Does prolonged operative time impact postoperative morbidity in patients undergoing robotic-assisted rectal resection for cancer?

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Abstract
Background Several studies have shown a correlation between longer operative times and higher rates of postoperative morbidity for open and laparoscopic surgery for rectal cancer. The aim of the study was to determine the impact of prolonged operative time on early postoperative morbidity in patients undergoing robotic-assisted rectal cancer resection.

Methods The study was a retrospective review of a prospectively maintained database conducted in two centers of the same institution. A total of 260 consecutive patients undergoing robotic-assisted resection for rectal cancer between 2007 and 2016 were included. Patients were divided into two groups regarding median operative time: > 300 min (prolonged operative time; n = 133) and ≤ 300 min (control; n = 127). Patient characteristics, operative and postoperative data were compared between groups. Univariate and multivariate analyses were performed to determine whether prolonged operative time was a predictive factor of 30-day postoperative morbidity.

Results Prolonged operative time was noted more frequently in males (p = 0.02), patients with higher BMI (p < 0.01), more severe comorbidities (p < 0.01), in tumors of the mid-rectum, and in surgery performed after neoadjuvant chemoradiation or upon surgeons’ learning curve. The two groups had similar overall postoperative morbidity (32 vs. 41%; p = 0.16) and severe morbidity (6 vs. 6%; p = 0.92) rates. Prolonged operative time was associated with longer hospital stay (3.8 ± 2.5 vs. 5.0 ± 3.7 days; p = 0.004) in univariate analysis. Prolonged operative time was not independently associated with postoperative morbidity or with increased hospital stay on multivariate analysis.

Conclusion In our study, prolonged operative time was not associated with an over-risk of morbidity in patients undergoing robotic resection for rectal cancer. These results suggest that more difficult robotic procedures do not lead to increased postoperative morbidity.

Keywords Robotic surgery · Rectal cancer · Operative time · Proctectomy · Postoperative morbidity

Curative treatment for advanced rectal cancer relies on surgical resection including total mesorectal excision, complemented by neoadjuvant chemoradiotherapy, and/or adjuvant chemotherapy, when necessary. Numerous countries currently recommend laparoscopy to perform total mesorectal excision [1]. Compared to open surgery, laparoscopic total mesorectal excision offers similar survival and better short-term outcomes including faster recovery and decreased pain [2–7]. However, rectal resection remains a challenging surgery when performed with laparoscopy. Moreover, the recently published AL-CART and ACOSOG Z6051 trial failed to demonstrate the non-inferiority of laparoscopic approach as compared to open surgery based on surrogate endpoints of completeness of mesorectal excision and margin positivity rates [8, 9]. Despite the lack of long-term oncologic outcomes, these studies have called into question laparoscopic proctectomy for rectal cancer.

Robotic-assisted surgery was developed to overcome the technical limitations of conventional laparoscopy, offering the ability to retract and control the camera without an assistant and potentially greater precision of dissection within narrow spaces. Due to these perceived advantages, robotic-assisted surgery is being increasingly used for rectal cancer

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resection [10]. Comparative studies and meta-analyses have demonstrated that robotic-assisted surgery achieves similar results as compared to conventional laparoscopy in terms of postoperative complications and oncologic outcomes [11–15]. Some authors have also reported a trend toward lower conversion rate and lower incidence of genito-urinary complications after robotic-assisted rectal resection [14, 16, 17]. However, the disadvantages of longer operative times and increased costs with robotic-assisted surgery remain a barrier to the implementation of the technique for some surgeons.

Prolonged operative time has been reported to be associated with increased postoperative complications in colorectal surgery, especially anastomotic leakage [18–20]. Moreover, prolonged operative time over 240 min has recently been reported as an independent risk factor for postoperative complications following conventional laparoscopic rectal cancer resection [20]. As prolonged operative time is known to reflect more challenging cases [21], these data suggest that the difficulty of the procedure correlates with postoperative morbidity in open and laparoscopic rectal cancer surgery. Whether the advantages of robotic approach could overcome the postoperative complications related to procedure difficulty remains unknown. No study has explored the impact of prolonged operative time on postoperative outcomes following robotic surgery.

In this study, we aimed to determine if prolonged operative time was associated with increased postoperative complications following robotic-assisted rectal cancer resection.

**Methods**

**Patients**

A retrospective review of a prospectively maintained database was conducted. All consecutive patients operated on for primary rectal cancer with robotic-assisted rectal resection between January 2007 and August 2016 at Mayo Clinic (Rochester and Jacksonville) were included. Patients who underwent synchronous hepatic resection of liver metastasis, patients operated on for palliative intent, and patients with recurrent rectal cancer were excluded. Patients were separated into two groups according to the median operative time (defined as time from skin incision to completed skin closure): ≥ median operative time (prolonged operative time) and < median operative time (control). We further defined operative time exceeding the 75th percentile of our series to be considered ‘very long operative time.’ The Mayo Clinic Review Board approved this study. Mayo Clinic was the sole support for this study.

Patients were staged according to the TNM classification system as outlined by the National Comprehensive Cancer Network [22]. Locoregional staging was performed using endorectal ultrasound and/or pelvic MRI. Staging for distant disease was performed using abdomino-pelvic CT scan. Patients with locally advanced rectal tumors (≥ T3) and/or regional lymph nodes (N+) received long-course radiochemotherapy followed by surgery 6–8 weeks later.

**Procedure and postoperative care**

All robotic-assisted rectal resections were performed by experienced board-certified colorectal surgeons in a standardized total mesorectal excision manner. The lymph node resection involved the transection of the inferior mesenteric artery 1–2 cm from its origin and the inferior mesenteric vein which was divided at the lower border of the pancreas. The mobilization of the splenic flexure and control of the vessels were performed robotically with the pelvic dissection in a single-stage procedure in patients operated on with the Da Vinci® Xi robot. With the previous version of the robotic system (Da Vinci® Si; Intuitive Surgical Inc., Sunnyvale, CA, USA), the splenic flexure was performed using conventional laparoscopy before or after performing the robotic-assisted pelvic dissection.

Rectal cancers involving the external anal sphincter were treated with an abdomino-perineal resection and endcolostomy. A tumor-specific excision with resection of the mesorectum 5 cm below the lower border of the tumor was performed for high rectal cancers. A total mesorectal excision was performed for mid and low rectal cancers. Reestablishment of intestinal continuity was performed with either a colorectal or hand-sewn coloanal anastomosis, as appropriate. The indication for diverting ileostomy was left to the surgeon’s discretion.

Operations were performed by nine different consultants. All colon and rectal surgeons involved were experienced in laparoscopic pelvic surgery, (> 50 pelvic laparoscopic operations) prior to beginning their robotic experience. Patients operated during the learning curve of the surgeons were included in the study. The learning curve was considered achieved for a surgeon after the first 30 cases of robotic-assisted rectal resection. It should be noted that most robotic cases are performed with the aid of residents and fellows in general and colorectal surgery given the educational mission of this institution.

The postoperative care at both institutions followed a standardized enhanced recovery pathway (ERP) [23]. ERP allowed for general oral intake and mobilization on the first postoperative day. Urinary catheter was removed the first postoperative day by 8 am. In cases of urinary dysfunction, intermittent catheterization was utilized until the return of spontaneous voiding. Discharge was allowed as soon as postoperative pain was controlled, appropriate bowel movement or ostomy output occurred, and diet was tolerated.
Data collection

Preoperative patient characteristics and postoperative outcomes were reviewed and compared between each group. Comorbidities were scored using the American Society of Anesthesiology (ASA) classification. Morbidity was defined as any complications occurring within 30 days of the operation. Severity of complications was graded according to Clavien–Dindo classification [24]. Severe complications were defined as Clavien–Dindo ≥ 3 complications. Surgical morbidity included anastomotic leak, reoperation, postoperative hemorrhage, anemia requiring transfusion, prolonged ileus, wound infection or disunion, and urinary complications. Medical morbidity included cardio-pulmonary complications and renal failure. Anastomotic leak was defined as any feculent or purulent drain output or any pelvic abscess or contrast extravasation on CT scan. Urinary retention was defined as the need for ongoing urinary catheterization at the time of dismissal. Prolonged ileus was defined as no return of bowel function after 5 days and/or insertion of nasogastric tube.

Statistical analysis

Statistical analysis was performed using JMP® software (version 10.0.0; JMP®, SAS Institute Inc., Cary, NC). Data were expressed as mean values ± standard deviation. Univariate analysis was performed using a Student’s t test or a Mann–Whitney U test, as appropriate, for continuous variables, and a Fischer’s exact test or a χ² test, as appropriate, for categorical variables. The variables considered relevant in the univariate analysis (p < 0.20) were included into a multivariate logistic regression model. A value of p < 0.05 was considered statistically significant.

Results

Patients

From 2007 to 2016, a total of 260 patients (84 women) underwent a robotic-assisted resection for rectal cancer and met the inclusion criteria. The mean age of the cohort was 58 ± 13 years. Median operative time was 300 min (110–680 min). One hundred and twenty-seven (49%) patients were included in the control group (operative time ≥ 390 min). The cut-off for very long operative time (75th percentile) was 390 min. Neoadjuvant chemo-radiotherapy was administered in 158 (61%) patients. The rectal resection consisted of a tumor-specific mesorectal excision, a total mesorectal excision, or an abdominoperineal resection in 51 (20%), 135 (52%), and 74 (28%) patients, respectively. Non-restorative surgery was performed in 77 (30%) patients and included Hartmann procedure (n = 3) and APR (n = 74). Conversion to open surgery was required in 6 (3%) patients due to obesity (n = 2), bleeding (n = 2), or a bulky tumor (n = 2). Patient characteristics are detailed in Table 1.

There were significantly more male patients with severe comorbidities (ASA ≥ 3) and/or increased BMI (BMI ≥ 25 kg/m²) in the prolonged operative time group as compared to control group (Table 1). Rectal resections performed for tumor of the mid-rectum, surgeries performed during the surgeons’ learning curve, and/or associated with colorectal or colorectal anastomosis were associated with prolonged operative time. In the subgroup of patients operated on with a colorectal or coloanal anastomosis, temporary diversion significantly prolonged operative time.

Postoperative outcomes

The overall morbidity rate was 40%. Complications are detailed in Table 2. Seventeen (6%) patients suffered from severe complications (Dindo ≥ 3). One patient died from postoperative hemorrhage. Intraoperative complications included 5 (2%) intraabdominal bleeding requiring intraoperative blood transfusion. Reoperation was required in 9 (3%) patients due to anastomotic leak (n = 7), postoperative hemorrhage (n = 1), or small bowel obstruction (n = 1). The only severe medical complication was a myocardial ischemia requiring a cardiac catheterization (n = 1). The most frequent complications in the overall cohort included urinary retention, prolonged ileus, and perineal/abdominal wound infection in 38 (15%), 35 (13%), and 11 (4%) patients, respectively. Pelvic abscess or anastomotic leak were reported in 13 (7%) of the 183 patients operated on with rectal resection and colorectal or coloanal anastomosis. The mean length of hospital stay was 4.4 ± 3.2 days. 30-day readmission rate was 11% (n = 30), including 20 (13%) patients with ileostomy and 10 (9%) without ileostomy.

Impact of operative time on postoperative morbidity

Prolonged operative time over 300 min during robotic-assisted rectal resection was not associated with increased postoperative morbidity in univariate analysis (Table 2). Likewise, very long operative time (≥ 390 min) was not associated with postoperative morbidity [25 (38%)] as compared to control [70 (36%)] (p = 0.7). Postoperative overall and severe morbidity rate did not significantly differ between quintiles of operative time (p = 0.46 and p = 0.49, respectively) (Fig. 1). Surgical and medical morbidity rates, as well as severe morbidity rate, were similar between prolonged operative time and control groups. When considering the
183 patients operated on with rectal resection and colorectal or coloanal anastomosis as a subgroup, the rate of anastomotic leak was similar in the prolonged operative time and control groups (8 vs. 3%; \( p = 0.47 \)). However, prolonged operative time was associated with increased postoperative ileus in univariate and multivariate analysis (OR 2.75; 95% CI 1.17–7.11; \( p = 0.02 \)).

Male gender and increased BMI were the only factors significantly associated with postoperative morbidity in univariate analysis. Age, ASA score, previous abdominal surgery, neoadjuvant radiotherapy, tumor location, surgical procedure (restorative or not), conversion, robot generation, prolonged operative time, surgeon experience, tumor stage, and positive resection margins were not associated with postoperative morbidity. Increased BMI was the only independent risk factor of postoperative morbidity in multivariate analysis (Table 3).

Impact of prolonged operative time on other postoperative outcomes

Hospital stay was significantly longer in the prolonged operative time group in univariate analysis (Table 2). However, prolonged operative time was not independently associated with increased hospital stay (≥ 5 days) in multivariate analysis (Table 4). On univariate analysis,
increased hospital stay (≥ 5 days) was significantly more probable in patients older than 75 years, overweighted, with ASA score ≥ 3, or presenting with postoperative prolonged ileus. Gender, preoperative history of abdominal surgery or neoadjuvant therapy, nature of surgery, learning curve period, conversion, or other postoperative complications were not associated with increased hospital stay (≥ 5 days). Postoperative prolonged ileus was the only independent risk factors for increased hospital stay (≥ 5 days) (Table 4).

Table 2 Postoperative outcomes in ‘prolonged operative time’ and ‘control’ patients operated on with robotic-assisted rectal cancer resection

<table>
<thead>
<tr>
<th></th>
<th>Overall cohort n = 260</th>
<th>Control group ≤ 300 min n = 127</th>
<th>Prolonged operative time &gt; 300 min n = 133</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall morbidity</td>
<td>105 (40)</td>
<td>41 (32)</td>
<td>54 (41)</td>
<td>0.164</td>
</tr>
<tr>
<td>Surgical morbidity</td>
<td>90 (35)</td>
<td>40 (31)</td>
<td>50 (38)</td>
<td>0.301</td>
</tr>
<tr>
<td>Medical morbidity</td>
<td>15 (6)</td>
<td>4 (3)</td>
<td>11 (8)</td>
<td>0.109</td>
</tr>
<tr>
<td>Severe complications (Dindo grade ≥ 3)</td>
<td>16 (6)</td>
<td>8 (6)</td>
<td>8 (6)</td>
<td>0.924</td>
</tr>
<tr>
<td>Intraoperative complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative hemorrhage</td>
<td>5 (2)</td>
<td>2 (2)</td>
<td>3 (2)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reoperation</td>
<td>9 (3)</td>
<td>6 (5)</td>
<td>3 (3)</td>
<td>0.325</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>38 (15)</td>
<td>21 (17)</td>
<td>17 (13)</td>
<td>0.389</td>
</tr>
<tr>
<td>Ileus</td>
<td>35 (13)</td>
<td>8 (6)</td>
<td>27 (20)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Wound infection</td>
<td>11 (4)</td>
<td>4 (3)</td>
<td>7 (5)</td>
<td>0.541</td>
</tr>
<tr>
<td>Abscess/anastomotic leak†</td>
<td>13/183 (7)</td>
<td>6/82 (7)</td>
<td>7/101 (7)</td>
<td>0.757</td>
</tr>
<tr>
<td>Infectious abdominal complications</td>
<td>25 (10)</td>
<td>10 (8)</td>
<td>15 (11)</td>
<td>0.352</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>4 (1)</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>0.622</td>
</tr>
<tr>
<td>Readmission rate</td>
<td>30 (11)</td>
<td>13 (10)</td>
<td>17 (13)</td>
<td>0.520</td>
</tr>
<tr>
<td>Hospital stay (days)†</td>
<td>4.4 ± 3.2</td>
<td>3.8 ± 2.5</td>
<td>5.0 ± 3.7</td>
<td>0.004*</td>
</tr>
<tr>
<td>Positive resection margins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumferential margin</td>
<td>5 (2)</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td>0.678</td>
</tr>
<tr>
<td>Distal margin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Resected lymph nodes</td>
<td>25 ± 12</td>
<td>26 ± 13</td>
<td>25 ± 11</td>
<td>0.543</td>
</tr>
</tbody>
</table>

*p value significant <0.05; Variables expressed as n (%) except †expressed as mean±SD; ‡Percentage and statistical analysis calculated only on the 183 patients operated on with rectal resection and colorectal or coloanl anastomosis

Fig. 1 Overall and severe morbidity rates reported according to operative time quintiles
Table 3 Multivariate analyses of predictive factors for postoperative morbidity

<table>
<thead>
<tr>
<th>Characteristics†</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.81</td>
<td>0.96–3.48</td>
<td>0.069</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>1.78</td>
<td>0.77–4.16</td>
<td>0.177</td>
</tr>
<tr>
<td>BMI ≥ 25 kg/m²</td>
<td>3.15</td>
<td>1.62–6.50</td>
<td>0.001*</td>
</tr>
<tr>
<td>History of abdominal surgery</td>
<td>0.57</td>
<td>0.28–1.11</td>
<td>0.103</td>
</tr>
<tr>
<td>Operative time ≥ 300 min</td>
<td>1.18</td>
<td>0.68–2.05</td>
<td>0.543</td>
</tr>
</tbody>
</table>

†American Society of Anesthesiology score, neoadjuvant radiotherapy, tumor location, surgical procedure (restorative or not), conversion, robot generation, learning curve period, tumor stage, and positive resection margins were not included in the multivariate model due to p value ≥ 0.1 in univariate analysis

BMI body mass index

Table 4 Multivariate analyses of predictive factors for prolonged hospital stay (≥ 5 days)

<table>
<thead>
<tr>
<th>Characteristics†</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 75 years</td>
<td>1.63</td>
<td>0.48–5.57</td>
<td>0.432</td>
</tr>
<tr>
<td>ASA score ≥ 3</td>
<td>1.63</td>
<td>0.67–3.94</td>
<td>0.280</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.05</td>
<td>0.74–5.67</td>
<td>0.165</td>
</tr>
<tr>
<td>BMI ≥ 25 kg/m²</td>
<td>0.76</td>
<td>0.29–2.00</td>
<td>0.580</td>
</tr>
<tr>
<td>Learning curve period</td>
<td>1.94</td>
<td>0.70–5.34</td>
<td>0.201</td>
</tr>
<tr>
<td>Conversion</td>
<td>3.84</td>
<td>0.40–36.78</td>
<td>0.243</td>
</tr>
<tr>
<td>Operative time &gt; 300 min</td>
<td>0.61</td>
<td>0.24–1.60</td>
<td>0.319</td>
</tr>
<tr>
<td>Prolonged ileus</td>
<td>84.66</td>
<td>24.72–289.95</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

†Body mass index, preoperative history of abdominal surgery and surgical procedure (restorative or not) were not included in the multivariate model due to p value ≥ 0.1 in univariate analysis

ASA American Society of Anesthesiology

Discussion

Our study revealed that prolonged operative time is not a risk factor for postoperative morbidity following robotic rectal resection for cancer. Postoperative morbidity rate did not differ between operative time quintiles. These results confirm the safety of robotic surgery even when the operative time is prolonged over 300 min. This is critical for teaching institution which by the very nature of education will require longer operative times in order to educate young surgeons. According to our data and previous studies, operative time for robotic-assisted rectal resection is increased significantly during the surgeons’ learning curve, though without an increased risk for postoperative complications [25–27].

The only postoperative outcome impacted by increased operative time in our study was prolonged ileus. Increased operative time has been demonstrated to be associated with postoperative ileus following colorectal surgery [28, 29]. Several items of the enhanced recovery protocol proposed in our study aim at decreasing postoperative ileus [30]. However, Grass et al. recently demonstrated that prolonged operative time contributed to high ileus rate and remained an independent predictive factor of prolonged ileus even after implementation of enhanced recovery protocol [28]. Despite the increase in operative time with robotic surgery, the postoperative ileus rate is demonstrated to be similar between robotic and laparoscopic approaches [12]. In our study, 13% of patients suffered from ileus following rectal cancer resection. This rate appears high compared to the results obtained from recent prospective series of minimally invasive rectal resection which reported postoperative ileus in 5–10% of patients [8, 11, 12]. However, a comparison is difficult since no consensus has been achieved for postoperative ileus definition. Ileus is sometimes defined as excessive time to return of bowel movement (varying from 4 to 7 days) or oral intake intolerance or insertion of nasogastric tube. Postoperative ileus was the main predictive factor of increased length of stay on multivariate analysis. Despite the higher rate of postoperative ileus observed in our study, the hospital stay remained very low. Indeed, the mean hospital stay was 4 days in our study, compared to 6–12 days in recent published series of minimally invasive rectal resection [8, 11, 12].

The fundamental reasons for increased operative time are illusive but could include multiple issues such as increased set-up time, patient population, tumor biology, robotic platform, inexperienced nursing and surgical technician team, or an intrinsic inefficiency of the surgeon’s technique. Our study identified one technical factor associated with prolonged operative time: surgeon experience. We chose to define the learning curve as the first 30 cases operated by a surgeon. Previous data showed that surgeons are able to progress beyond the learning curve for robotic rectal surgery after 25–74 cases [25, 26, 31]. In these studies, the learning curve was determined according to the operative time analysis. Internally, we confirmed that for a single senior surgeon starting robotic rectal surgery, operative time can be expected to be significantly longer for the first 30 patients as compared to those that follow. Despite this learning curve, it appears to be without the cost of increasing morbidity. Beyond surgeons’ learning curve, male gender, increased BMI, and low rectal tumors were also significantly associated with longer operative time. These three factors are known to be pitfalls in open and laparoscopic rectal surgery [32]. In these three groups of patients, constitutive narrow pelvis, abdominal adiposity, and tumor location, respectively, increase the difficulty to perform rectal dissection. The prolonged operative time observed in increased BMI, male patients, and low tumor in our study probably reflects...
that these anatomical aspects are also the more challenging with robotic surgery.

In laparoscopic and open surgery series of rectal resection for cancer, overweight (BMI ≥ 25 and < 30 kg/m²) and obesity (BMI ≥ 30 kg/m²) are independently associated with increased postoperative morbidity, and especially increased rate of anastomotic leak [19, 20]. Recent robotic series did not show any association between obesity and major complications [32–34]. Due to these results, the authors suggested that robotic surgery is a promising tool in rectal surgery, with the potential to sufficiently manage intraoperative difficulties associated with obesity. In previous studies, the impact of robotic surgery on minor postoperative complications was not reported [32–34]. According to our results, an increased postoperative morbidity, and especially increased BMI (≥ 25 kg/m²) was the only reliable risk factor for overall postoperative morbidity. Thus, further studies are required to better characterize the postoperative complications impacted by the increase of body mass index, separating overweight patients from obese patients.

The main limitation of our study is its retrospective nature although based on a prospective database. This limit could have resulted in an underestimation of postoperative morbidity and readmission rates. The analysis did not demonstrate any association between prolonged operative time and anastomotic leak. However, the low rate of anastomotic leak could have led to a type 2 error regarding anastomotic complications. We included in the study all patients undergoing robotic-assisted rectal dissection, including abdominoperineal resection and anterior rectal resection with colorectal or coloanal anastomosis. Although complication profile and operative challenges vary between each procedure, the nature of the surgical procedure did not influence postoperative morbidity nor hospital stay.

Conclusion

In our study, prolonged operative time did not impact overall nor severe postoperative morbidity following robotic rectal resection for cancer. These results suggest that operating on more difficult cases with a robotic approach is not associated with an over-risk of morbidity.

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Compliance with ethical standards

Disclosures Drs Emilie Duchalais, Nikolaos Machairas N, Scott R. Kelley, Ron G. Landman, Amit Merchea A, Dorin T. Colibaseanu, Kellie L. Mathis, Eric J. Dozois and David W. Larson have no conflicts of interest or financial ties to disclose.

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