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ORIGINAL ARTICLE

Does VATS Lobectomy Avoid Delay and Increase Compliance in Adjuvant Chemotherapy?

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OBJECTIVE

Adjuvant chemotherapy compliance and full dose delivery of agents are superior after videothoracoscopic Video-Assisted Thoracic Surgery lobectomy (VATS-L) for operable non-small cell lung carcinoma (NSCLC), compared with thoracotomy. Our aim was determining the role of VATS-L on inception timing and percentage of patients provided with the planned chemotherapy regimen.

METHODS

Clinical files of patients undergoing pulmonary resection for NSCLC between January 2010 and January 2018 were reviewed retrospectively. Analyses were performed only on patients receiving sole post-operative adjuvant chemotherapy subsequent to the final pathology. Chemotherapy protocol was planned according to Adjuvant Navelbine International Trialist Association trial. Analyzed variables were the duration between operation and initial chemotherapy day, with the planned and received chemotherapy doses. Patients with positive N2 nodes necessitating adjuvant RT were excluded from the study.

RESULTS

Eighty-four patients underwent adjuvant chemotherapy for NSCLC, either after videothoracoscopic surgery (n=36) or thoracotomy (n=48). Patients undergoing VATS-L had a shorter mean length of hospital stay (4.1 versus 7.3 days; $p<0.001$), which lead significantly reduced time delay on chemotherapy commencement (29.1 versus 36.9 days; $p<0.005$). VATS-L group received 82.9% of planned Cisplatin and 81.7% of Navelbine doses. In thoracotomy group, compliance to planned doses of Cisplatin and Navelbine was 77.6% and 75.0%, respectively. Tolerance for both drugs was increased in the VATS-L group (Cisplatin $p=0.004$; Navelbine $p=0.004$).

CONCLUSION

Besides the known advantages of VATS-L over conventional open surgery, our data demonstrated that it also allows more complete and rapid adjuvant chemotherapy, in terms of treatment initiation timing and compliance, by enabling quick post-operative recovery.

Keywords: Adjuvant chemotherapy; adjuvant navelbine international trialist association; chemotherapy compliance; lung cancer; thoracotomy; video-assisted thoracic surgery.

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INTRODUCTION

The first-line method of treatment is surgery in cases of early-stage non-small cell lung cancer (NSCLC) and a lobectomy is most performed through an open thoracotomy, while Video-Assisted Thoracic Surgery (VATS) resections with the developed camera systems and surgical instruments can be done more rapidly through shorter incisions and are safe and an applicable alternative, with a gradually increasing frequency of use.[1-3]

In addition to the safety of thoracoscopic lobectomy procedures suggested in many studies in literature, their various advantages have been demonstrated through comparisons with the conventional thoracotomy approach, including shorter hospital stays and chest tube duration, lower post-operative pain, better preservation of pulmonary functions, lesser release of cytokines, and lower rates of general complications.[4-7] Long-term results such as general mortality and recurrence were also demonstrated to be similar or superior in patients who underwent a VATS lobectomy when compared to those who underwent an conventional lobectomy.[8,9]

Disease-free survival and recurrence rates were found to be similar in the comparison of the VATS lobectomy and conventional thoracotomy approaches in the ACOSOG Z0030 (ALLIANCE) study.[10] The incidence of development of a second primary lung cancer has been reported to be similar after lobectomies performed through a thoracoscopy and conventional methods in a study by Flores et al.[11] in which it was demonstrated that thoracoscopic lobectomy was oncologically acceptable.[2,10-12]

A positive effect of adjuvant chemotherapy on survival has been reported in randomized studies in cases of NSCLC.[13-16] Patients who have undergone a VATS lobectomy and require adjuvant chemotherapy following pathological staging are expected to be more compliant to treatment, as post-operative complications are observed at a lower rate and patients return to social life more rapidly. There are only a limited number of studies in the literature addressing this issue, and so the present study makes a comparison of the adherence of patients who have undergone thoracoscopic or conventional lobectomy to adjuvant chemotherapy.

MATERIALS AND METHODS

This research is a retrospective and observational study. E-46418926-050.01.04--3065. It was carried out in our clinic following the approval of the ethics committee on the January 15, 2021.

Patient Selection

A total of 2903 patients diagnosed with NSCLC who underwent an anatomical lung resection by video-thoracoscopic (n=163) method or by thoracotomy (n=2740) were analyzed retrospectively between January 2010 and January 2018.

Patients who underwent adjuvant chemotherapy postoperatively under the Adjuvant Navelbine International Trialist Association (ANITA) protocol with Cisplatin 75 mg/m^2 and Nevalbine 25 mg/m^2 were included in the study. Patients who received adjuvant chemotherapy or who completed the adjuvant chemotherapy protocol at another center, patients who underwent pre-operative neoadjuvant or adjuvant chemotherapy and/or radiotherapy, who had a positive indication of RT for postoperative positive N2 involvement or chest wall involvement, who had a bilobectomy/pneumonectomy and extended lung resection, or who had post-operative complications were excluded from the study. The starting time of chemotherapy, doses of chemotherapy, reduced dosages, and delayed doses were regulated by the medical oncologist.

A total of 84 patients with similar comorbid and demographic specifications who underwent a lobectomy by thoracoscopy (n=36) or thoracotomy (n=48) were included in the study. The age, gender, tumor localization, dimensions, and N status were similar in both groups. The age, gender, operated site, type of operation, tumor type, dimension of tumor, N status, duration of hospital stay, duration of initiation of chemotherapy, chemotherapy doses applied, and rate of completion of the chemotherapy protocol were analyzed retrospectively.

Staging and Surgical Technique

All patients were evaluated through a thoracic and upper abdominal computed tomography, a positron emission tomography, and cranial magnetic resonance imaging. A cervical mediastinoscopy was performed for mediastinal lymph node evaluation before lung resections.

All patients in the study underwent a lobectomy and a mediastinal lymph node dissection; and patients who underwent a bilobectomy, pneumonectomy, sleeve lobectomy, or extended resection were excluded from the study.

A conventional thoracotomy was performed through entry to the thorax through the fifth intercostal space by a serratus anterior muscle-preserving posterolateral thoracotomy.

A thoracoscopic lobectomy was performed biportal. The thoracoscope was placed at the sixth or seventh intercostal space on the posterior axillary line and a

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Table 1 Patient demographics

	VATS (n=36)		TOR (n=48)		p*
	n	%	n	%	
Age, year	58.3 (56.0-60.7)		59.2 (57.1-61.9)		0.2
Gender					0.64
Female	9	10.7	10	11.9	
Male	27	32.1	38	45.2	
Tumor localization					0.83
RUL	9	10.7	14	16.6	
RML	5	5.9	3	3.5	
RLL	6	7.1	7	8.3	
LUL	6	7.1	10	11.9	
LLL	10	11.9	14	16.6	
Tumor histologic subtype					
Adenocarcinoma	29		26		0.01
Squamous cell carcinoma	7		22		
Hospital length of stay	4.1 (3.6-4.7)		7.3 (6.7-8.2)		<0.001
Time until initiation of chemotherapy	29.1 (25.7-32.6)		36.9 (34.1-39.8)		0.002
Cause of initiation of chemotherapy					0.54
T stage	26		34		
N stage	10		14		
Ratio of planned dose application of chemotherapy agent (%)					
Cisplatin	82.9 (81.4-84.5)		77.6 (71.0-78.6)		0.004
Nevalbine	82.4 (79.9-84.9)		74.8 (44-100)		0.004

*: Independent samples t-test. VATS: Video-assisted thoracoscopic surgery; TOR: Thoracotomy; RUL: Right upper lobectomy; RML: Right middle lobectomy; RLL: Right lower lobectomy; LUL: left upper lobectomy; LLL: Left lower lobectomy.

utility thoracotomy was performed at the anterior part of the fourth intercostal space, 4-7 cm in length. No retractor was used in any patient.

An intraoperative mediastinal lymph node dissection was performed on patients who underwent a thoracoscopy and thoracotomy.

Statistical Analysis

SPSS 26 (IBM Corp, 2019, IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY) was used to process the data obtained in the study. The conformity of the data to the normal distribution was evaluated with histograms, Q-Q plots, and the Shapiro-Wilk test. Continuous data conforming to the normal distribution are expressed as the mean and standard deviation, non-conforming data are expressed as the median and quartile range of 25-75%, and nominal variables are expressed as frequency and percentage. An intergroup comparison t-test was used for continuous data with normal distribution and the Mann-Whitney U test was used for data that did not fit. The Chi-square and, where necessary, Fisher's Exact tests were used to compare nominal variables.

RESULTS

The results included in the study were 84 patients who underwent adjuvant chemotherapy following a lobectomy due to the presence of a NSCLC. Among the patients undergoing a lobectomy, 36 were through thoracoscopy and 48 through thoracotomy.

The mean age of the sample was 59.0 (57.3-60.7) years in the total series, and 58.3 (56.0-60.7) years in the VATS group and 59.5 (57.1-61.9) years in thoracotomy group. Gender distribution was as follows: 27 males and nine females in the VATS group and 38 males and 10 females in the thoracotomy group, corresponding to 65 males and 19 females in the total series. Among the operations, 43 were applied on the right and 41 on the left sides of the patients. The demographics of both groups were similar (Table 1).

The mean duration of hospital stay was 4.1 days (3.6-4.7) and 7.3 (6.7-8.2) days in the VATS and thoracotomy groups, respectively. The duration of hospital stay was statistically significantly shorter in the VATS group ($p<0.001$).

A histopathological evaluation revealed a squamous cell carcinoma and adenocarcinoma in 29 and 55 patients, respectively. Of the patients diagnosed with adenocarcinoma, 29 were in the VATS group 26 in the thoracotomy group, while seven and 22 patients who had a squamous cell carcinoma were in the VATS and thoracotomy group, respectively. Considering the distribution of cancer histopathology, adenocarcinoma cases were significantly higher in the VATS group (p=0.01); squamous cell cancer was similar in both groups, there was statistically significant difference. Survival study between groups was not performed due to histological difference.

In the VATS group, 26 of the patients received chemotherapy due to tumor dimension and 10 due to N1 lymph node involvement, while 34 and 14 patients in the thoracotomy group received chemotherapy due to tumor dimension and lymph node involvement, respectively. The reason of received chemotherapy was similar in both groups, with no statistically significant difference (p>0.05).

The duration until the initiation of chemotherapy was 29.1 (25.7-32.6) days in the VATS group and 36.9 (34.1-39.8) days in the thoracotomy group (p=0.002). Adjusted to the ANITA protocol, the ratio of application of the cisplatin dose was 82.9 (81.4-84.5)% in the VATS group and 77.6 (75.1-80.1)% in the thoracotomy group (p=0.004), while the ratio of application of the Nevalbine dose was 82.4 (79.9-84.9)% in the VATS group and 74.8 (71.0-78.6)% in the thoracotomy group (p=0.004) (Table 1). Duration until the initiation of chemotherapy, dose application ratio of Cisplatin and Nevalbine were statistically significantly different in two groups.

DISCUSSION

Developments in medicine have led to improvements in the treatment of disease and decrease in mortality and morbidity, thus increasing patient comfort and satisfaction. Advances in minimal invasive surgery over the past two decades can be evaluated as an indicator of this approach.

The thoracoscopic lobectomy approach gained popularity following the introduction of the first VATS series in 1993.[1] The VATS lobectomy technique was defined as: No intercostal retractors; maximum utility thoracotomy length of 8 cm; separate dissection of the vein, arteries, and bronchi for the lobectomy; and standard lymph node sampling or dissection in line with the Cancer and Leukemia Group B 39802 Study of 2007.[17] All patients underwent a biportal VATS lobectomy in our present series. The mean length of the utility thoracotomy incision was 4.7 cm and all patients underwent a mediastinal lymph node dissection.

The advantages of a thoracoscopic lung resection are decreased blood loss,[2,18] decreased pain,[4,12,18-20] shorter hospital stay and duration of chest tube placement,[6,12,19,20] preservation of post-operative pulmonary functions,[2,12,21,22] diminished inflammatory response,[13] lower rate of general complications,[2,6] and earlier return to post-operative activity.[12] A thoracoscopic lobectomy is an approved surgical approach in selected cases of NSCLC.[23] In our study, the hospital stay of patients who underwent a thoracoscopic lobectomy was significantly shorter (p<0.001), which was consistent with the literature.

Adjuvant chemotherapy on behalf of resected NSCLC has been applied at the beginning of the 2000s. Several randomized and clinical studies performed over the past decade have identified the positive effect of post-operative cisplatin-based adjuvant chemotherapy for Stage IIA-IIIA NSCLC on survival.[13-16] The rate of use of adjuvant chemotherapy, namely, compliance with chemotherapy, has been demonstrated to be associated with increased survival.[4] Compliance with chemotherapy can be increased through surgical resection techniques that improve the administration of chemotherapy. In the present study, 36 patients who underwent a thoracoscopic lobectomy were compared with 48 patients who underwent a lobectomy by thoracotomy. Among patients received more than 66% of the total planned dose of Vinorelbine and Cisplatin, respectively, in ANITA trial.[13] Especially, the ratio of patients who received the total planned dose ranged from 40% to 78.4%.[24,25] In our study, the ratio of cisplatin drug dose administration rate was 82.9% and 77.6% in the VATS and thoracotomy groups, respectively (p=0.004); while the Nevalbine drug dose ratio was 82.4% and 74.8% in the VATS and thoracotomy groups, respectively (p=0.004). Although the drug doses applied were compatible with the literature for both groups, the dose applied in the VATS group was significantly higher than in the thoracotomy group. The results of the VATS lobectomy, including the duration of hospital stay, the initiation of chemotherapy and compliance with chemotherapy, have been shown to be superior to the lobectomy by thoracotomy approach in many studies published in the literature.[4,26,27] The duration between operation and the initiation of chemotherapy was significantly shorter in VATS group (Table 2) (p=0.002). The duration of hospital stay, the time until the initiation of chemotherapy, and the dose ratio of Cisplatin and Nevalbine were found to be significantly

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Table 2 Comparison of different variables between groups

	N	Mean	IQR	p*
Hospital LOS (days)				
VATS	36	4.1	3.6-4.7	<0.001
TOR	48	7.3	6.7-8.2	
C%				
VATS	36	82.9	81.4-84.5	0.004
TOR	48	77.6	75.1-80.1	
N%				
VATS	36	82.4	79.9-84.9	0.004
TOR	48	74.8	71.0–78.6	
Time to chemotherapy (days)				
VATS	36	29.1	25.7–32.6	0.002
TOR	48	36.9	34.1–39.8	

*: Independent samples t-test. IQR: interquartile range; LOS: length of stay; VATS: video-assisted thoracoscopic surgery; TOR: thoracotomy; C: Cisplatin; N: Navelbine

superior in the VATS group when compared to the lobectomy by thoracotomy group in the present study. Definitely, a meaningful higher rate of patients chemotherapy compliance in case of thoracoscopy compared to thoracotomy.[24,26]

CONCLUSION

The thoracoscopic lobectomy approach has been known to offer several advantages over the lobectomy and thoracotomy approaches. The data obtained in the present study have showed us that the VATS lobectomy approach is a more accurate and quicker in the initiation of chemotherapy and chemotherapy compliance.

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Ethics Committee Approval: The study was approved by the University of Health Sciences Hamidiye Scientific Research Ethics Committee (no: E-46418926-050.01.04--3065, date: 15/01/2021).

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