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Defining the Role of Minimally Invasive Proctectomy for Locally Advanced Rectal Adenocarcinoma

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Objective: National examination of open proctectomy (OP), laparoscopic proctectomy (LP), and robotic proctectomy (RP) in pathological outcomes and overall survival (OS).

Background: Surgical management for rectal adenocarcinoma is evolving towards utilization of LP and RP. However, the oncological impacts of a minimally invasive approach to rectal cancer have yet to be defined.

Methods: Retrospective review of the National Cancer Database identified patients with nonmetastatic locally advanced rectal adenocarcinoma from 2010 to 2014, who underwent neoadjuvant chemoradiation, surgical resection, and adjuvant therapy. Cases were stratified by surgical approach. Multivariate analysis was used to compare pathological outcomes. Cox proportional-hazard modeling and Kaplan–Meier analyses were used to estimate long-term OS.

Results: Of 6313 cases identified, 53.8% underwent OP, 31.8% underwent LP, and 14.3% underwent RP. Higher-volume academic/research and comprehensive community centers combined to perform 80% of laparoscopic cases and 83% of robotic cases. In an intent-to-treat model, multivariate analysis demonstrated superior circumferential margin negativity rates with LP compared with OP (odds ratio 1.34, 95% confidence interval 1.02–1.77, P = 0.036). Cox proportional-hazard modeling demonstrated a lower death hazard ratio for LP compared with OP (hazard ratio 0.81, 95% confidence interval 0.67–0.99, P = 0.037). Kaplan–Meier analysis demonstrated a 5- year OS of 81% in LP compared with 78% in RP and 76% in OP (P=0.0198).
Conclusion: In the hands of experienced colorectal specialists treating selected patients, LP may be a valuable operative technique that is associated with oncological benefits. Further exploration of pathological outcomes and long-term survival by means of prospective randomized trials may offer more definitive conclusions regarding comparisons of open and minimally invasive technique.

Keywords: laparoscopic, proctectomy, rectal adenocarcinoma, robotic, total mesorectal excision

In 2017, an estimated 39,910 new cases of rectal adenocarcinoma will be diagnosed.1 The cornerstone of treatment for locally advanced rectal cancer continues to be total mesorectal excision (TME) in conjunction with preoperative neoadjuvant multimodal therapy. The application of minimally invasive techniques for proctectomy appears to offer equivalent morbidity, mortality, length of stay, and anastomotic leak when compared with open methods.2,3

It remains controversial, however, if equivalent oncological yield and overall survival (OS) are achieved with minimally invasive techniques. While the Comparison of Open versus laparoscopic for mid or low REctal After Neoadjuvant chemoradiotherapy (COREAN) trial and the Colorectal Cancer Laparoscopic or Open Resection II (COLOR II) trial have reported equivalent pathological yield and long-term overall survival, the early findings of the Australian Laparoscopic Cancer of the Rectum Trial (ALaCART) and ASOCOG Z6051 trials have suggested

that the early oncologic outcomes of laparoscopic surgery are not equivalent to open surgery.4–7 It is important to note that the long-term overall survival data from these latter 2 trials is still pending.

As these findings reflect a smaller subset of surgeons, the oncological outcomes of the national surgical community with open and minimally invasive technique remain uncertain. Therefore, our objective in this study was to use a large national cancer dataset to examine the utilization and outcomes of open, laparoscopic, and robotic techniques in elective proctectomy for locally advanced rectal adenocarcinoma. Our study was principally directed at 2 outcomes: pathologic margin status and long-term OS.

METHODS

Database

The National Cancer Database (NCDB) is a clinical oncological database jointly sponsored by the American College of Surgeons (ACS) and the American Cancer Society. Data included in NCDB are sourced from over 1500 Commission on Cancer (CoC)- accredited facilities, representing more than 70% of newly diagnosed cancer cases nationwide and more than 34 million historical records. Permission to use NCDB was acquired from the CoC, a multidisciplinary program of the ACS, and the institutional review board at the University of California, Irvine.

Patient Selection

A retrospective review of NCDB data was performed to identify patients with nonmetastatic locally advanced rectal adenocarcinoma treated from 2010 to 2014. International Classification of Diseases for Oncology, Third Edition (ICD-O-3) primary site codes C19.9 and 20.9 with histological subtypes 8140, 8210, 8211, 8261, 8262, 8283, 8480, and 8481 were used to define rectal adenocarcinoma. Patients with locally advanced rectal adenocarcinoma were included, as defined by having received neoadjuvant chemoradiation. After completion of surgical intervention, only patients who completed adjuvant chemotherapy were included in the study. Patients with metastatic disease were excluded. Proctectomy was defined by Facility Oncology Registry Data Standards (FORDS) codes to include partial proctectomy (low anterior resection, Hartmann procedure), total proctectomy with colo-anal anastomosis, and abdominoperineal resection (APR). Cases were stratified by operative approach into 3 groups: open proctectomy (OP), laparoscopic proctectomy (LP), and robotic proctectomy (RP).

Outcome Variables

For selected cases, patient age, sex, ethnicity, insurance status, Charleson-Deyo comorbidity score, and primary facility type were reviewed. Pathological tumor characteristics including tumor size, clinical stage, and pathological stage were reviewed. Pathological variables that were analyzed included: total node yield, positive node yield, and overall margin outcomes including complete (R0) resection, positive microscopic margins (R1), and positive macroscopic margins (R2). The overall margin variable was a composite variable that included assessment of available (proximal, distal) margins in the resected specimen with microscopic and macroscopic assessment. A separate circumferential resection margin (CRM) variable was coded as well and included separately in NCDB as part of the Collaborative Stage Site-Specific Factors (CS-SSF). CRM specifically examined the radial margin of the specimen. A positive CRM was defined as a margin <1mm or the presence of tumor. Thirty-day mortality, 90-day mortality, and mean duration from diagnosis to index surgery were reviewed as well. Multivariate analysis of postoperative

outcomes was performed using both an as-treated method and an intent-to-treat method. For survival analysis, an intent-to-treat model was applied and cases were stratified based on initial operative approach regardless of conversion. All-cause survival time was calculated from the date of diagnosis to the date of death, or if censored, the date of last contact.

Statistical Methods

For pathological outcome variables including nodal yield, overall margins, circumferential margins, 90-day mortality, and mean duration to surgery, multivariate analysis was performed to determine risk-adjusted outcomes. Pertinent covariates included in our model were age, sex, ethnicity, Charleson-Deyo score, tumor size, pathological tumor stage, and pathological nodal status. Cox proportional-hazard modeling was used to examine death hazard ratios (HRs) for operative approach, and also key patient characteristics (age, sex, ethnicity, Charleson-Deyo score). Kaplan–Meier estimates of the survival curve were created with log-rank test of equality of survival. Five-year survival probabilities were generated for each operative approach with estimated length in years to 80th percentile survival. Data management was completed using SAS (Version 9.4. Cary, NC, 2016), and all analyses were completed using the computing and programming environment R (Vienna, Austria, 2016). Chi-square test for categorical variables and Student t test for continuous variables were used to perform univariate analysis. The OP subset was utilized as a baseline for univariate analysis. A P value <0.05 was deemed significant.

RESULTS

From 2010 to 2014, in all, 6313 cases met our inclusion criteria for nonmetastatic rectal adenocarcinoma patients who underwent neoadjuvant chemoradiation, surgical intervention, and adjuvant chemotherapy. Of this group, 3399 (53.8%) underwent OP, 2009 (31.8%) underwent laparoscopic proctectomy, and 905 (14.3%) underwent RP (Fig. 1). Of all laparoscopic resections, 283 (14%) underwent unplanned conversion to OP. Of all robotic cases, 64 (7%) were converted to OP. Key patient demographic characteristics are reviewed with univariate analysis in Table 1. Open cohort was used as baseline for analysis in Tables 1–3. Charleson-Deyo comorbidity scores were statistically similar in all 3 subsets. Higher-volume academic/research and comprehensive community centers combined to perform 80% of laparoscopic cases and 83% of robotic cases.

Operative/pathological characteristics were analyzed in Table 2. The frequency of partial proctectomy, including low anterior resection (LAR), was significantly higher in the laparoscopic (63%) and robotic (62%) groups compared with the open group (56%). The frequency of abdominoperineal resection was significantly higher at
26% in the OP group compared with 21% in the LP group and similar to the RP group (25%). Similar distribution of tumor size, overall clinical stage, and overall pathological stage was noted. The frequency of ypT3/ypT4 was significantly higher at 54% in the open cohort, compared with 47.9% in the laparoscopic group and 48.9% in the robotic group.

Descriptive review of pathological outcomes was performed in Table 3. Univariate analysis demonstrated a significantly higher rate of overall margin R0 resection in the laparoscopic (95%) and robotic group (96%) compared with the open subset (92%; $P <0.05$). Rates of microscopic positivity (R1) were significantly lower in laparoscopic proctectomy (2.8%) and RP (1.8%) compared with open resection (3.9%). Rates of CRM positivity were highest in the open intervention subset at 7.62% compared with 4.87% after laparoscopy and 4.75% after robotic intervention. Statistically equivalent rates of complete pathological response were noted at 20% in the open arm, 21% in the laparoscopic arm, and 20% in the robotic arm. Multivariate risk-adjusted

analysis of each operative approach was reviewed in Table 4 applying an as-treated approach for which conversions were assessed separately and an intent-to-treat protocol based on initial operative approach regardless of conversion (Table 4).

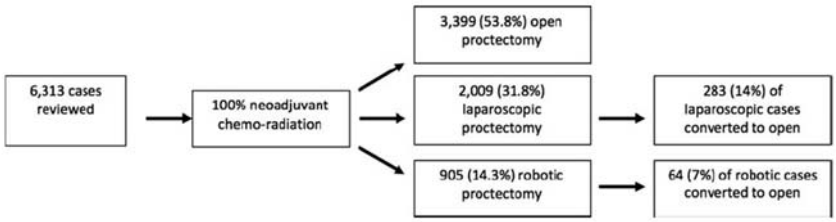


FIGURE 1. Study flowchart.

As-treated

Using an as-treated approach, overall margin R0 resection in laparoscopic [odds ratio (OR) 1.35, 95% confidence interval (CI) 1.01–1.81, P = 0.04] and RP (OR 1.56, 95% CI 1.04–2.32, P = 0.03) were found to be superior to OP. Similarly, odds of negative circumferential margin acquisition were superior for LP (OR 1.50, 95% CI 1.10–2.04, P < 0.01) and RP (OR 1.58, 95% CI 1.06–2.36, P = 0.026) compared with open intervention. RP yielded an equivalent overall negative margin rate (OR 1.15, 95% CI 0.74–1.79, P = 0.54) and negative circumferential margin rate (OR 1.05, 95% CI 0.67–1.66, P = 0.82) when compared with laparoscopy. LP was associated with superior overall negative margin acquisition (OR 2.0, 95% CI 1.23–3.22, P < 0.01) and superior negative circumferential margin acquisition (OR 1.96, 95% CI 1.18–3.23, P < 0.01) when compared with converted cases. RP similarly correlated with an improved overall negative margin rate (OR 2.40, 95% CI 1.37–4.21, P < 0.01) and an improved negative circumferential margin rate (OR 2.12, 95% CI 1.20–3.75, P < 0.01) when compared with conversion.

Intent-to-treat

Applying an intent-to-treat model to our multivariate analysis on pathological outcomes, gravitation towards a null effect was noted for minimally invasive interventions on certain data points. Laparoscopic surgery demonstrated superior negative CRM acquisition (OR 1.34, 95% CI 1.02–1.77, P = 0.036) compared with open resection. Laparoscopic resection (OR 1.16, 95% CI 0.89–1.50, P = 0.27) and robotic resection (OR 1.40, 95% CI 0.96–2.03, P = 0.07) demonstrated statistically equivalent rates of overall margin R0 resection compared with open intervention. RP trended towards a superior negative CRM rate (OR 1.38, 95% CI 0.96–2.01, P = 0.08), but did not achieve statistical significance. RP was equivalent with LP in terms of overall margin R0 resection (OR 1.21, 95% CI 0.81–1.80, P =0.35) and negative CRM (OR 1.03, 95% CI 0.69–1.55, P =0.885).

Survival Analysis

Using intent-to-treat populations, survival analysis featuring Cox proportional-hazard modeling and Kaplan–Meier estimates of survival curves was performed. Cox proportional-hazard modeling demonstrated a significantly lower death HR for the laparoscopic approach when compared with open resection (OR 0.81, 95% CI 0.67–0.99, P = 0.037) (Table 5). LP demonstrated an equivalent death HR when compared with RP (OR 0.99, 95% CI 0.72–1.37, P = 0.97). No statistical difference in death hazard ratio could be established between RP and OP (OR 0.82, 95% CI 0.61–1.09, P = 0.18). Incremental increase in age by 10 years (OR 1.21, 95% CI 1.12–1.31, P<0.01) and increase in Charleson-Deyo score by 1 (OR 1.26, 95% CI 1.10–1.45, P < 0.01) were both associated with a higher death hazard ratio. Probability of OS at 5 years was 81% for LP, 78% for RP, and 76% for OP. Kaplan–Meier estimates of survival curves demonstrated a

trend towards superior survival for robotic and laparoscopic cohorts compared with open resection; log-rank test of equality for survival was significant at 0.0198, (Fig. 2). Median survival could not be estimated, as curves did not cross the 50th percentile.

DISCUSSION

In our retrospective review of NCDB from 2010 to 2014, study arms were defined to include nonmetastatic locally advanced rectal adenocarcinoma with the following treatment algorithm: neoadjuvant chemoradiation, surgical intervention, and adjuvant chemotherapy. The majority of laparoscopic and robotic cases were performed at higher-volume academic/research and comprehensive cancer institutions. Compared with a 7.62% CRM positivity in OP, LP yielded a lower rate at 4.87%. LP, through intent-to-treat multivariate analysis, was associated with higher odds of negative CRM acquisition. For 5-year overall survival, laparoscopy was significantly higher at 81% compared with OP at 76%. Ultimately, our findings suggest that beneficial oncological outcomes can be achieved when proficient colorectal experts employ LP and RP on appropriately selected patients.

TABLE 3. Pathological Outcomes by Operative Approach

	Open (n = 3399)	Laparoscopic (n = 1726)	Robotic (n = 841)	Converted (n = 347)
Nodes examined (no.), mean	14.8 ± 8.3	15.2 ± 8.8	15.7 ± 8.7*	15.2 ± 8.0
Positive nodes (no.), mean	5.93 ± 20.8	6.46 ± 22.2	4.97 ± 18.9	5.2 ± 18.7
Overall margins, %				
Negative (R0)	92	95*	96*	90
Microscopic (R1)	3.9	2.8*	1.8*	5.2
Macroscopic (R2)	0.24	0.23	0	0.58*
Positive residual tumor (NOS)	3.1	1.6*	2.1	4.3
CRM, %				
Positive (<1 mm)	7.62	4.87*	4.75*	10.3
1–2 mm	1.7	1.1	2	0.58
2–3 mm	1	1	1.4	0.29
3–4 mm	1.4	0.98	0.71	0.86
4–5 mm	1.6	1.5	2.1	0.86
>5 mm	28	30	32*	28
Negative CRM (NOS)	26	29*	28	26
Complete pathological response	20	21	20	22
30-d mortality, %	0	0.16	0	0
90-d mortality, %	0.25	0.4	0.37	0.4
Days to surgery (no.), mean	134.8 ± 38.7	135.9 ± 34.8	138.4 ± 34.1*	133.5 ± 31.5

*Denotes a *P*-value of < 0.05. Open cohort was used as baseline group for statistical comparison.

Similar rates of short-term outcomes such as postoperative morbidity, mortality, anastomotic leak, and return of bowel function have been demonstrated between open and laparoscopic techniques. 2,3,8,9 In the setting of obese patients with a BMI >30 kg/m2, a minimally invasive approach to proctectomy has been associated with nearly a 35% reduction in surgical site infection rates.10 However, the equivalency of oncological outcomes continues to be questioned. Findings from the Medical Research Council Conventional versus Laparoscopic-assisted Surgery in Colorectal Cancer (MRC-CLASSICC) have previously demonstrated short-term and long-term outcomes supporting the equivalence of laparoscopic techniques for colonic malignancy, thereby allowing potential consideration of minimally invasive techniques in rectal cancer.4,11 Although laparoscopic TME may arguably be more challenging due to the use of in-line instrumentation in the pelvis, the benefits of improved access and visualization in the mid to low rectum must be considered as well.12 Moreover, robotic systems offer additional technical benefits including 3-dimensional visualization, endo-wrist instrumentation with 7 degrees of freedom, tremor filtering, and improved dexterity in the lower pelvis with multiple mechanical arms.13 In addition, robotic techniques have been shown to demonstrate similar distal margin positivity and CRM positivity rates when compared with laparoscopic intervention.14 Nonetheless, performing laparoscopic TME adequately has been deemed challenging and associated with a learning curve as high as 50 to 150 cases to achieve consistent results.15 Prior

studies featuring NCDB demonstrated equivalent rates at best for proximal/distal margin negativity and CRM margin negativity when examining open and laparoscopic low anterior resection for rectal adenocarcinoma.16

TABLE 4. Multivariate Analysis of Short-term Outcomes by Operative Approach

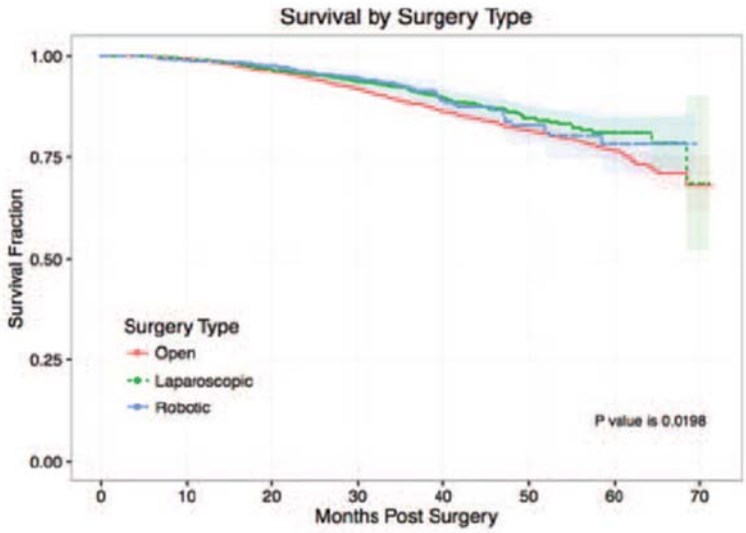
As-treated	OR/RM	95% CI	*P*	Intent-to-treat	OR/RM	95% CI	*P*
Negative overall margin				Negative overall margin			
Laparoscopic vs open	1.35	1.01–1.81	0.04	Laparoscopic vs open	1.16	0.89–1.50	0.27
Robotic vs open	1.56	1.04–2.32	0.03	Robotic vs open	1.4	0.96–2.03	0.07
Robotic vs laparoscopic	1.15	0.74–1.79	0.54	Robotic vs laparoscopic	1.21	0.81–1.80	0.354
Laparoscopic vs converted open	2	1.23–3.22	<0.01				
Robotic vs converted open	2.4	1.37–4.21	<0.01				
Negative circumferential margin				Negative circumferential margin			
Laparoscopic vs open	1.5	1.10–2.04	<0.01	Laparoscopic vs open	1.34	1.02–1.77	0.036
Robotic vs open	1.58	1.06–2.36	0.026	Robotic vs open	1.38	0.96–2.01	0.086
Robotic vs laparoscopic	1.05	0.67–1.66	0.82	Robotic vs laparoscopic	1.03	0.69–1.55	0.885
Laparoscopic vs converted open	1.96	1.18–3.23	<0.01				
Robotic vs converted open	2.12	1.20–3.75	<0.01				
Ninety-d mortality				Ninety-d mortality:			
Laparoscopic vs open	1.69	0.55–5.22	0.36	Laparoscopic vs open	1.42	0.46–4.39	0.54
Robotic vs open	1.5	0.31–7.20	0.61	Robotic vs open	2.09	0.55–7.99	0.28
Robotic vs laparoscopic	0.89	0.17–4.75	0.89	Robotic vs laparoscopic	1.47	0.34–6.34	0.61
Laparoscopic vs converted open	1.01	0.10–10	0.99				
Robotic vs converted open	0.91	0.07–11.64	0.94				
Positive nodes				Positive nodes			
Laparoscopic vs open	1.06	0.85–1.31	0.61	Laparoscopic vs open	1.03	0.84–1.26	0.77
Robotic vs open	0.87	0.65–1.17	0.35	Robotic vs open	0.91	0.69–1.20	0.49
Robotic vs laparoscopic	0.82	0.60–1.13	0.15	Robotic vs laparoscopic	0.88	0.66–1.18	0.4
Laparoscopic vs converted open	1	0.93–1.06	0.9				
Robotic vs converted open	1	0.93–1.07	0.98				
Days to surgery				Days to surgery			
Laparoscopic vs open	1.01	1.00–1.03	0.17	Laparoscopic vs open	1.01	0.99–1.03	0.209
Robotic vs open	1.5	0.31–7.20	0.61	Robotic vs open	1.02	1.00–1.04	0.021
Robotic vs laparoscopic	0.89	0.17–4.75	0.89	Robotic vs laparoscopic	1.01	0.99–1.03	0.198
Laparoscopic vs converted open	1.02	0.99–1.04	0.28				
Robotic vs converted open	1.03	1.00–1.06	0.053				

Robotic versus open.

TABLE 5. Cox Proportional Hazard Model

Death Hazard Ratio	OR	95% CI	*P*
Patient characteristics			
Age (10 yrs)	1.21	1.12–1.31	<0.01
Female vs male	0.9	0.76–1.07	0.23
Black vs Caucasian	1.3	0.98–1.74	0.07
Charleson-Deyo score increase by 1	1.26	1.10–1.45	<0.01
Operative approach			
Laparoscopic vs open	0.81	0.67–0.99	0.037
Robotic vs open	0.82	0.61–1.09	0.18
Laparoscopic vs robotic	0.99	0.72–1.37	0.97

With the introduction of laparoscopy, the treatment of rectal cancer has evolved as well. Neoadjuvant chemoradiotherapy has previously been independently associated with improvement in OS and is now considered standard of care for locally advanced rectal cancer.17,18 Two primary pathological outcomes were assessed in our study, overall margins and CRM. Adequacy of TME has been principally assessed through the CRM that has been found to be an independent predictor of recurrence and survival.19–21 Complete TME has been established as the cornerstone of rectal cancer surgical management as it has been associated with a reduction in local recurrence from 45% with traditional techniques to less than 10% with TME and less than 6% with TME and neoadjuvant chemoradiation. 22–25



Operative Approach	5-year OS (%)	80th Percentile - Years
Open	76	4.47
Laparoscopic	81	5.36
Robotic	78	4.87

FIGURE 2. Kaplan–Meier estimates of survival curve by operative approach. Intent-to-treat populations utilized. Probability of 5-year OS (overall survival) and years for 80th percentile survival reported.

The COREAN trial previously confirmed equivalency of minimally invasive technique for TME by examining open and laparoscopic resection for locally advanced rectal adenocarcinoma in 340 patients. The COREAN study demonstrated similar complete/near complete TME rates (OP 88%, LP: 92%, P ¼ 0.55), leading to a conclusion in support of equivalency, justifying the usage of minimally invasive technique.5 The COREAN trial, however, was conducted in only 3 referral hospitals in Korea by a limited number of surgeons. The COLOR II trial, performed by over 30 treatment centers in 8 countries, demonstrated equivalent overall survival at 86.7% after LP and 83.6% after OP, indicating equivalency between both techniques.26 Critics of findings in COLOR II have indicated that only 59% of the laparoscopic cohort and 58% of the open subset received neoadjuvant chemoradiation with a large subset of the study population with pathological stage 1 disease. In comparison, our study examined cohorts with equivalent distribution of clinical and pathological stage who had received the current standard for multimodal therapy for locally advanced rectal adenocarcinoma in the United States.

Recent findings from the ASOCOG Z6051 trial and the ALaCART have suggested that LP has not met the criteria for noninferiority when compared with open intervention in terms of pathological outcomes. In the Z6051 trial, 462 patients with clinical stage II to III rectal cancer were evaluated for the quality of pathological specimen and adequacy of the TME. Though successful resection was demonstrated in 81.7% of laparoscopic cases and 86.9% of open cases, this difference did not meet the predefined difference for noninferiority.6 The ALaCART used a similar composite endpoint composed of 3 variables: complete TME, clear circumferential margin, and a clear distal margin. Successful resection was acquired in 82% of the laparoscopic group and 89% of the open group, not meeting the criteria for noninferiority.7 No long-term data on recurrence and survival are currently available in Z6051 or ALaCART. Additionally, the role of robotic proctectomy was not reviewed.

Prior RCTs raise the question of external validity, as their findings may be representative of outcomes from only a small subset of practicing surgeons. By using a national database, our current study offers an assessment of operative practices in the overall surgical community. Understanding pathological outcomes at the national level is especially crucial considering recent findings that rates of positive CRM continues to remain critically high in the United States when compared with contemporary international studies.22,27 From a national perspective, compliance with evidence based treatment guidelines has been found to suboptimal, further emphasizing the need for critical review of oncological yield from operative techniques.28

In our study, CRM positivity was found to be 7.62% following open proctectomy compared to 4.87% after laparoscopic intervention and 4.75% after robotic intervention. This reflects a higher national CRM positivity rate when compared with CRM positivity rates in the COREAN trial (open 4%, laparoscopy 3%) and ALaCART (open 3%, laparoscopy 7%). In the ASOCOG Z6051 trial, CRM positivity was 7.7% of open cases and 12.1% of laparoscopic cases. The COLOR II yielded an equivalent CRM positivity rate in the overall cohort (open 10%, laparoscopy 10%), but for low pelvic tumors positioned at <5 cm from the anal verge, COLOR II associated laparoscopy with a 9% positive CRM, whereas open proctectomy was associated with a 22% positive CRM. In our study, Kaplan–Meier estimates of survival curves established a trend of superior OS in the laparoscopic and robotic cohorts with a significant log-rank test of equality. In comparison, 3-year OS rates have previously been reported as equivalent in the COREAN study (OP 90.4%, LP 91.7%).

Despite trends towards superior CRM acquisition in the robotic arm, statistical significance could not be defined. Taking into account the obvious effect of attrition bias from conversion cases, as-treated analysis still substantiated the potential efficacy of minimally invasive intervention in achieving negative overall margins and negative CRM. While the findings from an as-treated methodology can only suggest potential efficacy, our intent-to-treat assessment appears to demonstrate improved CRM negativity in the laparoscopic group. This finding has been corroborated by Rickles et al,22 who, in their 2010 to 2011 NCDB review, noted a 22% reduction in CRM positivity for laparoscopic resection against open approach.

The discrepancy between our intent-to-treat and as-treated multivariate analyses stems from the effect of conversion cases that demonstrated a high CRM positivity rate (10.3%) and low rate of overall margin R0 resection (90%). This confirms previous findings that suggest inferior oncologic yield after conversion to OP.29 Multivariate as-treated analysis demonstrated inferior odds of negative overall margin and negative CRM acquisition. Conversion occurred in 14% of the laparoscopic subset and 7% of the robotic subset, corroborating prior studies that have reported a higher conversion rates (3%–29%) after LP.12,30 These findings confirm the hypothesis from the RObotic versus LAparoscopic Resection for Rectal Cancer trial (ROLARR) trial that RP was associated with a lower conversion rate. ROLARR reported a higher 12.2% conversion rate with laparoscopy compared with 8.1% conversion rate with RP, but this finding was not statistically significant (P ¼ 0.158).31 Conversion itself may be a potential marker for case complexity, difficult anatomy, or surgeon inexperience with laparoscopic techniques; nonetheless, occurrence of conversion appears to be consistently associated with an inferior pathological outcome. This additionally suggests that only surgeons adept at minimally invasive techniques should consider laparoscopic and robotic methods, as conversion portends poorer outcomes.

Despite the statistical significance of our findings, the unavailability of key variables in NCDB including body mass index, surgeon skill level, TME completeness, distance of the tumor from the anal verge, recurrence rates, and disease-free survival exposes a degree of uncertainty

regarding any overall conclusions. The higher rate of APR in the open cohort might suggest a bias towards a higher proportion of technically difficult, low rectal tumors in this group, especially without additional information on tumor location. However, it has been demonstrated that among specialized colorectal surgeons at high-volume centers, the overall frequency of sphincter-preserving surgery for rectal adenocarcinoma has increased.32–34 As such, our study correspondingly demonstrates a higher rate of partial proctectomy in the laparoscopic and robotic cohorts that were predominantly treated at high-volume academic/research and comprehensive community cancer centers. In effect, this may suggest a fundamental difference in skill level between surgeons performing open and minimally invasive proctectomy that is subsequently difficult to characterize, especially in the absence of additional data that describes individual surgeon skill level and volume.

Moreover, despite equivalent overall clinical stage and pathological stage among all 3 groups after neoadjuvant chemoradiation, it was noted that frequency of ypT3/ypT4 was higher in the open cohort. Given the variable effect of tumor regression after neoadjuvant therapy based on tumor cell biology, it is plausible that higher-risk, more resistant tumors with minimal regression after chemoradiation may have preferentially undergone open resection.35 NCDB does not currently offer tumor regression grades after neoadjuvant therapy. This finding does ultimately highlight the importance of careful patient selection for minimally invasive proctectomy.

CONCLUSIONS

In our retrospective review of the NCDB, patients identified with nonmetastatic locally advanced rectal adenocarcinoma who underwent neoadjuvant chemoradiation followed by proctectomy and adjuvant chemotherapy were stratified based on operative type. When performed by surgeons proficient in minimally invasive technique on select patients, laparoscopic proctectomy appears to have a role in rectal cancer management associated with beneficial oncological outcomes.

Given the limitations of our database and the uncertainty surrounding key factors, it ultimately would not be reasonable to derive a comparison of open and laparoscopic techniques from our data. Instead, it should be recognized that minimally-invasive proctectomy is a challenging technique with a steep learning curve that should only be pursued by surgeons with sufficient experience. Given the evidence of oncological benefit from our study, continued examination of minimally invasive techniques through randomized clinical trials is clearly warranted.

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assisted with design of study plan, manuscript revisions, assistance with result interpretation, and recommendations on study statistics. He has assisted with study revisions. He has given final approval. Dr Michael J. Stamos has assisted with design of study plan, interpretation of results, drafting and revision of the manuscript. He has given final approval. Dr Alessio Pigazzi has assisted in facilitating usage of the NCDB database, design of the study plan, drafting of our NCDB data analysis protocol, interpretation of results, and drafting/ revisions of our manuscript. He has given final approval.

DISCUSSANTS

Dr J.W. Fleshman (Dallas, TX):

Mr President, Fellows, and guests, thank you for the opportunity to review this study comparing minimally invasive proctectomy with open proctectomy for rectal cancer. I also thank the authors for the chance to review this manuscript before the meeting.

This review of the NCDB is timely in that recent publication of randomized controlled trial data from 4 different study groups has shown mixed results with 2 studies showing equivalent results and 2 unable to reach noninferiority for MIS approaches compared with open proctectomy for rectal cancer.

In these studies, the greatest difference in surgical outcome, measured by quality of the surgical specimen and margin negativity, was found in the low rectal cancer close to the anal verge and especially in patients undergoing abdominal perineal resection. Unfortunately, the NCDB, while it is a tremendous resource for clinical cancer research, only recently added the distance of the tumor from the anal verge and the quality of the total mesorectal excision to the data collected for rectal cancer. This deficit, I believe, hinders the author's ability to conclude equivalence or improvement with the use of minimally surgery techniques for rectal cancer.

I would ask the authors to consider these issues:

Can you tell us how many abdominal perineal resections, in other words, low rectal cancers, were included in each group and if there were any perforations of the rectum during the procedure usually caused by a standard coned-in pelvic floor dissection? Number 2, CRM positivity is obviously less likely in T-1 and T-2 lesions. In my read of the paper, there was a significant difference in T-3/4 and T-1/2 lesions between the groups with deeper invasion in the open groups. Therefore, how does selection bias affect your conclusion?

Number 3, do you know how many specialty and general surgeons perform the procedures? And was open operation the default procedure for inexperienced operators?

Finally, a multidisciplinary team approach with appropriate assignment of cases to neoadjuvant therapy has been shown to reduce local recurrence and improve survival in cases of locally advanced rectal cancer. Was it possible to determine whether open and minimally invasive surgery cases were equally treated in a multidisciplinary approach given the fact that all patients in your study received neoadjuvant therapy and there is a wide variation in tumor stage as opposed to what you suggested?

I would, therefore, like to offer an alternative hypothesis for your data. MIS cases were performed for earlier, more favorable cancers by specialty surgeons in academic institutions in multidisciplinary settings and yielded better surgical outcomes. Thank you for the privilege of the

floor, and congratulations on an excellent presentation and a profound effort. Thank you very much.

Response from Dr A. Pigazzi (Irvine, CA):

Thank you, Dr Fleshman, for your comments. I think they are all excellent ones, and I'll try to answer them in order.

With respect to the perforation rate for abdominoperineal resection, that data are, unfortunately not available in the database. With respect to the distribution of the different T stages and the different cohorts that we analyzed, while it is true that there were some subtle and small differences between the T-3 and T-4 proportions of patients, in the open group being slightly higher, the overall stage 2 and stage 3 groups were the same across the cohorts. There were no differences.

Also, the clinical stage of patients, the preoperative clinical stage, was no different across the cohorts, arguing against, I think, a strong selection bias of the patients.

With respect to the specialty operators, obviously, we have no specific information regarding the experience of the surgeons. This is 1 of the limitations of the database for which we could not adequately account for. However, if we look at the type of institutions that perform these studies, there were no differences, whether they were community cancer centers or academic centers and so on.

The use of the multidisciplinary team, obviously, we have no information in the database, but we intentionally selected patients who had received neoadjuvant chemoradiation therapy to try to eliminate the possibility that neoadjuvant treatment played a strong role in the possible outcomes that we encountered. So I think that we can possibly suggest that MIS was performed in centers of excellence with greater expertise, and there is no way to deny that. But I think that in terms of patient selection, given what I said about the pathological stages and the multivariate analyses that we performed, I think that we can argue the patients were very similar.

Dr J. Guillem (New York, NY):

I, too, enjoyed your presentation and applaud your efforts in trying to answer the question of relative superiority of robotic approach versus the open approach. I agree with the comments that have been made. However, I have a concern with your opening comment about the applicability of this data to the general nonspecialist surgeon since it appears that your data is primarily from highvolume centers and only 7% from the community surgeon. Although I believe that this technique does provide superior visualization and access to the pelvis, your data reflect primarily the experience of high-volume centers, and the results may or may not be the same in the nonspecialist surgeon hands.

Another concern I have is the rapid uptake of this technique by the nonexperienced, nonhigh-volume surgeons who are launching into practice with this approach and performing their first series of rectal cancer surgeries at the same time that they are learning robotic techniques.

Response from Dr A. Pigazzi (Irvine, CA):

Yes, I couldn't agree more with that. I think our data support that. Again, we have no way to know exactly what the level of experience of the different operators were, and there's no doubt the minimally invasive proctectomy is an exceedingly difficult procedure with a very long learning curve. But by the same token, I think it would be wrong to argue that open proctectomy is easy

and, therefore, it's okay to perform that procedure in centers that are not highly experienced. I think that high volume results in better outcomes regardless of the procedure, and good surgeons get good outcomes if they do a lot of 1 procedure, according to good pathologic criteria. That's what we can say.

Dr P. Allen (New York, NY):

I have a brief question regarding your survival analysis, and I may have missed it on the earlier slides. But over the study time period, was the percentage of patients who underwent robotic approaches, did that increase significantly and, therefore, was it possibly a shorter median length of follow-up in that group of patients which would have led to a length time bias in the survival analysis?

Response from Dr A. Pigazzi (Irvine, CA):

It's possible. The number of robotic patients did increase over time, yes.

Dr M. Kalady (Cleveland, OH):

I congratulate you and your team on excellent work and pushing the limits on minimally invasive surgery for rectal cancer.

I have 2 points and questions. The first is that everybody got chemoradiation in this study. The response to chemoradiation affects your outcome to some degree because it's going to shrink tumors in a lot of cases, and in some cases it might not have much of an effect. Those people that didn't have a good response may be ones that are inclined to have a positive margin or inclined to undergo a conversion to open because of the big, bulky tumors. Conversely, the patients that had a great response, and in particular those that were complete responders aren't going to have margin positive at all because there's no tumor left. So my first question is, do you have any information on the pathologic AJCC response scores as that would influence outcomes?

The second question, as kind of a corollary to that, is do you have any ideas or thoughts regarding studying patients who didn't get neoadjuvant chemoradition as a separate study to determine the effect of your technique on people without that confounding factor of chemoradiation response?

Response from Dr A. Pigazzi (Irvine, CA):

Great question. We don't have information in terms of their response grade in this patient. As you saw, the overall, the complete path of responders were the same across all the cohorts, about 20%. So I think that's pretty much consistent with the overall literature on neoadjuvant chemoradiation therapy. And we will definitely consider your second option for a study.

Dr S. Strasberg (St. Louis, MO):

You mentioned that the database did not give information on BMI. Did it give information on weight? And can you tell us about the weight in the 2 groups?

Response from Dr A. Pigazzi (Irvine, CA):

No difference.

Dr F. Greene (Charlotte, NC):

First, thank you for using the participant user file from the NCDB, the National Cancer Data Base. There are more than 30 million cases in the NCDB, and the data files are open to any clinical research group that wants to apply for use.

You mentioned FORDS, the Facility Oncology Data Standards Manual. We are currently revising FORDS to update diagnosis and treatment codes that cancer registrars use for cancer reporting. My recommendation is that everyone should review the FORDS manual located in the cancer registry in your hospital and to familiarize yourselves with the operative codes and additional codes relating to your cancer specialty interest. Unless we as clinicians become involved in updating these codes, relevant diagnostic and management codes will be missing from the NCDB as alluded to by Dr Fleshman. I just recommend that we all look at the FORDS manual. Again, I salute you for using these data.

Response from Dr A. Pigazzi (Irvine, CA):

Thank you.