	Atelectasis (1), atrial fibrillation (3), pneumonia (2), reoperation (1), prolonged air leak (6), chylothorax (1), vocal cord paralysis (3)	
LOS (day)	7.2±4.6	8.9±4	0.021
LOS without postoperative complications (day)	5.4±1.8	6.4±2.1	0.011

Values are presented as mean±standard deviation. LOS, length of hospital stay.

written informed consent before enrollment. The study was approved by Marmara Ethics Board (decision no. 09.2015.224).

Results

Between April 2012 and August 2014, 229 anatomic lung resections for NSCLC and benign diseases were performed at our institution. Thirty-four patients were identified as having clinical T2 NSCLC and underwent a planned VATS resection (group 1). These patients were compared to clinical T2 thoracotomy patients (group 2).

Demographic factors and patient characteristics are summarized in Tables 1 and 2. The groups were evenly divided with respect to age, sex, functional capacity (comorbidities and pulmonary function tests), preoperative staging, and type of resection.

1) Perioperative findings

Six VATS patients were converted to lateral thoracotomy because of intraoperative difficulties. The VATS patients had no major postoperative complications, fewer postoperative complications (n=9 versus n=17, p=0.046), and shorter length of hospital stay (LOS) (Table 3). There was no 30-day mortality in either group. One patient from group 2 died within 90 days of the operation (Fig. 1).

2) Pathology results and early survival findings

On the basis of the pathology results, 4 patients from the VATS group were upstaged as T3 and 6 patients from the thoracotomy group were downstaged to T1. Nine VATS and 6 thoracotomy patients had nodal upstaging, but all patients remained in the op-

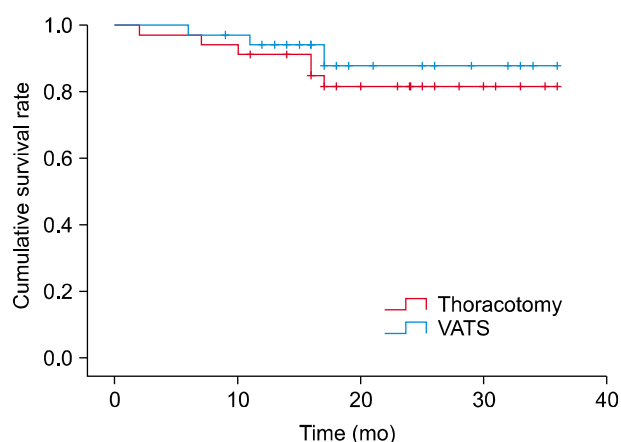


Fig. 1. Survival curves for VATS and thoracotomy patients. VATS, video-assisted thoracoscopic surgery.

erability range.

The total number of lymph node stations dissected did not differ between the groups (VATS: n=6±1.7, thoracotomy: n=6±2.2; p=0.1). The total number of lymph nodes (nodes that were dissected during the operation and sent separately from the specimen, counted as 1 per lymph node station due to en bloc resection and the nodes that were dissected from the specimen during the grossing process in the pathological workup) tended to be lower in VATS patients (8.1±2.3 versus 9.8±4.1) but this trend failed to reach statistical significance. Patients who were converted to open surgery were excluded from the lymph node count analysis.

A total of 21 VATS and 23 thoracotomy patients were offered adjuvant chemotherapy on the basis of the pathology results. Timely chemotherapy completion rates were found to be similar between the groups (VATS [n=17] versus thoracotomy [n=16],

p=0.8).

The overall survival rate in the VATS and the thoracotomy group was 33.2% and 31.5%, respectively, with a median follow-up period of 20 months (p=0.4).

Discussion

VATS anatomic lung resections are being adopted worldwide as the procedure of choice for early-stage lung cancers. The learning curve for this minimally invasive approach has been studied, and various reports have found this approach to be safe even with limited open surgery experience. Most studies have reported that 50 cases are needed for the first plateau performance, at which the incidence of complications becomes comparable to that of the supervising surgeons [9]. Patient cohorts in these reports usually have very early-stage tumors, and some have ground-glass opacities. Although these types of tumors are projected to become more frequent in the practice of a thoracic surgeon, a large percentage of patients present with larger tumors and are inoperable at the time of presentation.

The study population in this article was largely male and mostly consisted of smokers. This aligns with statistics from other developing countries, where smoking is still prevalent and patients present in later stages of cancer, because of an absence of large-scale screening programs. During the study period, 71 patients were referred to the VATS team, 34 of whom had clinical T2 tumors. All assigned patients were routinely started with VATS, unless they were presumed to need pneumonectomy, sleeve resection, or chest wall resection. Nine patients were converted to thoracotomy, 6 of whom were clinical T2 patients. Even though this represents a high percentage, there was no in-hospital mortality in either group and the VATS team could complete the learning curve in 1 year, as demonstrated by the last conversion for a clinical T2 patient happening in month 13 of the program.

VATS resection was marginally more favorable in terms of complication rates (p=0.046) than thoracotomy, and showed a similar distribution of complication types. Moreover, VATS patients had shorter LOS when they had no postoperative complications, which is concurrent with the established literature.

We did not observe a tendency for shorter hospital stays in clinical T2 patients during the progression of the learning curve.

With respect to the oncological quality of the resections, VATS T2 patients did not show statistically significant differences in comparison to thoracotomy T2 patients, as demonstrated by the number of lymph node stations dissected and the overall survival rate. Despite the fact that VATS patients had a tendency for fewer cumulative lymph nodes, the incidence of nodal upstaging was slightly higher than in some other study populations [10,11]. Since an increased number of dissected lymph node stations and the T stage have been reported as a predictive factor for nodal upstaging, this fact can be interpreted as the proof of adequacy of lymph node sampling for cT2 tumors during the learning curve.

The limitations of the present study include the small sample size and the possible patient selection bias. Despite the facts that a single team routinely started the operations with VATS, excluding patients with chest wall invasion, possible pneumonectomy, or sleeve resection, and that all consecutive patients were included in the selection pool, patterns of patient referral might have confounded the analysis. The sample size was small, but it might more accurately represent a thoracic surgery practice outside a major surgical center; it has been reported that 21% of centers perform close to 70% of the anatomic resections per year [12].

There are no high-quality evidence-based guidelines outlining the appropriate starter cases for VATS oncologic resections, which would complement an individual surgeon's discretion. Given the nature of the newly established programs, a single-institution study might not be sufficiently all-encompassing to answer such a need. Since its inception, the types of VATS operations have steadily expanded (sleeve resections, T3 tumors, pneumonectomy, etc.) and the technique itself has become more sophisticated (3-dimensional surgery, uniportal VATS, etc.). A multi-institutional study is needed to clarify the outlines of a graded experience for VATS surgeons.

In summary, our results suggest that in a newly established VATS program, it may be safe to offer clinical T2 patients VATS surgery, without compromising safety of oncological outcomes. Most of the cT2 patients will still benefit from minimally invasive

surgery in terms of decreased hospital stay and better postoperative function. This approach may shorten the time required to achieve proficiency for surgeons working in populations with high smoking rates and a low accessibility of screening programs, resulting in cumulative benefits for the community.

Conflict of interest

No potential conflicts of interest relevant to this article are reported.

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