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Reviewer A

This study evaluated the outcomes of robotic assisted lung lobectomy at an NCI-CC to those of open, VATS, or robotic lobectomy in the NCDB. NCI-CC patients had higher nodal yield, higher rates of mediastinal lymphadenectomy, and lower conversion rates compared with the date of NCDB patients.

Authors concluded that robotic assisted lobectomy for NSCLC appears to provide improved perioperative outcomes with comparable long-term OS compared to open and VATS lobectomies.

I have the following concerns.

- In this paper, the surgical data is compared between robotic surgery at NCI-CC and open surgery and VATS at NCDB, but these are not clear and confusing. Only data comparing robotic surgery at NCI-CC and NCDB is needed. Reply 1: The surgical data comparison between robotic surgery and open/VATS surgeries are presented to potentially support that robotic surgery has advantages over open/VATS, as there has really been no definitive paper that answers that question. To address the confusion, we have revised the table format such that the other tabular comparisons (originally tables 3, 4, 5, 6) have been transferred to the bottom of the manuscript as Supplementary tables.
- In table 5, 'laparoscopic' should be corrected to 'thoracoscopic'. Reply 2: The correction from laparoscopic to thoracoscopic has been made.

Reviewer B

The authors demonstrated that RATS lobectomy for non–small cell lung cancer appears to provide improved perioperative outcomes with comparable long-term OS compared to open and VATS lobectomies.

The manuscript was well-written throughout. It will attract the readers' interests. I have added some points below that if addressed may increase the educational value of the manuscript.

Thank you for the kind words.

Major comments:

1. Please describe the authors' robotic settings in detail such as port placement, instrument, model of da Vinci surgical system, CO2 insufflation and dividing fissures by robotic stapler.

Reply 1. A description of the operative technique has been added to the manuscript

revision.

Changes in the text: (page 6, line 7-22) Operative technique

All robotic lobectomies were performed using the Intuitive daVinci robotic surgical system. From 2010 to December 2011, the S model was used. The Si model was then used from January 2012 to December 2016. From 2017 onwards, the Xi system was henceforth used. There are three surgeons in the NCI-CC who perform robotic lobectomies. Two of these surgeons use four-arm technique, and one use a threearm technique. The port placement and technique of the surgeons did not vary with the laterality, or the lobe being resected. The first 8-mm trocar is placed, and the remaining trocars are placed under thoracoscopic guidance. Temporary insufflation with warm humidified CO2 is used to a maximum pressure of 8-10 mmHg to improve visualization of the surgical field. Robotic stapling is performed through either the anterior or posterior 12-mm trocars. The dissection is standardized, regardless of the laterality or the lobe. The inferior pulmonary ligament is divided, and this is followed by a posterior hilar dissection which includes a thorough lymphadenectomy of stations 7, 8, and 9. We then follow with an anterior hilar dissection, after which division of the vein, artery, and bronchus is performed. The sequence of division of these structures as well as the fissure differ depending on the lobe being removed. A complete mediastinal and hilar lymphadenectomy then follows – stations 2 and 4 on the right and stations 5 and 6 on the left. Stations 10 and 11 are dissected out as well. A single 28 French chest tube is inserted, and postoperative care follow the ERAS protocol.

2. A high rate of T4 case (27.4%) was confirmed in the RL group. Please described the reason in detail. Also please provide a breakdown of the T4 such as tumor size, the other organ invasion.

Reply 2. I apologize but there was in fact a mistake in the table. The rate of T4 cases was only 3.4% (35/1021). Of these, 5 were due to tumor size and the rest (30) were separate tumor nodule in an ipsilateral lobe.

Changes in the table (changes have been made in the other tables as well):

T stage	Tis	11 (1.1%)
	T1	534 (52.3%)
	T2	353 (34.6%)
	Т3	88 (8.6%)
	T4	35 (3.4%)

3. In Table 1, stage 3 was 19.8% even though 26.1% of the cases were T4. This is inconsistent with the fact that T4 cases must be at stage 3 or higher. Is there a confusion between surgical stage and pathological stage? Please describe it in detail. Reply 3. Corollary to reply 2. Stage III was 19.8% even though only 3.4% of the cases were T4 because 15.1% of all patients had N2 disease, making them at least a stage III. The staging used throughout the paper was pathological stage.

Changes in table: none

4. The conversion rate can vary considerably depending on the criteria of conversion to thoracotomy. Please describe the criteria at the authors' institution. Also, please discuss the comparisons with other institutions. For example, two articles describe the criteria for conversion well: PMID 21840547 and PMID 36245576. PMID 21840547 showed that the authors convert to thoracotomy if the operation time exceeds 4 hours. PMID 36245576 showed no conversion, probably because it did not take into account the operation time.

Reply 4: Our group's criteria are now mentioned in the discussion.

Changes in text: (page 11, line 4-9) Each group's criteria for conversion to thoracotomy varies considerably. In our institution, in cases of bleeding that cannot be controlled or treated with robotic surgery, then conversion to thoracotomy happens. Other criteria would be injuries to airway that cannot be repaired robotically, as well as severe pleural symphysis from prior surgeries that cause difficulty in entering the pleural space. There are no criteria regarding operative duration beyond which a conversion to open is necessary, as opposed to other institutions.

5. In this study, the authors described that "evidence from a previously published study shows that pathologic upstaging for stage I NSCLC is common and is associated with a greater number of lymph nodes sampled, among other variables". However, several articles showed that the number of lymph nodes sampled is not associated with the pathologic upstaging. For example, two articles described well PMID 34297835 and PMID 36083513. We believe that the association is still controversial. Please elaborate on this point.

Reply 5: We agree that the association between number of lymph nodes and pathologic upstaging is still controversial and will need further studies in the future. An elaboration has been added in the text.

Changes in text: (page14, line 7-20). Although our data do not include information on pathologic upstaging after surgery, evidence from a previously published study shows that pathologic upstaging for stage I NSCLC is common and is associated with a greater number of lymph nodes sampled, among other variables.⁷Another paper by Zirafa and colleagues compared nodal upstaging between their consecutive cN0 NSCLC patients who underwent OL and RL, and found that although the number of lymph nodes harvested were similar between the OL and RL cohorts, there was a statistically higher number of nodal stations in RL compared to OL, and nodal upstaging was observed in 20.8% of RL patients and in 17.9% of OL patients.²² Other papers however report a conflicting finding. For instance, in a recent article by Haruki et al, the median total LN numbers, though significantly different between RL and VL, were not associated with overall nodal upstaging.²³ The article by Shindo et all mirrors these results in cN0 patients.²⁴ The association between lymph node assessment and pathologic upstaging is still currently controversial and needs to be further studied. Suffice it to say that these differences, if any, in lymph node

assessment and upstaging between the different approaches have not been found to translate to differences in long-term oncologic outcomes

6. A high rate of prolonged air leak was observed. What accounted for the high rate? Please describe it in discussion.

Reply 6: I think what accounted for the high rate is the high incidence of COPD and smoking history as well in our cohort. A discussion of this has been added.

Changes in text: (page 15, line 1-6) It is also important to note that the most common postoperative complication in our database is prolonged air leak, and this had an incidence of 20.4% in our cohort of RL patients. Note however that 24.8% of the patients had a diagnosis of COPD, and that 22.8% were either currently smoking or recently quit within 90 days of surgery. These are two of the main risk factors for prolonged air leak after lung resections and could potentially explain the reason behind the relatively higher incidence of prolonged air leak in our cohort, and relatively longer duration of chest tube use.

Minor comment:

- 1. In Table 5 legend, laparoscopic \rightarrow VATS
 - Reply 1: The correction from laparoscopic to thoracoscopic has been made.

Reviewer C

- 1021 patients with robotics were presented in the abstracts but it was 667 patients in table of main text. Which is correct? Please correct them with right numbers. Reply 1: A total of 1021 patients underwent robotic lobectomy in the database who got a robotic lobectomy from 2010 to 2020. In order to have enough follow up data for at least a 5-year overall survival, however, we then compared chronological cohorts from the MCC database and NCDB, and a total of 667 patients were matched to NCDB's 122,467 OL patients from 2010-2017. These 667 patients were as well matched to 45,193 VL and 15,816 RL patients in the NCDB.
- 2. The conclusions in the abstract and in the main text seems to be different in tone. Please use consistent conclusions

Reply 2: As this is more of a benchmarking study, the authors made appropriate revisions to the conclusions both in the abstract and in the main text. Changes in text:

(Abstract conclusion, page 3 line 13-15): **Conclusion:** Robotic-assisted lobectomy for non–small cell lung cancer performed in an NCI-CC appears to have improved perioperative outcomes with comparable long-term OS compared to national benchmarks in open, video-assisted thoracoscopic and robotic lobectomies.

(Main text conclusion, page 16 line 13-18): Conclusion: The frequency of RL for NSCLC has remarkably increased over the years, and compared to national benchmarks of OL, VL and RL as presented in the NCDB, RL performed in an NCI-CC appears to provide improved perioperative outcomes and comparable long-term

OS. Although these results need to be verified in a prospective randomized trial with a long-term follow-up to confirm oncologic outcomes, this study provides a preponderance of evidence suggesting the suitability of RL in resectable lung cancers.

- Authors used "improved perioperative outcomes." There are only postoperative outcomes. Please show the preoperative outcomes.
 Reply 3: There are no preoperative outcomes in the paper. With perioperative outcomes, the authors were referring to surgical outcomes, i.e., number of examined nodes, performance of mediastinal lymphadenectomy, conversion to thoracotomy, LOS, and 30-day mortality. Among these, only 30-day mortality was no better in the RL MCC cohort.
- Please show clear indication of the Robotic lobectomy. Moreover, show the data of open or VATS in the study period to avoid the debate of selection bias. Reply 4: All patients with resectable NSCLC requiring a lobectomy underwent

robotic surgery by the three surgeons. The patients who needed chest wall resection or sleeve lobectomy were excluded. This group only have a few of cases of open/VATS cases, so there is clearly a selection bias, as we reserve open lobectomy for larger tumors (>8cm), in addition to most tumors involving the chest wall of requiring formal sleeve lobectomies. We recently started performing sleeve lobectomies robotically but these patients are not yet included in this database. Changes in text:

Limitations (page 16, line 7-9): There is selection bias in our study, since all three surgeons reserve open lobectomies for large tumors (>8cm), tumors requiring chest wall resection, and sleeve lobectomies. Thoracosopic lobectomies (VL) were only performed before the robotic platform became available.

5. Surgical outcomes of the paper were superior to those of NCDB. If there were no selection bias, please present the causes for it.

Reply 5: All lobectomies performed by the three surgeons included in this retrospective analysis only performed robotic lobectomies for early-stage lung cancers. Open lobectomy was reserved for those who required chest wall resection, sleeve lobectomy, and for tumors > 8 cm in size. Thoracoscopic lobectomies were only performed before the robotic platform became available. There is clearly selection bias in the paper, and this was included in the discussion (please refer to changes in text to comment #4). We believe that surgical outcomes of the paper were superior to those of NCDB for several reasons: 1) our institution perform more robotic lobectomies than most institutions, so there is more experience, 2) there are dedicated OR nursing team and dedicated OR bedside assistants, and 3) there is a dedicated telemetry ward for our postoperative inpatients, and we follow ERAS and clinical pathways for all of our patients.

Changes in text:

Discussion (page 15, line 1-8): Generally, our paper's surgical outcomes were

superior to those of NCDB counterparts, in terms of nodal yield, rates of reported mediastinal lymphadenectomy, and conversion rates. Median LOS, 30-day mortality and 5-year OS were similar. Although there is clearly selection bias in the paper, our group suggests that surgical outcomes were superior for several reasons: 1) our institution perform more robotic lobectomies than most institutions, so there is more experience, 2) there are dedicated OR nursing teams and dedicated OR bedside assistants for robotic thoracic surgical procedures, and 3) there is a dedicated telemetry ward for our postoperative inpatients, and we follow ERAS and clinical pathways for all of our patients.

- 6. Your data and that of NCDB are gathered and managed in the different manner. Such a data could be compared. Statement of statistician is required. Reply 6: Thank you for an important comment. First, we evaluated the data points reported in the NCDB and designed our data collection in a parallel fashion to make our database as identical and comparable as possible to that of the NCDB. During the selection process, we eliminated NCDB patients treated at our institution to avoid duplication since identification of these patients is reported per the location of performing the surgical resection. We followed the same standards of data reporting including staging and scale scoring (such as Charlson Comorbidity Index) to minimize reporting bias and make the matching and outcome comparison process as standardized as possible.
- Authors compared theirs and NCDB's. Were there common groups? If no, how did authors exclude them? Please refer to answer #6.

Reviewer D

The research addresses the important question of differences in outcomes between approaches used in lobectomy. The datasets and the analytical approaches used in the study are robust; however, the connection between study rationale, study objectives and the methods may require more clarity.

• The introduction, rationale, and study objective refer to lack of data on comparing outcomes of Robotic, VATS and open lobectomy in patients with NSCLC and evaluating these data in a head-to-head comparison. However, the study methodology introduces the database from the Moffitt Cancer Center (MCC) and the rest of the study feels a benchmarking study comparing outcomes of MCC to the national benchmarks available from the NCDB. Based on the study objectives, this study could have been done by doing a propensity score matched analysis of Robotic, VATS and open lobectomies from NCDB. Comparing MCC vs NCDB which are 2 different databases with potentially differences in variable operationalization especially for outcomes such as Overall Survival may introduce bias which could be avoided by comparing the 3

approaches within NCDB. I would recommend the authors to justify the use of the MCC data or revise the rationale and study objectives.

Reply: This paper is more of a benchmarking study, comparing the outcomes in an NCI-CC to those of national benchmarks. The authors have revised the rationale and study objectives as follows:

Changes in text: (Introduction, page 5, line 1-6) The goal of this retrospective study is to compare the perioperative and long-term oncologic outcomes of RL for NSCLC in a comprehensive cancer center to OL,VL and RL as reported in the National Cancer Database (NCDB). More than 1500 accredited centers across the US territories submit data to this program, and it is thought to capture around 70% of all newly diagnosed lung cancer cases in the US annually⁷. The authors aim to provide perspectives on how outcomes in an NCI-designated cancer center compares to national benchmarks as presented in the NCDB.

• The following variables were used by the researchers in the propensity score model: age, sex, race/ethnicity, Charlson score, histology, tumor grade, laterality, TNM stage, and the receipt of any type of neoadjuvant therapy. A few other critical variables such as smoking status, COPD, and year of procedure were not included in the propensity score model. I would recommend adding these variables to the model. At the minimum, the authors should at least show that these variables were balanced after propensity matching. It would be also helpful to clarify the use of MCC data from 2018-2020. I am assuming that these procedures were not included in the analysis which is the appropriate approach. Please clarify. Also, if this is accurate, I am not sure if the data from 1021 patients should be presented in the manuscript – authors should focus on the MCC cohort from 2010 -2017.

Reply: A total of 1021 patients underwent robotic lobectomy in the database who got a robotic lobectomy from 2010 to 2020. In order to have enough follow up data for at least a 5-year overall survival, however, we then compared chronological cohorts from the MCC database and NCDB, and a total of 667 patients were matched to NCDB's 122,467 OL patients from 2010-2017. These 667 patients were as well matched to 45,193 VL and 15,816 RL patients in the NCDB. Again, to clarify, the MCC data from 2018-2020 were not included in the propensity match and in the analysis. The propensity matching was just done with our 2010-2017 patients, along with chronological cohorts from NCDB.

Regarding the adjustment for risk factors such as smoking and COPD, unfortunately the NCDB does not report on these variables which, admittedly, is an inherent shortcoming of such our study and similar registry-based research analyses. Our attempt to compensate for potential reporting bias was to apply strict matching conditions while also aiming for a large sample size to dilute possible unreported differences between the study groups.

• Are the AJCC staging editions comparable between the MCC and NCDB? Based on some of the results, it seems like the MCC data is using AJCC 8th edition while the NCDB is using the AJCC 7th edition. These need to be normalized before conducting

the propensity matching or the results will be biased (some of the differences can be seen in T4 distributions). May also be helpful to include actual tumor size as a variable in the propensity model or at least show the balance post matching.

Reply: We agree that there are expected biases due to the AJCC staging switch. The MCC data was updated to reflect AJCC 8th edition while the NCDB uses the AJCC 7th edition. We do have the actual T stage as a variable in Table 1. The T stage and N stage were well-balanced post matching, and these are shown in Table 3, as well as Supplementary Tables 1 and 3. In addition, the NCDB staging was adjusted prior to matching and data analysis to reflect the AJCC 8th version standards by resorting to basic pathologic tumor characteristics (e.g., tumor size, number of nodes examined, number of nodes involved, etc.) and apply respective staging. A similar adjustment was applied to our patients diagnosed and treated before the implementation of AJCC 8th version classification.

• To clarify, is the MCC data using clinical or pathological staging? In SEER, for patients undergoing surgery, pathological staging is reported (except for those receiving neoadjuvant therapy). I am assuming NCDB uses a similar approach. Please confirm the comparability of staging approaches between MCC and NCDB.

Reply: Yes, NCDB uses a similar approach. The MCC data as well use the pathologic staging.

• This may have to checked with a Biostatistician. However, balance post propensity matching is generally checked through Standardized Mean Differences (SMD), with an absolute SMD of less than 0.1 indicating adequate balance. The authors have included standard deviation (not SMD) and p values in their tables for comparing balance before and after propensity matching. P values will be affected drastically by sample sizes and should not be used as a metric to evaluate balance.

Reply: Thank you for an important comment. After the matching process, standardized mean difference was checked for all matching variables with a target of <0.1 given our caliper width for the nearest neighbor matching condition was set at 0.1. Indeed, all variables demonstrated an SMD of <0.1 but given the size of the reported data these results were not reported in the matching tables and we elected to only report the p value to demonstrate to our readership that significant baseline differences were resolved upon matching.

• If this is a benchmarking study, the key comparison is of the MCC RL cohort to the NCDB RL cohort. This analysis can provide perspectives on how MCC compares to national benchmarks. All the other comparisons seem a bit convoluted (a direct comparison of the approaches within NCDB would have been the straightforward analytical approach). The conclusions focus heavily on comparability of RL, VL and OL as opposed to benchmarking of MCC data. I would recommend ensuring the alignment of objectives, methods and conclusions in a future revised version.

Reply: The surgical data comparison between robotic surgery and open/VATS surgeries are presented to potentially support that robotic surgery has advantages over

open/VATS, as there has really been no definitive paper that answers that question. To address the confusion and highlight the key comparison, we have revised the table format such that the other tabular comparisons (originally tables 3, 4, 5, 6) have been transferred to the bottom of the manuscript as Supplementary tables. Only the comparison between MCC RL and NCDB RL are in the main text/tables. Also, the objectives and conclusions have been aligned to reflect that this is a benchmarking study.

Reviewer E

Thank for the opportunity to review this work comparing robotic assisted lobectomy between a single high volume tertiary care center and those reported in the NCDB. This an important topic of investigation and the authors show that their institutional experiences compares favorably to that reported in the NCDB. I have several questions regarding the study methodology and outcomes.

1. The authors present data on their institutional peri-operative morbidity. Air leak >5 days was the most common morbidity and occurred in roughly 10% of cases. This and duration of chest tube use (~4days) and length of stay is higher than what is typically observed and was has previously been reported for robotic assisted lobectomy. Can the authors comment on this finding? Did it change over time during the study's 10 year course?

Reply 1: I think what accounted for the high rate is the high incidence of COPD and smoking history as well in our cohort. A discussion of this has been added. There has been no significant change over the study's 10 year course.

Changes in text: (page 14, line 17-22) It is also important to note that the most common postoperative complication in our database is prolonged air leak, and this had an incidence of 20.4% in our cohort of RL patients. Note however that 24.8% of the patients had a diagnosis of COPD, and that 22.8% were either currently smoking or recently quit within 90 days of surgery. These are two of the main risk factors for prolonged air leak after lung resections and could potentially explain the reason behind the relatively higher incidence of prolonged air leak in our cohort and relatively longer duration of chest tube use.

2. In the propensity match the authors lose 26% of their institutional study population. This is much higher than expected. Can the authors comment on why a quarter of their patient population could not be matched to NCDB patients.

Reply 2: A quarter of our patient population could not be matched to NCDB patients presumably because we used a number of perioperative variables (age, sex, race/ethnicity, Charlson score, histology, tumor grade, laterality, TNM stage, and the receipt of any type of neoadjuvant therapy) during the matching.

3. The authors have observed that lymph node harvest in robotic assisted lobectomy is

higher compared to open or video assisted surgery. The quality metric during the time of the study that was frequently used was 10 nodes during time of lobectomy. Did the authors use this as a binary cutoff (e.g. met 10 node criteria or not). There is a fairly wide standard of error and expect that data is quite skewed.

Reply3: The 3 thoracic surgeons whose patients are included in the database perform a complete thoracic lymphadenectomy and not only lymph node sampling. The dissection is standardized. For right-sided resections, lymphadenectomy of stations 2R, 4R, 7, 8, 9, 10, 11 is performed, while for left-sided resections, lymphadenectomy of stations 5, 6, 7, 9, 10, 11 is performed. The authors did not use 10 nodes as binary cutoff but instead evaluated all accessible nodes and recorded the number of nodes and nodal stations harvested.

4. How did the authors define adequate mediastinal lymphadenectomy? Mention of the recently endorsed 3+1 mediastinal sampling should be mentioned in the discussion why this may not have been possible to track in the retrospective study.

Reply 4: The authors used either performance of mediastinal lymphadenectomy or not as variable for this portion. The recently endorsed 3+1 mediastinal sampling was not utilized. Although the MCC database has the information to evaluate adherence of the CoC quality metric, the comparison with the NCDB database would not be possible due to missing data.

Changes in text: (page 13, line 8-13) Recently, the Commission of Cancer (CoC) of the American College of Surgeons defined one of the quality metrics of lung cancer resection as having a specific minimum number of lymph nodes separate from the tissue specimen. This quality metric is defined as the presence of lymph nodes from at least 3 mediastinal lymph node stations and at least one hilar lymph node station. It is yet unknown as to how the adherence to the CoC metric will influence long-term outcomes of lung cancer.

(page 14 line 22-23, page 15 line 1-2) approaches have not been found to translate to differences in long-term oncologic outcomes. It will be interesting to see if the recently released CoC quality metric translates to differences in outcomes in the long run. This was not possible to track in our retrospective study that compares it to NCDB due to a high percentage of missing data.

Reviewer F

Thank you for the great opportunity to review the interesting research entitled "Perioperative and oncologic outcomes of robotic-assisted lobectomy for non-small cell lung cancer in a National Cancer Institute–Designated Cancer Center compared to the National Cancer Database" by Baldonado, et. al. By comparing their institutional data with National Cancer Database (NCDB) data, the authors concluded that improved short-term and comparable long-term outcomes in patients with non-small cell lung cancer (NSCLC) who underwent Robotic-assisted lobectomies. I think the manuscript is written well and reaches the required quality of "Journal of Thoracic Disease".

However, the manuscript includes some minor revision points.

1. I (reviewer) was unable to understand why HR is shown in table 4, 6 and 8. I suppose that chi-squared test or Fisher's exact test would be used in comparison between two groups for categorical data, and t-test or Mann-Whitney U test for continuous data. Reply 1: Conditional logistic regression and mixed-effect modeling were used for these comparisons because we were analyzing matched case-control data, which is the reason why HR were shown.

2. Are T, N and M factors and stage shown in Table 1, 3, 5 and 7 clinical or pathological? Reply 2: The TNM factors refer to pathologic staging.

3. If possible, please show the information on the postoperative adjuvant therapy. Reply 3: Unfortunately, this would not be possible because majority of the patients in our institution do not establish care with medical oncology at Moffitt. Most of them go back to their referring physicians and so we do not have the complete data regarding adjuvant therapy.

4. Please show the current for Robotic-lobectomy for NSCLC in your institution. Reply 4: I apologize but I do not understand the question very well. Could you please clarify which data from our robotic lobectomy database need to be shown?

5. Please show the version of TNM classification adopted in this study, ie, 7th or 8th ? Reply 5: We used the AJCC v8 edition.

Location in text: (page 8, line 1-6) The mean tumor size was 2.96 ± 1.73 cm (median, 2.5 cm), and most tumors were clinical stage I (N = 609 [59.6%]) based on the American Joint Committee on Cancer, eighth edition of TNM staging for NSCLC. From the operative standpoint, 36 patients (3.5%) experienced conversion to OL; 28 patients (2.7%) had an additional anatomic lobectomy; and 382 (37.4%) had an additional resection (ie, wedge resection or mediastinal mass resection). The mean estimated blood loss was 170 ± 353 mL (median, 100 mL) and the mean operative time was 173 ± 54 minutes (median, 163 minutes). Table 1 summarizes the clinical, demographic, and intraoperative characteristics of the MCC RL cohort.