



## Comparison of awake and intubated video-assisted thoracoscopic surgery in the diagnosis of pleural diseases: A prospective multicenter randomized trial

*Plevral hastalıkların tanısında uyanık ve entübasyonlu video-yardımlı torakoskopik cerrahinin karşılaştırılması: Prospektif çok merkezli randomize bir çalışma*

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### ABSTRACT

**Background:** This study aims to compare the safety and diagnostic accuracy of awake and intubated video-assisted thoracoscopic surgery in the diagnosis of pleural diseases.

**Methods:** This prospective randomized study was conducted between October 2016 and April 2018 and included 293 patients (201 males, 92 females; mean age 53.59 years; range, 18 to 90 years) from five medical centers experienced in video-assisted thoracoscopic surgery. The patients were randomized into two groups as awake video-assisted thoracoscopic surgery with sedoanalgesia (non-intubated) and video-assisted thoracoscopic surgery with general anesthesia (intubated). Patients with undiagnosed pleural effusions and pleural pathologies such as nodules and masses were included. Conditions such as pain, agitation, and hypoxia were indications for intubation. The groups were compared in terms of demographic data, postoperative pain, operative time, complications, diagnostic accuracy of the procedures, and cost. All patients completed a follow-up period of at least 12 months for samples that were non-specific, suspicious for malignancy or inadequate.

**Results:** Awake video-assisted thoracoscopic surgery was performed in 145 and intubated video-assisted thoracoscopic surgery was performed in 148 patients. Pleural disease was unilateral in 83% (243/293) and bilateral in 17% (50/293) of the patients. There was no difference between the groups in terms of presence of comorbidity ( $p=0.149$ ). One patient in the awake video-assisted thoracoscopic surgery group (0.6%) was converted to general anesthesia due to refractory pain and agitation. As postoperative complications, fluid drainage and pneumonia were observed in one patient in the awake video-assisted thoracoscopic surgery group (0.6%) and fluid drainage was detected in one patient in the video-assisted thoracoscopic surgery group (0.6%). There were no differences in pain intensity measured with visual analog scale at postoperative 4, 8, 12, or 24 hours ( $p>0.05$ ). Distribution and rates of postoperative pathological diagnoses were also similar ( $p=0.171$ ). Both operative cost and total hospital cost were lower in the awake video-assisted thoracoscopic surgery group ( $p<0.001$ ,  $p=0.001$ ).

**Conclusion:** Our study showed that awake video-assisted thoracoscopic surgery is safe, has similar reliability and diagnostic accuracy compared to video-assisted thoracoscopic surgery performed under general anesthesia, and is less costly. Awake video-assisted thoracoscopic surgery can be the first method of choice in all patients, not only in those with comorbidities.

**Keywords:** Awake, local anesthesia, pleural effusion, thoracoscopy, video-assisted thoracoscopic surgery.

### ÖZ

**Amaç:** Bu çalışmada, plevral hastalıkların tanısında uyanık ve entübasyonlu video-yardımlı torakoskopik cerrahinin güvenliği ve tanısal doğruluğu karşılaştırıldı.

**Çalışma planı:** Bu prospektif randomize çalışma Ekim 2016 ve Nisan 2018 tarihleri arasında yapıldı ve çalışmaya video-yardımlı torakoskopik cerrahide deneyimli beş tıbbi merkezden 293 hasta (201 erkek, 92 kadın; ort. yaş 53.59 yıl; dağılım, 18-90 yıl) dahil edildi. Hastalar sedoanaljezi ile uyanık video-yardımlı torakoskopik cerrahi (entübasyonsuz) ve genel anestezi ile video-yardımlı torakoskopik cerrahi (entübasyonlu) olarak iki gruba randomize edildi. Tanısı konulmamış plevral efüzyonları ve nodüller, kitleler gibi plevral patolojileri olan hastalar dahil edildi. Ağrı, ajitasyon ve hipoksi gibi durumlar entübasyon için endikasyon idi. Gruplar demografik veriler, ameliyat sonrası ağrı, ameliyat süresi, komplikasyonlar, işlemlerin tanısal doğruluğu ve maliyet açısından karşılaştırıldı. Tüm hastalar nonspesifik, malignite şüpheli veya yetersiz örnekler için en az 12 aylık takip süresini tamamladı.

**Bulgular:** Uyanık video-yardımlı torakoskopik cerrahi 145, entübasyonlu video-yardımlı torakoskopik cerrahi 148 hastada uygulandı. Hastaların %83'ünde (243/293) plevral hastalık tek taraflı iken %17'sinde (50/293) iki taraflı idi. Gruplar arasında komorbidite varlığı açısından farklılık yoktu ( $p=0.149$ ). Uyanık video-yardımlı torakoskopik cerrahi grubunda bir hasta (0.6%) dirençli ağrı ve ajitasyon nedeniyle genel anesteziye geçildi. Ameliyat sonrası komplikasyonlar olarak uyanık video-yardımlı torakoskopik cerrahi grubunda bir hastada sıvı drenajı ve pnömoni gözlemlendi (0.6%) ve video-yardımlı torakoskopik cerrahi grubunda bir hastada sıvı drenajı saptandı (0.6%). Ameliyat sonrası 4, 8, 12. veya 24. saatte görsel analog ölçeği ile ölçülen ağrı yoğunluğunda farklılık yoktu ( $p>0.05$ ). Ameliyat sonrası patolojik tanıların dağılımı ve oranları da benzerdi ( $p=0.171$ ). Hem ameliyat maliyeti hem de toplam hastane maliyeti uyanık video-yardımlı torakoskopik cerrahi grubunda daha düşük idi ( $p<0.001$ ,  $p=0.001$ ).

**Sonuç:** Çalışmamız uyanık video-yardımlı torakoskopik cerrahinin güvenli, genel anestezi altında uygulanan video-yardımlı torakoskopik cerrahiye kıyasla benzeri güvenilirliği ve tanısal doğruluğu ve daha düşük maliyetli olduğunu gösterdi. Uyanık video-yardımlı torakoskopik cerrahi sadece komorbiditesi olan hastalarda değil, tüm hastalarda tercih edilen ilk yöntem olabilir.

**Anahtar sözcükler:** Uyanık, lokal anestezi, plevral efüzyon, torakoskopi, video yardımlı torakoskopik cerrahi.

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The first use of anesthesia during a surgical procedure was by William T.G. Morton in 1846, using ether. The first non-intubated thoracic surgery (NITS) procedures were reported by Vischnevski using local anesthesia and Buckingham using thoracic epidural anesthesia.<sup>[1,2]</sup> Single-lung ventilation in thoracic surgery was implemented by Carlens in 1952.<sup>[3]</sup> The use of double-lumen endobronchial tubes permitting single-lung ventilation has facilitated lung preparation and provided room to maneuver surgical instruments. In addition, the development of thoroscopic screening and endoscopic devices has also contributed to the increasing popularity of NITS in recent years.

Although the risks of general anesthesia have decreased, they are still important. Awake surgery, which is performed under spontaneous breathing with mild to moderate levels of anesthetic agents, further minimizes the potential risks of anesthesia. For this reason, awake video-assisted thoroscopic surgery (AVATS) is now gaining popularity. Awake VATS procedures are usually employed for pleural disease, wedge resections, and mediastinal biopsies.<sup>[4-7]</sup> Coughing and poor maneuverability due to diaphragm and lung movements limit its use for major surgical procedures. The experience of the surgical team can also be a factor.<sup>[8]</sup> In this study, we aimed to compare the safety and diagnostic accuracy of AVATS and intubated VATS in the diagnosis of pleural diseases.

## PATIENTS AND METHODS

This prospective, randomized study was performed between October 2016 and April 2018 with the participation of five centers, namely, Dicle University Medical Faculty, Trakya University Medical Faculty, Ondokuz Mayıs University Medical Faculty, and the thoracic surgery departments of the Health Sciences University Kartal Chest Diseases and Thoracic Surgery Training and Research Hospital and Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital. The study included 293 patients (201 males, 92 females; mean age 53.59 years; range, 18 to 90 years). The study protocol was approved by the Ethics Committee (version no. 3148/2016). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients who had undiagnosed pleural fluid or mass/nodule/thickening in the parietal pleura were included. Patients under 18 years old, those with pathologies of the visceral pleura or lung parenchyma, and those who did not consent to undergoing AVATS or did not have capacity to consent to the planned procedure were not

included. In addition, patients with pleural pathology for whom AVATS was preferred due to the high risk associated with their comorbidities were also excluded.

All patients were examined preoperatively by a pulmonologist and their routine laboratory tests, electrocardiograms, pulmonary function tests, chest X-rays, and thoracic computed tomography scans were evaluated. Cytologic, pathologic, microbiological, and biochemical evaluations of the pleural fluid samples were not diagnostic. Fiberoptic bronchoscopy and closed pleural biopsy were also performed on some patients but a diagnosis could not be established.

All cases were reviewed by a multidisciplinary council and the decision was established to perform biopsy for diagnosis. During the study period, patients with undiagnosed pleural pathologies had preoperative anesthesia consultation. Additional consultations were performed when needed and in the presence of comorbidities, and it was ensured that all patients could receive general anesthesia if required. Patients considered high-risk for general anesthesia were not included in the study.

The operating surgeon explained the study in detail to patients who were evaluated as candidates for both anesthetic methods. Patients were assigned sequentially to the two groups as 145 patients in AVATS and 148 in VATS groups. Oral intake was suspended for six hours before and for six hours after the operation. A single dose of 1.5 g cefuroxime axetil (Zinnat<sup>®</sup>) was given approximately 30 min before surgery as antibiotic prophylaxis.

Procedures were performed in the operating room with an anesthesiologist and anesthesia technician in attendance. Patients were placed in lateral decubitus position, the surgical site was cleaned three times with iodine, the entire area was covered with sterile drapes, and a sterile surgical field was prepared prior to the procedure. The surgeon performed aseptic surgical scrub and gowning, and preparations were made to enable conversion to general anesthesia if needed.

Patients underwent sedation induced by 0.05 mg/kg midazolam (Dormicum<sup>®</sup>), followed by remifentanyl (Ultiva<sup>®</sup>) 0.5 mg/kg bolus and 6 mg/kg/h infusion or propofol (Diprivan<sup>®</sup>) 0.5 mg/kg bolus and 3 mg/kg/h infusion. As a local anesthetic, 2.5 mL of 0.5% bupivacaine (Marcaine<sup>®</sup>) was applied to the incision site. Using a VATS approach, the pleural fluid was completely drained through a single incision approximately 2 cm in length and samples were obtained for cytologic, microbiologic, and biochemical analyses. A biopsy sample was then obtained from the

area of the pleura with apparent pathology, and a chest tube was placed through the existing incision. After all procedures, 2.5 mL 0.5% bupivacaine was applied to the port incision for local anesthesia. The mild sedation allowed communication between the patient and surgical team to be maintained periodically.

Patients in both groups underwent the same surgical procedures using the same surgical technique. The only difference between the procedures was that patients in the AVATS group had local anesthesia and sedoanalgesia while those in the conventional VATS group had general anesthesia. Patients who underwent general anesthesia were intubated using a double-lumen endobronchial tube.

In all patients, it was decided to immediately discontinue the procedure and terminate the operation if a life-threatening cardiac arrhythmia was detected intraoperatively. In the event of massive bleeding complication, thoracotomy under general anesthesia was planned for both groups to prevent life-threatening complications. For AVATS patients, intubation and conversion to general anesthesia were planned in the event of intraoperative severe pain, noncompliance, agitation, and hypoxia that would prevent proper completion of AVATS.

Postoperative pain was assessed using a visual analog scale (VAS) at 4, 8, 12 and 24 h after surgery. Postoperatively, patients were given tenoxicam once a day and 10 mg paracetamol infusion solution twice a day as analgesics and a weight-based dose of

enoxaparin sodium was given subcutaneously as an antithrombotic agent.

Awake VATS and VATS patients were compared in terms of operative time, reason for conversion to general anesthesia, complications, diagnostic accuracy, procedure cost, and patient satisfaction. Preoperative tests and analyses were not included in the calculation of cost. Operative cost included costs associated with the procedure performed and materials used in the operating room. In addition, postoperative cost was calculated based on the cost per bed-day and all procedures performed and medical materials used between surgery and discharge.

### Statistical analysis

Descriptive statistics were used in comparisons of demographic and clinical characteristics between the groups, while chi-square test, t-test, Mann-Whitney U test, and Kruskal-Wallis test were used to compare operative data, postoperative pathology, VAS values, and operative and total hospital costs. Statistical analyses were performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA) with *p* value <0.05 accepted as statistically significant.

### RESULTS

One hundred eighty-six (63.4%) patients had at least one comorbidity (hypertension, ischemic heart disease, diabetes mellitus, chronic obstructive pulmonary disease, renal failure). There was no difference between the groups in terms of presence of comorbidity (*p*=0.149).

**Table 1. Baseline characteristics of patients**

	Awake VATS			VATS			<i>p</i>
	n	%	Mean±SD	n	%	Mean±SD	
Total patients	145			148			
Age (year)			55.1±17.2			52.2±15.7	0.112
Gender							
Male	93	64.1		108	73		0.103
Comorbidities	47	32.4		60	40.5		0.149
Pleural disease							0.312
Unilateral	117	80.7		126	85.1		
Bilateral	28	19.3		22	14.9		
ASA score							0.172
1	31	21.4		37	25		
2	64	44.1		59	39.9		
3	42	29		50	33.8		
4	8	5.5		2	1.4		

VATS: Video-assisted thoracoscopic surgery; SD: Standard deviation; ASA: American Society of Anesthesiologists.

**Table 2. Comparison of operation characteristics of groups and visual analog scale pain scores**

	Awake VATS (n=145)		VATS (n=148)	
	Mean±SD		Mean±SD	<i>p</i>
Duration of surgery (min)	20.8±10.0		35.0±24.1	<0.001
Duration of anesthesia (min)	32.2±15.3		54.3±28.8	<0.001
Resected pleural tissue (cm <sup>2</sup> )	12.2±12.1		17.0±15.9	<0.001
VAS pain score				
at 4 hour	4.8±1.5		4.6±1.7	0.229
at 8 hour	3.7±1.7		3.5±1.4	0.910
at 12 hour	3.2±1.7		3.3±1.5	0.207
at 24 hour	2.5±1.7		2.7±1.7	0.144

VATS: Video-assisted thoracoscopic surgery; SD: Standard deviation; VAS: Visual analog scale (1-10).

American Society of Anesthesiologists (ASA) scores of physical performance were also similar between the groups (*p*=0.172). Pleural disease was unilateral in 83% (243/293) and bilateral in 17% (50/293) of the patients (Table 1).

Operative time and anesthesia time were shorter in the AVATS group (*p*<0.001 for both). Mean amount of pleura removed was 12.2 cm<sup>2</sup> (0.5-54 cm<sup>2</sup>) in the AVATS group and 16.97 cm<sup>2</sup> (1-90 cm<sup>2</sup>) in the VATS group (*p*<0.001). In the AVATS group, one patient (0.6%) was converted to general anesthesia due to refractory pain and agitation. Other than this case, there were no intraoperative complications in either group. As postoperative complications,

fluid drainage and pneumonia were observed in one patient in the AVATS group (0.6%) and fluid drainage was detected in one patient in the VATS group (0.6%). There were no differences in pain intensity measured with VAS at postoperative 4, 8, 12, or 24 h (Table 2).

The most common postoperative diagnosis in both groups was nonspecific pleuritis, in 54.6% (160/293) of the patients. This was followed by malignancies in 29.6% (87/293), tuberculous necrotizing pleuritis in 12.6% (37/293), and non-necrotizing granulomatous pleuritis in 2.7% (8/293) (*p*=0.171) (Table 3). Both operative cost and total hospital cost were lower in the AVATS group (*p*<0.001, *p*=0.001) (Table 4).

**Table 3. Postoperative diagnosis between two groups**

	Awake VATS (n=145)		VATS (n=148)		<i>p</i>
	n	%	n	%	
Postoperative diagnosis					
Non-specific pleuritis	88	60.7	72	48.6	
Malign disease	36	24.8	51	34.4	
Tuberculosis	18	12.4	19	12.8	0.171
Granulomatous disease	3	2.1	5	3.4	
Suspicious for malignancy	-	-	1	0.6	

VATS: Video-assisted thoracoscopic surgery.

**Table 4. Cost analysis of surgical procedures and total hospital stay**

	Awake VATS (n=127)		VATS (n=166)	
	Mean±SD (TL)		Mean±SD (TL)	<i>p</i>
Surgical cost	135.3±5.4		246.2±374.8	<0.001
Total hospital cost	589±448.8		911.2±893.6	0.001

VATS: Video-assisted thoracoscopic surgery; SD: Standard deviation; TL: Turkish lira (1 Turkish lira ≈ 0.2 USD).

## DISCUSSION

Video-assisted thoracoscopic surgery is a diagnostic and therapeutic tool used in the management of pleural, parenchymal, and mediastinal diseases. Although the risks of general anesthesia have been reduced to a minimum, AVATS has been reported to have significant cost advantage and offer a valuable alternative for patients with poor tolerance for general anesthesia.<sup>[4-7]</sup>

In our study, we considered it appropriate to use the term “awake VATS” for the surgical procedure we performed without general anesthesia. Terms such as “medical thoracoscopy” (MT) found in various publications are preferred by authors working in the field of interventional pulmonology. In some Turkish centers as well, AVATS is referred to as MT and performed by pulmonary medicine specialists. However, as the procedure is completely surgical, we believe using the term “medical” may be misleading. The term “medical” is used for noninterventional and noninvasive therapies. “Local anesthetic thoracoscopy” or “pleuroscopy” are other terms proposed for the procedure.<sup>[9]</sup>

A guideline published by the British Thoracic Society stated that because there are few thoracic surgeons in the UK and patients face long waiting times for surgery, thoracoscopy under local anesthesia can be performed by pulmonary medicine specialists on patients with pleural effusion who are awaiting diagnosis. This would reduce diagnostic delays and allow patients to undergo palliative treatments such as pleurodesis.<sup>[9]</sup> A report from the Mayo Clinic stated that collaboration between pulmonologists and thoracic surgeons is key in AVATS and the indication should be decided in conjunction with surgeons, and it was concluded that this technique can accelerate diagnosis and reduce the burden on the surgical ward.<sup>[10]</sup>

In Turkey, lack of thoracic surgeons is not an issue; in fact, it could be said that we have a surplus. Thoracic surgeons are easily accessible throughout Turkey, and waiting times for examination and surgery are not long. However, it is against legal, ethical, and medical principles for a doctor not trained in surgery to perform VATS, which is a surgical procedure. The doctor performing the procedure must be trained on how to respond to the potential complications and have both theoretical education and technical training. The Pulmonary Medicine Core Training Program of the standard Turkish medical curriculum does not include any training on this subject.<sup>[11]</sup>

Although the procedure seems simple, fatal complications can develop at any time. There are more risks and limitations if the AVATS procedure is performed outside the operating room. When a life-threatening complication occurs, interventions cannot be performed anywhere but in an operating room. In some publications, it is noteworthy that the pulmonologist performing the procedure is called the ‘operator’.<sup>[12]</sup> In a study performed in Turkey in 2013, a 41.4% complication rate was described as safe for this procedure. The authors stated that the complication rate and the fact that even minor complications require additional treatment increased the total procedure cost, and that high-risk cases must be handled by experienced physicians.<sup>[13]</sup>

In a meta-analysis including 47 studies, major complications (empyema, hemorrhage, port-site metastasis, bronchopleural fistula, postoperative pneumothorax, prolonged air leak, and pneumonia) were reported in 86 patients and death in 16 patients in a series of 4736 thoracoscopic procedures performed under local anesthesia. Minor complications included emphysema, minor hemorrhages, surgical site infection, intraoperative hypotension, fever, and atrial fibrillation reported in 177/2411 patients in 31 studies.<sup>[9]</sup>

When a port incision is performed in AVATS under spontaneous ventilation, intrapleural pressure and atmospheric pressure are equalized, causing a decrease in lung volume to the level of functional residual capacity. The intrapleural space resulting from this volume reduction provides adequate space for maneuvering surgical instruments. However, this space should not be expected to be as large as the total lung collapse created in general anesthesia. Diaphragmatic and mediastinal movements that can occur due to coughing and pain can make the procedure difficult. Moreover, the presence of dense pleural adhesions may make the procedure even more challenging.<sup>[6]</sup> Constant communication between the surgeon and anesthesiologist during the procedure is critical.<sup>[14]</sup>

The presence of extensive and dense pleural adhesions is considered the main contraindication for some awake surgical procedures.<sup>[14]</sup> Although some AVATS studies in the literature reported no need to convert to general anesthesia,<sup>[15]</sup> the conversion rate usually ranges between <1% and 9% (mean 2.4%).<sup>[16,17]</sup> In a series of 101 patients who underwent AVATS due to pleural effusion, conversion to general anesthesia was required due to refractory cough in three patients and dense pleural adhesions in one patient.<sup>[18]</sup> Pompeo et al.<sup>[19]</sup> cited patient’s refusal of awake anesthesia and radiologic evidence of extensive pleural adhesions with

pleural scarring and calcifications as contraindications for awake bullaplasty, and reported conversion to general anesthesia in one of 39 patients due to severe adhesion. We also observed similar situations in our cases but encountered no complications because the procedure involved only pleural biopsy and all of the operating surgeons were experienced. No patients in our study required conversion to general anesthesia due to pleural adhesion; only one patient was converted due to intraoperative anxiety and pain.

Although the application of local anesthetic to the pleural cavity to alleviate pain during AVATS has been reported, it is not recommended because its analgesic effect is still controversial.<sup>[20]</sup> Another factor that limits the use of local anesthetic is that its absorption in the pleural cavity is not uniform, which can lead to toxicity.<sup>[21]</sup> We attribute our low conversion rate (0.8%; 1/127) to the fact that pleural biopsy is a relatively simple procedure compared to the other AVATS procedures in the literature.

Awake VATS has been proposed as the method of choice for older patients and those with comorbidities, particularly ASA III-IV patients.<sup>[17,22]</sup> AVATS involves less surgical stress and faster postoperative recovery.<sup>[4,5,23]</sup> These are clear advantages in patients of advanced age. The technique was also reported to have more positive effects on the immune system, lymphocytes, and natural killer cells.<sup>[24]</sup> Considering that lymphocytes provide resistance against postoperative infections and natural killer cells likely play a role in first-line defense against neoplasia, we can say that awake surgery is much less traumatic for the immune system and enables more rapid healing.

In a study by McDonald *et al.*<sup>[25]</sup> comparing AVATS and VATS in the diagnosis of pleural effusion, rates of nonspecific pleuritis diagnosis were 43.8% and 24.2%, respectively. The authors defined nonspecific biopsy results as acute or chronic inflammation, reactive mesothelial cells, pleural fibrosis, organizing fibrinous pleuritis, and normal pleura. They reported that malignant disease was detected in 10-20% of patients diagnosed with nonspecific pleuritis within 24 months of follow-up, emphasizing the importance of clinical follow-up. In the present study, we did not observe transformation to malignant or specific disease in any patients with nonspecific pleuritis during at least 12 months of clinical follow-up. Patients with malignant pleural effusion usually have comorbidities and therefore, intubation can be risky in these patients.<sup>[26]</sup> Based on our experience, AVATS can easily be performed in these patients because lung

collapse accompanies a chronic process in patients with malignancy.

Our study has some limitations. Because it was a multicenter study, the procedures were performed by multiple surgeons. Furthermore, extending clinical follow-up time in patients with nonspecific pleuritis may have led to specific diagnoses.

In conclusion, our study showed that awake video-assisted thoracoscopic surgery is safe, has similar reliability and diagnostic accuracy compared to video-assisted thoracoscopic surgery performed under general anesthesia, and is less costly. Therefore, it can be the first choice not only in patients with comorbidity, but in all patients.

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