Video-assisted thoracoscopic lobectomy mitigates adverse oncological effects of delayed adjuvant chemotherapy for non-small cell lung cancer patients

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Summary

Purpose: Delaying adjuvant chemotherapy initiation >8 weeks after radical lobectomy for non-small cell lung cancer (NSCLC) adversely affects overall survival. The effect of video-assisted thoracoscopic lobectomy (VATS) on adjuvant chemotherapy initiation is yet unclear. This study aimed to determine if using VATS for NSCLC resection affected the timing of adjuvant chemotherapy and oncological outcomes.

Methods: Patients who underwent radical lobectomy for pathological stage II or IIIA NSCLC and received adjuvant chemotherapy between January 2009 and January 2016 were identified from a prospectively maintained lung cancer database. Patients were categorized according to surgical approach: open lobectomy or VATS. Patient demographics, clinicopathological data, postoperative complications, time from radical lobectomy to adjuvant chemotherapy initiation, and long-term survival outcomes were compared.

Results: Age, gender, American Society of Anesthesiologists (ASA) class, comorbidity, TNM stage, and postoper-

ative complications were similar between VATS and open cases; however, length of stay was shorter in VATS cases. No difference was observed in the proportion of patients who received adjuvant chemotherapy >8 weeks after radical lobectomy between the two groups. In the open group, a delay in adjuvant chemotherapy after radical lobectomy was associated with decreased overall survival (OS) and disease-free survival (DFS). However, delay in chemotherapy did not affect OS or DFS in the VATS group.

Conclusions: The benefits of quicker recovery after VATS did not result in earlier adjuvant chemotherapy initiation in this retrospective study. However, VATS negated the inferior oncologic outcomes associated with delayed adjuvant chemotherapy initiation.

Key words: adjuvant chemotherapy, lobectomy, minimally invasive surgery, non-small-cell lung cancer, video-assisted thoracoscopic surgery

Introduction

Current treatment guidelines for pathological stage II and IIIA NSCLC suggest radical lobectomy followed by adjuvant chemotherapy, which increases OS and DFS in these patients [1-6]. Previous studies have shown that delaying adjuvant chemotherapy initiation >8 weeks after radical lobectomy adversely affects prognosis [6-8]. A number of demographic, clinical, and systemic factors have been associated with delay in adjuvant che-

motherapy initiation, including age, comorbidity, postoperative complications, and postoperative length of hospital stay [8-13].

Oncological outcomes for NSCLC are reportedly the same between VATS and open lobectomy [14-18]. However, patients who undergo VATS benefit from better cosmesis, decreased postoperative narcotic analgesia use, decreased length of hospital stay, and faster recovery [14-18]. Al-

though it has been well-established that VATS is associated with decreased length of hospital stay and recovery time [14-18], the effect of VATS on the time to adjuvant chemotherapy initiation has not been studied. Therefore, this study aimed to determine if using VATS for NSCLC resection affected the timing of adjuvant chemotherapy and subsequent oncological outcomes.

Methods

Patient selection

This retrospective study was approved by our local ethics committees and performed according to the Declaration of Helsinki. The requirement for informed consent from patients was waived because of the retrospective nature of the study.

A prospectively maintained lung cancer database from a single institution was queried for patients with pathological stage II or IIIA NSCLC who underwent radical lobectomy between January 2009 and January 2016. The resulting patient list was then cross-referenced with a prospectively maintained oncology database of adjuvant chemotherapy regimens. Patient data present in both databases were extracted for analysis. Records without information regarding the timing of chemotherapy were excluded. Patients were categorized according to surgical approach: open lobectomy or VATS.

Patient characteristics and outcomes

The resulting cohort of patients was analyzed for clinicopathological data, including age, gender, comorbidity, ASA class, TNM stage, tumor location, and tumor cell differentiation. Postoperative complications, severity of postoperative complications, time interval from radical lobectomy to adjuvant chemotherapy initiation, and long-term survival outcomes were included in the analysis. The TNM stage was based on the 7th edition of the TNM classification of lung cancer, which was proposed by the American Joint Committee on Cancer, the Union Internationale Contre le Cancer, and the International Association for the Study of Lung Cancer [19-22]. Postoperative complications were graded to be either major or minor using the Clavien–Dindo classification based on the following definitions: Grade 1: oral medication or bedside medical care required; Grade 2: intravenous medical therapy required; Grade 3: radiologic, endoscopic, or operative intervention required; Grade 4: chronic deficit or disability associated with the event; and Grade 5: death associated with surgical complication. Major complications were defined as grades 3, 4, and 5, whereas minor complications were classified as grades 1 and 2 [23-25]. OS was assessed from the date of surgery until the last follow-up or death by any cause. DFS was calculated from the date of surgery until the date of cancer recurrence or death by any cause [26-30]. The last follow-up was on February 2016.

Statistics

All statistical analyses were performed using SPSS 14.0 software (SPSS Inc., Chicago, ILL, USA). Variables following a normal distribution were analyzed using the *t*-test and are presented as means and standard deviations, whereas those following a non-normal distribution were compared using Mann-Whitney U test and are expressed as medians and ranges. Differences between semiquantitative results were analyzed using the Mann–Whitney *U* test and those between qualitative results were analyzed using the chi-square or Fisher's exact test. Survival rates were analyzed using the Kaplan–Meier method, and differences between the two groups were analyzed using the log-rank test. A probability (*P*) value <0.05 was considered to be statistically significant.

Results

Clinical and pathological data

Of the 362 cases included in this study, 193 (53.3%) underwent VATS. There was no difference in age, gender, ASA class, or comorbidity between the open and VATS groups (Table 1). Similarly, pathological TNM stage, tumor location, pathological subtype, postoperative complications, and severity of postoperative complications did not differ between the two groups (Tables 1 and 2). Length of postoperative hospital stay was shorter

Table 1. Patient characteristics

Characteristics	VATS group (N=193)	Open group (N=169)	p value
Age, years (range)	64 (46-72)	59 (47-66)	0.520
Gender (Male: Female)	129:64	109:60	0.689
ASA score			0.734
I	148	128	
II	42	34	
III	3	7	
Comorbidity	51	45	0.724
Chronic obstructive pulmonary disease	5	6	
Prior tuberculosis	2	4	
Hypertension	22	19	
Angina pectoris	8	7	
Diabetes mellitus	8	7	
Liver cirrhosis	6	2	
Number of comorbidities			0.869
0	148	128	
1	39	37	
2	6	4	

Table 2. Tumor and postoperative characteristics

Characteristics	VATS group (N=193)	Open group (N=169)	p value
Pathological TNM stage			0.580
IIA	70	65	
IIB	87	76	
IIIA	36	28	
Tumor location			0.795
Right lobe	102	87	
Left lobe	91	82	
Pathological subtype			0.088
Adenocarcinoma	121	91	
Squamous cell carcinoma	72	78	
Surgical margin (R0/R1/R2)	193/0/0	169/0/0	1.000
Postoperative complications	32	37	0.199
Severity of postoperative complications (Clavien–Dindo system)			
Major complications	5	7	0.411
Minor complications	27	30	0.327
Length of postoperative stay, days (range)	8 (5-12)	13 (6-23)	0.022
Chemotherapy regimens			0.639
Gemcitabine + Cisplatin	96	73	
Paclitaxel+Carboplatin	81	80	
Vinorelbine+Cisplatin	11	10	
Others	5	6	

Table 3. Factors associated with delay in initiation of adjuvant hemotherapy

Factors	≤ 8 weeks (N=264)	> 8 weeks (N=98)	p value
ASA score			0.000
I	225	51	
II	38	38	
III	1	9	
Length of postoperative stay, days (range)	9 (6-23)	10 (5-20)	0.103
Postoperative complications	41	28	0.005
Severity of postoperative complications (Clavien–Dindo system)			
Major complications	4	8	0.005
Minor complications	37	20	0.138

in the VATS group compared with the open group (Table 2).

Initiation of adjuvant chemotherapy

Overall, the median time to adjuvant chemotherapy initiation after radical lobectomy was <8 weeks (48 days, range: 26-102). The median time to adjuvant chemotherapy initiation was simi-

lar between the open and VATS groups (50 vs 45 days, p=0.490, respectively). Of the 362 patients, chemotherapy was initiated >8 weeks postoperatively in 98 patients. There was no difference in the proportion of patients who received adjuvant chemotherapy >8 weeks after radical lobectomy between the two groups (30.1% in VATS group vs 23.7% in open group, p=0.173).

Delay in adjuvant chemotherapy initiation was associated with a higher ASA score. The postoperative complication rate and major complication rates were greater for patients who received adjuvant chemotherapy >8 weeks after radical lobectomy, compared with those who received treatment in <8 weeks (Table 3).

overall and disease-free survival

OS was decreased in patients who initiated adjuvant chemotherapy >8 weeks following radical lobectomy (p=0.019). This effect varied according to the surgical approach. In patients who underwent VATS, a delay in adjuvant chemotherapy was not associated with a decrease in OS (Figure 1, p=0.276). For patients who underwent open lobectomy, a delay in adjuvant chemotherapy was associated with a decrease in OS (Figure 2, p=0.030).

DFS was decreased in patients who initiated adjuvant chemotherapy >8 weeks following radical lobectomy (p=0.010). This effect varied accord-
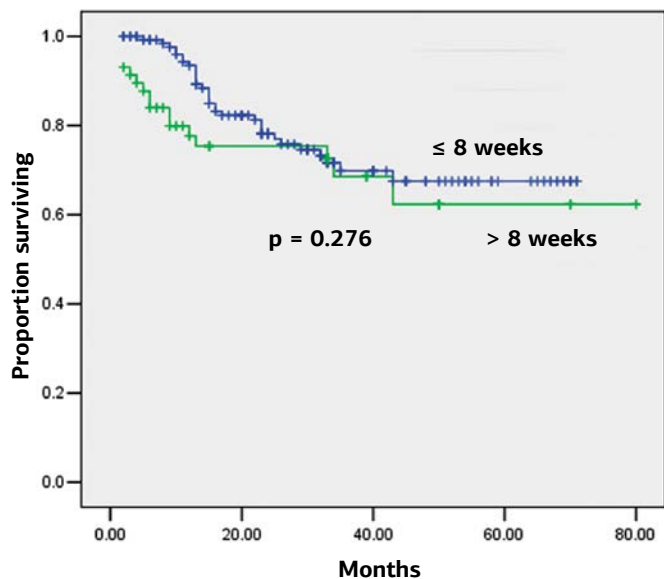
Figure 1. Kaplan-Meier plots of overall survival based on time to initiating adjuvant chemotherapy after radical lobectomy for patients treated by VATS approach (p=0.276).
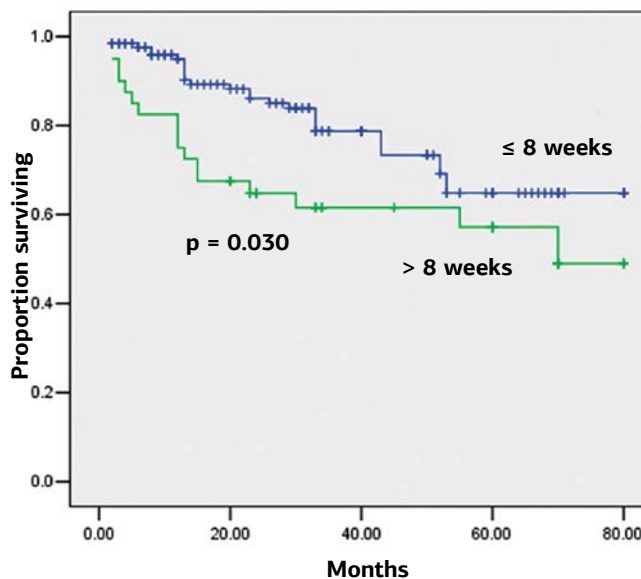

Figure 2. Kaplan-Meier plots of overall survival based on time to initiating adjuvant chemotherapy after radical lobectomy for patients treated by open approach (p=0.030).
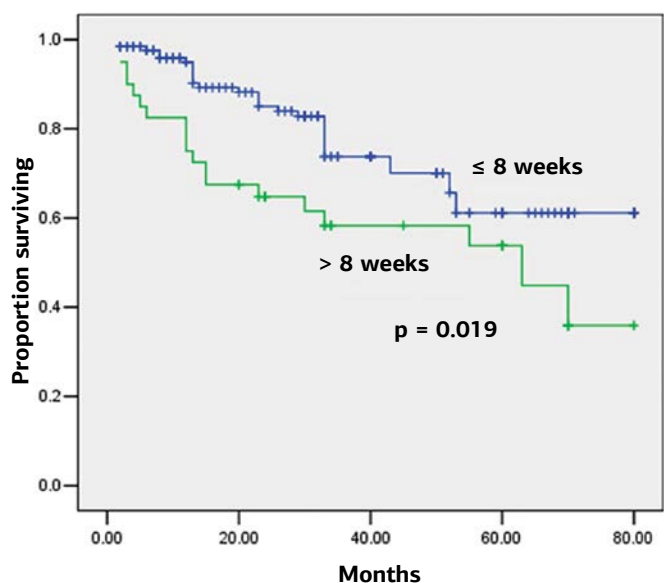

Figure 3. Kaplan-Meier plots of disease-free survival based on time to initiating adjuvant chemotherapy after radical lobectomy for patients treated by open approach (p=0.019).
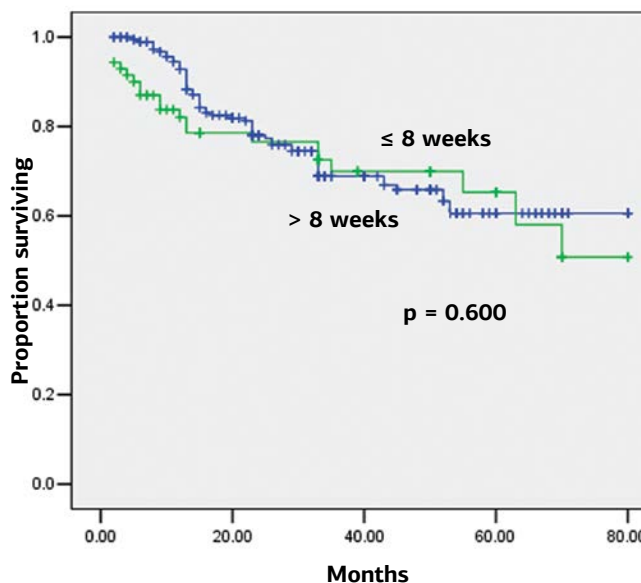

Figure 4. Kaplan-Meier plots of disease-free survival based on time to initiating adjuvant chemotherapy after radical lobectomy for patients treated by VATS approach (p=0.600).

ing to the surgical approach. In patients who underwent open lobectomy, a delay in adjuvant chemotherapy was associated with a decrease in DFS (Figure 3, p=0.019). In contrast, there was no difference in DFS between patients who received adjuvant chemotherapy before or after 8 weeks postoperatively in the VATS group (Figure 4, p=0.600).

Discussion

As expected, the VATS group had a short-er length of hospital stay than the open group. However, this did not result in earlier administration of adjuvant chemotherapy following VATS in this nonprotocoled retrospective study. A delay in adjuvant chemotherapy was associated with differences in OS and DFS based on the surgical approach. There was no decrease in OS or DFS among patients who underwent VATS when adjuvant chemotherapy initiation was >8 weeks. However, delayed adjuvant chemotherapy was associated with decreased OS and DFS in patients who

underwent open lobectomy. These findings may indicate an additional benefit of VATS for NSCLC.

In the literature, the proportion of patients who delayed adjuvant chemotherapy initiation ranges from 20-56% [8-13], which is consistent with our study because approximately one-fourth received adjuvant chemotherapy >8 weeks after radical lobectomy. A number of factors have been associated with a delay in adjuvant chemotherapy resulting in several confounding variables [8-13]. Age, race, length of postoperative hospital stay, postoperative complications, and systematic factors, such as waiting lists for appointments and waiting lists to initiate adjuvant chemotherapy, were associated with delayed initiation of adjuvant chemotherapy following surgery [8-13]. When designing this study, we anticipated that adjuvant chemotherapy would have been initiated earlier after radical lobectomy in patients who underwent VATS than those who underwent open resections. However, this hypothesis was not confirmed in this retrospective study because the timing of radical lobectomy depended on several uncontrolled and not recorded variables [8-13,31]. There was a slightly higher percentage of patients who underwent radical lobectomy >8 weeks after VATS compared with open lobectomy. However, this trend was not statistically significant because of small sample size.

Decreased OS in patients who received adjuvant chemotherapy >8 weeks after radical lobectomy has been demonstrated in several studies [6-8]. However, none of these previous studies examined the effect of VATS on OS after a delay in adjuvant chemotherapy. The paucity of data regarding the effect of VATS on the timing of adjuvant chemotherapy renders previous studies less generalizable to current surgical care and emphasizes the relevance of our study.

A relatively unexpected and novel finding of this study was that prognosis did not appear to be worse among patients who underwent VATS if adjuvant chemotherapy was delayed by >8 weeks after radical lobectomy. The advantages of VATS

have been widely reported and include decreased postoperative pain, decreased length of postoperative hospital stay, and quicker recovery. Another advantage of VATS is improved immunologic response to surgical stress compared with open surgery [32-34]. Several studies have reported a diminished inflammatory response in patients who underwent VATS [32-34]. Decreased stress response to VATS may result in improved immunologic function and oncologic benefits. These findings may be a possible explanation for the relatively improved OS and DFS for VATS cases with delayed chemotherapy compared with open cases.

We recognize that there were limitations to this study. The retrospective nature of this study is subject to confounding variables that may influence the timing of adjuvant chemotherapy. Various patients who underwent surgery at our institution received adjuvant chemotherapy elsewhere. This pattern of patients receiving adjuvant therapy at outside institutions prevented analysis of several variables that could delay adjuvant chemotherapy. Systematic variables should be included in future analyses of causes of delay in adjuvant chemotherapy.

In summary, although the benefits of quicker recovery after VATS did not result in earlier administration of adjuvant chemotherapy in this retrospective study, it is rational to examine this theory in a prospective fashion. VATS negated the inferior prognosis of patients who received delayed adjuvant chemotherapy. These results require validation in larger studies and, if confirmed, underlying potential causes of the differences in oncologic outcomes warrant exploration.

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Conflict of interests

The authors declare no conflict of interests.

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