NIF-GUIDED SEGMENTAL RESECTION FOR LUNG CANCER

THE ROLE OF NEAR-INFRARED GUIDED ANATOMIC SEGMENTAL RESECTION FOR EARLY-STAGE NON-SMALL CELL LUNG CANCER

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TITLE: The Role of Near-Infrared Guided Anatomic Segmental Resection for Early-Stage Non-Small Cell Lung Cancer

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Abstract

Robotic-assisted segmentectomy is a pulmonary resection procedure that is emerging as an alternative to lobectomy for the treatment of early-stage lung cancer tumours less than 2 cm in maximal diameter. Segmentectomy offers better lung function after surgery by only removing a few segments of the lobe that contain the tumour, and sparing remaining healthy lung tissue. As tumours are being more frequently detected in their early-stages, segmentectomy has gained considerable attention for its potential as a primary treatment option for suspected nodules less than 3 cm in maximal diameter. However, there is a reluctance in adopting segmentectomy due to technical challenges while performing the operation, and the lack of high-quality prospective data compared to lobectomy, which is the current standard of care.

From a technical standpoint, segmentectomy is difficult to perform because the pulmonary lines that separate segments, or intersegmental planes, are invisible. This poses a challenge for the operating surgeon in determining where to resect the lung tissue to obtain adequate margin distance from the tumour. Near-infrared mapping (NIF) with indocyanine green dye (ICG) is a recent advancement in robotic-assisted segmentectomy that provides a complete delineation of the intersegmental plane. Previous work at our center has also shown that this technique was associated with an increase in the oncological margin distance compared to the surgeons' initially estimated resection line. Given that segmentectomy is associated with a learning curve, we evaluated whether this was observed due to our early experience in robotic-assisted segmentectomy, and hypothesized that the added benefit of ICG would diminish as more cases were performed. In Chapter 2, we used a temporal analysis to

monitor surgeon experience over time, and found that the clinical utility of NIF mapping diminished after approximately 42 cases with ICG, and the surgeon began to identify the location of the intersegmental plane more accurately and consistently without ICG injection since.

The second barrier in the adoption of segmentectomy is the lack of high quality-prospective data. Current evidence pertaining to the effectiveness of segmentectomy in terms of cancer-related outcomes is inconclusive and difficult to generalize to the current lung cancer population. In Chapter 3, we performed a secondary analysis of a prospectively collected database of participants who underwent robotic-assisted segmentectomy or lobectomy for tumours less than 3 cm. The oncological efficacy of segmentectomy can be evaluated by the measuring the number of lymph node stations sampled intraoperatively and rates of nodal upstaging, and comparing these outcomes to pulmonary lobectomy. These are important surrogate outcomes that can be readily evaluated, and have been shown to predict overall survival after lung resection. We observed that these outcomes, including overall survival, were similar between patients who underwent segmentectomy and lobectomy for tumours less than 3 cm. While these findings were consistent for patients that underwent segmentectomy for tumours between 2 and 3 cm, recurrence-free survival was found to be significantly lower after segmentectomy compared to lobectomy.

In conclusion, the clinical utility of near-infrared mapping diminishes over time, which is indicative of an improved ability to perform robotic-assisted segmentectomy as more cases were attempted. Second, adequate lymph node evaluation can be expected after segmentectomy, reducing the likelihood of missing positive lymph nodes. Although patients who underwent segmentectomy for tumours greater than 2 cm may be at a greater risk of experiencing recurrence compared to lobectomy, this population did not experience any reductions in overall survival.

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Table of Contents

Chapter 1: Evaluating the Role of Segmentectomy for Early-Stage Non-Small Cell Lung Cancer

1.1 Rationale

The most common type of lung cancer is non-small cell lung cancer (NSCLC), accounting for more than 80% of lung cancer cases.[1] Lung cancer is the leading cause of mortality and accounts for nearly a quarter of all cancer deaths reported in Canada.[2] As more jurisdictions implement organized lung cancer screening programs,[2,3] small nodules are being frequently detected and the demand for surgical resection is rising rapidly.[4,5] Patients with early-stage NSCLC typically undergo curative-intent surgery with lymph node harvesting to detect nodal metastases. Pulmonary lobectomy, which involves the total removal of the diseased lobe, is the most frequently used resection procedure, and is generally regarded as the gold standard for early-stage lung cancer.[6] Pulmonary segmental resection, or segmentectomy, is emerging as an alternative to lobectomy for tumours less than 2 cm in maximal diameter. The role of pulmonary segmentectomy in the current landscape of early-stage NSCLC care has yet to be fully investigated.

1.2 Surgical Resection for Lung Cancer

Both human lungs consist of ten bronchopulmonary segments, and each segment has its own pulmonary arterial and venous supply. Subcentimeter nodules can be fully removed by only resecting the target segment(s) in which they are contained, instead of resecting the entire lobe. Segmentectomy preserves post-operative lung capacity and may also provide several advantages compared to lobectomy, including shorter operative time and length of hospital stay. Segmentectomy also allows patients with multiple bilateral evolving nodules to undergo future resections if needed. However, there is a reluctance in adopting segmentectomy as it is challenging to perform and is associated with a demanding learning curve.[7,8] This is due to multiple variations in each segment's bronchopulmonary anatomy,[9–11] difficulties maneuvering surgical equipment,[12] and a restricted field of view during critical portions of the operation.[13–15] Furthermore, pulmonary intersegmental planes (ISP), which divide bronchopulmonary segments, are invisible to the naked eye, adding a layer of complexity to the operation. The intersegmental plane is often estimated by the operating surgeon, which may result in an inability to ensure adequate surgical margins.[16] When the ISP cannot be adequately estimated, the traditional "inflation-deflation" (ID) technique requires an additional 20 minutes of operating room time, and is difficult to employ in patients with pre-existing pulmonary conditions, such as chronic obstructive pulmonary disorder.[13]

Robotic-assisted thoracoscopic surgery has addressed many technical limitations encountered during video-assisted thoracoscopic surgery. The robotic platform is equipped with three-dimensional (3D) optics and higher instrument precision, enabling thoracic surgeons to perform more complex operations. The advantages of the robotic platform are especially apparent during anatomic segmentectomy, which requires meticulous intraparenchymal dissection to expose the segmental bronchus and vessels.[17] Near-infrared (NIF) mapping with indocyanine green (ICG) dye is a recent advancement in minimally invasive segmentectomy that permits the intraoperative identification of the intersegmental plane.[15] After ligating the corresponding bronchus and vessels to the target segment, ICG is injected intravenously and perfuses through all lung tissue except the isolated segment. A clear demarcation between the isolated segment and the rest of the lung can be observed within a few seconds under near-infrared light, providing a clear delineation of the intersegmental plane. We have previously reported our initial experiences with NIF-guided robotic-assisted segmentectomy.[16] We observed that ICG injection was associated with an increase in the oncological margin distance, by correcting the surgeons' cautery-marked estimate of the location of the intersegmental plane by an average of 2 cm away from the tumour. We reasoned that this benefit of ICG injection in securing margin distance would diminish as more cases were performed. In Chapter 2, we describe our findings pertaining to the relationship between the added value of indocyanine green dye injection and surgeon experience during robotic-assisted segmentectomy.

1.3 Evaluating the Efficacy of Lung Cancer Surgery

A renewed assessment of segmentectomy compared lobectomy is warranted due to substantial improvements in the diagnostic pathway for NSCLC, and ongoing consolidation of minimally invasive techniques.[18] Mediastinal lymph node (LN) involvement in patients with lung cancer is an important prognostic factor and influences therapeutic decisions.[19,20] While it is agreed that nodal staging must be as precise as possible, there is no consensus surrounding the optimal degree of lymph node assessment, or the number of lymph nodes that should be evaluated following lung resection.[19] Adequate LN sampling decreases the likelihood of missing positive lymph nodes, which permits a more precise staging.[21,22]

Lobectomy has been established as the gold standard surgical treatment since a randomized control trial in 1995 comparing lobectomy to sublobar resection.[6] This trial found that sublobar resections were associated with a 3-fold increase in local recurrence rates, and that they should only be used in patients with compromised lung function who could not tolerate the removal of an entire lobe. In recent years, several retrospective investigations and meta-analyses have challenged this finding, and segmentectomy is being increasingly used as the primary treatment option for early-stage NSCLC less than 2 centimeters in diameter.[23,24] However, the quality of evidence guiding this shift in surgical practice is low, and there is a demand to validate these results through prospective methodology.[23] Furthermore, the role of segmentectomy for tumours greater than 2 cm and less than 3 cm (T1cN0M0), which are still considered early-stage, remains fully undefined.[25]

Despite the known prognostic role of mediastinal nodal involvement, recent investigations comparing segmentectomy to lobectomy for these tumours seldom report the oncological quality of the resection procedure, and instead emphasize long-term recurrence and survival outcomes.[18,23,24] Indeed, those are important endpoints to study, yet they are difficult to validate in the absence of short-term data pertaining to surgical quality and the extent of lymph node sampling which are predictive of those endpoints.[19,23,24,26] Furthermore, the extent of lymph node assessment can be influenced by the clinical indication for sublobar resection, and the operating surgeon's technical ability in minimally invasive surgery.[23,27–29]

The oncological efficacy of robotic segmentectomy can be evaluated against robotic lobectomy by measuring differences in the number of lymph node stations sampled and rate of nodal upstaging.[21,28,30] From a research methodology perspective, these outcomes are advantageous to study as they can be readily collected and analyzed in a prospective manner. Analyzing these surrogate outcomes may also provide insights on the potential impact of lymph node dissection on long-term clinical endpoints. We hypothesized that in patients undergoing robotic-assisted segmentectomy with LN sampling for tumours less than 3 cm, the number of lymph node stations sampled, and rate of nodal upstaging will be similar to robotic-assisted lobectomy. In Chapter 3, we compare the oncological efficacy of robotic-assisted segmentectomy and evaluate the impact of segmentectomy on overall survival for non-small cell lung cancers.

In Chapter 4, we will present a summary of our methods and findings, observations, and how this thesis contributes to current knowledge surrounding the optimal surgical treatment for early-stage non-small cell lung cancer.

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Chapter 2: Segmental Resection for Lung Cancer: The Added Value of Indocyanine Green Dye Injection Diminishes with Surgeon Experience

Abstract

Introduction: Robotic-assisted segmentectomy is emerging as a standard operation for early-stage non-small cell lung cancer. Near-infrared fluorescence (NIF) mapping with indocyanine green (ICG) dye facilitates the identification of the true intersegmental plane of resection in the lung, which is often different from the plane predicted by the operating surgeon. We hypothesized that as surgeons gain more experience in segmentectomy, the measured distance between the true plane and the predicted plane will approach zero.

Methodology: This study is a phase 2, single-arm, prospective trial in patients undergoing robotic-assisted segmentectomy for lung tumours < 3 cm. At the time of surgery, the predicted intersegmental plane was identified by consensus between 2 thoracic surgeons prior to ICG injection. Then, the true plane was mapped by intravenous ICG injection. The average distance between the true plane and the predicted plane was recorded and compared across temporal tertiles. The first tertile comprised of 30 participants, which is the required number of cases to attain proficiency with the robotic platform, and the remaining participants were divided equally for the second and third tertile. A Kruskal-Wallis test was used to compare differences between tertiles.

Results: A total of 190 consecutive patients were enrolled from October 2016 to June 2021. Median (interquartile range) age was 68 (62-72), and 42% were men. The planned intervention with ICG was completed in 61% (115/190) of the participants, and intersegmental plane visualization was achieved in 88.7% (102/115). The mean measured distance between the true plane and the predicted plane was 19.4±4.2 mm in the first tertile, 2.18±2.6 mm in the second, and 2.48±1.5 mm in the third ($p<0.001$). Locally estimated scatterplot smoothing revealed that this distance approaches zero as the surgeon performs more cases.

Conclusion: In robotic-assisted segmental resection for lung cancer, the added value of NIF-mapping diminishes with surgeon experience.

2.1 Introduction

2.1.1 Background

Anatomic segmental resection is emerging as an alternative to lobectomy as the standard surgical treatment for non-small cell lung cancer tumours. With the advent of low-dose CT screening, subcentimeter pulmonary nodules are being frequently detected and the demand for pulmonary segmentectomy is rising rapidly. Segmentectomy is a valuable resection procedure that preserves viable sublobar lung tissue and is being increasingly utilized for suspected nodules less than 2 cm, with no clinical evidence of lymph node metastasis at clinical staging (stage T1bN0M0 or below according to the eight edition TNM classification system[1]). However, segmentectomy is difficult to perform because of the high level of dissection into the lung parenchyma required to isolate the diseased segment, and lack of visible pulmonary intersegmental planes. Furthermore, variations in segmental anatomy from patient to patient adds a layer of complexity to the operation.[2,3]

2.1.2 Near-Infrared Mapping during Minimally Invasive Segmentectomy

When performing anatomic segmentectomy, it is important for surgeons to identify the correct anatomic intersegmental plane, to avoid unnecessary parenchymal resection and preserving maximum pulmonary function.[4,5] Near-infrared (NIF) mapping with indocyanine green dye (ICG) allows for the identification of the invisible intersegmental plane in a deflated lung state following the isolation of the target segment containing the tumour. This technique was initially described in two cases undergoing robotic anatomic segmentectomy by Pardolesi and colleagues.[6] Indocyanine green dye has since been extensively evaluated, and has a reported a success rate from 90-100% in demarcating the intersegmental plane during video-assisted surgery.[4,5,7–9] However, there is a paucity of literature on the clinical utility of NIF-guided segmentectomy during robotic-assisted surgery.

The clinical benefit of indocyanine green dye injection is that it clarifies the actual margin of the tumour from the intersegmental plane, which is often selected as the resection line.[5] In a pilot study conducted at our center, we aimed to assess the reproducibility of NIF mapping and whether it provided any added oncological margin distance from the tumour to the staple line, compared to the surgeons' best judgment.[10] In the cohort of 31 patients who underwent the planed NIF-guided segmentectomy procedure, ICG provided an average 2 centimeters of additional oncological margin distance in a majority of cases where it was used. Given that segmentectomy is an operation with a known learning curve, we suspected that this could have been observed because of our early experience in the procedure. We hypothesized that as more cases were performed, the plane mapped by ICG will become closer to the surgeons' predicted plane marked by electro-cautery.

2.2 Objective

The objective of this study is to determine the potential relationship between surgeon experience and added utility of NIF mapping (measured by added oncological margin distance) in patients undergoing robotic-assisted segmentectomy with ICG dye for suspected or confirmed early-stage non-small cell lung cancer tumours.

2.3 Methods

2.3.1 Study Design

This is a prospective trial of robotic-assisted thoracoscopic segmental resections for non-small cell lung cancer (NSCLC) between October 2016 and June 2021. Informed consent was obtained from all participants. Eligible patients were older than 18 years of age, with suspected or confirmed non-small cell lung cancer or isolated metastases to the lung, and peripheral tumours less than 3 cm in maximal diameter. Preoperative computed tomography (CT) was used to confirm that the tumour was isolated to 1 or more bronchopulmonary segments amenable to segmental resection. The exclusion criteria were hypersensitivity to contrast dye, pregnant or breastfeeding women, or women of child-bearing potential not taking adequate birth control. Patients were prospectively enrolled in the study and were followed for 30 days post-operatively.

2.3.2 Research Ethics Approval and Trial Registration

This study was granted a no objection letter from Health Canada authorizing the off-label use of ICG (#184323) and was approved by the Hamilton Integrated Research Ethics Board. The study was carried out in compliance with the Canadian Tri-Council Policy Statement on Ethical Conduct for Research Involving Human Subjects.[11] Informed consent was obtained from all participants for the surgical procedure and the experimental nature of the ICG intervention. This trial was registered on www.clinicaltrials.gov (#NCT02570815).

2.3.3 Surgical Technique

Operations were conducted by one surgeon on the DaVinci Si and Xi (Intuitive Surgical, Sunnyvale, Calif) robotic platform, using the Completely Portal 4-Arm approach,[12] and Firefly Fluorescence Imagine camera (Intuitive Surgical) as a NIF light source. Following ligation of the corresponding segmental artery, vein, and bronchus, the attending surgeon identified the predicted intersegmental plane (Dp) via consensus, which was marked by cautery for future reference. Next, ICG was reconstituted into distilled water to produce a 2.5mg/mL solution, and a volume of 6 to 10 mL (dose of 15-20 mg) was injected in a peripheral intravenous catheter, followed by a 10-mL flush of sterile normal saline. After injection, the surgical field was visualized with the integrated fluorescence imaging capability of the Firefly camera. The target segment, isolated from the pulmonary vasculature, exhibited no fluorescence, and remained dark. The remainder of the lung, perfused with ICG, exhibited bright green fluorescence. The true intersegmental plane (Dt) was identified as the line separating the dark lung parenchyma from the green lung parenchyma. The true plane was then marked by cautery and stapled across to complete the division of the lung, and extract the diseased tissue.

2.3.4 Intraoperative Outcome Measures

All cases that received near-infrared mapping with indocyanine green dye injection were scored using a 7-item binary scale previously described by our center, which indicated the safety, feasibility, and reproducibility of the technique.[10] To summarize, a score of 1-5 indicated a non-successful segmentectomy following intravenous ICG injection, a score of 6 or 7 indicated a successful segmentectomy. A score of 6 indicated that the intersegmental plane mapped by ICG matched the previously marked plane by electrocautery. A score of

7 indicated that ICG corrected the surgeon's estimate of the intersegmental plane, for which the average distance between the true plane and the predicted plane (Dt-Dp) was measured and reported in millimeters (mm). Dt-Dp could also be considered an assessment of the added-value as the added distance from tumour to the resection edge of the specimen thanks to ICG. A difference less than 0 mm would theoretically increase the amount of lung tissue preserved, however, for oncological considerations, the surgeon did not follow Dt when it was closer to the tumour than Dp. As such, the definition for the 7th item on the binary scale was adjusted to only reflect a positive difference in Dt-Dp. (Figure 1) This was different from the original definition, which reflected the added-value of ICG by whether the NIF-guided plane was different at all from the predicted plane.[10] Dt-Dp was the primary outcome of this study. (Figure 2)

All cases were attempted robotically at the beginning of the operation. Intraoperative switches to lobectomy were mandated when N1 disease was suspected or confirmed on intraoperative frozen section, when positive margins were suspected on the resection specimen, or when the tumour was not found in the resection specimen. Conversions to thoracotomy occurred due to intraoperative complications or inability to progress robotically.

2.3.5 Data Items

Following enrollment, baseline data on patient demographic characteristics, medical history, social history, diagnosis, preoperative tests, and preoperative staging were collected. Preoperative variables included age, sex, smoking status, medical history, tumour size and location, pulmonary function, planned resection and complexity. Segmentectomy complexity was defined as “simple” or “complex”. Segmentectomy that creates one linear intersegmental plane were defined as simple, which included segmental resection of superior segment (S6) or lingula (S4+S5) on any side, as well as left upper lobe divisions (S1+S2+S3). Segmentectomy that creates several or intricate intersegmental planes were defined as complex, which essentially included all non-simple segments (e.g., S3 segmentectomy, S9+S10 segmentectomy, S1+S3 on the left). The decision to perform either operation was based on tumour location and size based on pre-operative CT scan. Intraoperative variables included date of operation, post-operative diagnosis, tumour stage and maximal diameter, pulmonary resection type, additional resections, switches to lobectomy, conversions open thoracotomy, additional resections, total operative time, and operative time on the robotic console. Safety variables included any intraoperative or post-operative complications. Any serious adverse events resulting as a direct consequence of ICG administration was to be reported to the local institutional review board. Postoperative variables included hospital length of stay, duration of chest tube drainage and postoperative complications and/or adverse events for up to 3 weeks post-operatively (assessed using the Ottawa Thoracic Morbidity & Mortality System[13]).

2.3.6 Statistical Analysis

A per-protocol analysis was used, analyzing patients who received the ICG intervention. Descriptive statistics (median, [interquartile range]) was used to present the data. The percentage of successful cases was calculated as the sum of the number of cases scoring either a 6 or a 7 on the rating scale, divided by the total number of procedures where ICG was used. To assess the presence of a learning curve, all cases were divided into three temporal intervals. Tertile 1 (t1) comprised the first 30 "training" cases, and the remaining cases were divided evenly between Tertile 2 (t2) and Tertile 3 (t3). We used the Kruskal-Wallis test to compare differences between tertiles for non-parametric data and one-way analysis of variance for parametric data. A Chi-square test was used to compare categorical variables across tertiles. To observe the effects of a learning curve, a locally estimated scatterplot smoothing (LOESS) where ICG case number (X-axis) was plotted against Dt-Dp. Statistical tests were two-sided, and the level of significance was set at $\alpha = 0.05$.

2.3.7 Secondary Analysis

A Mann-Whitney U test was used to compare differences in our primary outcome between complex and simple segmentectomy. A binomial logistic regression to determine factors associated with Item #7 on the 7-item binary scale, the ability of indocyanine green to correct the surgeon's predicted plane to be farther from the tumour. These factors included case number, age at surgery, body mass index, forced expiratory volume %, console time, segment location & complexity and tumour size.

2.4 Results

2.4.1 Study Population

A total of 190 consecutive patients were enrolled in this study between October 2016 and June 2021. The median age was 68 (interquartile range [IQR] 62-72), and 42% (n=81) were men. (Table 1) Of this sample, 17% (n=33) never smoked, 54% (n=103) were former smokers, and 28% (n=54) were active smokers. Previous cancer was reported in 47.4%

(n=90) patients, and 8.9% (n=17) had a history of lung cancer. Median tumour size was 1.7 cm (IQR 1.2-2.2). Tumour location was most prevalent in the left upper lobe (34.7%). The most commonly resected segmentectomy were the left upper lobe apicoposterior (S1+S2) segment (16.8%), followed by the posterior segment (S6) of the right lower lobe (13.2%).

The first tertile (t_1) comprised of 30 cases (October 2016 – January 2018, 454 days), the second tertile **(**t_2) comprised of 80 cases (January 2018 – December 2019, 713 days) and the third tertile (t_3) comprised the remaining 80 cases (December 2019 – June 2021, 525 days). (Table 2) Twenty-nine participants underwent completion lobectomy (15.2%; n=20 via robotic, n=9 via open thoracotomy), and the proportion of these decreased significantly across tertiles, with 30.0% (9/30), 13.8% (11/80) and 11.3% (9/80) occurring in t1, t2, and t3 respectively (p=0.046). Eleven (11/29, 37.9%) were due tumour or nodal upstaging, and 12 (12/29, 41.4%) more were due to difficult resections. Three more cases (3/29, 10.3%) were converted after ICG injection. Conversion to open thoracotomy (n=19, 10.0%) occurred primarily due to dense adhesions or patient inability to tolerate single-lung ventilation (n=9). Conversion to open thoracotomy also occurred due to injury of the pulmonary artery or to safely access the pulmonary artery to perform a dissection and arterioplasty (n=6; 1 in t1, 5 in t2, 0 in t3). Post-operatively, major complications occurred in 8.9% of participants. One participant died three days after surgery due to a left middle cerebral artery stroke. Operative measures and complications grades are summarized in Table 3 and Table 4.

2.4.2 Perioperative Outcomes

Indocyanine green injection after vascular ligation occurred in 115 participants (60.5%), and all were included in the temporal analysis. The median length of hospital stay (LOS) was 3 days (IQR 2-5) and the median duration of chest tube drainage was 2 days (IQR 1-4). Operating room time and console time did not differ significantly across tertiles ($p=0.075$ and $p=0.053$ respectively), yet skin-to-skin procedure time decreased by approximately 18 minutes after t2 ($p=0.014$). There were no ICG-related adverse events. Five patients (4.34%) experienced intraoperative complications, and 52 patients (45.2%) experienced post-operative complications during the hospital stay.

There were no significant differences in the number of patients who received ICG in each tertile (t1: n=18/30 (60.0%); t2: 49/80 (61.3%); t3: n=48/80 (60.0%); $p=0.985$). Successful intersegmental plane visualization using ICG was achieved in 102 out of 115 participants (88.7%), indicated by a score of 6 or 7 on the binary scale. Unsuccessful intersegmental plane visualization occurred in 13 cases (11.3%) due to: no demarcation of a dark segment after ICG injection (7-item binary score of 1/7; n=5), inability to resect along the intersegmental plane (7-item binary score of 2/7; n=1), inability to localize tumour in resected specimen (n=5), and no confirmation of tumour-free margins or the segmental vein by the on-site pathologist (7-item binary score of 3 or 4/7; n=5 and n=2 respectively). Most unsuccessful cases were for right-sided resections, primarily in the right lower lobe (n=8 right lower lobe, n=3 right upper lobe, n=2 left lower lobe).

2.4.3 Added Value of NIF-guided ICG Mapping

All cases were scored using a 7-item binary scale modified to assess the clinical utility of indocyanine green dye injection in ensuring surgical margin. A score of 7/7 was achieved in 45 out of 102 (44.1%) successful cases, where ICG corrected the surgeon's estimate of the intersegmental plane by a mean of 17.1 ± 1.68 mm away from the tumour. This distance diminished significantly in t3 (10.00 ± 0.99 respectively ($p<0.0001$)), when compared to t1 and t2 (23.6 ± 3.9 mm and 19.1 ± 2.41 mm respectively). The proportion of cases scoring 7/7 decreased significantly across tertiles ($p=0.002$). A score of 6/7 was achieved in the remaining 57 out of 102 (55.9%) cases, in which ICG did not add any distance from the tumour compared to the surgeons' initial estimate of the location of the intersegmental plane. When considering all 102 cases with successful NIF mapping, ICG increased the added distance from the tumour by a mean of 7.3 ± 2.2 mm away from the tumour. This distance diminished significantly across all tertiles, initially at 23.6 ± 3.9 mm in t1, to 4.2 ± 4.2 mm in t2, and 2.01 ± 2.2 mm in t3 ($p<0.0001$) (Figure 5).

A locally estimated scatter plot smoothing (LOESS) was performed with ICG case number as the independent variable to examine the relationship between surgeon experience with ICG and the ability to predict the location of the invisible intersegmental plane. The plot shows a steady decline in Dt-Dp until approximately the 42nd case with ICG (series case 77), followed by a local minimum at 0.0 mm for the next 43 to 62 cases (case 78-103). There is a subsequent increase in Dt-Dp by a few millimeters above zero around the 80th case (total case 131, max 3.3 mm) before returning to 0.0 mm. A linear regression analysis revealed a strong negative association in Dt-Dp and ICG case number, when ICG case number was less than 42. Specifically, Dt-Dp decreased by 0.82 ± 0.41 mm/case until the

42nd consecutive case with ICG ($p<0.0001$). After the 42nd case, this finding was no longer significant ($p=0.727$). The slight subsequent increase in Dt-Dp, including high variability among cases which made up the second tertile (cases 18-67), was hypothesized to be due to introduction of more complex resection. On the contrary, further inspection of LOESS plots stratified by simple or complex segmentectomy revealed that this is more likely to be associated with simple resections. (Figure 4)

2.4.4 Additional Findings

Dt-Dp differed significantly based on segment complexity, which was 8.8 ± 2.0 mm during simple segmentectomy (n=61, 32.1%), compared to 2.20 ± 2.0 mm (n=127, 66.8%). (Table 6) A binary logistic regression model was performed to determine factors associated with clinical utility of NIF mapping with ICG in successful cases (n=102). Case number and right upper lobe resections were significantly associated with a decrease in ICG utility ($p=0.011$ and $p=0.09$ respectively), whereas left side upper and lower complex resections were associated with a non-significant increase in ICG utility ($p=0.053$). (Table 5)

2.5 Discussion

We have previously reported the results of our pilot study assessing the safety and reproducibility of near-infrared mapping with intravenous indocyanine green dye injection to identify the intersegmental plane.[10] In our initial study, ICG often identified the true intersegmental plane to be up to 2 cm farther from the tumour than the cautery-marked plane predicted by consensus between two thoracic surgeons. In this study, we sought to evaluate whether this effect would persist beyond the learning period reflected in our initial experience in robotic segmental resection. The aim of this study was to examine the utility of NIF-mapping during robotic-assisted segmentectomy over time, and to determine factors associated with its added value. Our study demonstrates that surgeon experience is associated with an improved ability in identifying the invisible pulmonary intersegmental plane, and this effect was consolidated after approximately 42 cases with ICG.

The success rate of intravenous ICG injection in delineating the intersegmental plane was 89%, which is on the lower end of reported success rates in the existing literature, ranging between 90% to 100%.[4,14,15] This finding was likely observed because of our larger sample size, which included more participants undergoing complex segmentectomy, where the majority of unsuccessful cases occurred. One of the apparent caveats in segmentectomy are patients requiring complex resections, and the debates to perform segmentectomy or lobectomy in these cases remain ongoing.[19] In this study, the first two complex resections of the right upper lobe were included on the 43rd and 65th case. In these two cases, indocyanine green dye could not be used due to difficulties in isolating the target segment, which was likely a result of atypical patterns of division in the right upper lobe that the operating surgeon was unfamiliar with.[2] On the 85th case, later in tertile 2, the first successful right upper segmentectomy with ICG was performed with adequate intersegmental plane prediction. In our sample, the clinical utility of ICG dye was marked in only a quarter of right upper lobe resections when it was used successfully. In approximately half of unsuccessful right upper lobe resections, ligation of the corresponding pulmonary veins proved difficult, which prompted an intraoperative switch to lobectomy or wedge resection to complete the operation. This finding points to the potential value of pre-operative planning and intraoperative utility of three-dimensional reconstruction technology for right upper lobe and other complex segmental resections.[15]

A noticeable finding in our study is the reproducible utility of indocyanine green dye for simple resections of the superior segment (S6), in both the left and right lung. In this subset, ICG corrected the surgeon's estimate of the intersegmental plane by nearly a centimeter, and its added utility persisted for these tumours even after proficiency was achieved. This may have been observed due to the inherently simple nature of this resection procedure, leaving minimal clues for surgeons to accurately locate the intersegmental plane and ensure adequate margins. Since correct identification and dissection of pulmonary veins is far simpler in S6 resections, evidenced by a high success rate of these cases in our sample, it appeared that ICG injection may be sufficient on its own as an intraoperative adjunct. Overall, simple cases benefited most from NIF-mapping across our study period, and resulted in a slight increase in oncological margin length attributable to ICG after the learning curve was overcome.

The standard method of identifying the intersegmental plane is by the inflation-deflation technique, which has been optimized in recent years but requires between 5-20 minutes before it can be visualized.[16,17] Furthermore, the lung may not be able to deflate well in patients with emphysema and other chronic lung diseases, which consequently results in greater operative time, more complications, and may impede recovery.[18] Other centers have also demonstrated that NIF-mapping can be performed by transbronchial injection, which has been reported to be particularly advantageous in the lower lobes as it provides clearer staining.[7,14] Transbronchial injection may therefore have been ideal in the cases where ICG visualization was unsuccessful in our sample, which occurred primarily during lower lobe resections. However, this anticipated advantage should be subject to further research.

There are limitations to be addressed. Primarily, this study reflects a single-surgeon experience, potentially limiting the generalizability of our findings to other surgeons seeking to train in segmentectomy. The specific number of cases to achieve proficiency in robotic segmental resection ranges between 25-49 cases.[20–22] While our study does highlight the presence of a learning curve, a more rigorous analysis for segmentectomy may be helpful to determine the utility of ICG as an educational tool. Our study also lacked a control group and had a short follow-up duration, preventing cost-utility analyses.

Our study is strengthened by its large sample size and reproducibility. We also present a modification of the 7-item rating scale to objectify the clinical value of indocyanine green dye solely to when it increases the oncological margin length from the tumour. This instrument allowed us to fully capture the added benefit of NIF-mapping with respect to segment complexity, highlighting areas where technological advancements and imaging techniques could improve our ability to plan and perform segmental resections.

2.6 Conclusion

In robotic segmentectomy resection for lung cancer, the added value of near-infrared mapping with indocyanine green dye diminishes with surgeon experience. NIF-guided mapping is a useful tool early in surgical experience. Future studies may also highlight the potential benefit of ICG as an educational tool for teaching segmentectomy to surgical trainees.

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Appendix A

Figure 1: Modified 7-Item Binary Scale to Evaluate the Utility of ICG Injection

7-Item Scale
Item #1 - Visualization of fluoresced lung by NIF imaging
The lung fluoresces with a green hue at the time of exposure to near infrared light
The lung does NOT fluoresce with a green hue at the time of exposure to near infrared light
Item #2 - Demarcation of a dark segment and inter-segmental plane
A dark segment is demarcated from the rest of the lung
A dark segment is NOT demarcated from the rest of the lung
Item # 3 - Completion of a dark segment and inter-segmental plane
The dark segment is successfully resected along the dark inter-segmental plane
The dark segment is NOT successfully resected along the dark inter-segmental plane
Item #4 - Ex-vivo localization of lesion
The lesion is found in the resected lung tissue as confirmed by on-site pathologist
The lesion is NOT found in the resected lung tissue as confirmed by on-site pathologist
Item #5 - Ex-vivo confirmation of tumour-free margins around lesion
Tumour-free margins are confirmed by on-site pathologist
Tumour-free margins are NOT confirmed by on-site pathologist
Item #6 - Ex-vivo confirmation of adequate anatomical inter-segmental planes
Confirmation of the presence of the segmental vein within the specimen
NO confirmation of the presence of the segmental vein within the specimen
Item #7 - Added value of NIF-guidance
The staple line marked by ICG increases the oncological margin length from the tumour compared to cautery marked plane
The staple line marked by ICG does NOT increase the oncological margin length from the tumour compared to the cautery marked plane

Figure 2: ICG Injection and Outcome Measurement Protocol

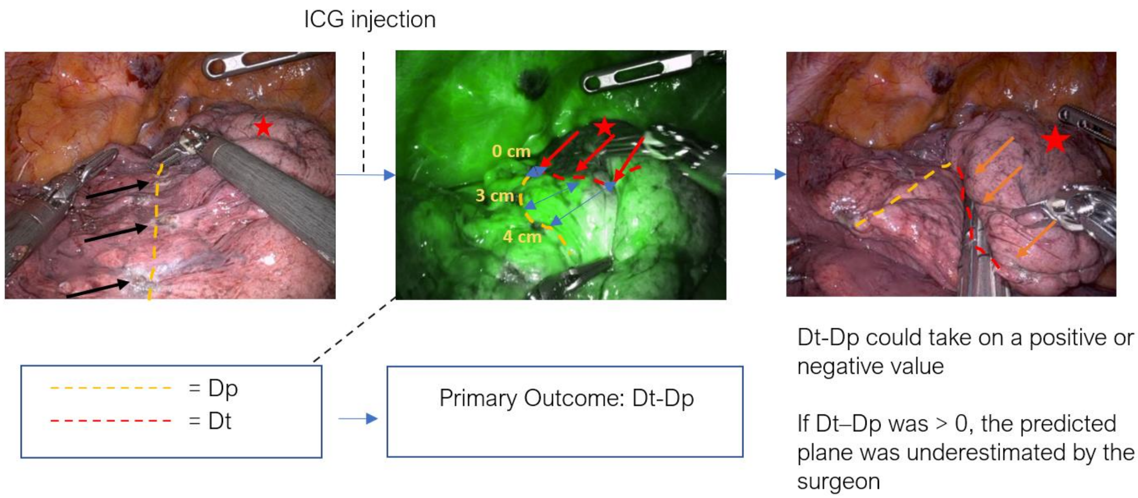

Table 1: Patient Demographics

Characteristic		No. (%) or Median [IQR]
Age at Surgery (years)		68 (62-72)
BMI		28.32 (24.84-31.74)
Gender	Female	109 (57)
	Male	81 (42)
Smoking Status	Former Smoker	103 (54)
	Never Smoker	33 (17)
	Current Smoker	54 (28)
ASA Category	II	2 (1)
	III	110 (57)
	IV	78 (41)
Tumour Size (cm)		1.7 (1.2-2.2)
Tumour Location	Left Lower Lobe	36 (18)
	Left Upper Lobe	66 (34)
	Right Lower Lobe	49 (25)
	Right Middle Lobe	3 (1)
	Right Upper Lobe	36 (18)
Segmentectomy Complexity	Simple	83 (44)
	Complex	105 (55)
Malignant Histology	Adenocarcinoma	107 (56)
	Adenosquamous Carcinoma	3 (1)
	Carcinoid Tumour	9 (4)
	Large Cell Carcinoma	2 (1)
	Squamous Cell Carcinoma	18 (9)
	Small Cell Carcinoma	1 (0)
	Other	4 (2)
Benign		17 (8)
Metastatic		29 (15)
Pulmonary Function	FEV1 %, predicted	87.5 (73-102)
	DLCO %, predicted	78 (64-89)
ICG Injected		115 (60)

Table 2: Characteristics of the Included Sample Across Tertiles

Characteristic	**No. (%) or Median [IQR] per Tertile**			
	Tertile 1 (n=18)	Tertile 2 (n=49)	Tertile 3 (n=48)	p-value
Age in years, median (IQR)	66 (61-69)	68 (61-74)	69 (62-72)	0.765
Gender, *n* (%)				0.679
Male	18 (60.0%)	40 (57.1%)	38 (54.3%)	
Female	12 (40.0%)	30 (46.9%)	32 (44.7%)	
Smoker Status, *n* (%)				0.023
Current Smoker	5 (16.6%)	20 (28.6%)	23 (32.9%)	
Former Smoker	15 (50%)	44 (62.9%)	33 (47.1%)	
Never Smoker	10 (33.3%)	6 (8.57%)	14 (20.0%)	
Characteristics, *n* (%)	21 (70.0%)	22 (31.4%)	21 (30.0%)	0.711
COPD	21 (70.0%)	22 (31.4%)	21 (30.0%)	0.552
Diabetes	9 (30%)	16 (22.9%)	14 (20.0%)	0.942
History of Stroke	2 (6.7%)	6 (8.6%)	6 (8.6%)	0.067
Renal Disease	0 (0.0%)	0 (0.0%)	3 (4.3%)	0.87
Atrial Fibrillation	1 (3.3%)	4 (5.7%)	4 (5.7%)	0.339
Previous Cancer, *n* (%)	13 (43.3%)	33 (47.1%)	32 (45.7%)	0.94
Pulmonary Function Tests				
FEV1% median (IQR)	88 (76-101)	89 (70-102)	88 (72-100)	0.625
DLCO% median (IQR)	82 (75-87)	75 (62-88)	78 (60-92)	0.94

Table 3: Operative and ICG Outcomes

Characteristic		**No. (%) or Median [IQR] per Tertile**			
		Tertile 1 (n=18)	Tertile 2 (n=49)	Tertile 3 (n=48)	p-value
ICG injected, % of total sample		18 (60)	49 (61)	48 (60)	1.00
Operative Time, minutes		174 (164-192)	176 (159-202)	165 (149-189)	0.205
Procedure Time		131 (115-150)	138 (122-160)	120 (102-140)	0.014
Console Time		88.5 (74-98)	96 (82-120)	91 (68-107)	0.682
Dt-Dp (mm)		19.9 (9-30.2)	0 (0.0-13.33)	0 (0.0-10.0)	<0.001
Complex Segmentectomy, % complex		4 (30)	26 (53)	32 (66)	0.005
Binary Scale Score	Score = 7	14 (78)	14 (29)	17 (35)	0.002
	Score = 6	3 (17)	28 (57)	26 (54)	
Binary Score < 6		1 (6)	7 (14)	5 (10)	0.408
Additional Wedge Resection For Margins		2 (11)	6 (12)	13 (27)	0.067

Table 4: Complications Grade

AE Grade	Tertile (1)	Tertile (2)	Tertile (3)	Total
1 - any complication without need for pharmacologic treatment or other intervention	4	12	11	27
2 - any complication that requires pharmacological or minor intervention only	13	52	62	127
3a - any complication that requires surgical, radiological, endoscopic intervention, or multi-therapy, does not require general anesthesia	0	2	6	8
3b - any complication that requires surgical, radiological, endoscopic intervention, or multi-therapy - requires general anasthesia	0	2	0	2
4a - any complication requiring ICU management and life support - single organ dysfunction	0	2	5	7
5 - any complication leading to death of the patient	0	1	0	1
Total	**17**	**71**	**84**	**172**

Table 5: Univariate Analysis of Factors Predictive of Dt-Dp being greater than 0 cm.

Regression Factors	Univariate (n=102)		
	B	exp(B)	p-value
Case #	-0.01	0.99	**0.011**
Age at surgery			0.965
BMI			0.182
FEV1%			0.786
Console time			0.467
Total number of L.N. stations sampled			0.254
Tumour size (mm)			0.294
Superior segment (S6)	0.738	2.091	0.11
Simple Left Upper Lobe	0.346	1.414	0.419
Left Side Complex	1.317	3.733	**0.053**
Right Upper Lobe	-0.957	0.384	**0.09**
Right Side Complex	0.712	2.038	0.294

Figure 3: Added Value of Indocyanine Green Dye Over Surgeon Case Number

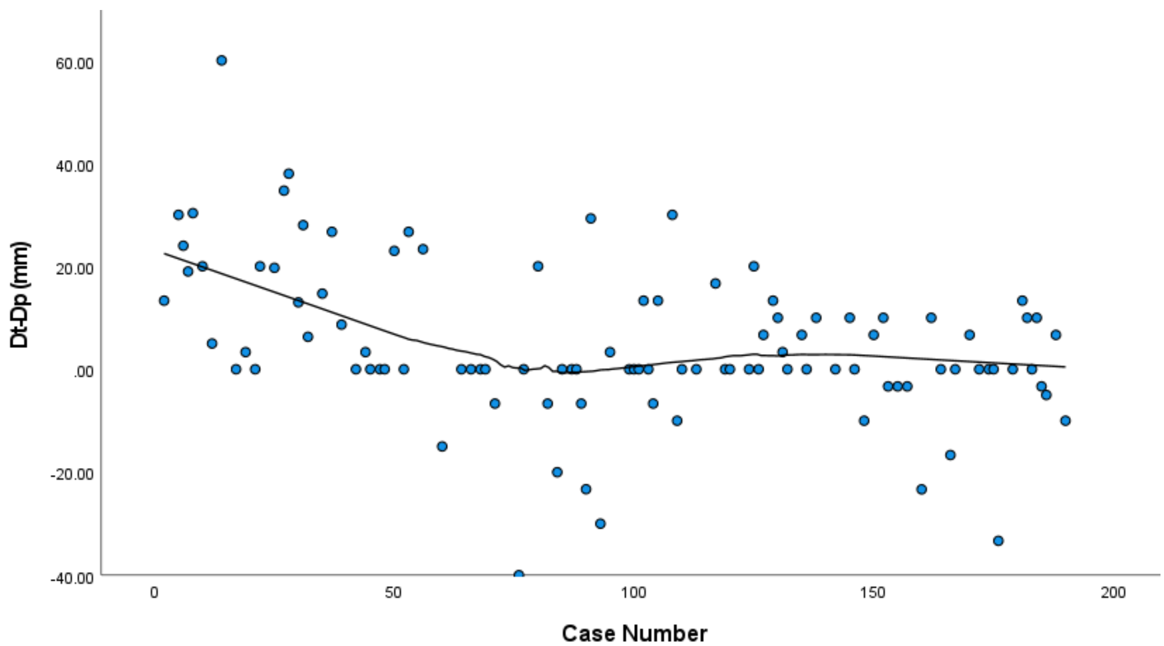

Figure 4: Added Value of Indocyanine Green Dye Stratified by Segment Complexity

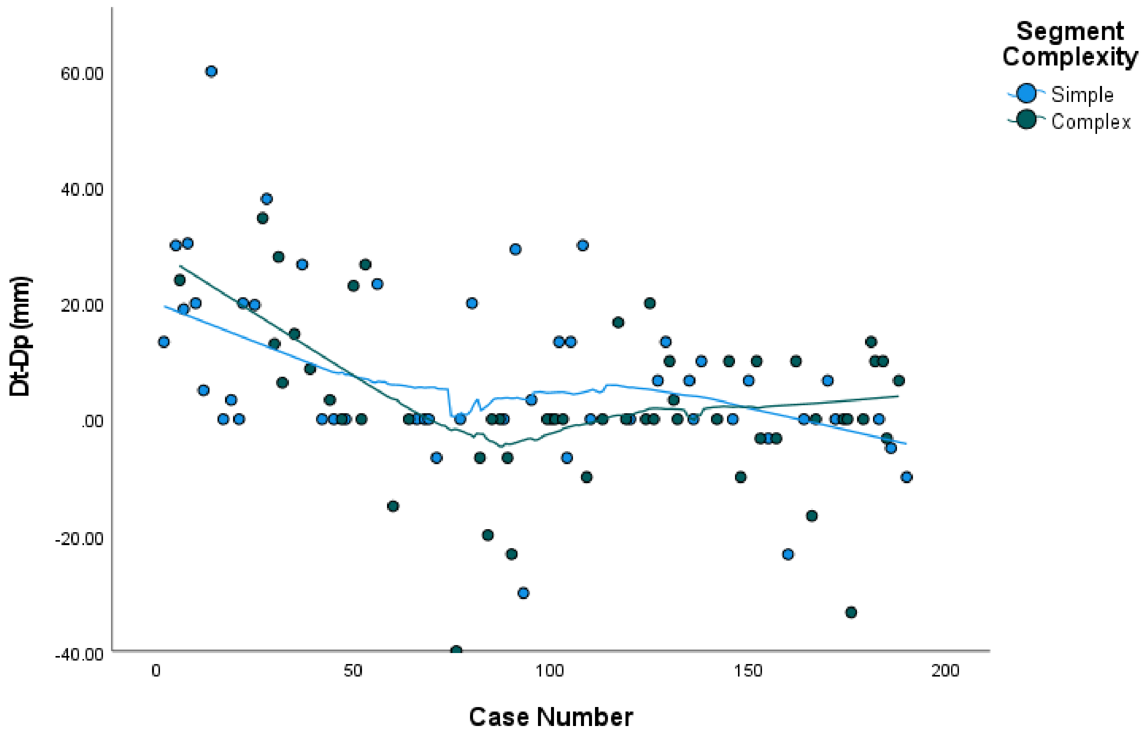

Figure 5: Dt-Dp Across Tertiles

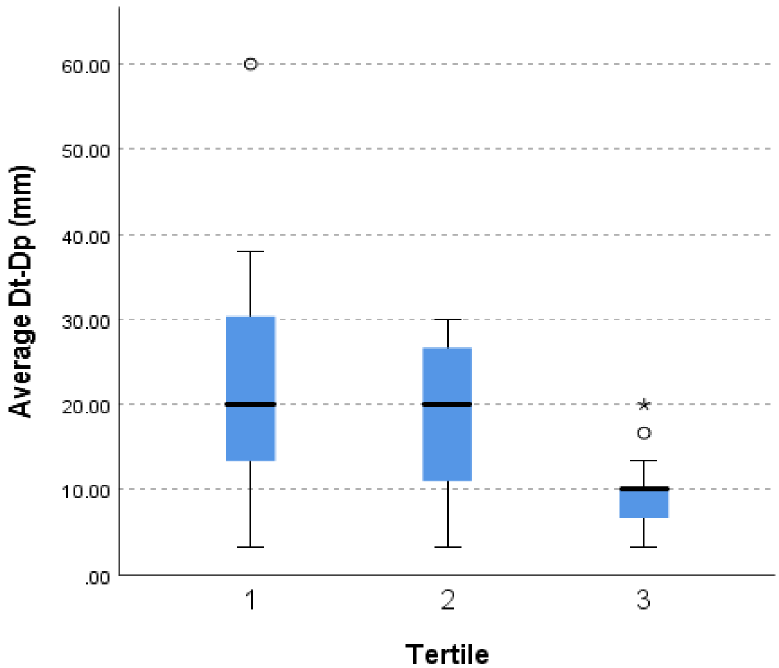

Table 6: Added oncological distance owing to ICG injection based on resected segments.

Removed Segments	Average Added Distance (mm)	Number of Cases (n)
LS1LS2	**5.39**	**17**
Score < 7	-8.70	9
Score = 7	21.25	8
LS1LS3LS2	**8.51**	**8**
Score < 7	-14.99	2
Score = 7	16.35	6
LS3	**-3.33**	**1**
Score < 7	-3.33	1
LS3LS4LS5	**0.00**	**2**
Score < 7	0.00	2
LS4LS5	**6.38**	**7**
Score < 7	0.00	5
Score = 7	22.34	2
LS6	**0.83**	**8**
Score < 7	-1.11	6
Score = 7	6.67	2
LS6LS9	**-5.00**	**2**
Score < 7	-5.00	2
LS8LS9	**0.00**	**1**
Score < 7	0.00	1
LS8LS9LS10	**6.85**	**9**
Score < 7	-1.33	5
Score = 7	17.08	4
LS9LS10	**-40.00**	**1**
Score < 7	-40.00	1
RS1	**0.83**	**8**
Score < 7	-2.22	6
Score = 7	10.00	2
RS1RS2	**-3.33**	**3**
Score < 7	-8.34	2
Score = 7	6.67	1
RS1RS3	**5.00**	**2**
Score < 7	-3.33	1
Score = 7	13.33	1
RS2	**1.67**	**2**
Score < 7	0.00	1
Score = 7	3.33	1

RS2RS6	**0.00**	**1**
Score < 7	0.00	1
RS3	**-16.67**	**2**
Score < 7	-16.67	2
RS5	**10.00**	**1**
Score = 7	10.00	1
RS6	**13.33**	**18**
Score < 7	0.00	5
Score = 7	18.46	13
RS6RS9RS10	**16.67**	**1**
Score = 7	16.67	1
RS7RS8	**-20.00**	**1**
Score < 7	-20.00	1
RS7RS8RS9	**20.00**	**1**
Score = 7	20.00	1
RS7RS8RS9RS10	**6.20**	**5**
Score < 7	-7.50	2
Score = 7	15.33	3
Grand Total	**4.84**	**102**

Chapter 3: A Comparison of Oncological Outcomes after Robotic-Assisted Segmental Resection versus Lobectomy for Early-Stage (< 3 cm) Non-Small Cell Lung Cancer Tumours

Abstract

Introduction: The debate to perform segmentectomy versus lobectomy for early-stage tumours less than 3 cm remains ongoing. The number of lymph node (LN) stations sampled is an important surrogate measure for assessing the oncological completeness of lung cancer surgery. The aim of this study is to compare the extent of intraoperative lymph node sampling, recurrence-free and overall survival in patients undergoing robotic segmentectomy compared to robotic lobectomy for NSCLC tumours between 2 and 3 cm.

Methodology: This study is secondary analysis of a prospectively collected database of all robotic-assisted procedures for lung cancer at a single center. Patients undergoing robotic-assisted segmentectomy or lobectomy for suspected cancers less than 3 cm in maximal diameter were included in the analysis. A per-protocol analysis was performed, comparing participants based on the intervention that was received, regardless of the initially planned procedure. Comparisons of the number of lymph node stations sampled were done using a Mann-Whitney U test. Cumulative time-to-event probabilities were estimated for recurrence-free (RFS) and overall survival (OS), which were assessed using the Kaplan-Meier method. A log-rank test was used to compare survival distributions between segmentectomy and lobectomy. A sub-analysis was also performed for tumours between 2 cm and 3 cm in maximal diameter. All statistical tests were two-sided, and the level of significance was set at $\alpha = 0.05$.

Results: Three-hundred and eighty-eight participants were eligible for the analysis, after excluding cases that were converted to open thoracotomy, or switched to wedge resection. Of these participants one-hundred and fifty-seven ($n=157$) participants received robotic segmentectomy (41%) and 231 received robotic lobectomy (59%). Median age was 67 (interquartile range [IQR], 61-73) and 59.0% were women. A median number of 6 (IQR: 5-7) LN stations were sampled during segmentectomy, compared to 5 (IQR: 4-6) during lobectomy ($p<0.001$). This finding was consistent for tumours between 2 and 3 cm. At a median follow-up of 2.43 years (IQR: 0.98-3.92), overall survival was 93.2% in the segmentectomy group compared to 85.4% in the lobectomy group ($p=0.155$), and this was consistent for tumours greater 2 cm ($n=122$, $p=0.164$). However, segmentectomy was associated with inferior recurrence-free survival compared to lobectomy (92% compared to 97%, $p=0.004$), and this finding was statistically significant for patients undergoing segmentectomy for tumours > 2 cm ($p=0.019$).

Conclusion: While the extent of lymph node evaluation is similar in patients undergoing segmentectomy versus lobectomy for early-stage tumours, patients who received segmentectomy for early-stage tumours experienced a greater risk of local recurrence compared to lobectomy. However, this did not translate to any reductions in overall survival.

3.1 Introduction

3.1.1 Background

Surgical resection is the standard treatment for early-stage lung cancer. Sublobar resections, which include segmentectomy and wedge resection, are parenchyma-sparing procedures that preserve pulmonary function by only resecting a limited amount of lung tissue containing the nodule. Due to their associated long-term mortality and recurrence rates, sublobar resections have only been indicated for patients with poor pulmonary function who could not tolerate the removal of an entire lobe.[1] With the advent of low-dose CT screening, small subcentimeter nodules are being frequently detected and the demand for segmental resection is rising rapidly.

3.1.2 The Role of Robotic-Assisted Segmentectomy

Today, segmentectomy is being increasingly used to treat non-small cell lung cancer tumours less than 2 cm with no evidence of lymph node metastasis at clinical staging (<T1bN0M0).[2,3] Recent advancements in robotic surgery have addressed many barriers during video-assisted thoracoscopic surgery, and the benefits associated with the robotic platform are especially apparent during segmentectomy.[4] The implications of these developments are apparent from our center's experience, where surgeons are increasingly willing to perform complex segmental resections as they become more proficient with the robotic platform. The advent of low-dose screening has also broadened patient eligibility for surgical resection, and a renewed assessment of segmentectomy versus lobectomy is warranted to better serve this population. Furthermore, the oncological validity of

segmentectomy for early-stage tumours greater than 2 cm and less than 3 cm (T1cN0M0), which are still considered early-stage, have yet to be explored in a prospective fashion.[5]

3.1.3 The Surgical Quality of Lobectomy and Segmentectomy versus Wedge Resection

The key limitation of the initial and controversial trial by Ginsberg et al.,[1] which set lobectomy as the gold standard for NSCLC, is that the sublobar resection group included both segmentectomy and wedge resection participants. In terms of oncological quality, sublobar segmentectomy differs significantly from a wedge resection in that it is an anatomical resection with sufficient margins and is accompanied by intraoperative lymph node assessment.[6,7] This is different from a wedge resection, where nodal assessment is not necessarily performed as the division of the hilum is not required (and is a non-anatomic resection). Therefore, segmentectomy could have been considered an alternative to lobectomy in terms of curative capacity.[8] While the authors note that the observed increase in local recurrence rates in the sublobar group could be due to unidentified nodal metastases, they fall short in demonstrating how this could have been influenced by the sublobar resection procedure. This example highlights the importance of reporting intraoperative outcomes pertaining to lymph node assessment and its potential impact on recurrence and overall survival. This is further substantiated by a study conducted by Ajmani et al.,[9] which reported a positive correlation between the surgical quality of wedge resection (assessed by measuring the number of lymph nodes examined and surgical margin distance) and overall survival. Although mediastinal lymph node dissection (MLND) is the most rigorous form of lymph node assessment (by sampling all lymph node stations), most patients undergo mediastinal lymph node sampling (MLNS), based on sampling recommendations and the ability to safely reach a particular lymph node station. The effectiveness of robotic segmentectomy can be evaluated against robotic lobectomy by measuring differences in the number of lymph node stations sampled and rates of nodal upstaging.[9–12] The purpose of this study is to evaluate the extent of intraoperative lymph node harvesting during robotic-assisted segmentectomy compared to lobectomy for patients with NSCLC tumours less than 3 cm in maximal diameter.

3.2 Primary and Secondary Objectives

The objective of this study is to compare the number of lymph node stations sampled and rate of nodal upstaging during segmentectomy versus lobectomy in patients undergoing robotic-assisted surgery for non-small cell lung cancer tumours less than 3 cm. The secondary objective of this study is to evaluate the impact of tumour size greater than 2 cm long-term overall and recurrence-free survival after robotic-assisted segmentectomy, compared to robotic-assisted lobectomy.

3.3 Methods

3.3.1 Study Design

This study is a secondary analysis of a prospectively collected database of all robotic-assisted procedures at a single center (St. Joseph's Healthcare Hamilton; SJHH). We analyzed all cases that were assigned to robotic segmentectomy or lobectomy for clinical stage N0 NSCLC tumours less than 3 cm in maximal diameter. The primary outcome of this study is the number of lymph node stations sampled and the secondary outcome was the rate of nodal upstaging. The primary- and secondary- endpoints of this study is overall survival (OS) and recurrence-free survival (RFS) respectively. This study was approved by the local institutional review board. This database included available data of two ongoing trials at SJHH, and their protocols can be identified on www.clinicaltrials.gov (NCT02570815 "ICG Segmentectomy", NCT05270616 "RAVAL Lobectomy").

3.3.2 Inclusion and Exclusion Criteria

Participants were included in the primary analysis if they met the following criteria:

1) Age ≥ 18 years of age.
2) Pre-operative staging assessed by low dose computed tomography (LDCT).
3) Suspected or confirmed clinical stage IA NSCLC (tumour size ≤ 3.0 cm with disease-free lymph nodes).
4) Received robotic segmentectomy or robotic lobectomy.

Participants were excluded from the analysis if they satisfied one of these criteria:

1) Clinical stage IIA or greater (tumour size > 3.0 cm with or without lymph node involvement, or tumours < 3.0 cm with lymph node involvement).

Patients with a history of lung cancer surgery were included, yet only the outcomes of the first robotic-assisted operation were used. In patients undergoing segmentectomy, no limits were placed on the number of segments removed, nor if an extended resection into an adjacent segment or separate lobe was warranted to secure margin distance.

3.3.3 Oncological Outcomes Measurement and Definitions

Pathology-confirmed nodal status was collected from post-operative pathology reports via a standardized data collection form. The location of each unique LN station sampled was reported intraoperatively by the operating surgeon. The number of LN stations examined was measured as the number of unique lymph node stations that contained confirmed nodal tissue by the attending pathologist. The total number of LN examined was measured by calculating the sum of all lymph nodes examined, including peribronchial lymph nodes contained within the lung specimen. Nodal upstaging was defined as the pathology-confirmed presence of lymphadenopathy compared to disease-free lymph node status determined at the pre-operative clinical encounter (cN0 → pN1 or cN0 → pN2). Additional measures included tumour size, location of tumour, tumour focality, tumour histology and subtype.

3.3.4 Overall Survival and Recurrence-Free Survival Definitions

Overall survival (OS) was measured as the length of time between the date of admission for lung resection until date of death or date of last follow-up. Local recurrence was defined as cancer relapse to the surgical margin, ipsilateral lung, or to the chest wall. Regional recurrence was defined as cancer relapse to a regional lymph node area (mediastinum or hilar), or contralateral lung. Recurrence-free survival (RFS) was measured as the length of time between the date of surgery for the initial lung resection until the date local recurrence was suspected or confirmed.

3.3.5 Data Items

Baseline data on patient demographic characteristics, medical history, social history, diagnosis, preoperative tests, and preoperative staging was collected. Preoperative variables included age, sex, smoking status, medical history, tumour location, pulmonary function, planned resection procedure. Intraoperative variables included date of operation, lobes resected, additional resections, total operative time, operative time on the robotic console (console time), intraoperative complications and lymph node stations harvested. Postoperative variables included hospital length of stay, duration of chest tube drainage and postoperative complications or major adverse events for up to 3 weeks post-operatively.

3.3.6 Data Analysis Plan

A per-protocol analysis was used to compare the outcomes of participants who received robotic segmentectomy versus robotic lobectomy for suspected early-stage NSCLC. Patients converted to open thoracotomy were excluded from the analysis as this may have influenced the results of our primary and secondary outcome. All eligible participants were included in the analysis of the primary and secondary outcomes. The analysis of secondary study endpoints (overall and recurrence-free survival) included participants with pathology-confirmed malignant non-small cell lung cancer.

Descriptive statistics (median, interquartile range) were used to present the data for continuous variables, and numbers and percentages (n, %) for categorical variables. Continuous parametric variables were compared using a Student's T test and non-parametric variables was compared using a Mann-Whitney U test. Nominal variables were compared using a Chi-square test, or a Fisher's exact test if the expected cell counts in the contingency table were less than 5. Cumulative time-to-event probabilities were estimated using the Kaplan-Meier method. A log-rank test was used to compare survival distributions between segmentectomy and lobectomy. A sub-analysis was also performed for tumours greater than 2 cm in maximal diameter. All statistical tests were two-sided, and the level of significance was set at $\alpha = 0.05$.

3.3.7 Additional Analyses

An analysis of intraoperative, hospitalization and safety outcomes was performed, based on the planned resection procedure. Adverse events were graded according to the Ottawa Thoracic Morbidity & Mortality System (TM&M).[13] Intraoperative variables included operative time, number of chest tubes used, frequency of complications, and frequency of conversions from robotic to open thoracotomy and switches from robotic segmentectomy to lobectomy or wedge resection. Important post-operative outcomes included length of hospital stay, chest tube duration, rate of pulmonary, pleural, cardiac, or gastrointestinal complications, major adverse events, and status at discharge.

3.4 Results

3.4.1 Study Population

Five-hundred and twenty-seven (n=527) participants enrolled to undergo robotic-assisted thoracoscopic surgery for lung cancer were screened over a study period of 7.1 years (May 2014 and July 2021). Patient demographics are summarized in Table 1. Of these, 77.6% met the inclusion criteria and were included in this study (n=409). More cases were initially planned for robotic lobectomy (n=229, 56.0%). Among the remaining 180 cases planned for robotic segmentectomy, 5.9% (n=24) were intraoperatively switched to lobectomy, and 4.0% (n=7) were switched from segmentectomy to wedge resection. One patient was switched from lobectomy to wedge resection. The rate of conversion to thoracotomy was 10.3%, and did not differ significantly between both groups (15.2% versus 9.1% in segmentectomy, p=0.072). Additional operative results are summarized in Table 2 and Table 4.

After excluding participants who were converted to open thoracotomy or switched to robotic wedge resection, 388 cases remained for the primary analysis. One-hundred and fifty-seven participants underwent robotic segmentectomy (n=157, 40.5%) and 231 received robotic lobectomy (59.5%). Median age was 67 (interquartile range [IQR], 61-73) and 59.0% were women. Tumour size was different between both groups, with a median of 1.7 cm (IQR: 1.2-2.2) in the segmentectomy group and 1.8 cm (IQR: 1.3-2.5) in the lobectomy group (p=0.48). The most common tumour location was the right upper lobe (n=103, 26.5%), followed by the right lower lobe (n=86, 22.2%).

3.4.2 Extent of Lymph Node Evaluation and Rates of Nodal Upstaging

Mediastinal and hilar lymph node sampling was performed in 93% of the study sample. A median of 6 (IQR: 5-7) lymph nodes stations were sampled during segmentectomy, compared to 5 (IQR: 4-6) during lobectomy (p<0.001). (Figure 4) Positive lymph nodes were detected in 7.3% of patients, 5.1% of these cases were N0 to N1 and 2.2% were N0 to N2.

The number of LNs examined from lymph node stations was significantly higher during segmentectomy compared to lobectomy ($p<0.001$). The number of mediastinal lymph node stations sampled from mediastinal stations did not differ significantly between segmentectomy and lobectomy (median 3 LNs [IQR: 2-4], $p=0.420$). The number of hilar lymph nodes sampled was significantly higher in the segmentectomy group, with 3 LNs (IQR: 2-4) sampled compared to 2 LNs (IQR: 1-3) in the lobectomy group ($p<0.001$). Owing to the presence of peribronchial lymph nodes, the total number of lymph nodes examined statistically favored the lobectomy group. (8 LNs [IQR: 5-10] vs 7 LNs [IQR: 5-9], $p<0.001$). Overall, the observed differences in the lymph node sampled/examined did not translate to any differences in the rate of nodal upstaging between groups (4.2% vs 9.1% during segmentectomy and lobectomy respectively, $p=0.122$). These observations were consistent across all variables for participants with tumour size > 2 cm. Figure 5 summarizes the number of lymph node stations sampled based on the resected lobe.

3.4.3 Overall and Recurrence-Free Survival

Three-hundred and sixteen participants (81.4%) were included in the analysis of survival endpoints after excluding benign (n=33) and metastatic cases of non-pulmonary origin (n=39). Baseline differences in tumour size were no longer significant in this subset of patients ($p=0.164$). Follow-up time was significantly longer in the lobectomy group (2.64 [IQR: 1.08-4.51] versus 1.96 [IQR: 1.02-3.03], $p=0.003$) since segmentectomy was only routinely performed since the start of the ICG Segmentectomy trial, which began in October 2016, nearly 2 years after the conception of this research database.

At a median follow-up of 2.43 years (IQR: 0.98-3.92), overall survival was 93.2% in the segmentectomy group compared to 85.4% in the lobectomy group. (Figure 1) A log-rank test revealed no significant differences in overall survival times between segmentectomy and lobectomy (p=0.155), and this was consistent for tumours > 2 cm (n=122, p=0.164). Over the study period, the rate of mortality was significantly lower in the segmentectomy group (7.0% versus 13.4% in lobectomy, p=0.046), yet the proportion of locoregional recurrence was similar (12.6%) in both groups (p=0.166 and p=0.322 respectively). In terms of disease-free years, segmentectomy was associated with inferior recurrence-free survival compared to lobectomy (96.5% compared to 91.5%, p=0.003; Figure 2), and this finding was statistically significant for patients undergoing segmentectomy for tumours > 2 cm (p=0.019; Figure 3).

3.5 Discussion

Adequate lymph node dissection permits a more accurate staging, which allows surgeons to appropriately indicate whether further treatment is necessary. Especially as cancers are being detected more frequently in their earlier stages, intraoperative lymph node assessment is becoming an increasingly important component of any pulmonary resection performed with curative intent.[9,10,14] However, despite its well-known predictive properties for overall survival, the extent of lymph node dissection is seldom reported in the literature, and this is a consistent limitation in most retrospective comparisons of segmentectomy versus lobectomy for NSCLC.[2,5,9,10,14]

The aim of this study was to compare the extent of lymph node evaluation and rate of nodal upstaging during robotic-assisted segmentectomy compared to lobectomy for tumours less than 3 cm in maximal diameter. Our results indicate that segmentectomy can be performed with comparable oncological completeness to lobectomy, demonstrated by approximately 6 distinct nodal stations sampled, and comparable rates of nodal upstaging in both cohorts. These outcomes were also consistent for patients undergoing segmentectomy for tumours between 2- and 3 cm, suggesting that robotic segmentectomy is technically feasible for this population. In terms of long-term endpoints, tumours less than 3 cm experienced lower recurrence-free survival after segmentectomy compared to lobectomy. More importantly, we observed statistically significant reductions in recurrence-free survival in participants that received segmentectomy for tumours between 2- and 3 cm. However, the increased risk of local recurrence did not translate to any significant reductions in overall survival in this subgroup, and experienced similar survival to patients who underwent robotic lobectomy.

A recent systematic review identified a critically low number of articles that evaluated segmentectomy versus lobectomy for early-stage tumours between 2 and 3 cm, which are instead analyzed under the umbrella of tumours stage IA.[2] Existing comparative designs are also subject to a considerable degree of bias due to their retrospective nature, leading to results that are difficult to externalize.[15–17] For example, segmentectomy has been traditionally reserved for patients with compromised cardiopulmonary status or undergoing palliative care for metastatic disease. These patients are generally older and are unable to tolerate a complete lobectomy, resulting in uneven comparisons that are difficult to extrapolate to today's population of NSCLC patients, even after rigorous matching techniques are used.[15–19] Furthermore, patients undergoing segmentectomy at the time would likely not have had an extensive number of lymph nodes harvested as the clinical indication did not warrant it and/or potential safety considerations in doing so for frailer patients.[12] As a result, contrary to our observations, segmentectomy has long been associated with inferior lymph node evaluation compared to lobectomy.[2] It is possible that we observed similar overall survival rates between segmentectomy and lobectomy because of similar patterns of lymph node evaluation in both groups.[6,15–18]

Until the results of the long-awaited JCOG0802/WJOG4607L phase III trial (J/W trial) became recently available, the quality of evidence guiding the emergence of segmentectomy for tumours less than 2 cm was also low.[2,6] The J/W trial recently reported the results of a two-arm trial comparing segmentectomy to lobectomy for tumours 2 cm, and found that segmentectomy was associated with a significantly higher overall survival, but observed two-fold increased risk of recurrence. We also observed similar patterns of recurrence in our sample, yet this finding was not statistically significant when patients with tumours less than 2 cm were assessed separately. Instead, lowered recurrence-free survival was mostly observed in the cohort of participants who received segmentectomy for tumours between 2 cm and 3 cm. However, given that these participants experienced similar overall survival compared to lobectomy, the role of segmentectomy for these tumours may still be well-justified.

It should be noted that within the category of tumours less than 3 cm (T1 or stage IA), higher recurrence rates are associated with tumour size larger than 2 cm, and this observation has served as the basis of stratifying these tumours into 3 size descriptors (T1a-c; a=0-1 cm, b=1.1-2.0 cm, and c=2.1-3.0 cm) for the 8th edition of the lung cancer staging system.[19–21] While smaller tumours tend to be more peripherally located and are less prone to nodal metastases, larger tumours have an increased likelihood of extending onto invisible pulmonary intersegmental planes, posing a challenge in securing adequate margins during segmentectomy.[5,15,19,21] During robotic-assisted segmentectomy, this concern was slightly alleviated by using near-infrared mapping with indocyanine green dye to locate the intersegmental plane, which provided a degree of intraoperative guidance to determine whether additional resections were needed to secure margin distance prior to wound closure.[4] However, based on our results for T1c tumours, it is unlikely that this conferred any added protection in terms of local cancer control. It is therefore possible that whenever adequate surgical margins are difficult to attain, a switch to lobectomy in patients with acceptable pulmonary reserve may be better suited to reduce the likelihood of developing local metastases. This possibility should be subject to future evaluation.

There are some limitations to be addressed. First, a longer follow-up duration and larger sample size for the segmentectomy group may have been necessary to fully substantiate our findings, especially for tumours between 2 and 3 cm. Second, pulmonary function was not assessed post-operatively to suggest any improvements in pulmonary capacity compared to lobectomy following segmental resections of more than two segments. Second, as the 8th edition of the TNM classification system became standard midway through our study period (January 2017), we opted to define our inclusion criteria based solely on tumour size and clinical nodal staging, since the data collection was performed at a single timepoint in a prospective manner, and it was not feasible to retrospectively revise pathological staging based on the updated system. Lastly, the extent of lymph node evaluation could have been influenced by preselection bias (i.e., predispositions to being allocated to segmentectomy or lobectomy), which may have impacted the accuracy of the conclusions drawn by this study's evaluation of long-term endpoints. Future studies should aim to evaluate how refinements of the diagnostic pathway for NSCLC impacts the clinical indication for segmentectomy, prior to the initiation of a potential large-scale randomized controlled trial. In an ancillary analysis performed in this study (not shown), a Cox regression analysis showed no significant effects (protective or harmful) of resection type (segmentectomy or lobectomy), number of lymph node stations sampled, or tumour size on OS or RFS.

Our study is strengthened by its large sample size and prospective methodology. Although we employed a non-randomized study design, both groups were well-matched for age, BMI, baseline pulmonary function status and tumour size, enabling us to provide a full depiction of our center's experience in robotic-assisted segmentectomy. We also refrained from excluding sublobar resections of more than 2 segments from our segmentectomy group, which we believe reflects current practice more appropriately, as it is often challenging to perform segmentectomy exactly as planned. Lastly, this study overcomes a key limitation of previously published studies by analyzing the extent of lymph node evaluation during robotic segmentectomy versus lobectomy as our primary outcome, allowing more robust interpretations of long-term endpoints to be made.

Conclusion

During robotic-assisted segmentectomy for early-stage non-small cell lung cancer, the extent of lymph node evaluation is comparable to robotic lobectomy, as evidenced by a greater number of lymph node stations sampled and similar rate of nodal upstaging. Furthermore, our study suggests that segmentectomy could confer comparable overall survival for tumours greater than 2 cm, despite a higher risk of local recurrence in this population.

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Appendix B

Table 1: Patient Characteristics

Characteristics		**Lobectomy** (n=229)		**Segmentectomy** (n=180)		**Total** (n=409)		
		Count (%)	**Median (IQR)**	**Count (%)**	**Median (IQR)**	**Count (%)**	**Median (IQR)**	**p-value**
Gender	**Female**	140 (61)		106 (59)		246 (60)		
	Male	89 (39)		74 (41)		163 (40)		
Age at Surgery			67 (61 - 74)		68 (61 - 73)		67 (61 - 73)	
BMI			27.4 (24 - 32)		28.32 (25 - 32)		27.93 (25 - 32)	
Smoking Status	**Former Smoker**	112 (49)		95 (53)		207 (51)		
	Non-Smoker	44 (19)		34 (19)		78 (19)		
	Smoker	72 (31)		50 (28)		122 (30)		
	unknown	1 (0)		1 (1)		2 (0)		
ASA	**II**	4 (2)		2 (1)		6 (1)		
	III	149 (65)		104 (58)		253 (62)		
	IV	73 (32)		74 (41)		147 (36)		
	unknown	3 (1)		0 (0)		3 (1)		
FEV1 % Predicted			88 (73 - 100)		89 (73 - 102)		88 (73 - 101)	
DLCO % Predicted			76 (66 - 87)		79 (65 - 90)		78 (66 - 88)	
Location of Primary Tumor	**LLL**	39 (17)		39 (22)		78 (19)		
	LUL	29 (13)		59 (33)		88 (22)		<0.001
	RLL	37 (16)		51 (28)		88 (22)		=0.003
	RML	38 (17)		3 (2)		41 (10)		<0.001
	RUL	86 (38)		28 (16)		114 (28)		<0.001
Complex Segmentectomy	**0**	N/A		69 (39)				
	1	N/A		110 (61)				
Disease	**Benign**	18 (8)		18 (10)		36 (9)		
	Malignant	195 (85)		134 (74)		329 (80)		=0.007
	Metastatic	16 (7)		28 (16)		44 (11)		=0.005

Figure 1: Overall Survival Plot for Tumours < 3 cm

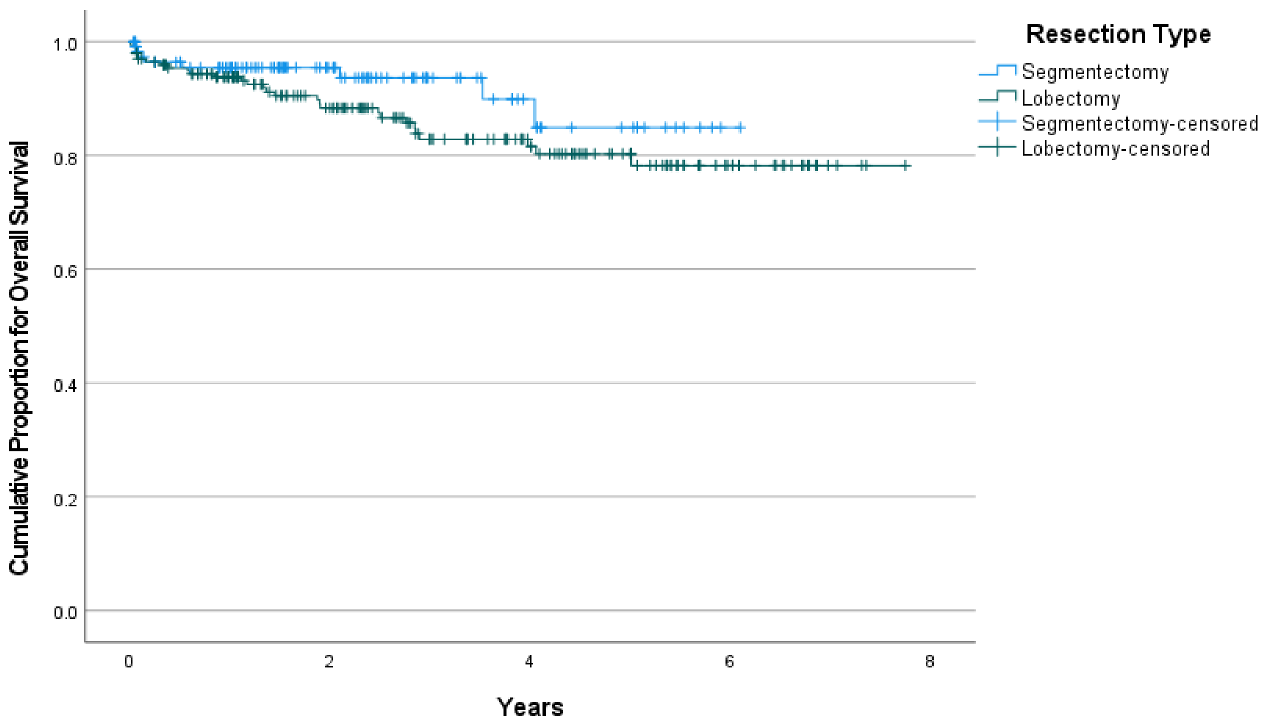

Figure 2: Recurrence-Free Survival for Tumours < 3 cm

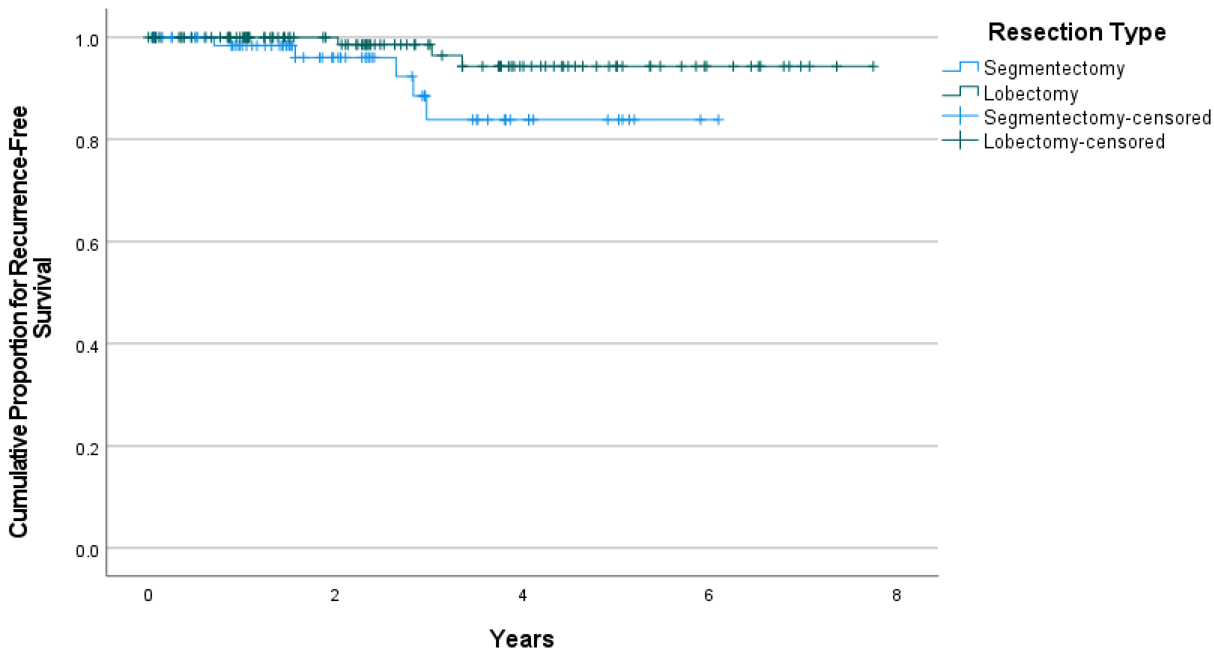

Figure 3: Recurrence-Free Survival for Tumours > 2cm and < 3cm

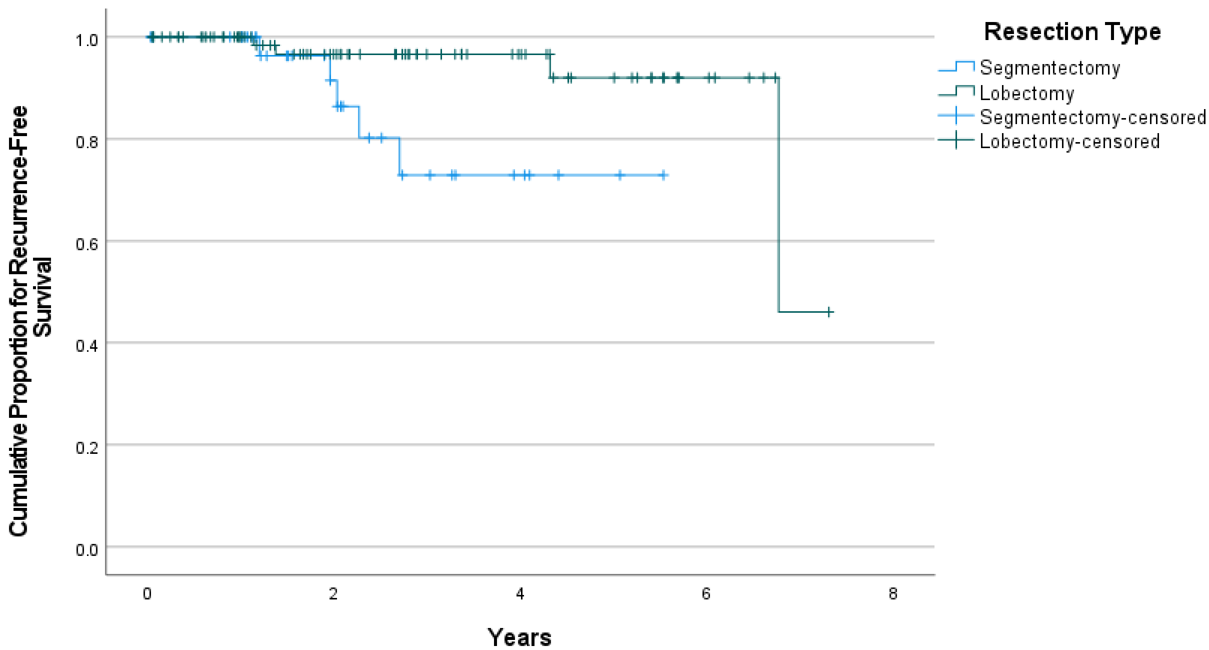

Figure 4: Number of Lymph Node Stations Sampled Based On Robotic Procedure

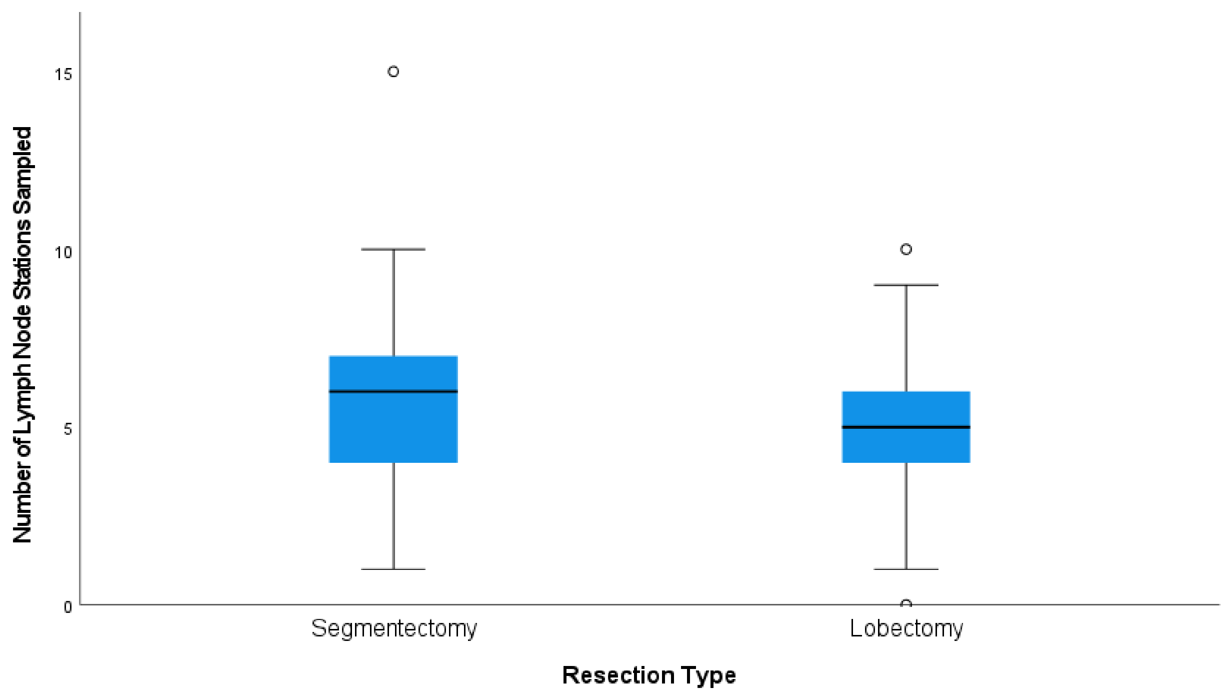

Figure 5: Number of Lymph Node Stations Sampled based on Resected Lobe

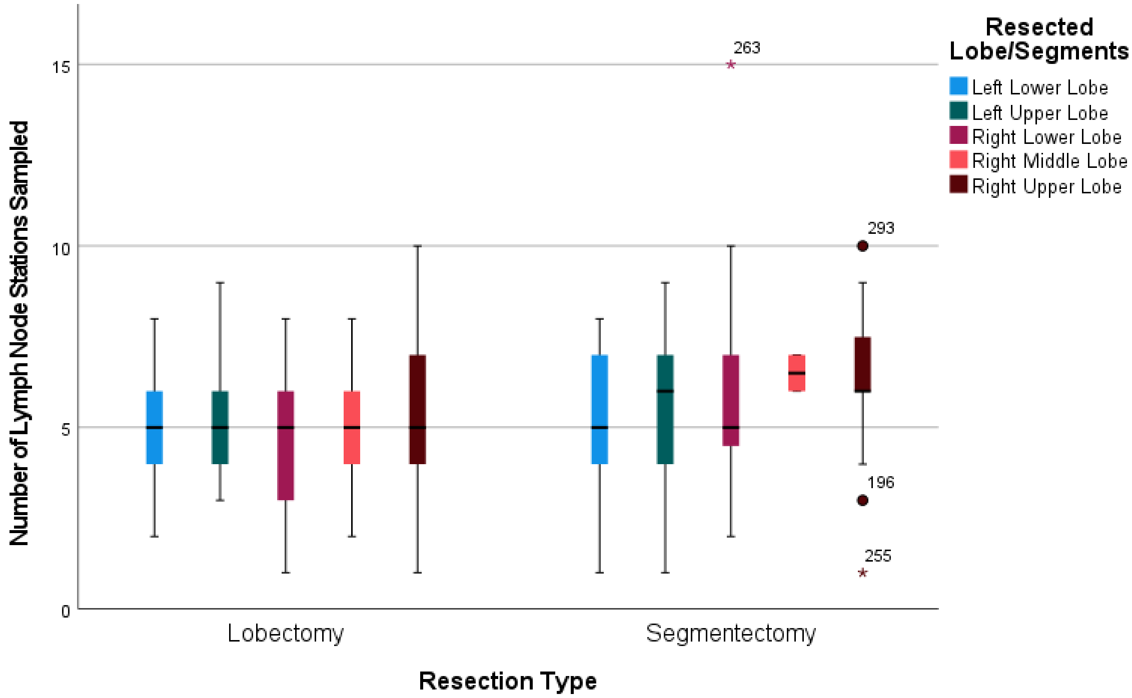

Table 2: Operative Outcomes After Planned Robotic Lobectomy and Robotic Segmentectomy

Operative Characteristics		**Lobectomy** (n=229)		**Segmentectomy** (n=180)		**Total** (n=409)		
		Count (%)	**Median (IQR)**	**Count (%)**	**Median (IQR)**	**Count (%)**	**Median (IQR)**	**p-value**
OR Time			195 (164 - 237)		169 (150 - 192)		180 (157 - 211)	<0.001
Procedure Time			144 (119 - 179)		125 (106 - 150)		135 (113 - 164)	<0.001
Console Time			92 (69 - 120)		88 (68 - 104)		89 (68 - 113)	=0.026
Switch Type	Lobectomy to Segmentectomy	1 (0)		0 (0)		1 (0)		
	Segmentectomy to Lobectomy	0 (0)		24 (13)		24 (6)		
	Segmentectomy to Wedge	0 (0)		7 (4)		7 (2)		
Blood loss amount (ml)			150 (100 - 200)		100 (50 - 200)		100 (50 - 200)	=0.001
Chest Tube Duration			2 (1 - 4)		2 (1 - 4)		2 (1 - 4)	
Converted	**Open Thoracotomy**	29 (13)		13 (7)		42 (10)		

Table 3: Patients that Experienced Study Outcomes or Endpoints

	Resection Type		
	Segmentectomy (n=157)	Lobectomy (n=231)	p-value
Nodal Upstaging	7 (4)	18 (8)	0.122
N0 → N1	4 (3)	13 (6)	
N0 → N2	3 (2)	5 (2)	
Locoregional Recurrence	23 (15)	33 (14)	0.920
Local	12 (8)	10 (4)	0.166
Regional	10 (6)	21 (9)	0.332
Local and Regional	2 (1)	2 (1)	1.00
Distant Recurrence	3 (2)	4 (2)	1.00

Table 4: Planned Robotic Resection with Switches or Conversions

	Planned Robotic Resection	
Pulmonary Resection	**Lobectomy (n=329)**	**Segmentectomy (n=198)**
Robotic Assisted (n,%)	**279 (84.8)**	**180 (90.9)**
Lobe Removed	179 (54.4)	
Left Lower Lobe	34 (10.33)	
Left Upper Lobe	18 (5.47)	
Right Lower Lobe	27 (8.2)	
Right Middle Lobe	33 (10.03)	
Right Upper Lobe	67 (20.36)	
Segments Removed		**153 (77.27)**
LS1LS2		32 (16.16)
LS1LS2LS3		10 (5.05)
LS1LS4LS2		1 (0.5)
LS3		1 (0.5)
LS3LS4LS5		3 (1.51)
LS4LS5		11 (5.55)
LS6		13 (6.56)
LS6LS9		2 (1.01)
LS7LS8LS9		1 (0.5)
LS7LS8LS9LS10		1 (0.5)

LS8	1 (0.5)
LS8LS9	1 (0.5)
LS8LS9LS10	8 (4.04)
LS9LS10	3 (1.51)
RS1	8 (4.04)
RS1RS2	3 (1.51)
RS1RS2RS3RS4*	1 (0.5)
RS1RS3	3 (1.51)
RS2	4 (2.02)
RS2RS3	1 (0.5)
RS2RS6	1 (0.5)
RS3	2 (1.01)
RS4	1 (0.5)
RS5	1 (0.5)
RS6	23 (11.61)
RS6RS10	2 (1.01)
RS6RS9RS10	1 (0.5)
RS7RS8	2 (1.01)
RS7RS8RS9	1 (0.5)
RS7RS8RS9RS10	9 (4.54)
RS8RS9	1 (0.5)

RS9	1 (0.5)
Switch to Robotic Lobectomy	**20 (10.1)**
LS1LS2	1 (0.5)
LS6	3 (1.51)
LS8LS9LS10	3 (1.51)
RS1RS2	1 (0.5)
RS1RS3	1 (0.5)
RS2	3 (1.51)
RS2RS3	1 (0.5)
RS2RS6	1 (0.5)
RS4	1 (0.5)
RS6	2 (1.01)
RS7RS8RS9RS10	1 (0.5)
RS9RS10	1 (0.5)
Switch to Robotic Wedge	**7 (3.53)**
LS1LS2	1 (0.5)
LS3	1 (0.5)
LS8	1 (0.5)
RS3	1 (0.5)
RS3RS6	1 (0.5)

RS7		1 (0.5)
RS9		1 (0.5)
Converted to Open	50 (15.19)	**18 (9.09)**
As Planned	49 (14.89)	11 (5.55)
Lobectomy	31 (9.42)	
Left Lower Lobe	9 (2.73)	
Left Upper Lobe	3 (0.91)	
Right Lower Lobe	3 (0.91)	
Right Middle Lobe	5 (1.51)	
Right Upper Lobe	11 (3.34)	
LS1LS2		1 (0.5)
LS1LS3LS2		1 (0.5)
LS3		1 (0.5)
LS4LS5		1 (0.5)
LS6		2 (1.01)
RS2		1 (0.5)
RS3		1 (0.5)
RS6		3 (1.51)
Switch to Segmentectomy	**1 (2)**	
Left Upper Lobe	1 (2)	
Switch to Open Lobectomy		**6 (3.03)**

LS1LS2	2 (1.01)
LS3LS4LS5	1 (0.5)
RS6	2 (1.01)
RS8	1 (0.5)
Switch to Open Wedge	**1 (0.5)**
RS10	1 (0.5)

Chapter 4: Summary of Findings and Future Directions

4.1 Added Value of This Work

The most prominent clinical question in the field of thoracic surgery pertains to the role of segmentectomy for early-stage non-small cell lung cancer, which is emerging as an alternative to lobectomy. Segmentectomy is a valuable lung resection procedure that preserves pulmonary function by only resecting the few anatomical segments containing the tumour, while sparing the remainder of the lobe. Prior to this work, the role of robotic-assisted segmentectomy had not been fully investigated. To address this gap in the literature, we focused our efforts on evaluating how intraoperative adjuncts have helped overcome technical challenges associated with segmentectomy, and ascertain the potential relationship between the clinical utility of these innovations and surgeon experience. Next, we compared the immediate and long-term oncological impacts of robotic-assisted segmentectomy against the standard of care, by generating a dependable control group from a prospectively collected database of participants undergoing robotic-assisted lobectomy.

4.2 NIF-Guided Robotic-Assisted Segmentectomy

The robotic surgical platform is equipped with three-dimensional optics and higher instrument precision, enabling thoracic surgeons to perform more complex operations. The advantages of the robotic platform are especially apparent during anatomic segmentectomy, which requires meticulous intraparenchymal dissection to expose the segmental bronchus and vessels.[2] From a technical standpoint, segmentectomy is difficult to perform because the pulmonary lines that separate segments, or intersegmental planes, are invisible. This poses a challenge for the operating surgeon in determining where to resect the lung tissue to obtain adequate margin distance from the tumour. Near-infrared mapping (NIF) with indocyanine green dye (ICG) is a recent advancement in robotic-assisted segmentectomy that provides a complete delineation of the intersegmental plane. Previous work at our center has also shown that this technique was associated with an increase in the oncological margin distance compared to the surgeons' initially estimated resection line. Given that segmentectomy is associated with a learning curve, we evaluated whether this was observed due to our early experience in robotic-assisted segmentectomy, and hypothesized that the added benefit of ICG would diminish as more cases were performed. In Chapter 2, we used a temporal analysis to monitor surgeon experience over time, and found that the clinical utility of NIF mapping diminished after approximately 42 cases with ICG, and the surgeon began to identify the location of the intersegmental plane more accurately and consistently without ICG injection since. This finding supported our initial hypothesis, and confirmed the presence of a learning curve associated with the robotic procedure, which has been documented through previous, albeit limited, reports on robotic-assisted segmentectomy.[4,5]

4.3 Extent of Lymph Node Assessment during Robotic Segmentectomy

While it is agreed that nodal staging must be as precise as possible, there is no consensus surrounding the optimal degree of lymph node assessment, or the number of lymph nodes that should be evaluated during lung resections.[6] Adequate LN sampling decreases the likelihood of missing positive lymph nodes, which permits a more precise staging and appropriate treatment to be indicated if needed.[7,8] Traditionally, segmentectomy was associated with reduced oncological effectiveness, due to poorer rates of lymph node dissection, and higher recurrence rates compared to lobectomy.[9–11] In our study, we observed that when segmentectomy is offered as curative-intent surgery, adequate lymph node harvesting can be performed with comparable rates of nodal upstaging compared to lobectomy. Furthermore, prior to this work, the role of segmentectomy for tumours greater than 2 cm and less than 3 cm (T1c), which are still considered early-stage, had never been evaluated through prospective methodology.[12] In our study, we also found that segmentectomy is technically feasible for T1c tumours, and can be performed with adequate oncological outcomes despite the local invasiveness of these tumours. A finding that was rather unexpected was the significant reduction in local recurrence-free survival observed after segmentectomy for these tumours. However, given that this subgroup experienced similar overall survival compared to lobectomy, the role of segmentectomy may still be well-justified for these tumours.

4.4 Conclusions and Future Directions

Pulmonary segmentectomy has been limited to a unique subset of patients with early-stage non-small cell lung cancer, due to challenges in performing the operation and unknown long-term oncological impacts. In this thesis, we determined that experience on the robotic surgical platform, coupled with intraoperative guidance, has facilitated surgeon adherence to fundamental components of lung cancer surgery, such as maintaining enough surgical margin distance from the tumour, and performing a thorough lymph node evaluation, both of which are perceived to be compromised during segmentectomy. Although we found significant differences in recurrence-free survival after segmentectomy compared to lobectomy, this finding should be interpreted in the context of similar overall survival rates, which could be attributed to the preservation of pulmonary function. In light of these findings, the answer to the role of segmentectomy may ultimately lie within future prospective trials emphasizing patient-reported outcomes after lung cancer surgery.

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