



Robotic-Assisted Thoracoscopic Surgery for Non-Small Cell Lung Cancer



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Abstract

Minimally invasive thoracic surgery is the gold standard treatment for Non-Small Cell Lung Cancer (NSCLC). Robotic Assisted Thoracic Surgery (RATS) has increased its appeal in the last years. In this review, we analyzed RATS perioperative and long-term outcomes, the possibility to obtain radical resections and to perform an accurate RATS lymphadenectomy, the complication rates, the cost-benefit ratio and the training program.

Keywords: Minimally-Invasive Thoracic Surgery; Non-Small Cell Lung Cancer; Robotic-Assisted Thoracic Surgery; Lymphadenectomy; Radical Resection; Robotic Surgery; Oncological Staging

Abbreviations: NSCLC: Non-small cell lung cancer; RATS: Robotic-assisted thoracic surgery; VATS: Video-assisted thoracoscopic surgery; MIS: Minimally invasive surgery; AATS: American Association of Thoracic Surgeons; RP: Robotic Portal; MAL: Midaxillary Line; STS: Society of

Introduction

Non-Small Cell Lung Cancer (NSCLC) is the most diagnosed cancer worldwide (11.6% of the total cases) and the leading cause of death for cancer (18.4% of the total cancer deaths) in both sexes combined [1]. Surgery is the main therapeutic option, especially in early stages [2]. Nevertheless, NSCLC is still the “big killer”. Indeed, after treatment, the 5-year survival rate for people with NSCLC stage IA1, IA2, IA3 and IB is about 92%, 83%, 77% and 68% respectively, while IIA and IIB-stage patients have a 5-year survival rate of 60% and 53%, respectively [3].

Minimally invasive surgery (MIS)

The continuous need to reduce post-operative pain and, consequently, improve recovery after thoracic surgery with good oncological outcomes, has opened the way to a gradual adoption of minimally invasive techniques with Video-Assisted Thoracoscopic Surgery (VATS) [4]. The first thoracic surgical procedures in VATS were performed in the early 90's [5]. After these first attempts, the technique was abandoned because, according to some surgeons, it did not allow an oncological radicality [6] and because most of the devices used (i.e. stapler and optics) were not safe and comfortable for the operator [6,7].

In the early 2000's, surgeons gained new interest in VATS, first with McKenna, who also reported his experience in the 90s, then with Hansen and Petersen [8,9]. Hansen and Petersen proposed a triportal approach, with the camera-port in the lower anterior corner of the chest cavity. Single port access VATS pulmonary procedures were initially described by Rocco et al in 2004 and further developed by Gonzalez-Rivas et al, who performed the first single-port VATS lobectomy [10,11]. This approach showed some potential benefits over the traditional multiport technique, including ergonomics and a more direct view of the surgical field. According to early reports, though, uniportal video-assisted thoracoscopic lobectomy did not present better postoperative outcomes compared to other video-assisted thoracoscopic lobectomy techniques [12,13].

Nowadays, it has been demonstrated that Minimally Invasive Surgery (MIS) is the first choice for lung cancer treatment, especially for early stages [14-18]. Compared with traditional open surgery, VATS is less invasive as it avoids damage to the chest wall structure and rib distraction. VATS also has less postoperative pain, shorter postoperative drainage positioning and hospital stay. It might also improve the timing of adjuvant chemotherapy

delivery [19]. Following the widespread use of robotic assisted surgical technologies in urology, obstetrics, gynecology and cardiac surgery, this approach has been also proposed in thoracic surgery [20,21]. VATS instruments have a limited flexibility and an unmodifiable shape. Due to these limits, the 7 degrees-of-freedom of the main robotic instruments, their physiological tremor filtration, the motion scaling, the absence of the “fulcrum effect” and the 3D visualization of robotic surgery have a certain appeal for the surgeon. Indeed, robotic surgery offers better maneuverability, accuracy and stability over VATS [22,23]. Robotic instruments allow to easily reach deep and narrow spaces such as retrosternal and posterior mediastinal spaces [24].

Thanks to all the features of RATS, its use should probably also be encouraged in locally advanced NSCLC. Nevertheless, some surgeons have concerns about the use of RATS for chest wall invasive NSCLC, while others consider a robotic assisted muscle-sparing resection safe and radical, with a reduction of post-operative pain [25,26]. The absence of tactile feedback is a clear disadvantage of RATS technique, even if it could be overcome by the experience of the surgeon, that can “feel” tissue texture through the 3D visualization [27]. Moreover, Abiri A et al. studied a bimodal vibrotactile system with promising results [28].

Thanks to diagnostic improvements, many patients have early-stage disease that might be adequately treated with sublobar resections [29]. Segmentectomies are usually performed in open: in VATS they are a technically challenging procedure because of the little flexibility of the instruments [30]. RATS approach could be a minimally invasive solution for these resections: Pardolesi et al and Toker et al stated that RATS segmentectomies are feasible, safe and associated with few complications, and that an adequate number of lymph nodes can be removed [31,32].

Different RATS Techniques

According to the American Association of Thoracic Surgeons (AATS), a robotic thoracic operation is defined as a minimally invasive procedure that does not spread or lift any part of the chest or abdominal wall [33].

A Robotic Portal (RP) approach does not employ any utility incision during the operation (until the removal of the specimen). Robotic operations that include a utility incision are defined as Robotic Assisted (RA) procedures [33].

Robotic Portal (RP) Approach

Cerfolio's completely portal robotic lobectomy with 4 robotic arms consists of a 5-mm port located anteriorly in the mid-axillary line at the 7th intercostal space and the use of a 5-mm video-assisted thoracoscopic surgery camera to enable the surgeon to make all other incisions following thoracic anatomy [22]. With this technique, the surgeon could assist himself, reducing the influence of the assistants' expertise and different technical skills

[22].

Robotic Assisted (RA) Approach

The RATS technique consists of a 3 to 5 cm utility incision, usually at the fifth intercostal space anteriorly to the latissimus dorsi and three other ports. The remaining ports are placed under view guidance [23,34-37]. Although the two previously reported techniques are the most widely used, in daily practice a “surgeon-tailored” approach should be also considered, based on personal experiences and attitudes. The main open issues in literature for RATS are the perioperative and long-term outcomes, the oncological staging and lymphadenectomy, the possibility to obtain a radical resection, the complication rate, the cost-benefit ratio and the training program.

Outcomes

Perioperative outcomes

In the analysis of the Society of Thoracic Surgeons (STS) Database by Louie BE et al in 2016, the incidence of intraoperative bleeding, pneumonia, atrial fibrillation and prolonged air leak is similar between RATS and VATS [38]. Tchouta LN et al compared RATS and VATS complication rates in very low-volume centers (from one to three cases/year) versus high-volume hospitals (15 cases/year or more). Through multivariate analysis, the authors found that high volume centers are not always associated with lower complication rates [39]. However, this study has a selection bias, because more difficult cases are usually referred to more experienced centers and surgeons.

In 2011, Dylewski et al reported on 200 robotic lung resections performed using their approach involving chest cavity insufflation with CO₂ [40]. Perioperative results were satisfactory, with a mean postoperative stay of 3 days, mean duration of surgery 90 minutes, 2% 60-day mortality and 26% morbidity. Also, in 2011 Cerfolio et al. published their experience on a series of 107 four-arm robotic lobectomies, compared with 318 open surgery lobectomies [22]. The robotic group had better quality of life, shorter hospital stay and lower mortality and morbidity than the thoracotomy group. In 2012, Louie et al. published a case-control analysis of anatomic lung resections performed by robotic surgery or VATS [38]. Surgical and postoperative outcomes were similar in both groups, but patients who received robotic surgery had significantly shorter duration of narcotic use and earlier recovery than VATS patients [38].

Mahieu J et al demonstrated that perioperative complication rates are similar between VATS and RATS even in the learning curve, but the robotic approach seems to offer more operative safety with fewer conversions for uncontrolled bleeding [41]. On the other hand, in an early experience with robotic surgery, robotic-assisted lobectomies were associated with a higher rate of intraoperative injury and bleeding [42]. This analysis could be

misleading, as the authors did not consider the center volume and the surgeons' learning curve. Indeed, another study by Oh DS et al focused on the analysis of complication rates only of surgeons who performed 20 or more RP lobectomies. Data highlighted a lower conversion-to-open rate (4.8% vs 8.0%, $p=0.007$) and a lower 30-day complication rate (33.4% vs 39.2%, $p=0.0128$) compared to VATS [43].

Cerfolio et al. analyzed 502 RP lobectomies and 130 segmentectomies, with 16 patients having major vascular injuries (1.2%) [44]. The injury rate was higher for upper lobectomies; the conversion rate to thoracotomy gradually decreased as the team gained experience [44].

Oncological R0 resections can be achieved equally in RATS and VATS [38,45-47]. On a series of 1339 patients, R0 resection was obtained in all but three patients (microscopic R1) [47].

Long-term survival

Disease-free and long-term survival rates are similar for RATS, VATS and open surgery [48]. The incidence of total recurrences was 15%, while the local recurrence rate was 3% [49]. In a retrospective multicentric study, Park et al found a 5-year overall survival (OS) after RATS lobectomies of 91% and 88% for stages IA and IB, and 49% for stage II NSCLC [25]. The 3-year survival rate of N2 patients with adjuvant therapies was 43% [25]. These data, compared to other studies in VATS patients, are consistent both for 5-year OS and stage-related OS [3,50].

In another study by Yang H et al, the authors compared the long-term outcomes for Stage I among RATS, VATS and thoracotomic lobectomies [48]. The 5-year OS was not statistically different among the three techniques (77.6%, 73.5% and 77.9% respectively for RATS, VATS and open surgery). On the other hand, the 5-year disease-free survival was statistically different between RATS and VATS (72.7% and 65.5%), even if multivariate analysis found that the surgical approach was not independently associated with this outcome [48]. Cerfolio RJ et al enrolled 1339 patients in the widest long-term outcomes robotic lobectomy (both RP and RA) study [51]. The 5-year OS reported was 83% for stage IA, 77% for stage IB, 68% for stage IIA, 70% for stage IIB. Moreover, the authors also highlighted the 62% 5-year OS of stage IIIA and 31% for stage IIIB [51].

Staging and lymphadenectomy

A correct staging is crucial for patients' prognostic and therapeutic management [3]. Current guidelines recommend systematic mediastinal lymph node sampling (MLNS) or systematic mediastinal lymph node dissection (MLND) for accurate staging and management in patients with resectable primary lung cancer [52]. Due to the increasing experience in minimally invasive surgery, lymphadenectomy in VATS and RATS

is absolutely comparable to what is reported in literature for open approaches [27].

Toker et al in 2016 compared open, video-assisted and robotic approaches in the dissection of N1 and N2-level lymph nodes during anatomic resections for cancer and concluded that robotic-assisted thoracoscopic procedures dissected more lymph nodes at N1 level vs open thoracotomy, and also compared to VATS approach, even if in this case the difference was not significant. RATS yielded station #11 and #12 lymph nodes in more patients if compared to the other surgical techniques [53].

The upstaging rate after robotic lobectomy is similar to VATS; besides, as RATS upstaging it is often considered only the N1, but not the N2 stations involvement [39,54]. A recent single institution retrospective study demonstrated an increased number of nodal stations accessed by RATS compared to VATS but the upstaging, the 5-year OS and disease-free survival did not vary between the two groups [45].

In N1 positive patients, the dissection and preparation of the hilar elements could be challenging with traditional devices. Robotic surgery may be very helpful in these cases [23,53].

Cost-Benefits analysis

The significant capital outlay for purchasing and maintaining the robot itself and robotic instruments is the most relevant barrier to RATS spreading. Most studies that addressed the issue found that RATS lobectomy is associated with significantly higher costs than both open surgery and VATS, although two studies estimated lower costs for robotics than open surgery mainly due to reduced length of hospital stay [39,55,56]. About the RP technique, the direct costs for a RP lobectomy were about \$13,800 per patient, considering both direct costs, i.e. all the items used for patient management, and indirect costs [55]. Regarding RA surgery, according to the cost analysis made by Novellis et al, the mean additional cost of robotic surgery per operation was \$1,405 compared to VATS and \$1,730 compared to open surgery, while other previous studies have estimated from \$3000 to \$5000 additional costs for RP compared to VATS [55-59].

According to Kajiwara et al, following Japanese health society reimbursement paradigm, institutions would need to perform at least 150 procedures thoracic operation per year to have a positive cost-benefit ratio [60]. In a more recent single institute study from Paul S et al on 184 patients with similar comorbidities who underwent lobectomy or segmentectomy (69 by thoracotomy, 57 by robot, and 58 by VATS), authors found that overall costs (including system cost amortization), differed significantly between the groups [61]. VATS was the less expensive, and robotic surgery was the most expensive procedure. On average, robotic surgery cost \$3,182 more than VATS ($P<0.001$). Although hospital

stay was shorter for robotic patients, the differences between the groups were not significant, and the higher cost of robotic surgery was mainly due to robotic-specific supplies and depreciation. The authors commented that reducing operating times and costs of robotic consumables is needed for robotic surgery to be competitive [61].

The costs of training courses for surgeons and surgical teams also need to be considered. A simulator costs 35,000–158,000 US\$ and is typically sold with the machine, as with the latest Xi system robots [62]. Nevertheless, the sustainability could be achieved thanks to high surgical volumes, standardization and complex procedure performances [63]. One of the most relevant items is efficiency, and most of the times it can be achieved only changing working daily practice [63]. Implementation of protocols helped to effectively contrast unnecessary variations in practice and achieve standardization. For example, at the University of Pisa Multidisciplinary Robotic Center, savings were not obtained directly from innovation but by using innovation as a starting point to stimulate a more efficient organization [63]. Some hospitals purchased a da Vinci robot as a strategic choice unrelated to current cost, with the aim to stimulate clinical research, increasing publications, and enhancing their attractiveness to both patients and young surgeons. The purchase often follows an evaluation of the advantages and disadvantages of the robot system, but costs may be a non-critical aspect of this evaluation [63].

Training

The incidence of severe intraoperative complications during minimally invasive surgery (MIS) is low but potentially life-threatening. Thus, it is critical to perform robotic procedures only after dedicated training [64]. As the Thoracic Robotic Curriculum Development Committee stated, a standardized robotic training curriculum for robotic thoracic surgery should be divided into clearly defined sections as a staged learning pathway; the basic robotic curriculum should include a baseline evaluation, an e-learning module, a simulation-based training (including virtual reality simulation, Dry lab and Wet lab) and a robotic theatre (bedside) observation. Advanced robotic training should include e-learning on index procedures (right upper lobe) with video demonstrations, access to a video library of robotic procedures, simulation training, modular console training to index procedure, transition to full-procedure training with a proctor and final evaluation of the submitted video to certified independent examiners [64].

Training is crucial both for the surgeons and the operating room personnel [65,66]. The thorough knowledge of the console control and the use of simulators may shorten the learning time [67]. The use of a training console should also be considered in order to gain proficiency at switching the arms, using the endowrist instruments and suturing [68]. The learning curve for a

VATS-proficient surgeon should be of at least 20 RATS operations [68]. This is also due to the viewing angle of the hilum, because both in VATS and in RATS the approach is from an inferior point of view, while in open surgery the operator has both a posterior and an anterior view [27]. Veronesi et al, instead, demonstrated that only 20 RATS are also required for a surgeon experienced in major resections, regardless of their open or VATS approach [34]. According to Toker et al, adopting a 3-port RP technique, 14 cases are needed to reach the proficiency in robotic lung resections [69]. The standardization of patients' preparation, robot docking and surgical procedures is crucial for reducing operating times, complication and surgeons' learning curve [24,27]. Besides, a standardized port mapping, applicable to any kind of lung resection, would certainly reduce the learning curve and the overall operating time [70]. An interactive screen is also available for the experienced surgeon to draw on the screen and display optimal hand movements [27].

According to Ricciardi et al., the training program should consist of 3 steps: the use of the simulator; the observation of cases performed by a skilled surgeon and to perform operations proctored by proficient colleagues as the final step [24]. Veronesi et al., during the First international Workshop on Robotic Surgery in Thoracic Oncology, proposed the institution of a Robotic Chest Surgeons Network (ROCS-NET), in order to standardize and certify the robotic training, to monitor centers' quality performance and to enhance research in this field [63].

Conclusion

MIS, both VATS and RATS, is the gold standard for treatment of early stage NSCLCs. VATS and RATS are essentially comparable in terms of peri-operative and long-term outcomes. Different RATS techniques are employed without any difference on results. Standardization should be achieved to facilitate operators' choice. About the costs of RATS, we would like to highlight that RATS is only at its infancy. The same issues reported in the recent years for RATS have been discussed for VATS in 90's [71]. Nowadays, VATS is at its apex, and its role has been clearly established. What if it will be the same for RATS?

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