Ultrasonography for Detecting Adhesions: Aspirin Continuation for Lung Resection Patients

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Abstract. *Background/Aim: Aspirin reduces cardiovascular disease and/or stroke risks. However, perioperative aspirin use remains controversial. We assessed the efficacy of ultrasonography to facilitate video-assisted thoracic surgery (VATS). We analyzed the perioperative management of patients using aspirin and its association with bleeding events during lung cancer surgery. Patients and Methods: A total of 38 patients who underwent VATS after continuing or discontinuing aspirin were examined. Ultrasound was performed preoperatively to evaluate the pleural adhesions. Fisher's exact test was used to analyze correlations between the two groups. Results: Dense adhesions were found at VATS ports using ultrasonography (accuracy: 100%). No differences were detected in bleeding, thrombotic events, or operative times between the aspirin and non-aspirin groups. There were differences in bleeding ($p=0.009$) and operative times ($p=0.021$) between the dense adhesion and non-dense adhesion groups. Conclusion: Preoperative detection of pleural adhesions using ultrasonography was useful in selecting pulmonary resection patients who continued aspirin perioperatively.*

During the past two decades, video-assisted thoracic surgery (VATS) has been established as the preferred approach for almost all thoracic surgical procedures. Recently, several authors have reported the efficacy of uniportal VATS for

lobectomy (1, 2). However, there is no agreement regarding the limitations of this method. The most popular technical contraindications for VATS for pulmonary resection are dense pleural adhesions, incomplete interlobar fissures, previous chemotherapy and/or radiotherapy, perivascular and/or peribronchial fibrosis, tumors larger than 5 cm, chest wall involvement, centrally located tumor, severe comorbidity, advanced age, severe chronic obstructive pulmonary disease (COPD), and emphysema (3). For experienced surgeons, VATS in the presence of dense pleural adhesions is controversial. Furthermore, for inexperienced surgeons, VATS in the presence of dense pleural adhesions could lead to unexpected massive bleeding and/or lung injury (4). Preoperative transthoracic ultrasonography is useful for detecting pleural adhesions in patients scheduled to undergo thoracotomy (5-7). We speculated that preoperative evaluation of pleural adhesions is beneficial before surgical intervention.

In Japan, many elderly patients with lung cancer undergo pulmonary resection. However, they often have comorbidities, including cardiovascular and/or cerebrovascular diseases (8). Because aspirin has been used for decades as secondary prevention of myocardial infarction or stroke by patients with ischemic heart or cerebrovascular disease (9), increasing numbers of lung cancer patients with cardiovascular and/or cerebrovascular diseases are using aspirin. Major adverse cardiac and cerebrovascular events (MACCEs) are common causes of disabling and/or fatal outcomes after non-cardiac surgery (10, 11). Therefore, there is a clinical dilemma regarding patients who use aspirin before surgery in terms of whether aspirin treatment should be continued because of the risks of thromboembolic complications compared with the risks of coagulopathy. Recent data regarding the risk of discontinuing antiplatelet therapy by patients with coronary stents have highlighted the use of aspirin during the perioperative period (12, 13). Therefore, the routine withdrawal of aspirin 7-10 days before surgery has been

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questioned, and some recent publications have recommended that aspirin should not be stopped during the perioperative period (14, 15). However, these recommendations were not based on evidence from controlled trials that could elucidate the risks and benefits of aspirin in the setting of non-cardiac surgery.

Kanzaki *et al.* (4) demonstrated the feasibility of aspirin continuation during the perioperative period for lung cancer patients requiring pulmonary resection. However, they reported that 1 out of 20 patients who continued using aspirin had blood loss of 500 g intraoperatively and postoperative bleeding that required transfusion due to an intrathoracic adhesion. Considering their report, it is important to determine whether there are thoracic adhesions in patients who continue using aspirin. This study aimed to assess the efficacy of ultrasonography before VATS to analyze the efficacy of perioperative management with antiplatelet therapy, especially aspirin, for such patients and the relationship between aspirin and VATS regarding the incidence of MACCE and major bleeding events during lung cancer surgery.

Patients and Methods

Patients. Among 287 patients who underwent lung cancer resection at the Nara Medical University Hospital from January 2017 to December 2018, 38 who underwent lung cancer resection and were using aspirin were enrolled. The exclusion criterion for entry into the study population was the use of other anticoagulation drugs and/or antiplatelet drugs. All 38 patients underwent preoperative ultrasonography to evaluate the possible presence of pleural adhesions.

Of 38 patients who underwent lung cancer resection from January 2017 to September 2017, 10 stopped using aspirin 7 days before surgical intervention (group 1). The other 28 patients who underwent lung cancer resection from October 2017 to December 2018 had continued using aspirin before surgical intervention and did not have adhesions according to ultrasonography (group 2).

Patients and methods. We used VATS to resect the lung tumors. This involved four incisions: an incision along the anterior axillary line for a camera port (initial port) in the seventh or eighth intercostal space; a 1-cm incision along the anterior axillary line in the fourth or fifth intercostal space; a 1-cm incision along the posterior axillary line in the seventh or eighth intercostal space; and a 4- to 5-cm incision in the axilla for a working port in the fourth or fifth intercostal space.

The ultrasound study was performed within 2 weeks before the scheduled surgery. The LOGIQ E9TM (GE Healthcare, Chicago, IL, USA) ultrasound system was used. All patients were examined in the lateral position with the fourth or fifth intercostal spaces and the seventh or eighth intercostal spaces of the mid-axillary line undergoing respiration. We evaluated the lung sliding sign, which is the movement of visceral pleural sliding with breathing and is a hallmark of the absence of pleural adhesions. If pleural adhesions were detected during preoperative ultrasonography, then patients in group 2 stopped using aspirin 7 days before surgery. If there were no pleural adhesions during preoperative ultrasonography, then

patients in group 2 continued using aspirin. In group 2, no patient stopped using aspirin 7 days before surgery.

We checked whether there were adhesions and determined their locations during VATS. Loose adhesions and dense adhesions were considered blunt ablations that could or could not be removed easily. Prolonged air leakage was defined as an air leak lasting for more than 5 days postoperatively. The chest tube duration was measured in days.

The Ethics Review Board of our institute approved the study protocol and waived the requirement to obtain written informed consent from patients because individual patients were not identified in this retrospective study.

Statistical analyses. Either the Chi-square test or Fisher's exact test was performed, as appropriate, to analyze correlations between the two groups. All *p*-values were two-sided, and $p \leq 0.05$ was considered statistically significantly different. All analyses were conducted using EZR on R commander version 1.33 (Saitama, Japan) (16).

Results

No pleural adhesions were found using preoperative ultrasonography for patients in group 2; these patients were instructed to stop using aspirin before surgery. Table I shows the clinical characteristics of all patients. Ten adhesions were found at VATS ports. Adhesions could not be detected in nine patients. For these nine patients, we were able to remove these adhesions easily, without lung injury and massive bleeding, because they were loose. Visceral slide sonography detected the following adhesions: 1 true-positive adhesion; 9 false-negative adhesions; 0 false-positive adhesions; and 28 true-negative adhesions (sensitivity: 10.0% [1/10]; specificity: 100.0% [28/28]; accuracy: 76.3% [29/38]) (Table II). The lung sliding sign could distinguish between dense adhesions and non-dense adhesions (accuracy: 100% [38/38]) (Table III). At the initial port, we could not detect two adhesions (accuracy: 94.7% [36/38]) (Table IV). However, there were 19 adhesions at other sites, including the intrathoracic space and additional port sites. Adhesions were not estimated using ultrasonography at areas other than port sites in this group.

Table I shows the outcomes of surgical intervention. Surgery times for group 1 and group 2 were 109 ± 47 min and 116 ± 53 min, respectively ($p = 0.702$). Intraoperative bleeding in group 1 and group 2 comprised 21.2 ± 24.2 g and 23.3 ± 39.0 g, respectively ($p = 0.877$). No patients underwent blood transfusion intraoperatively or perioperatively. The chest tube durations for group 1 and group 2 were 1.5 ± 0.8 days and 3.1 ± 4.1 days, respectively ($p = 0.235$). Fortunately, there were no complications, such as postoperative bleeding, myocardial infarction, cerebral infarction, arrhythmia, and pneumonia, among all patients. Three patients in group 2 experienced prolonged air leakage (more than 5 days). Furthermore, we analyzed the outcomes of dense adhesions and of loose or no adhesions. Table V shows the outcomes of surgical

Table I. Clinical characteristics of all patients (n=38).

	All patients, n=38 (%)	Group 1, n=10 (%)	Group 2, n=28 (%)	p-Value
Age (years)	72.5±6.5	71.1±8.2	73.0±5.9	0.445
Gender				1.000
Male	30 (78.9)	8 (80.0)	22 (78.6)	
Female	8 (21.1)	2 (20.0)	6 (21.4)	
Indication for aspirin				0.890
CAD	26	8	18	
Cerebral infarction	13	3	10	
Peripheral vascular disease	2	0	2	
Others	1	0	1	
Procedure				0.888
Lobectomy	19 (50.0)	6 (60.0)	13 (46.4)	
Segmentectomy	2 (5.3)	0 (0.0)	2 (7.2)	
Wedge resection	17 (44.7)	4 (40.0)	13 (46.4)	
Thoracic adhesions observed				0.601
Dense	15 (39.5)	3 (30.0)	12 (42.9)	
Loose	5 (13.2)	2 (20.0)	3 (10.7)	
None	18 (47.4)	5 (50.0)	13 (46.4)	
Adhesions sites				NS
Ports	10	2	8	
Others	19	5	14	
Length of surgery (min)	114±51	109±47	116±53	0.702
Intraoperative bleeding (g)	22.7±35.3	21.2±24.2	23.3±39.0	0.877
Chest tube duration (days)	2.7±3.6	1.5±0.8	3.1±4.1	0.235
Postoperative complications	3 (7.9)	0 (0.0)	3 (10.7)	0.552
				(prolonged air leakage: >5 days)

CAD: Coronary artery disease; NS: non-significant.

intervention. Operative times for the dense adhesions group and for the loose or no adhesions group were 143±53 min and 97±46 min, respectively ($p=0.021$). Intraoperative bleeding for the dense adhesions group and for the loose or no adhesions group comprised 44.7±52.4 g and 7.2±8.8 g, respectively ($p=0.009$). No patients underwent blood transfusion intraoperatively or perioperatively. Chest tube durations for the dense adhesions group and for the loose or no adhesions group were 5.0±5.8 days and 1.7±1.2 days, respectively ($p=0.033$). Three patients had prolonged air leakage; these three were in the dense adhesions group.

Discussion

We demonstrated that preoperative detection of pleural adhesions using transthoracic ultrasonography could provide safe thoroscopic access without unexpected massive bleeding and/or lung injury and facilitate VATS among lung cancer patients who continue using aspirin during the perioperative period.

Aspirin (acetylsalicylic acid) is part of the salicylate family of drugs. Universally, it is used as an analgesic, antipyretic, and anti-inflammatory agent. However, primarily because of its antiplatelet effects, it is commonly used for

secondary prevention of cardiovascular and neurovascular morbidity of patients with known ischemic heart disease and cerebrovascular disease (*i.e.*, previous myocardial infarction, coronary artery disease, peripheral vascular disease, coronary stent implantation, previous cerebral vascular accident). Aspirin decreases the risk of cardiovascular disease and/or stroke through its antiplatelet characteristics in those at risk for thrombotic events. Within the perioperative period, aspirin use remains controversial. If withheld before surgery, then patients are at risk for cardiac and neurovascular events during the aspirin-free period. Several studies of major surgery (cardiac and non-cardiac) found that aspirin use was associated with increased bleeding; however, others showed minimal bleeding risks and improved outcomes (17-20).

Which patients should continue using aspirin during the perioperative period? The American College of Chest Physicians (ACCP) guidelines in 2012 (21) provided grade 1A recommendations for patients with established coronary artery disease, suggesting that long-term single antiplatelet therapy with aspirin is appropriate.

Oscarsson *et al.* (18) performed a randomized, double-blinded, placebo-controlled trial to evaluate the effects of aspirin on major adverse cardiac events (MACEs) and found no increase in perioperative bleeding between the aspirin and

Table II. Results after the lung slide sign were discovered using ultrasonography to detect pleural adhesions. All ports among all patients (n=38).

Adhesions predicted	Adhesions observed	
	Yes	No
Yes	1	0
No	9	28

Table III. Results after the lung slide sign were discovered using ultrasonography to detect pleural adhesions at port sites. Adhesion levels among all patients: dense adhesions vs. loose or no adhesions (n=38).

Adhesions predicted	Dense adhesions observed	
	Yes	No
Yes	1	0
No	0	37

Table IV. Results after the lung slide sign were discovered using ultrasonography to detect pleural adhesions. Adhesions in the initial port among all patients (n=38).

Adhesions predicted	Adhesions observed	
	Yes	No
Yes	0	0
No	2	36

non-aspirin groups. Mantz *et al.* (19) reported that no difference was detected in bleeding or thrombotic events between the aspirin and non-aspirin groups. The European Society of Cardiology (22) stated that continuation of aspirin by patients previously treated with aspirin should be considered during the perioperative period, but that discontinuation of aspirin therapy should be considered only for those in whom hemostasis is expected to be difficult to achieve during surgery.

We recognize that lung cancer surgery should be performed safely with less bleeding. However, resection of the pulmonary parenchyma may lead to unexpected bleeding due to dense adhesions. Kanzaki *et al.* (4) demonstrated the feasibility of aspirin continuation during the perioperative period for lung cancer patients requiring pulmonary resection. Furthermore, the need to continue aspirin therapy during the perioperative period should be evaluated on an individual basis. They reported that 1 out of 20 patients who

Table V. Clinical characteristics of patients who continued aspirin (n=28).

	Loose or no adhesions (n=16) (%)	Dense adhesions (n=12) (%)	p-Value
Age (years)	71.7±5.7	74.7±6.0	0.193
Gender			0.196
Male	11 (68.8)	11 (91.7)	
Female	5 (31.2)	1 (8.3)	
Procedure			0.769
Lobectomy	6 (37.5)	7 (58.3)	
Segmentectomy	2 (12.5)	0 (0.0)	
Wedge resection	8 (50.0)	5 (41.7)	
Length of surgery (min)	97±46	143±53	0.021*
Intraoperative bleeding (g)	7.2±8.8	44.7±52.4	0.009*
Chest tube duration (days)	1.7±1.2	5.0±5.8	0.033*
Postoperative complications	0 (0.0)	3 (25.0)	0.067
		(prolonged air leakage: >5 days)	

*Statistically significant.

continued using aspirin experienced intraoperative blood loss of 500 g and postoperative bleeding on postoperative day 1 that required transfusion due to an intrathoracic adhesion. Considering their report, it is important to determine whether patients who continue using aspirin have thoracic adhesions. Furthermore, it is important to preoperatively select appropriate lung cancer patients who would be at low risk for bleeding. Therefore, we evaluated thoracic adhesions using ultrasonography to select the appropriate patients. If patients are at high risk for bleeding, then they should not continue using aspirin because the risk of perioperative bleeding complications might be increased. However, if they are not at high risk for bleeding, then they should continue aspirin because the risk of perioperative thromboembolic complications might be increased due to discontinuing the use of aspirin.

Preoperative transthoracic ultrasonography was useful for detecting pleural adhesions in patients who have undergone thoracic surgery (5-7). When we could not detect adhesions in patients who, in fact, did have adhesions, the adhesions were not dense and could be removed easily without injuring the lung. Therefore, we used preoperative ultrasonography to evaluate the feasibility of aspirin continuation during the perioperative period before pulmonary resection to provide safe thoracoscopic access, without lung injury and/or unexpected massive bleeding, thereby facilitating VATS. The lung sliding sign can distinguish between dense adhesions and non-dense adhesions. If there were dense adhesions, then the lung would not slide with breathing. If

there were no adhesions or if there were loose adhesions, then the lung would slide with breathing. Regarding the safety of VATS, especially when there are adhesions, it is important to not distinguish between adhesions and no adhesions; instead, one should distinguish between easy cases and difficult cases and between high potential and low potential for complications.

In this study, no differences were detected in bleeding events, thrombotic events, and operative time between the aspirin group (group 2) and non-aspirin group (group 1). However, there were differences in bleeding and operative times between the dense adhesions group and the non-dense or no adhesion group. Therefore, using ultrasonography might be helpful when selecting appropriate lung cancer patients continuing aspirin who could experience fewer complications during VATS. Furthermore, the presence of adhesions might be a prognostic factor for prolonged postoperative air leakage.

Here, we used preoperative ultrasonography to determine the existence of adhesions in lung cancer patients and the severity of their coexisting cardiovascular or cerebrovascular diseases, type of stent implanted, and duration of stent use. Unfortunately, we did not research the expected port site adhesions. Detecting adhesions near the apex area when using ultrasonography is difficult. If we are careful when removing adhesions during VATS, then we can perform pulmonary resection safely, without massive bleeding in those continuing aspirin. However, discontinuing aspirin could lead to a higher risk of an unanticipated major adverse cardiac and cerebrovascular event (MACCE). Regarding the safety of VATS, and considering the risk of MACCE causing disabling and/or fatal outcomes after lung cancer surgery, we concluded that continuing aspirin is worthwhile because there were no differences in bleeding events, thrombotic events, and operative times between the aspirin group (group 2) and non-aspirin group (group 1). Ultrasound is a cost-effective imaging modality that permits clinicians to obtain information regarding the thorax without the risk of exposure to ionizing radiation, and it provides real-time and immediate results (23). Because it is easy to use, easy to learn how to use it, portable, and accurate when examining the pleural space, it has allowed for safer pleural procedures, including VATS.

This study had two main limitations. It was a single-institute study with a small sample size. Therefore, it is important and necessary to perform additional investigations involving a large multi-institutional cohort to validate these findings. As mentioned, we did not research the expected port site adhesions during this study, and detecting adhesions near the apex site when using ultrasonography is difficult.

In conclusion, preoperative detection of pleural adhesions using transthoracic ultrasonography was useful for appropriately selecting pulmonary resection patients who continued using aspirin during the perioperative period.

Conflicts of Interest

The Authors declare that they have no conflict of interest in regard to this study.

Authors' Contributions

MY is the corresponding Author and wrote the manuscript. RT, NM, and TH performed the ultrasonography diagnosis. TK, NK, NS, TT, and MY participated in the surgery and postoperative management. TT, JT, NH, and ST supervised the writing of the manuscript. All Authors read and approved the final manuscript.

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