Role of video-assisted thoracic surgery in T4 NSCLC

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Abstract: For many years, T4 lung tumors have been considered less suitable for surgery, because of their local extension invading central structures or vertebral bodies. To date, many studies have confirmed the advantages in terms of survival of a multimodality approach made up of surgical resection associated with neoadjuvant and/or adjuvant therapy for selected patients with advanced lung cancer. In those patients, in fact, minimally invasive surgery could improve overall survival rates while promoting faster recovery, faster access to adjuvant therapies and preserving a better functionality of the immune system. Because of the difficulty in collecting data on patients with T4 lung tumors amenable to minimally invasive surgery, published evidences only come from case reports which prove the feasibility and the possible advantages of video-assisted thoracic surgery (VATS) procedures. The aim of this literature review is to collect the published experiences of skilled surgeons dealing with T4 tumors invading central structures or chest wall, to analyze concerns and new opportunities of treatment and proving the feasibility and advantages of the VATS approach.

Keywords: T4 lung tumors; advanced lung cancer; video-assisted thoracic surgery (VATS); minimally invasive

Received: 02 April 2020; Accepted: 03 June 2020; Published: 20 July 2021.

doi: 10.21037/jovs-20-93

View this article at: http://dx.doi.org/10.21037/jovs-20-93

Introduction

The eighth edition of tumor, node and metastasis (TNM) classification for lung cancer has defined T4 tumors those >7 cm or invading the mediastinum, heart, diaphragm, great vessels, trachea, esophagus, spine, recurrent nerve, carina or separate tumor nodule(s) in a different ipsilateral lobe (1).

Because of the local extension of these tumors invading central structures or vertebral bodies, for many years they have been considered less suitable for surgery. To date, many studies confirm the advantage in terms of survival of a multimodality approach made up of surgical resection associated with neoadjuvant and/or adjuvant therapy for selected patients with locally advanced lung tumors (2-4).

In NSCLC, the pT factor does not significantly affect survival rate as the pN factor does, except in the case of the T4 disease, in which survival rates do not statistically differ in the setting of N1 or N2 node involvement (5). In this stage of the disease, 5-years survival rates range from 22 to 47% in patients without lymph node involvement and after complete surgical resection (6-13).

Advantages of the thoracoscopic approach have been widely discussed and proved and include decreased postoperative pain, shorter hospitalization and faster recovery (14-19). Along with technical and surgeons' skills acquirements, video-assisted thoracic surgery (VATS) has become a challenging opportunity to treat T4 lung tumors even if published evidence is still sparse. The availability of high definition cameras with wide-angle lens, new devices, more angulated staplers and topical hemostatic tools,

in fact, has made affordable the thoracoscopic approach even for locally advanced tumors (20,21). Under the assumption that complex procedures as sleeve lobectomies, vessel reconstructions, pneumonectomies, and chest wall resections should be done only by skillful surgeons (21), Nakanishi *et al.* (22) have suggested a learning curve of 25 cases for minimally-invasive T4 tumors resections for those expert surgeons who had already performed more than 100 VATS lobectomies in their career.

VATS for T4 lung tumors: still few evidences

No randomized controlled trials have been published yet about perioperative and long-term outcomes of VATS resections for T4 lung tumors. Because of the difficulty in collecting data on patients with T4 lung tumors amenable to minimally invasive surgery, published evidences only come from case reports which prove the feasibility and the possible advantages of VATS procedures. Moreover, the few existing evidences refer to advanced lung tumors as defined by the 7th American Joint Committee on Cancer TNM staging system: tumors greater than 4 cm, T3 and T4 tumors or tumors requiring neoadjuvant therapy (20,21). Hennon *et al.* (21) have published results about outcomes after thoracoscopic *vs*. open thoracotomy resection for advanced lung cancer. They proved no statistical differences in median blood loss, operative time, frequency of major complications, in-hospital stay and overall survival between the two approaches. The two groups only differ in the percentage of patients who could undergo adjuvant therapy postoperatively, which was significantly higher in the VATS group (37.2% *vs*. 5.3%); conversion rate was 23%. Similar findings have been reported by Chen *et al.* (23) when comparing thoracoscopic *vs*. open thoracotomy resection for advanced lung cancer. Interestingly, they also found a significant difference between the median blood loss and length of hospital stay, in favor of the thoracoscopic approach. It also seemed that more patients in the VATS group could tolerate all chemotherapy cycles at the fully planned dose than those in the open group (51.7% *vs*. 42.5%). Gonfiotti *et al.* (24) published their results on 3,266 *vs*. 454 patients undergoing VATS resections for early and locally advanced lung tumors, respectively. The hospital stay, mortality and complication rates were not statistically different between the two groups, while VATS resections for advanced-stage NSCLC were associated with a longer procedure time, higher blood loss and an increased incidence of conversion.

Conversion rates vary from 0% to 23% for advanced lung tumors, depending on case selection and surgeon expertise (25). Conversion to thoracotomy could be necessary during VATS procedures for advanced stages; the infiltration itself, in fact, can produce massive bleeding or difficulty in achieving a wide oncological resection forcing the surgeon to convert to thoracotomy. Gonfiotti *et al.* (24) proved that patients requiring conversion had a significantly higher operative time, blood loss, hospital stay and positive surgical margins, but not a higher overall morbidity rate.

Uniportal VATS (u-VATS) has also been proved to be a feasible approach for advanced lung tumors in skillful hands. Fan *et al.* (26) compared open and u-VATS groups in their analysis and they found results similar to those above mentioned, with significant differences in median blood loss, hospital stay and time to access adjuvant chemotherapy after the operation (29.6 *vs*. 43.3 days). Gonzalez-Rivas *et al.* (20) published an analysis on 43 u-VATS resections for advanced stage of NSCLC compared to 87 resections for early-stage lung cancer. They found no significant differences between the two groups in terms of in-hospital stay, chest tube removal and rate of complications; overall 30-months survival was 73.7%.

VATS, T4 and (neo)adjuvant therapies

The overall survival for patients with stage III NSCLC is less than 5% after 5 years in those undergoing single modality therapy with either radiotherapy or surgery alone (27). Induction therapy is considered the standard of care for patients with operable stage III NSCLC (28,29), with reported 5-year survival rates between 43% (30) and 56% (31) in IIIB stage patients who underwent preoperative chemoradiotherapy. Despite surgeons' concerns about adhesions and the difficult hilar and mediastinal dissection, VATS and u-VATS has proved to be feasible and safe procedures also after neoadjuvant therapies, showing no differences in perioperative outcomes, 30-day mortality and overall survival when compared to open thoracotomy (28,32-34).

Moreover, VATS approach could also promote a faster access to adjuvant therapies and to better tolerate them leading to improved survival rates. This is because VATS is less invasive and painful for patients, allowing a faster recovery. Many studies have highlighted the possible role of VATS in preserving a better functionality of the immune system, because of a less acute inflammatory response after a minimally invasive approach (21,35). Additionally,

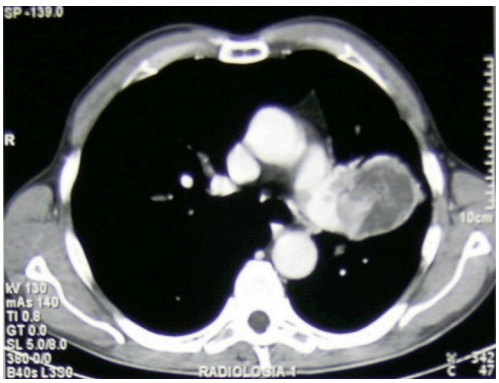


Figure 1 Chest computed tomography scans showing a large central lung cancer.

Peng *et al.* (36) found that VEGF release from tissues after surgery could have a proangiogenic effect and consequently promote tumor growth and metastasis formation; they also proved that after a VATS resection, levels of VEGF released were lower than after an open thoracotomy. D'Amico (37) published results about the delivery of adjuvant chemotherapy after VATS or open lobectomy for NSCLC; 93.9% of patients who underwent VATS lobectomy tolerate the complete 3-cycle adjuvant regimen *vs*. the 79.1% of those who underwent open thoracotomy.

Patient selection

Preoperative staging of T4 lung tumors is of paramount importance to plan the most adequate treatment. Since extended surgical resection could be connected with higher perioperative risks, it has to be indicated on an individual patient basis, excluding those with a marginal cardiopulmonary reserve and low performance status, with age <70 years (3). A multidisciplinary board should guide the correct treatment strategy, after nodal and systemic spread had been excluded along with international guidelines. In particular, thoracoscopic procedures should be considered when minimal invasion of adjacent organs occurs and excluded for superior sulcus tumors and bulky, nodal or systemic disease (22).

Along with perioperative assessment of lung function, preoperative TNM staging should include total-body CT scan and positron emission tomography (PET) to better detect unrecognized nodal or metastatic disease. T status may often result under or overstaged by CT-scan only, since infiltrated structures are not often detectable; in these cases, magnetic resonance (MRI), echocardiography or transesophageal ultrasounds could guide the clinicians' decision. Gdeedo *et al.* (38) proved that, in their case series, CT staging of T3 and T4 lung cancers was correct in almost 50% of cases; Cangemi *et al.* (39) reported similar results; in their series, CT-scan staging for T4 tumors was accurate only in 27% of cases. Other studies, reported that CT-scan sensitivity for chest wall invasion varies from 38 to 87% and the specificity varies from 40% to 90% (40) *vs*. MRI sensitivity ranging from 63 to 90% with a specificity of 84% to 86% (41). When used to predict mediastinal invasion, both CT scan and MRI have similar diagnostic accuracy (56–89% for CT and 50–93% for MRI), with no modality being considered superior. A recent study by Tang *et al.* (42) compared T staging accuracy of both MRI and CT-scan; they found that CT was more accurate when studying T1 and T2 NSCLC (100 % *vs*. 75 %, 96.4 % *vs*. 82.1 %), while MRI was superior in the identification of T3 and T4 tumors (80 % *vs*. 50 %, 100 % *vs*. 33.3 %).

An interesting suggestion is to use VATS to assess the real extent of the tumor, even if an open thoracotomy is planned, to exclude any contraindication to resection not evident in the preoperative radiological evaluation (43). VATS inspection, in fact, is a non time-consuming and economic procedure which could routinely be performed prior to the open approach. Cetinkaya *et al.* (44) conducted a study to compare preoperative and postoperative staging in NSCLC; interestingly, in patients with cT4 disease, downstaging occurred in 38.2% of cases. Mouroux *et al.* (45) routinely performed VATS inspection in the presence of inconclusive information of imaging techniques about extension and resectability. De Giacomo *et al*. (46) also performed a study on 64 patients with the clinical suspicion of stage IIIB lung cancer to evaluate the role of VATS in the assessment of the real extent of the tumor. They found that VATS is safe and effective for this purpose and it provided the correct staging for 91% of patients.

Tumors >7 cm

Adhesions, narrow spaces and difficulty to move the lobe, make VATS resection for large lung tumors still poorly practiced and discussed, and it still remains a challenging procedure to perform trough a minimally invasive approach (*Figure 1*). Hou *et al.* (47) reported a case report of a VATS left-upper lobectomy, bronchoplasty and angioplasty for a giant central lung cancer, showing how thoracoscopy had been useful firstly for an accurate dissection and then to provide better vision and better chances for recovery along

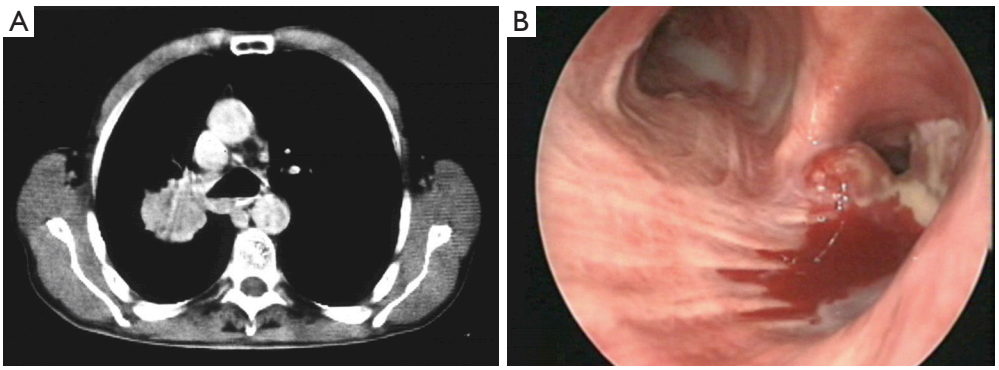


Figure 2 A Chest computed tomography scan showing a tracheal tumor involving the carina and the right main bronchus. B. Bronchoscopic view of the tumor involving the carina and the proximal part of the right main bronchus.

with a complete oncologic resection.

Tumors invading the great vessels, trachea or carina

In 2002, Santambrogio *et al.* (48) reported the first video-assisted bronchial sleeve resection and bronchoplasty. Since that, many studies have been published about the role of VATS in bronchoplastic procedures and vascular sleeve resections, sharing the experience and the tips and tricks of skilled surgeons (49-52). Because of its technical difficulty, airway reconstructions are still a challenge even for the most skilled surgeons, and few opportunities are still offered during thoracic training programs to practice endoscopic suturing.

Moreover, central lung cancer involving the carina is still a challenging procedure due to the technical difficulty of carina resection and airway management and reconstruction (*Figure 2*). Many authors have reported several case reports about thoracoscopic carina resection and reconstruction for central lung cancer, demonstrating the feasibility of this procedure although some issues remain unsolved. Firstly, the correct management of airways during the VATS reconstruction which has to be as much as less interfering with the surgical field while preventing hypercapnia o hypoxemia. Li *et al.* (53) shared their experience on a series of 12 patients who underwent VATS carinal or tracheal resection and reconstruction for benign or malignant diseases. At the beginning of their experience, after the tracheal resection, they shifted to cross-field ventilation by introducing the endobronchial tube directly through the 4-cm main operative port or an optional 10-mm port. As they became more skilled at the procedure, they also tried to simplify the surgery by using high-frequency jet ventilation (HFJV) or spontaneous breathing anesthesia (SRA). The outcomes of the three procedures have not been compared, but they reported no overall in-hospital mortality or major morbidity.

Cross-field ventilation is a time consuming procedure, since it requires periodical retraction during anastomosis, while it obstructs the view of the surgical field. On the other hand, HFJV may ventilate one lung without causing injury to the tumor, but it can cause moderate lung ventilation and increase the risk for postoperative ARDS (54,55). Three major issues have been described while dealing with SRA: management of airway, hypoxemia and hypercapnia. Jiang *et al.* (56) compared results on 18 *vs.* 14 patients who underwent thoracoscopic carina resection both through intubation or spontaneous anesthesia. They proved that SRA could help both the anesthetic and surgical procedure; the lack of an endotracheal tube, in fact, makes the trachea more flexible and allows a wider range of motion for the surgeon, along with a wider field of view; these factors lead to a global reduction of operative time. Ai *et al.* (57) reported two cases of neoplastic invasion of left main bronchus up to the bifurcation of the upper and lower lobe, the carina and the right main bronchus treated by using a bilateral combined VATS and open approach. Firstly, they performed a right posterolateral thoracotomy to resect and anatomize trachea and the right main bronchus; subsequently, they performed a VATS left sleeve pneumonectomy trough a four-port left thoracoscopy. Although no randomized trials have been performed on this topic and only few case reports have been published, all authors agree that the most important factor influencing the outcomes of such a complex thoracoscopic procedure is the

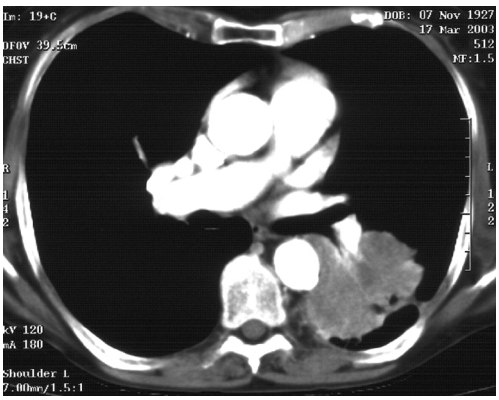
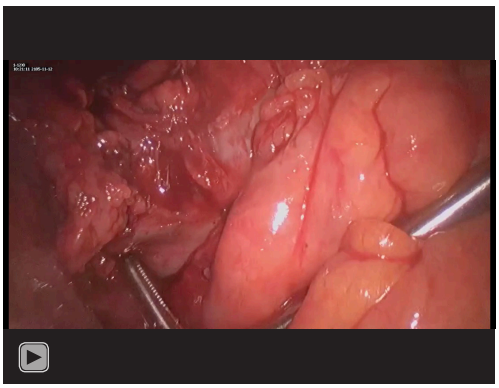


Figure 3 Chest computed tomography scan showing a lung tumor with aortic wall involvement.



Video 1 Right non-small-cell lung cancer involving the atrium: VATS atriotomy and closure of the atrium using a running suture. VATS, video-assisted thoracic surgery.

careful patient selection (53-57).

Endoscopic bronchial and tracheal anastomosis methods include intermittent, continuous, and continuous mixed with intermittent sutures (58-64). When performing a thoracoscopic procedure, most of authors agree on the usefulness of a complete continuous suture starting from the posterior part of the anastomosis to the anterior one, since it offers a clear operative view (53-57,65-67).

The first case report of a uniportal VATS sleeve resection has been published in 2013 by Gonzalez-Rivas *et al.* (64) and new attempts have been reported (68,69) confirming the possible advantages in terms of minimal invasiveness, lower postoperative pain and good postoperative outcomes. In a review published in 2015, Gonzalez-Rivas *et al.* (49) described their anastomotic technique for uniportal-VATS carina resection, using both a cross-field tube and HFJV.

To date, few cases have been reported about the possible role of VATS when managing tumors infiltrating the great vessels (70-75) (*Figure 3*). Surgery in these cases is still challenging both because of technical problems and difficulty in accomplishing a radical resection. VATS approach is unusual and complex in these cases, because of the limited working space and surgical field. In fact, different techniques have been described to perform safe vascular resections, including cardiopulmonary bypass (CBP), aorto-aortic passive shunt, direct clamping or thoracic aortic endograft (*Video 1*). Each technique should be chosen based on length, depth and site of aortic involvement and on the type of resection to be performed; if more than one fourth of the wall has to be resected a patching or a complete resection followed by an end-to-end anastomosis should be performed (76). Nakanishi *et al.* (71) reported their experience on a case series of 5 patients who underwent a VATS lobectomy with pulmonary artery (PA) angioplasty. They used a four-port approach, using a 7-cm utility thoracotomy incision in the 3rd or 4th intercostal space to insert the Satinsky clamps on the proximal and distal part of PA; after that, the infiltrated wall of the artery was resected by using scissors and reconstructed with a running Prolene suture. Xu *et al.* (72), instead, described their VATS technique when the side-wall of the pulmonary trunk is infiltrated, by performing an arterioplasty using a mechanical suturing technique. Gonzalez-Rivas *et al.* (49) suggested some tricks to perform uniportal-VATS angioplasty for advanced lung cancer: the use of bulldog clamps on the pulmonary vessels as they do not interfere with other instruments; the use of a double-vessel loop to clamp the distal artery for partial resections; to perform vascular reconstruction during the last step of the lobectomy in order to have a larger surgical field.

CBP should be used in case of aortic arch/supraortic vessel involvement, when the media is invaded and resection requires cross-clamping of the aorta to resect the infiltrated wall (77) and obviously it cannot be used in VATS. Marulli *et al.* (78) in 2008 firstly described a two-step use of a thoracic endovascular graft followed by delayed *en bloc* surgical resection of the tumor to avoid CBP, aortic clamping, resection and vascular graft anastomoses, lowering the peri- and postoperative complication rates (77). Since in the majority of cases aortic infiltration is confined to the adventitia, the preoperative thoracic endograft positioning could be used to perform a VATS *en bloc* resection of the tumor since no need for clamping or

CBP should be required. Unfortunately, no attempts have been performed in this field, yet. Additionally, since the techniques to perform safe and radical vessel resections are different and have to be chosen based on the entity of the infiltration, inspective VATS could be a helpful means to complete preoperative staging to decide what kind of procedure is the best to be planned.

Pancoast's and tumors invading the spine, chest wall or diaphragm

Many hybrid approaches have been proposed in Literature to obtain both an oncological and a minimally invasive resection for tumors involving the chest wall and Pancoast tumors (*Figures 4,5*). All these approaches agree on the first, important role of VATS: an initial thoracoscopy to evaluate the resectability and the real extent of the tumor. Additionally, the minimally invasive approach may be used to perform lobectomy and to better define the extent of chest wall resection.

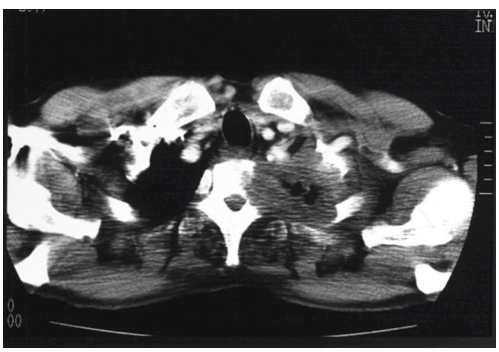


Figure 4 Chest computed tomography scan showing an apical chest wall tumor with spinal involvement.

Truin *et al.* (79) reported for the first time a hybrid VATS approach for superior sulcus tumors, combining VATS with a L-shaped transmanubrial incision according to Grunenwald to perform an anterior radical dissection. Rosso *et al.* (80,81) also proposed two hybrid combined approaches with both a limited Shaw-Paulson thoracotomy and a modified Grunenwald incision, paving the way to new creative minimally invasive approaches. Moreover, Caronia *et al.* (82) performed a comparative analysis of Pancoast tumor resection performed via VATS or open approaches. They used VATS to firstly observe the extent of the tumor, then they performed an anterior or posterior thoracotomy with video-assistance support or a VATS lobectomy followed by chest-wall resection. The two groups were equivalent regarding blood transfusion, chest drain duration and length of hospital stay, but there was a significant difference in intraoperative blood loss and in morphine requirement in favor of the VATS group.

Stoker *et al.* (83) reported their results on eight consecutive patients who underwent VATS or open thoracotomy with simultaneous posterior spine reconstruction (PSR) for invasive upper lobe lung cancer. Even if preliminary, they described encouraging results for this innovative technique, with lower perioperative complications and shorter in-hospital stay when comparing the VATS with the open approach.

Although many studies have proved the feasibility of a VATS approach for plication of the diaphragm after repair or eventration, (84-91) the first experience of a uniportal-VATS resection of NSCLC invading the diaphragm has been firstly described by Gonzalez-Rivas *et al.* (92) in 2019.

Through a single five-centimeter anterior incision at the fifth intercostal space, in 8 cases they resected the involved part of the diaphragm at the beginning or at the end of the surgery, closing the remaining defect with continuous non-

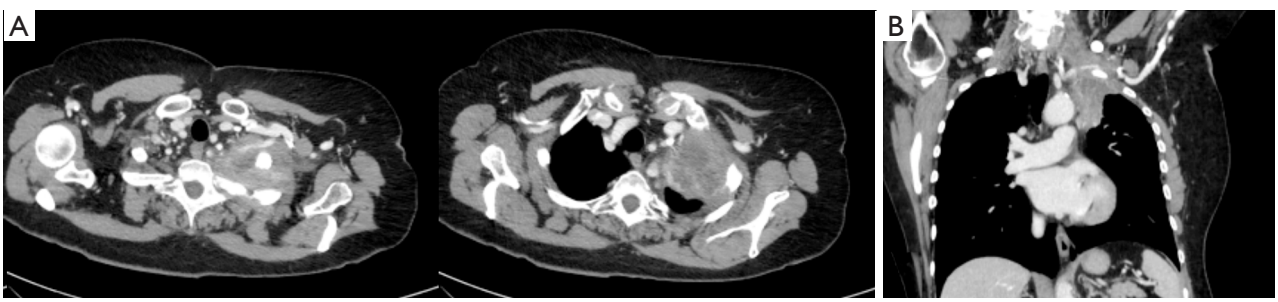


Figure 5 Pancoast tumor. Axial (A) and coronal (B) computed tomography scans reveal a superior sulcus tumor invading the ipsilateral subclavian artery.

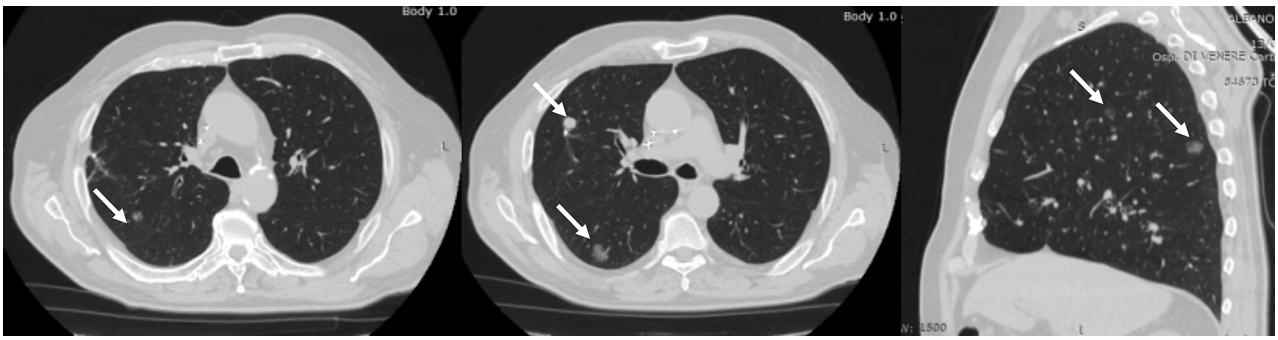


Figure 6 Chest computed tomographic images revealing simultaneous lung nodules and ground-glass opacities (white arrows) in the right upper and lower lobes.

absorbable sutures or synthetic patches on the basis of the entity of the defect itself.

Tumors with separate tumor nodule(s) in a different ipsilateral lobe

Surgical resection of multifocal NSCLC has been widely discussed and approved by several previous studies (93,94). Because of the type of surgery required (including lobectomy, sublobectomy, bilobectomy or pneumonectomy), this indication seems to be the most appropriate for a VATS approach. The extension of the resections has to be accurately evaluated for each patient, on both the basis of number, size and location of the lesions and of patients' adequate cardiopulmonary reserve and performance status (*Figure 6*). Many studies had also proved the feasibility of thoracoscopic pneumonectomy (95-99) as a safe procedure with equivalent results when compared to the open approach, but able to lower pain score since no chest retractor is used. Also, an animal study by Liu *et al.* (100) confirmed that postoperative stress was lower in pigs that underwent VATS pneumonectomy when compared with thoracotomy.

Conclusions

The role of VATS in T4 NSCLC is both for diagnostic and therapeutic purposes. In the hands of skillful surgeons, VATS resections for T4 tumors could be a promising instrument to perform complete resections, allowing lower postoperative pain, shorter hospitalization and faster recovery. Most of published studies have proved no statistical differences in median blood loss, operative time, frequency of major complications, in-hospital stay when comparing VATS and open approach for T4 tumors. Likely, VATS resections could increase the overall survival in advanced lung cancer allowing patients to better tolerate adjuvant treatments at the fully planned dose. Many attempts have been done during the last years to approach T4 tumors in a minimally invasive way and first results are promising, even if it is evident that these procedures have to be performed by skilled surgeons in specialized centers. Because of the exiguity of available cases, these evidences largely originate from cases reports or retrospective studies and more randomized clinical trials and comparative studies are needed to confirm these preliminary results.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Federico Rea) for the series "Alternative Surgical Approaches for Challenging Cases in Thoracic Surgery" published in *Journal of Visualized Surgery*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jovs.amegroups.com/article/view/10.21037/jovs-20-93/coif). The series "Alternative Surgical Approaches for Challenging Cases in Thoracic Surgery" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the Helsinki Declaration (as revised in 2013). The manuscript is waived from patient informed consent according to the ethics committee or institutional review board.

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doi: 10.21037/jovs-20-93
Cite this article as: Brascia D, De Iaco G, Schiavone M, Nicotra S, Signore F, Panza T, Geronimo A, Sampietro D, Marulli G. Role of video-assisted thoracic surgery in T4 NSCLC. J Vis Surg 2021;7:27.