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Current Status of Minimally Invasive Surgical Approaches for Early Stage Non-Small Cell Lung Cancer: Systematic Review

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Abstract

Resection is the principal mode of treatment for early stage non-small cell lung cancer and the only treatment that is potentially curative. As such, surgical approach can be a crucial factor in successful treatment. Over the past three decades, the surgical modalities within thoracic surgery have undergone massive changes, mainly through the introduction of minimally invasive surgical techniques, such as video-assisted thoracic surgery and robot-assisted thoracic surgery, into the field. The advent of minimally invasive surgical techniques ushered in several advantages over open thoracotomy in the forms of reduced post-operative length of stay, surgical morbidity, functional recovery, and pain. Despite these advantages, opponents of these techniques were weary of their effectiveness in measures such as number of lymph nodes resected, disease-free survivability, cost, and procedure duration. As these techniques developed and evolved, their acceptance has greatly increased as literature

suggests no reductions in oncologic effectiveness, nodal upstaging, disease-free survivability, or overall survivability. More recently, interest has been growing in robot-assisted thoracic surgery as some groups have published results indicating several preferences for the robot-assisted approach over the video-assisted approach when considering outcomes such as morbidity, blood loss, length of stay, and lymph node dissection. In this review, we attempt to explore the current literature surrounding these techniques in hopes of elucidating more about their differences based on recent studies.

Keywords: Lung cancer, Pulmonary Adenocarcinoma, Squamous Cell Carcinoma, Lung resection, Robotic surgery

Methods

PubMed was searched on July 14, 2020 for published articles in English utilizing, “robot,” “surgery,” and “lung” which yielded 1,104 results. Authors manually reviewed all publication results and irrelevant publications were excluded based on title and abstract content. Remaining studies underwent final evaluation in the form of full-text review to determine final inclusion in our study.

We included non-small cell lung cancer studies from 2000 to 2020 that met the following inclusion criteria: 1. Studies comparing video-assisted thoracic surgery (VATS) to robot-assisted thoracic surgery (RATS); 2. Studies evaluating the efficacy of VATS; and 3. Studies evaluating the efficacy of RATS. Studies that did not meet at least one of the inclusion criteria were excluded.

We then individually examined and analyzed studies for outcomes of variable of interest such as morbidity and mortality, lymph node dissection, blood loss and operating time, hospital stay duration, recurrence, and cost, primarily utilizing the differences in means as the principal summary measure.

Introduction

The emergence of Video-Assisted Thoracic Surgery (VATS) greatly increased the field’s interest in minimally invasive surgery (MIS). When compared to open thoracotomy, VATS

offered reduced morbidity, perioperative mortality, blood loss hospitalization duration, pain, and many other benefits[1]. As such, VATS's acceptance and further development ensued largely unhindered, allowing it to manifest into a plethora of Robot-Assisted Thoracic Surgery (RATS) systems.

The first use of a robotic system for pulmonary lobectomy occurred in 2002 with the da Vinci Surgical System (Intuitive Surgical Inc., Sunnyvale, CA, USA)[2]. Since then, several groups have gone on to study the use RATS as an alternative technique to VATS for performing pulmonary lobectomies. This shift in technique was largely due to the advantages RATS was theorized to bring. Although VATS' use in the 1990s allowed for the improved patient outcomes referenced above, shortcomings, such as instrument rigidity, lack of three-dimensional visual field, awkward hand-eye coordination, and a steep learning curve, restricted its ability to overcome open thoracotomy as the most common technique for pulmonary lobectomy[3]. As a result, the introduction of RATS to thoracic surgery, with its augmented dexterity, tele-surgery capabilities, tremor filtration, and three-dimensional field of view, brought several advantages over VATS [4].

Despite these purported benefits of RATS, the extent of the superiority of RATS over VATS was still debated as dissonant data generated by several groups not only con-founded RATS's efficacy, but also it brought to question its practicality; indeed, several variables, such as cost, robot accessibility, duration of surgery, and lack of haptic feedback, had seemingly counteracted the benefits touted by early proponents of RATS [5]. However, subsequent studies, such as those by Bao et al. and Swanson et al., pointed out that many of these drawbacks could largely be attributed to factors such as unfamiliarity with the robot, artificially elevated costs typically associated with novel technology, patient-load, geographical location, etc.

With the generation of larger data sets and a wider variety of trials, groups such as Mungo et al., Toker et al., and Taniguchi et al. generated results suggesting the divide between RATS, VATS, and open thoracotomy was not as wide as previously thought. As the proportion of operations being performed utilizing RATS increased, it became widely accepted that both RATS and VATS offer improved outcomes when compared with open thoracotomy, however, the difference in outcomes between RATS and VATS does not seem to be as apparent [6]. This study aims to elucidate a clearer depiction of the differences in outcomes in VATS vs RATS cases in terms of morbidity and mortality, lymph node dissection, blood loss and operating time, hospital stay duration, recurrence, and cost.

Morbidity and Mortality

It has been strongly supported that VATS and RATS result in improved outcomes in comparison to open thoracotomy when considering parameters including, but not limited to, supraventricular arrhythmias [n = 1397 (13.7%) vs n = 5536 (17.9%); P <0.001], myocardial infarctions [n = 30 (0.3%) vs n = 217 (0.7%); P = 0.011], deep venous thromboses [n = 48 (0.5%) vs n = 303 (1.0%); P = 0.008], and pulmonary embolisms [n = 57 (0.6%) vs n = 323 (1.0%); P = 0.018] [7]. However, when comparing VATS and RATS, the data are much less reliably skewed towards favoring one technique over the other. From their retrospective review following 69 patients from 2011-2012, Lee et al. found morbidity and mortality for RATS versus VATS to be 11% vs 18% (P = 0.46) and 0% vs 3% (P=0.49) [8]. Similarly, Kent et al. conducted a propensity-matched review of the State Inpatient Databases (SID) and, from a pool of 33,095 patients, also found RATS to be slightly in favor of VATS in that RATS was associated with reduction in mortality [n = 1 (0.2%) vs n = 14 (1.1%); P = 0.12] and overall complication rate [n = 180 (43.8%) vs n = 558 (45.3%); P = 0.67], however, these results were not statistically significant. Wei et al. also conducted a retrospective meta-analysis study on 60,959 patients which determined that RATS [n = 4,727] allowed for a significantly lower mortality rate compared to VATS [n = 56,232 (RR = 0.54, 95% CI 0.38-0.77; P = 0.0006)], however, upon comparison with the pooled result of six matched studies (RR = 0.12, 95% CI 0.01-1.07; P = 0.06), it was determined that the difference in morbidity between the two surgical approaches was not significant (RR = 0.97, 95% CI 0.85-1.12; P = 0.70)[3].

Although Toker et al. found similar results in terms of morbidity and mortality between the two techniques, they brought attention to the fact that most groups were comparing a brand new surgical technique to one that had already been established and finding them to be comparable [9]. The ability of new robotic surgeons to perform at the same level of surgeons with extensive VATS experience suggests that starting a robotic surgery program, unlike VATS, can be done safely and quickly without a steep learning curve [9].

Yang et al. were one of the first groups to explore a potential difference in Disease-Free Survival (DFS) between RATS and VATS patients, and with a study on the larger end [n = 498], they were able to show a significant difference in DFS between RATS and VATS from, however, only via univariate regression analysis and not multivariate [10].

As more studies suggested equivalency in terms of surgical capability, the proportion of lobectomies performed via RATS exponentially increased and, in 3 years, grew from 0.2% of all lobectomies in the US to 3.4% [6]. Currently, RATS is estimated as being utilized for approximately 25% of all lobectomies in the US [11]. The increasing utilization of RATS allowed for many more studies to be conducted such as the systematic review and meta-analysis by Emmert et al. who pooled a sample of 62,435 patients (3,758 underwent RATS and 58,677 underwent VATS) from six studies and found a combined mortality odds ratio of 0.52 (95% CI [0.29-0.92]) for RATS, or a 2-fold decrease compared to VATS [12].

Lymph Node Dissection

The extraction of lymph nodes for pathological examination in lung cancer patients is one of the cornerstones of lung cancer treatment and prognosis. As such, many studies have focused on determining whether open thoracotomy or VATS is superior for lymph node extraction. For example, Wang et al. and Sato et al. found that VATS is superior to open thoracotomy, however, in their studies, Denlinger et al., Ramos et al., and Merritt et al. concluded that open thoracotomy is the more effective approach [13–17]. With the introduction of RATS, however, it was found to be the superior method for lymph node dissection. In a study of 69 patients who underwent minimally invasive lobectomy between 2011 and 2012, Lee et al. found that median number of lymph nodes harvested via RATS to be 18 and via VATS to be 16 ($P = 0.42$) with no statistical difference in number of lymph nodes dissected, stations retrieved, or complication rate [8]. As RATS gained traction in the field and physicians became more accustomed to using it, further studies were carried out and subsequent groups comparing RATS and VATS tended to have more consistent results [6]. In a study of 270 subjects, Toker et al. found that not only did RATS produce more lymph nodes (14.9 ± 6.5) than either VATS (11.7 ± 4.7) or open thoracotomy (12.0 ± 6.4 ; $P = 0.0007$), but also the RATS approach was able to dissect more N1-level nodes than either VATS or open thoracotomy (6.8 ± 3.7 , 3.8 ± 2.1 , and 4.0 ± 2.7 , respectively; $P < 0.0001$). In their study, Cerfolio et al. demonstrated that even an inexperienced surgeon was able to dissect as many lymph nodes using RATS as an experienced surgeon would using open thoracotomy [18].

Blood Loss and Operating Time

As RATS was beginning to take traction in thoracic surgery, early retrospective studies comparing all three techniques from 2008 through 2012 found that RATS [$n = 57$], VATS [$n = 58$], and open thoracotomy [$n = 69$] average 223, 202, and 180 minutes of operating time,

respectively, with each method being statistically different from the other two (open vs RATS; $P < 0.001$, open vs VATS; $P = 0.02$, and RATS vs VATS; $P = 0.045$) [19]. Lee et al. also found there to be a statistically significant difference between the operating times of RATS and VATS and reported RATS upper and lower lobectomies to take 172 and 140 minutes, respectively, and VATS upper and lower lobectomies to take 134 and 123 minutes, respectively, with statistical significance only between upper RATS and VATS; $P = 0.001$ [8]. The difference in lower lobectomy operating times was not statistically significant between RATS and VATS [8]. Demir et al. also studied operating times of VATS and RATS, however, their study ranged from 2007-2014 [20]. Demir et al. found the two surgical approaches started off significantly apart in operation time, with RATS taking longer than VATS to perform [76 ± 23 vs 65 ± 22 ; $P = 0.018$]. However, despite using VATS for the full seven years of the study and RATS for only the last two years of the study, "...the duration of both operations reached similar levels as the maturity in robotic surgery increased" due to its relative ease of learning [20].

Taniguchi et al. documented an experience similar to Demir et al. such that their team also became accustomed to RATS and drastically reduced operation time [20]. Taniguchi et al. bifurcated their cases and assigned them to an initial period and a later period of using RATS (2011-2016) [21]. Initially, median operation time was 239.5 minutes with 179 minutes of console time, however, in the latter half of their study, operating and console times had shortened down to 215 and 159.5 minutes, respectively ($P = 0.0001$) [21]. Novellis et al. further bolster the notion that experience with RATS greatly increases efficiency with their retrospective study aimed at measuring operation time of RATS and VATS in teams that have attained full proficiency in their respective approach [22]. Novellis et al. report being early adopters of both VATS and RATS, and after comparing them with open thoracotomy, they found that VATS, RATS, and open thoracotomy occupied 191, 150, and 116 minutes of time, respectively ($P < 0.001$) [22]. Zhou et al. also noted similar experience with operation duration in that, from a sample of 130 subjects ([RATS, $n = 50$], [VATS, $n = 80$]), they also had a statistically significant shorter duration for RATS (89 minutes) than for VATS (115 minutes; $P = 0.005$) [23].

Additionally, Zhou et al. documented a statistically significant difference in the amount of blood lost during RATS (50 mL) and VATS (80 mL; $P = 0.000$) [23]. Taniguchi et al. also documented blood loss throughout their study and found that initial RATS phase blood loss median was 50 mL with a latter RATS blood loss median of 5 mL ($P = 0.008$) [21].

Length of Stay

Another theorized benefit of RATS is length of hospital stay. This is attributed to the greater level of control afforded by the 7 degrees of freedom which allow it to perform complex maneuvers and fit into tight spaces, arms that rotate around a fulcrum within the robot itself rather than the chest cavity and applying damaging torque as is possible with VATS, and vastly superior viewing capabilities composed of up to a 10x magnification lens and 3-Dimensional field of view [5]. As a result of a more dextrous system with lower risk for damaging structures, it has been observed that RATS patients tend to return to activities of daily living sooner, use few narcotics, and shorter hospital stays [24]. Early studies regarding the difference in length of stay (LOS) between RATS and VATS associated RATS with a reduction in mortality, LOS, and complication rate ([0.2% vs 1.1%; $P = 0.12$], [5.9 days vs 6.3 days; $P = 0.45$], and [43.8% vs 45.3%; $P = 0.68$], respectively), however, none of these associations were statistically significant [6]. Demir et al. also studied LOS and, from a sample of 99 subjects spread out from 2007-2014, also found RATS to be associated with improved outcomes over VATS in the forms of reduced chest tube drainage duration and postoperative stay ([3.53 ± 2.3 days vs 3.98 ± 3.6 day; $P = 0.90$] and [4.65 ± 1.9 days vs 6.16 ± 4.7 ; $P = 0.39$]), however, neither of these results was statistically significant [20].

In a retrospective study examining 133 patients, 80 of which underwent VATS while 53 underwent RATS, Mungo et al. found that RATS is associated with fewer conversions to open thoracotomy (13.2% vs 26.2%; $P = 0.025$), however, univariate regression analysis revealed no association between any measured variables and, "...conversion to open thoracotomy, LOS, perioperative events, or repeat operation" [10].

Novellis et al., however, report in their 2018 retrospective study involving 103 subjects that median LOS for RATS, VATS, and open thoracotomy are 4, 5, and 6 days, respectively ($P = 0.001$) [22]. In their retrospective review of 121 patient outcomes from 2014-2017, Li et al. also reported a statistically significant shorter LOS with RATS over VATS (4 vs 5 days; $P < 0.01$) [25]. In a very similar manner, Zhou et al. also reported a statistically significant shorter LOS for RATS than for VATS (4 vs 5 days; $P = 0.001$), respectively [23].

Recurrence

Recurrence of tumors following resection in early-stage NSCLC is dependent on numerous factors and, because currently surgery is the only potential cure for NSCLC and recurrence is estimated to occur in 30% to 55% of patients, it is of the utmost important to determine the

most efficacious surgical technique [26–28,29(p20)]. Park et al. conducted one of the first multi-institutional retrospective review on 325 patients who underwent resection via RATS from 2002-2010 and found their 5-year overall survivability (OS) rate to be 80% (95% CI = 73-88) [30]. Yang et al. also conducted a study on long-term survival of NSCLC, and from after analyzing the data of 470 patients who underwent resection between 2002 and 2012, it was determined the 5-year OS rates for RATS, VATS, and open thoracotomy were 77.6%, 73.5%, and 77.9%, respectively with no statistically significant difference [31]. Additionally, the 5-year DFS rates were 72.7%, 65.5%, and 69.0% for RATS, VATS, and open thoracotomy, respectively, all without a statistically significant difference following multivariate analysis besides from a slight preference for RATS over open thoracotomy (hazard ratio of 1.41; P = 0.063) .

A study that followed a more recent cohort of patients was conducted by Taniguchi et al. in which 44 patients from 2011-2016 underwent resection via RATS and produced a 5-year overall survival (OS) rate of 100% and a 5-year DFS rate of 88.9% [21]. In a similar light, Zhou et al. also followed a more recent cohort of patients, however, they focused on elucidating a potential difference in OS and DFS rates between RATS and VATS [23]. The RATS cohort has a median follow-up of 38 months and had zero recurrences, meanwhile, the VATS group had an 85-month follow-up and had 5 cases of recurrences; 2 local and 3 distant [23]. The two cohorts' 5-year OS rates were 100% and 98.75% for RATS and VATS (P = 0.642), respectively, and their 5-year DFS was 100% and 93.75% for RATS and VATS (P = 0.144), respectively [23].

Cost

A major concern commonly cited by opponents of RATS are the increased costs associated with the technique along with the barrier to entry due to its \$1,000,000-\$2,500,000 purchase price and \$100,000-\$170,000 annual maintenance cost [19,32–34]. Indeed, when Swanson et al. conducted a retrospective study of 15,502 individual patient records (n = 14,837 for operations done without robot assistance) for excision surgeries performed between 2009 and 2011, analyzing the costs for RATS and VATS revealed the two approaches cost \$25,040.70 vs \$20,476.60 (P = 0.0001), respectively [35].

Furthermore, despite the reduced postoperative stay RATS affords the patient (4 vs 5 days average LOS), the savings of one fewer hospital day admission still does not make up for the cost difference between RATS and VATS [22].

In addition, RATS must not only offer an improvement over VATS and open thoracotomy to make up for purchase price, procedure cost, and robot maintenance, but also to make up for the depreciation of the robot which Deen et al. calculated out to be \$1,200 US per case [19]. Deen et al. compared the costs of RATS, VATS, and open thoracotomy utilizing their area's relevant prices and determined the costs to be \$17,011.02, \$13,829.09, and \$15,036.32, respectively, with a statistically significant difference in costs between RATS and VATS ($P < 0.001$) (19).

Conclusion

The most recent literature continues to advocate surgery as the preferred treatment option for patients with NSCLC, however, over just the last decade or so, it appears a paradigm shift has occurred such that MIS techniques have been found to be not only as oncologically effective as open thoracotomy, but also more so. This difference is seen when comparing RATS to open in terms of morbidity and mortality, number of lymph nodes dissected, blood loss, and length of stay with less obvious discrepancies in recurrence and cost and open thoracotomy generally having a shorter operation duration. When comparing RATS to VATS, technique preference becomes less drastic, however, we tended to notice a general trend of RATS capabilities improving with time and eventually superseding the results of VATS cases. The most recent literature gravitates towards RATS resulting in superior outcomes when compared to VATS in terms of morbidity and mortality, number of lymph nodes dissected, blood loss, and length of stay with less obvious differences in operation duration and recurrence rate. Expenses tended to remain in favor of VATS.

Author Contributions:

(I) *Conceptualization*: MJ, BC, WV; (II) *Data Analysis and Interpretation*: MJ; (III) *Data Assembly*: MJ; (IV) *Data Curation*: MJ; (V) *Funding Acquisition*: WV; (VI) *Methodology*: MJ, BC, WV; (VII) *Project Administration*: WV; (VIII) *Review and Editing*: MJ, BC, WV; (IX) *Validation*: WV; (X) *Writing*: MJ

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