UNIVERSITA' degli STUDI dell'INSUBRIA

DOTTORATO di RICERCA in SCIENZE della VITA e BIOTECNOLOGIE

XXXII Ciclo

Evaluation of a new ultrasonic device for surgical dissection in lung lobectomy and lymphadenectomy for lung cancer

Docente guida: Prof. Andrea Imperatori

Tutor: Prof. Nicola Rotolo

Tesi di dottorato di

Maria Angela Cattoni

Mart:70083

Dipartimento di Biotecnologie e Scienze della Vita – Università degli Studi dell'Insubria

Anno Accademico: 2018-2019

Contents

Introduction

Lung cancer: overview of incidence, risk factors, treatment and survival

In the last century lung cancer incidence has progressively increased, becoming the most common diagnosed cancer (GLOBOCAN 2018 estimates: 11.6% of 18.1 million new cancer cases) and the leading cause of cancer-related death (GLOBOCAN 2018 estimates: 18.4% of 9.6 million cancer-related deaths), worldwide [1-3].

Focusing on our country, the estimated new cases of lung cancer in Italy in 2018 are 27,900 for men and 13,600 for women, for a total of 41,500 (11% of 373,300 new cancer cases) [4]. Thus, lung cancer is the third most commune cancer in Italy after colorectal (14%) and breast cancer (14%) [4].

Lung cancer rarely involves men and women <50 years old. If fact, concentrating on Italian data, only 5% and 2% of all cancer are represented by lung tumor respectively among men and women before their 50s [4]. Conversely, lung cancer is the 2nd most common cancer among men between 50-69 years old (14% of all cancers) and $\geq$70 years old (17% of all cancers) after bladder cancer [4]. Likewise, it is the 3rd most common cancer among women between 50-69 years old (7% of all cancers) and $\geq$70 years old (7% of all cancers) after breast and colorectal cancer [4]. Interestingly, the incidence of lung cancer among women has been continuously rising since the mid 1970s, leading its total annual incidence to increase of +1.7% between 2006 and 2014 [5]. This impressive rise is due to a simultaneous increase of female smokers' number which has reached 5.7 million (19.2% of all women) in 2018 [4].

As known, cigarette smoking is the main risk factor for lung cancer, with 85-90% of all lung tumors attributable to this habit [1-3,5]. Lung cancer risk increases with number of cigarettes smoked per day and smoking duration. In fact, it is about 14 times higher in smokers than never

smokers and more than 20 times higher in heavy smokers (people smoking ≥20 cigarettes per day) [1-3,5].

Other factors associated with increased lung cancer risk include ionizing radiation, environmental toxins, such as secondhand smoke, radon, metals (arsenic, chromium, and nickel) and polycyclic aromatic hydrocarbons [1-3,5-8]. Moreover, also history of pulmonary fibrosis, human immunodeficiency virus infection, and alcohol consumption have been defined as risk factors for lung cancer [1-3,5-8].

Regarding mortality, lung cancer is the leading cause of cancer-related death worldwide [1-3]. In detail, in Italy, it is the first cause of death for cancer among men (26% of all cancer deaths) and the 3rd cause of cancer-related death among women (11% of all cancer deaths) [5]. It has been estimated that 1 every 11 men and 1 every 46 women are at risk of dying for lung cancer during their life, with an overall of 33,836 deaths for lung cancer recorded in Italy in 2015 [5]. Unfortunately, the most of lung cancer cases (>50%) are detected in advanced stage, with few treatment options available and with a consequently poor survival (advanced lung cancer 5-year survival: 5%), despite significant advances continue to be made and treatment has become nuanced and specific for particular histologic subtypes, clinical patient characteristics and presence of specific genetic mutations [5-9]. This explain why lung cancer has one of the lowest survivals, with 5-year relative survival rate for all stages combined of 15.8% [5].

This suggest the importance of diagnosing lung cancer in early stage, when it is still asymptomatic and it hasn't yet spread to mediastinal lymph nodes and/or distant organs, in order to treat and cure it, improving patients' prognosis. To date, radical surgery is still the treatment of choice for lung cancer. In depth, there are two main forms of lung cancer: non-small cell lung cancer (NSCLC) (85% of all lung cancer patients) and small cell lung cancer (15% of all lung cancer patients). Small cell lung cancer, with its high proliferation rate, is

highly aggressive and most of patients already have distant occult metastases at time of presentation with surgery indicated only in selected cases and always as part of a multimodal therapy which combines surgery, chemotherapy and radiotherapy [10]. Conversely, surgery is the "gold standard" treatment for potentially resectable NSCLC. In detail, if at preoperative evaluation, no distant metastases has been detected and no mediastinal lymph nodes are involved by tumor (clinical stage I or II) or if tumor has already metastasized only to one ipsilateral mediastinal lymph node station (clinical stage IIIA "single station") tumor surgical resection is suggested as first treatment approach (NSCLC 8th edition TNM Staging System is explained at pages 38-40) [11,12,13]. Overall 5-year survival rate of NSCLC patients undergoing tumor surgical resection is more reassuring than that one of patients not fit for surgery, and is 80-90% for pathological stage IA disease, 73% for stage IB, 65% for stage IIA and 56% for stage IIB, with a worse prognosis for poorly differentiated tumor, tumor with size >4 cm, presence of pleura infiltration and/or neuro-vascular invasion [11,13].

Non-small cell lung cancer surgery: indications, surgical procedures and postoperative outcomes

After stating tumor surgical resection as the cornerstone of non-small cell lung cancer (NSCLC) treatment, we move our attention on principles of lung cancer surgery.

First, surgery should be considered only for potentially resectable NSCLC (clinical stage I-II disease and clinical stage IIIA disease only in selected cases), and it should be realized with the purpose of obtaining a R0 (no residual tumor) resection.

Thus, an accurate preoperative tumor staging by chest computed tomography scan, 18F-fluorodeoxyglucose positron emission tomography and brain computed tomography scan/magnetic resonance imaging is fundamental to assess the presence of lymph nodes and distant metastases (liver, adrenal glands, bones and brain) before surgery.

Whenever mediastinal lymph nodes are >1 cm in size at computed tomography scan and/or have positive uptake at 18F-fluorodeoxyglucose positron emission tomography and/or primary tumor is closed to lung hilar structures and/or it is >3 cm in size and/or hilar/intraparenchymal lymph nodes are suspicious for metastases, mediastinal lymph nodes assessment by endobronchial ultrasound-transbronchial needle aspiration or video-assisted mediastinoscopy is required [11,12,14].

If no distant metastases are detected and no mediastinal lymph nodes are involved by tumor (clinical stage I or II) or if tumor has already spread, but only to an unique ipsilateral mediastinal lymph node station (clinical stage IIIA “single station”), tumor surgical resection and hilar-mediastinal lymph nodes dissection is suggested as the first step in NSCLC treatment process [11,12].

After assessing tumor histology (small cell versus non-small cell) and extension (stage), it is mandatory to evaluate patient age, comorbidity and respiratory function in order to determine whether an individual patient is able to cope with reduced pulmonary and vascular reserve

capacity after surgical resection and to maintain an acceptable quality of life. For those patients who are not willing to accept surgery-related risks, or are at high risk for surgery, alternative local therapy as curative radiotherapy (either stereotactic ablative body radiation therapy or hypofractionated high-dose radiotherapy) or radiofrequency/microwave ablation should be offered [11,12].

Regarding surgical procedure itself, lung lobectomy (surgical resection of a single lung lobe) with hilar-mediastinal lymphadenectomy is still considered the standard surgical treatment of NSCLC [12].

However, two phase III randomized trial (CALGB 140503 and JCOG0802/WJOG4607L) comparing lung lobectomy to lung sublobar resection [either segmentectomy (surgical resection of a lung segment) or wedge resection (non-anatomical sublobar lung resection)] for NSCLC $\leq$2 cm are still ongoing and in the next years they are disclosing if lung sublobar resection is comparable to lung lobectomy in terms of disease-free survival, overall survival, patterns of tumor recurrence and postoperative pulmonary function, maybe changing surgical approach to NSCLC $\leq$2cm [14-16].

Concerning hilar-mediastinal lymphadenectomy, it is admitted that nodal staging of NSCLC should be as accurate as possible and intraoperative mediastinal lymph node assessment is mandatory to improve nodal staging itself and patients' survival. Though, the extent of mediastinal lymphadenectomy is still controversial and different techniques ranging from mediastinal lymph node sampling to systematic lymph node dissection could be employed.

Sampling is the removal of one or more lymph nodes guided by preoperative or intraoperative findings which are thought to be representative. Systematic sampling means a predetermined selection of the lymph node stations specified by surgeon. Systematic nodes dissection consists in dissecting and removing all the mediastinal tissue containing lymph nodes systematically

within anatomical landmarks. Finally, lobe-specific systematic nodes dissection is defined as the excision of mediastinal tissue containing specific lymph node stations depending on lobar location of primary tumor (i.e. in right upper lobe NSCLC cases, a part of subcarinal nodal station, upper and lower right paratracheal nodal stations should be dissected and removed) [17].

Since the management of lymph nodes during surgery is mainly dictated by the staging requirements for guaranteed "R0 resection" status, it is recommended that at least six nodes/stations, three of which should be mediastinal nodal stations (but always subcarinal station) should be excised as a minimum requirement [12,18,19].

While in stage I NSCLC overall survival, loco-regional and systemic recurrence rate are not influenced by intraoperative mediastinal lymph node assessment technique, systematic nodal dissection is recommended in stages II and IIIA despite it has been demonstrated that complete mediastinal lymphadenectomy adds little morbidity to pulmonary resection for lung cancer [12 ,20,21].

Whether surgery should be performed through standard open thoracotomy or video-assisted thoracoscopic surgery (VATS) procedure, is probably less significant from oncological perspective, since comparative margin clearance and nodal dissection can be achieved [12 ,22]. However, the introduction of VATS has led to reduction of postoperative morbidity, length of stay and, in some studies, of mortality when compared to open thoracotomy, probably as a consequence of tissue injury and stress response minimization due to the mini-invasive approach [23-25]. These promising results have allowed a rapid diffusion of this technique that is widely preferred to thoracotomy almost in all experienced centers.

Despite VATS improvement of patients' postoperative outcomes, mortality and morbidity at 30 days after VATS lobectomy for NSCLC are not negligible, ranging between 0-2.7% and 6-

36.6%, respectively [26-28]. The most frequent postoperative complications are atrial fibrillation (2.9-12%), persistent air leak (15-18%) pneumonia (6%), hemothorax (2.9%), chylothorax (0.7-2%) middle lobe torsion (0.09-0.4%), phrenic and recurrent laryngeal nerve injury (<1%) [26-29].

Video-assisted thoracoscopic surgery lobectomy and lymphadenectomy technique

Despite video-assisted thoracoscopic surgery (VATS) lobectomy and lymphadenectomy can be performed using up to five incisions, the fundamental steps to realize this procedure are similar even using different ports number and different approach (anterior\posterior).

In all anterior approaches, the camera port (5 to 10 mm) is typically placed low in the chest (7^{th} or 8^{th} intercostal space), either in the mid or anterior axillary line and 30 degrees camera is used to have a complete view of the surgical field [30-33]. A "utility" incision (3 to 6 cm) is usually placed anterior to latissimus dorsi muscle, over the anterior hilum and the major pulmonary vessels (4^{th} or 5^{th} intercostal space). A soft tissue retractor is often used at this incision to protect surrounding tissue [30-33]. Third, fourth and fifth incisions (10 mm) are placed either high in the mid-axillary line, or low in the chest in the posterior axillary line. In all cases, no rib spreading is used at any of incision sites and only monitor based vision is allowed (Figure 1) [30-33].

In case of uniportal VATS, a unique incision (3-6 cm) is performed anterior to latissimus dorsi muscle at 5^{th} intercostal space. A soft tissue retractor is used at this incision where camera is placed at the top and the other instruments at the bottom [34-35].

For the posterior approach "utility" incision is made anterior to latissimus dorsi muscle at 6^{th} or 7^{th} intercostal space instead of 4^{th} intercostal space and the camera port is made through the auscultatory triangle, instead of lower anterior incision [36].

Tissue dissection starts at lung hilum where mediastinal pleura is incised over the anterior and posterior aspect of the hilum to provide anatomic structure exposure. During this procedure vital structures such as phrenic and recurrent laryngeal nerves should be identified early and

preserved [30,33,34,36]. Tissue dissection is performed by dissectors, forceps, graspers, suckers, scissors, "sponge-sticks" and energy devices (Figure 2-3).

Pulmonary vessels (veins and arteries) and bronchi within the hilum are ligated with endoscopic staplers. Alternatively, small vessels (5-7 mm) can be clipped and dissected or coagulated and transected by energy devices [30,33,34,36].

Fissures are usually stapled unless complete, in which case cautery may be used. In order to better manage incomplete fissure and to minimize the risk of prolonged postoperative air leak, surgeons prefer to perform the "fissure-less technique". This technique consists in a progressive dissection of hilar structures and in stapling the involved fissure last with the visceral pleura intact as a seal above the parenchyma, giving a tighter closure within the stapling line, and no scars in the tissue next to the clips [30,33,34,36].

Specimen is removed using a specimen bag, to minimize contact with soft tissues at the "utility" incision site and to consequently reduce incidence of "port-site" recurrence.

Removal of hilar and lobar lymph nodes is performed during hilar structures ligation (Figure 4). For mediastinal lymph nodes, in right-sided procedures, the pleura is opened above and under the azygos vein. Right upper and lower paratracheal lymph nodal stations "en-bloc" dissection begins at the tracheobronchial angle and progresses upwards under the azygos vein in order to clean off all the fatty tissue of the superior mediastinum [30,33,34,36].

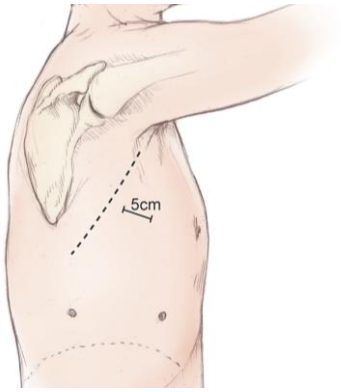
On the left side, lymph nodes are removed "en-bloc" from subaortic and paraaortic stations, excising the greasy tissue between the aorta and the main pulmonary artery, after recurrent laryngeal nerve identification.

In both right and left sides, subcarinal lymph nodes are approached after dividing the inferior ligament and opening the pleura on the posterior limit of the lung up to the carina. In this way subcarinal nodes are exposed and all the fatty tissue at this level is removed so that carinal bifurcation and opposite bronchus are clearly visible [30,33,34,36]. Finally, paraesophageal and

pulmonary ligament lymph nodes are removed during pulmonary ligament division and hilar structure dissection.

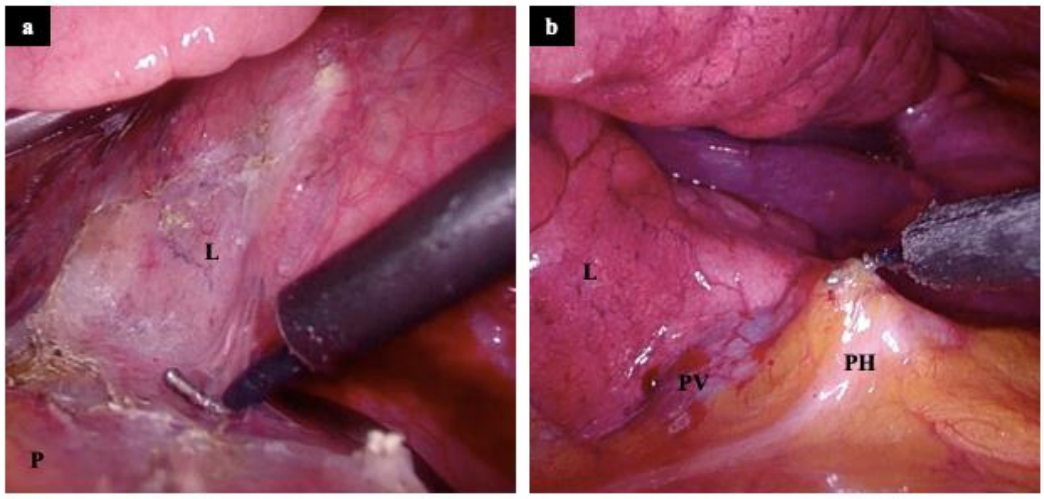
At the end f the surgical procedure, one intercostal drain is placed in through the camera incision or through “utility” incision if uniportal VATS is performed. The drainage is left in place till there is no air-leak and less than <5 mL/kg of fluid after 24 hours according to the last Italian enhanced recovery after surgery guidelines [37].

Figure 1 Three-port video-assisted thoracoscopic lobectomy and lymphadenectomy [33]



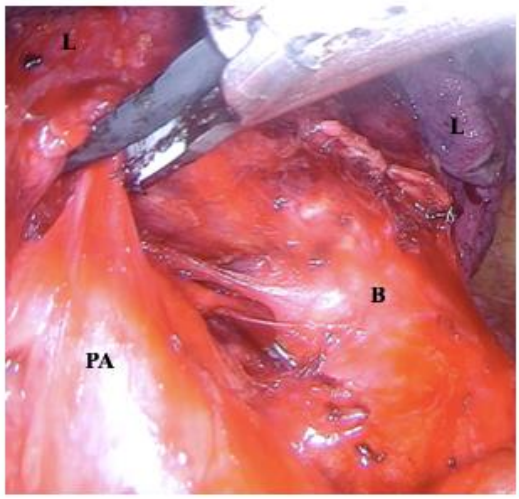
The 5 cm "utility" incision anterior to latissimus dorsi muscle at 4^{th}-5^{th} intercostal space and the other two incision at the bottom (the anterior one is the camera port).

Figure 2 The use of electric hook (monopolar device) in adhesiolysis (a) and hilar structure dissection (b).



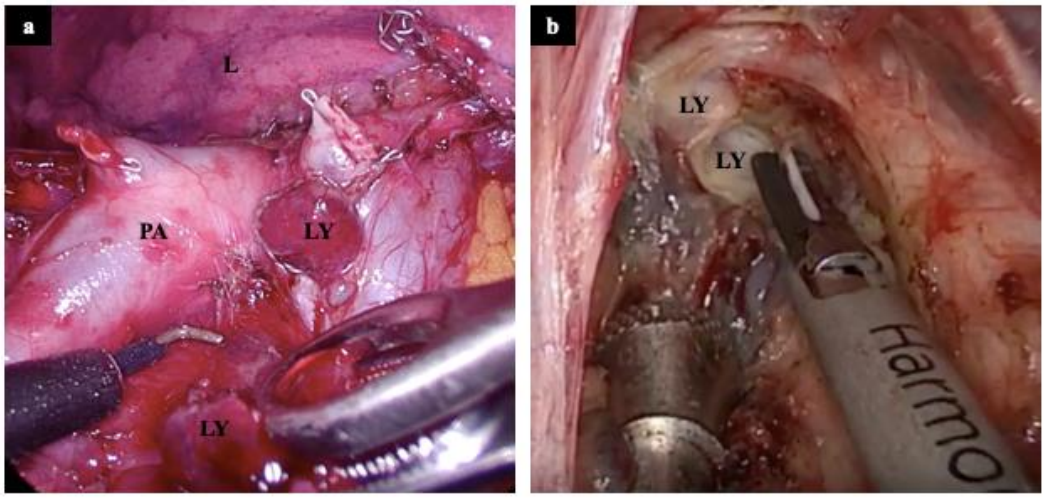
L=lung lobe; P=pericardium; PH=phrenic nerve; PV=pulmonary vein.

Figure 3 The use of the Harmonic ACE Plus® (ultrasonic device) in hilar structure dissection.



B=right upper lobe bronchus; L=lung lobe; PA=pulmonary artery.

Figure 4 Interlobar lymph nodes dissection by electric hook (monopolar energy device) (a) and by Harmonic ACE Plus® (ultrasonic device) (b).



L=lung lobe; LY=lymph node; PA=pulmonary artery.

Energy devices in video-assisted thoracoscopic lobectomy and lymphadenectomy: monopolar and ultrasonic instruments

Since the first electrosurgical unit was created by Dr William T. Bovie and Dr Harvey W. Cushing in 1920, there have been important improvements in energy device field and several different instruments have been introduced in thoracic surgeons' daily practice in order to cut, dissect tissue and seal vessels [38]. However, most surgeons are still not familiar with the technology behind them, or their applications [39,40].

During video-assisted thoracoscopic (VATS) lung lobectomy and lymphadenectomy, energy devices are employed with different purposes: division of pleural adhesions, hilar structures dissection, small vessels coagulation and transection and lymph nodes dissection and removal. Several devices with different technology have been using during this surgical procedure. In this session we are focusing only on the electric hook (Figure 4) and the Harmonic ACE Plus® (Figure 5) (Johnson & Johnson Medical).

The electric hook (Figure 4) is a monopolar energy device and it directly uses high-frequency electric current to cut tissue and coagulate vessels [41]. The electric current flows from the generator to the active electrode (the device itself) and, passing through the patient, concludes the electric circuit reaching the dispersive cautery pad [40]. In detail, heat production by electric current concentration in a small tissue area (the area touched by the instrument itself) leads to tissue thermal damage and to the majority of the tissue effects in electrosurgery: coagulation occurs when tissue is heated below the boiling point and undergoes thermal denaturation; desiccation when a slow temperature increase leads to vaporization of tissue water; fragmentation and cutting when a sudden increase in tissue temperature above the boiling point causes rapid explosive vaporization of tissue water [41]. Thus, electrocautery can be used for

tissue dissection, but alone it is inefficient and potentially inappropriate for larger (>3 mm) parenchymal blood vessels sealing and division.

One of the recent advancements in surgical devices for cutting and coagulating tissue has been the introduction of the Harmonic ACE Plus® (Johnson & Johnson Medical) (Figure 5): an ultrasonic surgical instrument for cutting and coagulating tissue, operating at a frequency of 55.5 kHz oscillations per second. There is no electrosurgical current generated. The combination of mechanical energy due to its blade tip oscillations and the heat that is generated causes protein denaturation and formation of a coagulum that seals blood vessels up to 5 mm in diameter and up to 7 mm in the new device version Harmonic ACE®+7 [42-45]. Moreover, the blade tip vibrations produce large transient pressure changes, which causes cellular low temperature water vaporization with consequently cells rupture, and tissue stretching with molecular bands separation, leading to an accurate cutting and dissection.

With their different technology, electric hook and Harmonic ACE Plus® have a different impact on target tissue but mainly on surrounding structures [46-50]. In evaluating energy device performance to test the lateral thermal spread is fundamental because it is a measurement of the device potential damage to surrounding sensitive structures including vessels and nerves [48-50]. The degree of lateral thermal spread varied by instrument type, power setting and application time. Recent studies have showed that monopolar instruments result in a greater degree of thermal damage when compared to ultrasonic devices which has a lateral thermal damage of about 3 mm [48-50]. However, this difference does not imply a higher risk of intraoperative complication due to energy device itself, suggesting that surgeon's awareness about instruments technology and application within the use of protected-tip cautery may balance these devices different effects [46-47].

In the literature, some study has been published with the aim of evaluating vessel sealing technology devices efficacy but no study focuses on comparing Harmonic ACE Plus® to the more commune electrosurgical devices, in terms of postoperative blood\lymph leaks, postoperative morbidity and postoperative length of stay after VATS pulmonary lobectomy and lymph node dissection for non-small cell lung cancer has been reported yet [42,51-55]. A similar study comparing bipolar to monopolar devices in VATS pulmonary lobectomy and lymph node dissection is still ongoing and it is going to reveal its first results after 2020 (NCT03125798) [56].

Figure 4 The surgical electric hook.

Figure 5 The Harmonic ACE Plus®.

Objectives

This study aims to assess and compare surgical electric hook vs Harmonic ACE Plus® impact on short-term postoperative outcomes after video-assisted thoracoscopic surgery pulmonary lobectomy and lymph node dissection for non-small cell lung cancer.

Materials and methods

We prospectively collected data of consecutive patients who underwent lung lobectomy and lymphadenectomy in our Center from October 1st 2016 to July 31th 2019. We excluded patients undergoing surgery for benign disease or for lung metastases; those requiring conversion from video-assisted thoracoscopic surgery (VATS) to thoracotomy or approached by thoracotomy; those undergoing extended resection to chest wall, mediastinum and another lung lobe and those requiring the use of more than one dissecting devices.

This study was approved by our Center Ethic Committee and individual patient consent was obtained for each patient.

All lung lobectomies and lymph node dissections were performed using the standardized three-port anterior approach [33]. All the procedures were performed by experienced surgeons who had already completed the learning curve for VATS lobectomy and lymphadenectomy. A chest tube of 28 French in size was left in place after surgery until no air-leak was observed and secretion quantities was $\leq$250 ml/day. During the postoperative stay all patients were managed according to our Center standardized protocol which provides: perioperative respiratory physiotherapy; epidural analgesia/paravertebral block in association with non-steroidal analgesic painkillers for pain control; antithrombotic prophylaxis; intravenous fluid restriction; early oral feeding (on the day of surgery or postoperative day 1); early urinary catheter removal (on postoperative day 1), early ambulation (on postoperative day one).

For each patient we collected the following records: age, gender, body mass index (BMI), smoking habit, comorbidities, forced expiratory volume in 1 second (FEV_1), diffusion capacity for carbon monoxide (DLCO), surgical procedure, surgery duration, tumor histology and size, number of dissected lymph nodes, tumor pathological stage according to the 8th edition TNM

staging system, pleural effusion volume during the first 48 postoperative hours, postoperative chest tube stay, postoperative length of stay and 30-day postoperative complications.

Patients were divided in two groups based on the device used for tissue dissection during surgery: the electric hook (Group A) or the Harmonic ACE Plus® (Group B). All surgical procedures were performed by experienced surgeons. The use of electric hook or Harmonic ACE Plus® was left to devices availability and to surgeon preference.

Patients' clinical and pathological characteristics were compared between Group A and Group B.

The benchmarks used to evaluate and compare the impact of electric hook to the one of Harmonic ACE Plus® on postoperative course were postoperative hemo/chylothorax incidence, pleural effusion volume during the first 48 postoperative hours and postoperative chest tube duration.

Univariable and multivariable analyses were performed in order to test energy device as possible independent risk factor for pleural effusion volume during the first 48 postoperative hours and for postoperative chest tube duration. Factors analyzed were age, gender, BMI, cardiac comorbidities, FEV_1, DLCO, pleural adhesiolysis, number of resected lymph nodes, energy device (Harmonic ACE Plus® versus electric hook), site of resection (upper/middle lobe lobectomy vs lower lobe lobectomy), surgery duration, postoperative persistent air-leak (>5 days after surgery).

Continuous data were reported as median with interquartile range (IQR) and compared using T-test for normally distributed data and Mann–Whitney U test for non-normally distributed

data. Categorical and count data were presented as frequencies and percentages and compared using Chi-square test or Fisher's exact test if any expected frequency was less than 5. Univariable and multivariable analyses were performed by binary logistic regression, using as cut-off value of dependent variable its median value. Significant factors at univariable analyses were included in multivariable analyses. A p-value <0.05 was considered significant. Statistical analysis was performed using SPSS 24.0 software (IBM Corp, Armonk, NY).

Results

During the study period, 184 patients underwent lung lobectomy in our Center. According to study exclusion criteria, 64 patients were excluded from the study for the following reasons: 43 patients were approached by thoracotomy, 10 patients underwent surgery for benign disease or for lung metastases, 6 patients required conversion from video-assisted thoracoscopic surgery (VATS) to thoracotomy (2 intraoperative bleeding, 2 locally advanced disease and 1 lung failure to collapse) and in 5 cases surgeon used both devices. Thus, 120 patients were left for statistical analysis.

All patients underwent VATS lung lobectomy and lymphadenectomy for non-small cell lung cancer. Tissue and lymph nodes dissection were performed by electric hook in 68 cases (Group A) and by Harmonic ACE Plus® in 52 cases (Group B).

Group A and B patients' clinical characteristics are listed in Table 1. No patients reported coagulopathy, liver cirrhosis or renal failure in their past medical history in both groups. No difference in terms of clinical data were detected between the two groups (Table 1).

Pleural adhesiolysis was required in 40 (33%) cases: 21 (31%) in Group A and in 19 (37%) in Group B (p-value=0.51). Surgery involved the right upper lobe in 38/120 patients (32%), middle lobe in 9 (7%), right lower lobe in 25 (21%), left upper lobe in 28 (23%) and left lower lobe in 20 (17%). Tumor lobe distribution was significantly different between Group A and Group B (p-value<0.01) with a lower rate of lower lobectomies in Group A (25% vs 54% Group B) (Table 2). A median of 3 (IQR: 3-4) N1 and N2 lymph node stations were dissected during surgery, with no difference in terms of overall number of lymph node excised between the two groups [Group A vs Group B: 8 (6-10) vs 8 (5-12); p-value=0.44]. Overall surgery duration was 195 minutes (IQR: 170-235). Surgical procedure lasted more time in Group B than in Group A: 214 (IQR: 190-261) vs 180 (IQR: 164-211) minutes, respectively (p-value<0.01).

Overall intraoperative leak was ≥100 ml in 29 (27%) patients with no differences between Group A and Group B [15 (23%) vs 14 (33%) patients respectively; *p*-value=0.26]. This data was not reported in 11 cases. No intraoperative complications due to energy device use were recorded in both groups.

Final pathological results are reported in Table 2. Group A and Group B tumor size, histology and pathological stage distribution were comparable (Table 2).

Overall 30-day mortality was 0.8% (1/120): 1 patient of Group A died of pulmonary embolism. However, no significant difference in term of 30-day mortality was detected between the two groups (1.5% vs 0%; *p*-value=1.00).

Overall 30-day morbidity was 31% (37/120). During postoperative stay 24/120 (20%) patients developed persistent air leak (>5 days), 8 (7%) pneumonia, 3 (3%) atrial fibrillation, 2 (2%) chylothorax. No postoperative hemothorax was reported. Chylothorax incidence was higher in Group A than Group B, with no statistically significant difference between the two groups (3% vs 0%, respectively; *p*-value=0.50).

Pleural effusion volume during the first 48 postoperative hours was significantly higher in Group B than in Group A: 253 ml (IQR: 149-405) vs 408 (IQR: 294-508) ml respectively; *p*-value<0.01. However, chest tube duration was similar in Group A and Group B: 4 (IQR: 3-8) days vs 5 (IQR: 4-8) days; *p*-value=0.39. Likewise, there was no difference in terms of postoperative length of stay between the two groups: 7 (IQR: 5-9) days vs 7 (IQR: 6-9) days; *p*-value=0.65.

At multivariable analysis energy device was not independently associated with pleural effusion volume during the first 48 postoperative hours and with postoperative chest tube duration (Table 3-4).

Discussion

The use of energy devices during surgical procedure has been increasing since their invention in 1920 [38]. To date several energy tools, some of which have similar applications but different technologies, have been introduced in different surgical fields. In thoracic surgery and particularly in video-assisted thoracoscopic (VATS) lobectomy and lymph nodes dissection, energy devices are employed during almost all the surgical procedure for adhesiolysis, hilar structures dissection, small vessels sealing and finally for lymph nodes removal.

Different energy tools can be used during this surgical procedure (i.e. electric hook, Harmonic ACE Plus®, LigaSure^{TM}, Enseal®). However, no studies have compared the performance of different energy devices in terms of short-term outcomes after VATS lobectomy and lymphadenectomy and only few studies have evaluated and compared their efficacy in sealing pulmonary vessels, in non-human and human models [42-45].

In this study we've compared the impact of electric hook (monopolar device) to Harmonic ACE Plus® (ultrasonic device) on short-term outcomes after VATS lobectomy and lymphadenectomy for non-small cell lung cancer.

The use of either electric hook or Harmonic ACE Plus® during adhesiolysis, hilar structure dissection and lymph nodes dissection is safe, with no intraoperative complications related to the use of one or the other energy device reported. During the postoperative stay, despite the significant pleural effusion volume increase during the first 48 postoperative hours after using Harmonic ACE Plus®, no statistically significant difference in terms of chylothorax incidence, chest tube duration and length of stay has been detected between electric hook and Harmonic ACE Plus®. Moreover, energy device was not recognized as an independent risk factor of either increased pleural effusion volume during the first 48 postoperative hours or prolonged postoperative chest tube duration.

In this study no intraoperative complications due to energy device have been recorded. This supports literature data which estimates that surgical energy injuries occur only in 1-2 per 1,000 operations (0.1-0.2%) [46]. Energy devices complications are generally due to four main causes: thermal burn, hemorrhage, mechanical failure, and fire. Thermal burn, that is the result of direct application, dispersive electrode burns or insulation failure, is the most common reason for both injury and death and it has an incidence of 3% in thoracic surgery [47]. In our study no intraoperative injuries due to thermal burn has occurred despite the well-known higher lateral thermal spread of monopolar than ultrasonic device [48-50]. This suggests that surgeon awareness of energy device application, technology and common injury patterns within the use of protected-tip cautery is essential to minimize complications due to these instruments.

No statistically significant differences were detected also in postoperative chylothorax and hemothorax incidence after using monopolar and ultrasound device. However, chylothorax rate was slightly higher after using electric hook than Harmonic ACE Plus® (3% vs 0%, respectively; *p*-value=0.50). This difference, despite not statistically significant, could be explained by devices application. Electric hook has been created with the aim of cutting and coagulating tissue, sealing vassels <3 mm, while Harmonic ACE Plus® has been created with the purpose of providing a strong and secure sealing in vessels up to 5 mm in diameter and up to 7 mm with its last version (Harmonic ACE®+7) [48,50,51]. This different performance could justify electric hook higher incidence of postoperative lymph leaks.

Conversely, a significantly higher pleural effusion volume during the first 48 postoperative hours was detected after using the ultrasonic tool. However, multivariable analysis identified lower lung lobectomies, increased surgery duration and cardiac comorbidities but not energy device as risk factors for increased fluid leak during 48 hours after surgery. This suggests that the higher pleural effusion volume detected during the first 48 postoperative hours after using

Harmonic ACE Plus® may be due to the higher rate of lower lung lobectomies and the prolonged surgery duration reported in the ultrasonic device group.

Additionally, chest tube duration was similar after using electric hook and Harmonic ACE Plus®, even when the two groups has been adjusted for other possible risk factors for prolonged postoperative chest tube stay at multivariable analysis. This suggests that, beside the two cases of chylothorax in monopolar device group, higher pleural effusion volume during the first 48 postoperative hours in Harmonic ACE Plus® group and devices slightly different purposes, both instruments have a comparable performance in controlling postoperative fluid production, that is generally due to both pleural irritation and hilar structures-lymph nodes dissection.
The similar chest tube duration resulted in an absence of difference in terms of postoperative length of stay between the two devices groups because, besides postoperative complications, the main factor driving discharge is chest tube length of stay.

The only difference we observed in the usage of monopolar and ultrasonic devices was surgery duration: surgery lasted longer in Harmonic ACE Plus® group. We try to explain this difference taking into consideration instruments and surgical procedure characteristics. Harmonic ACE Plus® with its curved tip and its ergonomic shape is easy to use, and surgeons in our and other Institutions has been using it from several years and in different fields without reporting any complains. This suggests that this surgery prolongation in time is not due to the device itself but probably to surgical procedure complexity. In fact, in the Harmonic ACE Plus® group a significantly higher rate of lower lung lobectomies, that could be more challenging that middle and upper lobe lobectomies, has been performed (54% versus 25% of the electric hook).

Finally, in terms of cost-effectiveness, Harmonic ACE Plus® with its innovative technology is more expensive than electric hook that is reusable: its prize is fourfold in our Institution. So, in

absence of Harmonic ACE Plus® positive impact in postoperative short-term outcomes, the use of electric hook may be useful in reducing operative costs. However, the safe use of the ultrasonic devices even in pulmonary vein and artery branches sealing could decrease the use of endoscopic staplers and ligating clips maybe reducing the overall operative costs which is mostly due the use of disposable equipment/devices [45,48,50-53]. In our study no data about the number of endoscopic staplers and charges saved in the Harmonic ACE Plus® group are available because no surgeons used the ultrasonic device to seal pulmonary vein and artery branches.

This study has some limits. The use of electric hook or Harmonic ACE Plus® was not dictated by a randomized process but by devices availability and surgeon's preference. However, patients had similar characteristics in both groups and a propensity score matching analysis was performed adjusting groups for those two factors which could have influenced study outcomes measurements: number of lymph nodes dissected and presence of postoperative air-leak. Secondly, no data have been reported about Harmonic ACE Plus® performance in sealing small vessels up to 5 mm because surgeons preferred to employ endoscopic staplers or clips. Finally, we did not report data about patients' intraoperative and postoperative cost. However, we evaluated indirect indicators of overall cost as devices cost, length of surgery, postoperative complications, postoperative length of stay. A strength of this study is its aim: the evaluation of electric hook and Harmonic ACE Plus® impact on patients' postoperative course.

To conclude, the use of either surgical electric hook (monopolar device) or Harmonic ACE Plus® (ultrasonic device) for adhesiolysis, hilar structure dissection and lymph nodes dissection in VATS lobectomy and lymphadenectomy is safe and these two devices are associated with similar postoperative chylothorax incidence, chest tube duration and length of stay. Further randomized and larger studies are needed in order to confirm our results and to compare these

two devices in terms of overall costs, maybe employing Harmonic ACE Plus® even in pulmonary vessels sealing.

Tables

Table 1 Patients' clinical characteristics: comparison between Group A (electric hook) and Group B (Harmonic ACE Plus®).

	Group A (n=68)	**Group B (n=52)**	***p*-value**
Male, n (%)	36 (53)	36 (69)	0.07
Age, median (IQR) year	69 (62-75)	72 (64-76)	0.47
BMI, median (IQR) kg/m^2	25 (22-28)	26 (23-28)	0.78
Current/former smoker, n (%)	51 (75)	39 (75)	1.00
FEV_1, median (IQR) %	99 (88-110)	106 (89-119)	0.22
DLCO, median (IQR)	83 (62-92)[a]	85 (77-96)[b]	0.07
COPD, n (%)	11 (16)	11 (21)	0.48
Previous myocardial infarction, n (%)	8 (12)	8 (15)	0.56
Diabetes mellitus, n (%)	9 (13)	9 (17)	0.54
Previous malignancy, n (%)	27 (40)	15 (29)	0.22

BMI=body mass index; COPD=chronic obstructive pulmonary disease; DLCO=lung diffusing capacity for carbon monoxide; FEV_1=forced expiratory volume in 1 second; IQR=interquartile range; [a]=data not available in 9 patients; [b]=data not available in 6 patients.

Table 2 Patients' pathological characteristics: comparison between Group A (electric hook) and Group B (Harmonic ACE Plus®).

	Group A (n=68)	**Group B (n=52)**	***p*-value**
Tumor size, median (IQR) cm	1.8 (1.5-2.9)	1.9 (1.5-3.0)	0.81
Tumor histology, n (%)			0.79
Adenocarcinoma	45 (66)	37 (71)	
Squamous cell carcinoma	11 (16)	8 (15)	
Neuroendocrine tumor	10 (15)	7 (13)	
Other histology	2 (3)	0	
Lower lobe tumor location, n (%)	17 (25)	28 (53)	<0.01
Dissected lymph nodes, median (IQR) n	8 (6-10)	8 (5-12)	0.44
Pathological stage, n (%)			0.46
I	52 (76)	44 (85)	
II	12 (18)	5 (10)	
III	4 (6)	3 (5)	

IQR=interquartile range.

Table 3 Risk factors for increased (>315 ml) pleural effusion volume during the first 48 hours after VATS lobectomy and lymphadenectomy in 120 patients: univariable and multivariable analyses by binary logistic regression.

Risk factor	**Univariable analysis**		**Multivariable analysis**	
	HR (95%CI)	***p***	**HR (95%CI)**	***p***
Age (continuous)	1.00 (0.96-1.03)	0.83	-	-
Gender (male vs female)	2.02 (0.96-4.24)	0.06	1.36 (0.58-3.17)	0.48
BMI (continuous)	1.00 (1.00-1.00)	0.21	-	-
FEV_1 (continuous)	0.99 (0.98-1.01)	0.54	-	-
DLCO (continuous)	1.00 (0.98-1.03)	0.74	-	-
Cardiac comorbidity (none vs yes)	**2.23 (0.96-5.19)**	**0.06**	**2.86 (1.09-7.45)**	**0.03**
Pleural adhesiolysis (none vs yes)	1.16 (0.54-2.48)	0.70	-	-
Site of resection (upper/middle vs lower)	**4.13 (1.86-9.16)**	**<0.01**	**3.28 (1.37-7.83)**	**<0.01**
N° of resected lymph nodes (continuous)	1.04 (0.96-1.12)	0.39	-	-
Energy device (ultrasonic vs monopolar)	0.33 (0.15-0.70)	<0.01	0.59 (0.25-1.42)	0.24
Surgery duration (≤195 vs >195 minutes)	**3.73 (1.75-7.94)**	**<0.01**	**2.93 (1.22-7.04)**	**0.02**
Postoperative air-leak>5 days (none vs yes)	1.36 (0.56-3.29)	0.50	-	-

BMI=body mass index; DLCO=lung diffusing capacity for carbon monoxide; FEV_1=forced expiratory volume in 1 second.

Table 4 Risk factors for prolonged (>5 days) postoperative chest tube duration after VATS lobectomy and lymphadenectomy in 120 patients: univariable and multivariable analyses by binary logistic regression.

Risk factor	**Univariable analysis**		**Multivariable analysis**	
	HR (95%CI)	***p***	**HR (95%CI)**	***p***
Age (continuous)	1.05 (1.00-1.09)	0.04	1.04 (0.99-1.10)	0.13
Gender (male vs female)	2.41 (1.10-5.29)	0.03	1.63 (0.60-4.39)	0.34
BMI (continuous)	1.00 (1.00-1.00)	0.35	-	-
FEV_1 (continuous)	0.99 (0.97-1.01)	0.39	-	-
DLCO (continuous)	0.99 (0.97-1.01)	0.38	-	-
Cardiac comorbidity (none vs yes)	0.67 (0.28-1.59)	0.36	-	-
Pleural adhesiolysis (none vs yes)	2.69 (1.23-5.88)	0.01	2.14 (0.80-5.73)	0.13
Site of resection (upper/middle vs lower)	0.91 (0.43-1.95)	0.81	-	-
N° of resected lymph nodes (continuous)	1.02 (0.94-1.11)	0.60	-	-
Energy device (ultrasonic vs monopolar)	0.79 (0.38-1.66)	0.54	1.32 (0.49-3.52)	0.59
Surgery duration (≤195 vs >195 minutes)	1.46 (0.70-3.04)	0.32	-	-
Postoperative air-leak >5 days (none vs yes)	**75.1 (9.62-586)**	**<0.01**	**63.5 (7.80-517))**	**<0.01**

BMI=body mass index; DLCO=lung diffusing capacity for carbon monoxide; FEV_1=forced expiratory volume in 1 second.

References

1. Duma N, Santana-Davila R, Molina JR. Non-Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment. Mayo Clin Proc 2019;94:1623-1640.

2. Barta JA, Powell CA, Wisnivesky JP. Global Epidemiology of Lung Cancer. Ann Glob Health 2019;85.

3. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.

4. www.demo.istat.it.

5. I numeri del cancro in Italia 2018. Intermedia Editore.

6. Alberg AJ, Samet JM. Epidemiology of lung cancer. Chest 2003;123:21S-49S.

7. Hubbard R, Venn A, Lewis S, et al. Lung cancer and cryptogenic fibrosing alveolitis: a population-based cohort study. Am J Respir Crit Care Med 2000;161:5-8.

8. Kirk GD, Merlo C, O' Driscoll P, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. Clin Infect Dis 2007;45:103-110.

9. Imperatori A, Harrison RN, Dominioni L, et al. Resection rate of lung cancer in Teesside (UK) and Varese (Italy): a comparison after implementation of the National Cancer Plan. Thorax 2016;71:230-237.

10. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Small Cell Lung Cancer. Version 2.2019. NCCN.org.

11. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-Small Cell Lung Cancer. Version 6.2019. NCCN.org.

12. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv1-iv21.

13. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016; 11:39-51.

14. Blasberg JD, Pass HI, Donington JS. Sublobar resection: a movement from the Lung Cancer Study Group. J Thorac Oncol 2010; 5:1583–1593.

15. https://clinicaltrials.gov/ct2/show/NCT00499330

16. Nakamura K, Saji H, Nakajima R et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607L). Jpn J Clin Oncol 2010;40:271–274.

17. Goldstraw P. Report on the international workshop on intrathoracic staging. Lung Cancer 1997;18:107-111.

18. Rami-Porta R, Wittekind C, Goldstraw P, et al. Complete resection inlung cancer surgery: proposed definition. Lung Cancer 2005;49:25–33.

19. Baltayiannis N, Chandrinos M, Anagnostopoulos D, et al. Lung cancer surgery: an up to date. J Thorac Dis 2013;5 Suppl 4:S425-S439.

20. Huang X, Wang J, Chen Q, et al. Mediastinal lymph node dissection versus mediastinal lymph node sampling for early stage non-small cell lung cancer: a systematic review and meta-analysis. PLoS One 2014;9:e109979.

21. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. Ann Thorac Surg2006;81:1013-1019.

22. Petrella F, Spaggiari L. The smaller the better: a new concept in thoracicsurgery? Lancet Oncol 2016; 17: 699–700.

23. Falcoz PE, Puyraveau M, Thomas PA, et al. Video-assisted thoracoscopic surgery versus open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of

outcome from the European Society of Thoracic Surgeon database. Eur J Cardiothorac Surg 2016; 49:602-609.

24. Stephens N, Rice D, Correa A, et al. Thoracoscopic lobectomy is associated with improved short-term and equivalent oncological outcomes compared with open lobectomy for clinical Stage I non-small-cell lung cancer: a propensity-matched analysis of 963 cases. Eur J Cardiothorac Surg 2014; 46:607-613

25. Cao C, Manganas C, Ang SC, et al. Video-assisted thoracic surgery versus open thoracotomy for non-small cell lung cancer: a meta-analysis of propensity score-matched patients. Interact Cardiovasc Thorac Surg 2013; 16:244-249.

26. Rueth NM, Andrade RS. Is VATS lobectomy better: perioperatively, biologically and oncologically? Ann Thorac Surg 2010;89:S2107-S2111.

27. Whitson BA, Groth SS, Duval SJ, et al. Surgery for early-stage non-small cell lung cancer: a systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. Ann Thorac Surg 2008;86:2008-2016;

28. Andrade RS, Maddaus MA. Thoracoscopic lobectomy for stage I non-small cell lung cancer. Semin Thorac Cardiovasc Surg 2010;22:14-21.

29. Ziarnik E, Grogan EL. Postlobectomy Early Complications. Thorac Surg Clin 2015;25:355-364.

30. Mitchell JD. Techniques of VATS lobectomy. J Thorac Dis 2013;5:S177–S181.

31. Fan PM, Zheng WP, Zheng LP, et al. Completely thoracoscopic right upper lobectomy and mediastinal lymph node dissection. J Thorac Dis 2013;5:851-854.

32. Rocco G, Internullo E, Cassivi SD, et al. The variability of practice in minimally invasive thoracic surgery for pulmonary resections. Thorac Surg Clin 2008;18:235-247.

33. Hansen HJ, Petersen RH. Video-assisted thoracoscopic lobectomy using a standardized three-port anterior approach - The Copenhagen experience. Ann Cardiothorac Surg 2012;1:70-76.

34. Gonzalez-Rivas D, Paradela M, Fieira E, et al. Single incision video-assisted thoracoscopic lobectomy: initial results. J Thorac Cardiovasc Surg 2012;143:745-747.

35. Gonzalez-Rivas D, Sihoe ADL. Important Technical Details During Uniportal Video-Assisted Thoracoscopic Major Resections. Thorac Surg Clin 2017;27:357-372.

36. Yan TD. Video-assisted thoracoscopic surgery. Ann Cardiothorac Surg 2014;3:131-132.

37. Gonfiotti A, Viggiano D, Voltolini L, et al. Enhanced recovery after surgery and video-assisted thoracic surgery lobectomy: the Italian VATS Group surgical protocol. J Thorac Dis 2018;10:S564-S570.

38. Goudie E, Tahiri M, Liberman M. Present and Future Application of Energy Devices in Thoracic Surgery. Thorac Surg Clin 2016;26:229-236.

39. Madani A, Watanabe Y, Vassiliou MC, et al. Impact of a hands-on component on learning in the Fundamental Use of Surgical Energy (FUSE) curriculum: a randomized-controlled trial in surgical trainees. Surg Endosc 2014;28(10):2772–82.

40. Feldman LS, Fuchshuber P, Jones DB, et al. Surgeons don't know what they don't know about the safe use of energy in surgery. Surg Endosc 2012;26(10):2735–9.

41. Taheri A, Mansoori P, Sandoval LF, et al. Electrosurgery: part I. Basics and principles. J Am Acad Dermatol 2014;70(4):591.e1–591.e 14.

42. Liberman M, Khereba M, Goudie E, et al. Pilot study of pulmonary arterial branch sealing using energy devices in an ex vivo model. J Thorac Cardiovasc Surg. 2014;148(6):3219-3223.

43. Okada M, Miyata Y, Takamochi K, et al. Prospective feasibility study of sealing pulmonary vessels with energy in lung surgery. J Thorac Cardiovasc Surg 2019;157:388-395.

44. Lesser TG, Wolfram F, Boltze C. Sealing of pulmonary arteries with LigaSure: in vivo and ex vivo examinations. J Thorac Cardiovasc Surg 2013;145:1525-1528.

45. Goudie E, Thiffault V, Jouquan A, et al. Pulmonary artery sealing with ultrasonic energy in open lobectomy: A phase I clinical trial. J Thorac Cardiovasc Surg. 2017;153:1600-1607.

46. Nduka CC, Super PA, Monson JR, et al. Cause and prevention of electrosurgical injuries in laparoscopy. J Am Coll Surg 1994;179:161e170.

47. Overbey DM, Townsend NT, Chapman BC, et al. Surgical Energy-Based Device Injuries and Fatalities Reported to the Food and Drug Administration. J Am Coll Surg. 2015;221:197-205.

48. Alkatout I, Schollmeyer T, Hawaldar NA. Principles and Safety Measures of Electrosurgery in Laparoscopy. JSLS 2012;16:130–139.

49. Družijanić N, Pogorelić Z, Perko Z, et al. Comparison of lateral thermal damage of the human peritoneum using monopolar diathermy, Harmonic scalpel and LigaSure. Can J Surg 2012;55:317-321.

50. Hefermehl LJ, Largo RA, Hermanns T, et al. Lateral temperature spread of monopolar, bipolar and ultrasonic instruments for robot-assisted laparoscopic surgery. BJU Int 2014;114:245-252.

51. Kondrup JD, Anderson F2, Sylvester B, et al. The New HARMONIC ACE®+7 Shears: A Game Changer in Ultrasonic Hemostasis. Surg Technol Int 2014;25:24-27.

52. Richardson MT, Backhus LM, Berry MF, et al. Intraoperative costs of video-assisted thoracoscopic lobectomy can be dramatically reduced without compromising outcomes. J Thorac Cardiovasc Surg 2018;155:1267-1277.

53. Schuchert MJ, Abbas G, Landreneau JP, et al. Use of energy-based coagulative fusion technology and lung sealants during anatomic lung resection. J Thorac Cardiovasc Surg 2012;144:S48-S51.

54. Harold KL, Pollinger H, Matthews BD, et al. Comparison of ultrasonic energy, bipolar thermal energy, and vascular clips for the hemostasis of small-, medium-, and large-sized arteries. Surg Endosc 2003;17:1228-1230.

55. Longo F, Crucitti P, Quintarelli F, et al. Bipolar sealing devices in video-assisted thoracic surgery. J Vis Surg 2017;3:13.

56. https://clinicaltrials.gov/ct2/show/NCT03125798?term=LIGASURE&rank=2

Appendix

8th edition of TNM Classification for lung cancer [13]

T – Primary Tumor Classification

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

T0 No evidence of primary tumor.

Tis Carcinoma in situ.

T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)

T1mi Minimally invasive adenocarcinoma.

T1a Tumor 1 cm or less in greatest dimension.

T1b Tumor more than 1 cm but not more than 2 cm in greatest dimension.

T1c Tumor more than 2 cm but not more than 3 cm in greatest dimension.

T2 Tumor more than 3 cm but not more than 5 cm; or tumor with any of the following features:

• Involves main bronchus regardless of distance to the carina, but without involving the carina

• Invades visceral pleura

• Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung.

T2a Tumor more than 3 cm but not more than 4 cm in greatest dimension.

T2b Tumor more than 4 cm but not more than 5 cm in greatest dimension.

T3 Tumor more than 5 cm but not more than 7 cm in greatest dimension or one that directly invades any of the following: chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or associated separate tumor nodule(s) in the same lobe as the primary.

T4 Tumors more than 7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe to that of the primary.

N – Regional Lymph Nodes Classification

NX Regional lymph nodes cannot be assessed.

N0 No regional lymph node metastasis.

N1 Metastasis in ipsilateral peri bronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension.

N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s).

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s).

M- Distant Metastasis

M0 No distant metastasis.

M1 Distant metastasis.

M1a Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion.

M1b Single extra thoracic metastasis in a single organ (thin includes involvement of a single distant, non-regional node).

M1c Multiple extra thoracic metastases in one or several organs.

Stage grouping for the 8th edition of TNM Classification for lung cancer [13]

Stage	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1a (mi)	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a	N1	M0
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
IIIA	T1a	N2	M0
	T1b	N0	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0

IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	Any T	Any N	M1a
	Any T	Any N	M1b
IVB	Any T	Any N	M1c