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Video-assisted thoracic surgery is associated with faster delivery to adjuvant chemotherapy after lung resection in patients with lung cancer

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Abstract

Background Rapid recovery after surgery is especially important for patients who are scheduled for adjuvant therapy.

This study aimed to investigate the effect of video-assisted thoracic surgery (VATS) on chemotherapy referral time and chemotherapy tolerance in patients who underwent lung resection for non-small cell lung cancer.

Methods The data of 612 patients who underwent lung resection with the diagnosis of non-small cell lung cancer in our clinic between January 2014 and December 2021 were reviewed. Patients who underwent lobectomy or bilobectomy with systematic mediastinal lymph node dissection and who received at least one cycle of adjuvant chemotherapy were included in the study. The characteristics of the patients, pathological data, postoperative follow-up findings, and the time between the operation and adjuvant chemotherapy were recorded.

Results A total of 144 patients who met the criteria were included in the study. The mean age was 61.6 ± 7.9 years. The mean visual analogue scale scores were found to be lower, and the length of hospital stay was found to be shorter in the VATS group compared to thoracotomy.

The mean time (days) to initiate chemotherapy after surgery was statistically shorter in the VATS group (48.9 ± 17.6 vs 58.1 ± 27.6, $p = 0.049$). However, there weren't seen any statistical differences between VATS and thoracotomy groups in terms of mean cycle completed, percentage of planned regimen received, and grade ≥ 3 toxicity rates ($p = 0.16$, $p = 0.18$, and $p = 0.22$, respectively).

Conclusions VATS provides faster recovery compared to open surgery and shortens the time for patients to refer to adjuvant chemotherapy.

Keywords Adjuvant chemotherapy, Chemotherapy tolerance, Thoracotomy, VATS

Background

Lung resections, which have relatively high mortality and morbidity, are the most important step in the treatment of patients with localized non-small cell lung cancer (NSCLC) [1]. The necessity and timing of chemotherapy in this patient group are decided by considering many parameters such as cancer stage, the patient's age, comorbidity, and performance status. Several studies including randomized studies and meta-analyses have demonstrated the survival benefit of cisplatin-based adjuvant chemotherapy in patients with stage II-III non-small

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cell lung cancer who have undergone complete resection [2–4]. Although their long-time prognostic importance is controversial, rapid recovery of patients after the operation, no delay in adjuvant treatment, and good tolerance of chemotherapy are desirable conditions.

The video-assisted thoracic surgery (VATS) has been shown in many studies to be associated with less postoperative pain, faster recovery, shorter drainage, and hospital stay compared to open thoracotomy [5–8]. Considering these advantages of VATS, it is expected that patients will adapt better to the planned oncological treatment process. This study aimed to investigate the effect of VATS on the referral time of patients to adjuvant therapy and their chemotherapy tolerance.

Methods

Study design and patient selection

This study was approved by the Institutional Review Board (KAEK-2021/75–73). The authors received no financial support for this study. This study was designed as a retrospective cohort and analyses were performed with routinely collected data. The data of 612 patients who underwent lung resection with the diagnosis of non-small cell lung cancer in our clinic between January 2014 and December 2021 were reviewed. Patients who underwent lobectomy or bilobectomy with systematic mediastinal lymph node dissection and who received at least one cycle of adjuvant chemotherapy were included in the study. Patients who received neoadjuvant therapy, who underwent pneumonectomy or extended lung resection, and who had a history of conversion to thoracotomy due to the development of intraoperative complications were excluded from the study. Patients who received radiotherapy in the postoperative period due to incomplete surgical resection were also excluded from the study. The characteristics of the patients, pathological data, postoperative follow-up findings, and the time between the operation and adjuvant chemotherapy were recorded.

Preoperative investigation

In the preoperative period, the patients routinely underwent chest X-ray, thorax computed tomography (CT), positron emission tomography, brain CT or magnetic resonance imaging, pulmonary function test, and fiberoptic bronchoscopy. The patient's respiratory performance status was examined with exercise tests (6-min walk test or ladder test), VO2max measurement, and quantitative lung perfusion scintigraphy if needed. Patients with suspicious mediastinal lymph nodes detected in preoperative imaging methods were evaluated with transbronchial needle aspiration, endobronchial ultrasonography, and/or cervical mediastinoscopy. Lung cancer staging was performed according to the 8th International Staging System for Lung Cancer.

Surgical technique

Although we do not have strict indications for VATS, thoracotomy was often preferred in tumors larger than 7 cm, in the presence of calcific or pathological hilar lymph nodes, and in the presence of thickened pleura secondary to previous infections.

The lung isolation was achieved by double-lumen endotracheal intubation.

Three portal approach was used in the VATS group with a non-rib-spreading technique. The 4–5 cm utility incision was placed between the anterior and posterior axillary line, over the 5-6th intercostal space (ICS). A 1.5 cm camera port was placed in the anterior axillary line (at the 7th ICS) to enable the anterior approach which required sequential dissection of hilar structures from anterior to posterior. The 30-degree thoracoscope and ultrasonic or bipolar energy devices were used routinely. The posterior port was often used for lung retraction and endoscopic stapler placement.

Open surgery was performed through the muscle-sparing lateral thoracotomy using a 15 to 20-cm lateral skin incision. The 5th or 6th ICS was used. The vascular structures were ligated and transfixed with non-absorbable sutures (mostly 2–0 or 1–0 silk). The lobar bronchus was transected and closed with a surgical stapling device.

Postoperative follow-up and adjuvant therapy

The patients were followed up in the intensive care unit on the first postoperative night. Operation-related chest pain managed with a multimodal treatment approach includes iv non-steroidal anti-inflammatory drugs, opiates, and epidural analgesia, modified according to the visual analog scale scores (VAS), and daily respiratory rehabilitation practices were performed in the postoperative period with the supervision of a physiotherapist. Minor and major complications within 30 days after surgery were described as postoperative complications. Chest tubes of the patients were removed when the air drainage ceased, and the 24-h fluid drainage decreased below 200 cc. Common discharge criteria were applied to all patients after the chest tube removal. These criteria are:

1. Absence of postoperative complications requiring hospitalization
2. Providing effective and adequate pain relief with oral medications (VAS < 3)
3. Patients able to mobilize out of bed without any assistance
4. No need for supplemental oxygen

The first follow-up after discharge was scheduled for 10 days. Adjuvant chemotherapy was planned for patients with an Eastern Cooperative Oncology Group performance status of 0–1 who completed the post-surgical recovery. The chemotherapy regimen differed according to the patient's age and comorbid conditions, and the personal preference of the oncologist. Chemotherapy regimens consisted of combinations containing platinum-based chemotherapeutics administered in 3-week cycles. The decision to reduce or delay the chemotherapy dose was made considering the developing hematological, neurological, gastrointestinal, and nephrological complications and the performance status of the patients. Chemotherapy dose reduction or delay was applied in case of toxicity over grade 2. Toxicity grades are defined according to the Common Terminology Criteria for Adverse Events.

Patient follow-up was planned every 3 months in the first year and every 6 months in the other years, for a total of 5 years.

Statistical analyses

The primary endpoint was defined as the mean time between surgery and adjuvant chemotherapy. Secondary endpoints were defined as chemotherapy toxicity rates and the percentage of planned regimen received.

Statistical analysis was performed using SPSS 28.0 (SPSS Inc., Chicago, IL, USA).

Continuous variables were expressed as mean value ± standard deviation (SD) while categorical variables were presented as counts and percentages. The Shapiro–Wilk test was used to assess the normal distribution of the continuous variables. The unpaired Student's t-test was performed to compare continuous variables. Levene's test was used to assess the homogeneity of the variance. The chi-square or Fisher exact test was used to compare categorical variables. Statistical significance was set at P-value < 0.05 (All P values presented were 2-sided).

Results

A total of 144 patients who met the criteria were included in the study. The mean age was 61.6 ± 7.9, the median age was 62 (range, 42–85) years. Fifteen patients were female and 129 were male. Lobectomy was performed in 124 patients and bilobectomy was performed in 20 patients. VATS lobectomy/bilobectomy was successfully performed in 42 (29.2%) patients. In order to evaluate the change in VATS preference rate over time, the patients were divided into two groups according to the date of operation (first 4 years vs. last 4 years). It was observed that the rate of preference for VATS was higher in the last 4 years (n = 25/73, 34.2%) compared to the first 4 years (n = 17/71, 23.9%), but this difference between the rates was not statistically significant (p = 0.17).

The characteristics of the patients, the types of resections, and the results of the pathological examination are presented in Table 1.

A significant difference was found between VATS and thoracotomy groups in terms of mean tumor sizes (Table 1).

When surgical results were evaluated, the mean VAS scores were found to be lower, and the length of hospital stay was found to be shorter in the VATS group compared to thoracotomy (Table 2). No statistically significant difference was observed in terms of postoperative complication rates. Readmission within ten days was observed in 15 (10.4%) patients. Although this rate was higher in the thoracotomy group, the difference was not statistically significant (V: n = 3, 7.1%; T: n = 12, 11.8%; p = 0.55). The most common reasons for readmission were severe chest pain and subcutaneous emphysema.

Table 1 Patient characteristics

Variables	VATS (n = 42)	Thoracotomy (n = 102)	*P* value
Age (year) (mean ± SD)	60.4 ± 8.4	62.1 ± 7.6	0.23
Gender (male), n (%)	37 (88.1)	92 (90.2)	1.0
Operation (n (%))			*
Right upper lobectomy	14 (33.3)	24 (23.5)	
Right lower lobectomy	9 (21.4)	16 (15.7)	
Middle lobectomy	0 (0.0)	2 (2.0)	
Left upper lobectomy	13 (31.0)	23 (22.5)	
Left lower lobectomy	4 (9.5)	19 (18.6)	
Bilobectomy superior	2 (4.8)	5 (4.9)	
Bilobectomy inferior	0 (0.0)	13 (12.7)	
Histologic type (n (%))			*
Squamous cell carcinoma	10 (23.8)	53 (52.0)	
Adenocarcinoma	26 (61.9)	40 (39.2)	
Large cell carcinoma	5 (11.9)	6 (5.9)	
Other[b]	1 (2.4)	3 (2.9)	
Tumor size (cm) (mean ± SD)	4.8 ± 2.4	5.6 ± 2.2	0.031
Nodal status (n (%))			0.47
N0	28 (66.7)	62 (60.8)	
N1	8 (19.0)	29 (28.4)	
N2	6 (14.3)	11 (10.8)	
Stage (n (%))			0.15
I	9 (21.4)	12 (11.8)	
II	17 (40.5)	58 (56.9)	
III	16 (38.1)	32 (31.4)	

SD: Standard deviation, VATS: Video-assisted thoracic surgery

[*] Due to the presence of cells with an expected value of less than 5, the chi-square test could not be performed, so the p value could not be given

[b] Adenosquamous carcinoma and sarcomatoid carcinoma

Table 2 Postoperative results

Variables	VATS ($n=42$)	Thoracotomy ($n=102$)	*P* value
Postoperative complication (yes), n (%)	11 (26.2)	22 (21.6)	0.66
Length of postoperative hospital stay (days) (mean ± SD)	5.4 ± 2.9	6.7 ± 3.8	0.032
VAS (mean ± SD)			
POD 1	3.6 ± 0.9	4.5 ± 1.1	0.00
POD 3	3.2 ± 1.0	4.1 ± 1.2	0.00
Time to initiation of adjuvant chemotherapy (days) (mean ± SD)	48.9 ± 17.6	58.1 ± 27.6	0.049

POD Postoperative day, *SD* Standard deviation, *VATS* Video-assisted thoracic surgery

Table 3 Chemotherapy regimens

Chemotheraphy	N (%)
Cisplatin + Vinorelbine	48 (33.3)
Cisplatin + Gemsitabine	15 (10.4)
Cisplatin + Etoposide	9 (6.3)
Cisplatin + Paclitaxel	6 (4.2)
Cisplatin + Docetaxel	3 (2.1)
Carboplatin + Vinorelbine	33 (22.9)
Carboplatin + Gemsitabine	9 (6.3)
Carboplatin + Etoposide	6 (4.2)
Carboplatin + Paclitaxel	6 (4.2)
Carboplatin + Pemetrexed	3 (2.1)

Table 4 Grade 3–4 chemotherapy-related toxicities

Toxicity grade ≥ 3	N (%)
Neutropenia	18 (12.5)
Anemia	6 (4.2)
Pancytopenia	4 (2.8)
Fatigue	3 (2.1)
Nausea	3 (2.1)
Pleural effusion	2 (1.4)
Lung infection	2 (1.4)

When the data of the oncological treatment process were examined, it was seen that the median time (days) for patients to be delivered to chemotherapy after surgery was 48 days (range, 10–156 days) and the most frequently administered chemotherapy regimen was Cisplatin + Vinorelbine in the form of 4 cycles (33.3%) (Table 3).

The mean number of chemotherapy cycles was 3.5 ± 0.8, and the rate of grade 3 and higher toxicity was 26.4% ($n=38$). The most common grade 3 and higher toxicity was neutropenia (12.5%) (Table 4).

The mean time (days) to initiate chemotherapy after surgery was statistically shorter in the VATS group (48.9 ± 17.6 vs 58.1 ± 27.6, $p=0.049$). However, there weren't seen any statistical differences between VATS and thoracotomy groups in terms of mean cycle completed, percentage of planned regimen received, and grade ≥ 3 toxicity rates ($p=0.16$, $p=0.18$, and $p=0.22$, respectively) (Table 5).

Discussion

Our study showed that VATS is superior to thoracotomy in terms of postoperative pain and hospital stay, which are important indicators of early postoperative recovery. While it was seen that this superiority contributed positively to the referral time of patients to chemotherapy, no significant difference was found in terms of chemotherapy tolerance (cycles completed, percentage of planned regimen received, toxicity grade ≥ 3) of the patients.

The survival benefit of adjuvant chemotherapy after curative surgical resection in patients with NSCLC was not shown until the early 2000s. However, evidence for the survival benefit of adjuvant treatment regimens with platinum-based chemotherapy agents and their combinations has accumulated in subsequent studies. Currently, adjuvant chemotherapy is recommended after curative surgical resection in patients with stage 2–3 NSCLC

Table 5 Comparison of VATS and thoracotomy groups in terms of parameter related with chemotherapy tolerance

	VATS ($n=42$)	Thoracotomy ($n=102$)	*P* value
Cycles completed, (Mean ± SD)	3.4 ± 0.9	3.6 ± 0.7	0.16
Percentage of planned regimen received	83.9 ± 22.6	88.7 ± 17.8	0.18
Toxicity grade ≥ 3	8 (19.0%)	30 (29.4%)	0.22

SD Standard deviation, *VATS* Video-assisted thoracic surgery

[2–4]. Thus, the importance of rapid recovery after surgery for patients scheduled for adjuvant chemotherapy has increased.

VATS lobectomy which is performed through the smaller incisions without rib spreading is shown to be associated with shorter drainage time and hospital stay and less postoperative pain compared to thoracotomy [5–11]. This relationship of VATS with early recovery after surgery has made it the first choice in suitable patients for lung cancer surgery. In addition to the positive results in the early postoperative period, some studies suggested better survival results in patients who underwent VATS compared to thoracotomy. The common hypothesis emphasized in these studies to explain the survival advantage of VATS was less inflammatory cytokine release and better tolerance of adjuvant therapy due to rapid recovery after surgery [12–15]. In our study, the duration of hospitalization was shorter and VAS scores were lower in the VATS group. While no difference was found between VATS and thoracotomy groups in terms of postoperative complication rates, we think that the most important reason for the difference in hospitalization times is severe pain requiring iv analgesic treatment. Short hospital stays and less postoperative pain are important indicators of early recovery after surgery and may explain the earlier initiation of adjuvant chemotherapy in the VATS group.

In a similar study comparing adjuvant chemotherapy tolerances in patients who underwent lung resection with VATS or thoracotomy Jiang et al. [16] suggested better compliance and fewer delayed or reduced doses of adjuvant chemotherapy in the VATS group. However, no significant difference was found between the VATS (V) and thoracotomy (T) groups in terms of time to initiate chemotherapy (V:33.7 ± 10.9, T:34.0 ± 13.3 days, p:0.904). In another study, Zhi et al. reported higher compliance to adjuvant docetaxel-carboplatin chemotherapy in patients who underwent VATS however they didn't find a difference between VATS and thoracotomy groups in terms of time from surgery to initiation of chemotherapy (V:32 ± 10, T:34 ± 9 days, $p = 0.4$) [17].

In the study performed by Petersen et al. [8], no significant difference was found between the chemotherapy-induced toxicity rates between VATS and thoracotomy groups, while dose reduction and dose delay rates were found to be lower in the VATS group.

Unlike these previous studies, in our study, no significant difference was found between VATS and thoracotomy groups in terms of chemotherapy-related toxicity and tolerance. The difference between the VATS and thoracotomy groups at the time of initiation of chemotherapy is likely to be due to the difference in postoperative hospital stay and the difference in recovery times after surgery, which we could not reveal objectively.

Our study has some limitations. First the number of cases included in the study relatively small. Some results can reach statistical significance by increasing the number of cases. Second, we did not include long-term follow-up survival results in our study. For this reason, the effect of the referral time to chemotherapy on prognosis was not included in the results of our study. Finally, the cases included in the study are not homogeneous in terms of the chemotherapy regimens applied. This may have caused erroneous results when comparing the toxicity rates of VATS and thoracotomy groups.

Conclusions

The results of this study showed that initiation time to adjuvant chemotherapy is shorter in patients who underwent VATS compared to thoracotomy. However, no significant difference was found in terms of chemotherapy tolerance and toxicity. Multicenter prospective studies are needed to reveal the possible effects of short surgery-adjuvant chemotherapy interval on prognosis in patients who underwent VATS.

Abbreviations

CT	Computed tomography
ICS	Intercostal space
NSCLC	Non-small cell lung cancer
VAS	Visual analogue scale
VATS	Video-assisted thoracic surgery

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Not applicable.

Authors' contributions

Author GB and author KCC have given substantial contributions to the conception or the design of the manuscript, author GB and author SOK to acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript, author SOK revised it critically. All authors read and approved the final version of the manuscript.

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Availability of data and material

The data that support the findings of this study are available from the corresponding author, GB, upon reasonable request.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board (Reg. no. 2020-KAEK-139).

Consent for publication

Informed consents were obtained for publication of the study.

Competing interests

The authors declare that there is no conflict of interest.

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