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Totally robotic vs hybrid abdominoperineal resection: A retrospective multicenter analysis

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Abstract

Introduction: Laparoscopic abdominoperineal resection (APR) for low rectal cancers is technically demanding. Robotic assistance may be of help and can be hybrid (HAPR) or totally robotic (RAPR). The present study describes outcomes of robotic APR and compares both approaches.

Material and methods: A multicentric retrospective analysis of rectal cancer patients undergoing either HAPR or RAPR was conducted. Patients' demographics, surgeons' experience, oncologic results, and intraoperative and postoperative outcomes were collected.

Results: One hundred twenty-five patients were included, 48 in HAPR group and 77 in RAPR group. Demographics and comorbidities were comparable. Operative time was reduced in RAPR group (266.9 ± 107.8 min vs 318.9 ± 75.1 min, $P = .001$). RAPR patients were discharged home more frequently (91.18% vs 66.67%, $P = .001$), and experienced fewer parastomal hernias (3.71% vs 9.86%, $P = .001$).

Conclusion: RAPR is safe and feasible with appropriate oncologic outcomes. Totally robotic approach reduces operative time and may improve functional outcomes.

KEYWORDS

abdominoperineal excision, abdominoperineal resection, rectal cancer, rectal surgery, robotic surgery

1 | INTRODUCTION

Rectal cancer surgery encompasses different types of surgical resections. Their indications and techniques are subject to constant debate and evolution.¹ When reconstruction is not feasible for oncologic, technical, or patient-related reasons, abdominoperineal resection (APR) with permanent colostomy remains the only alternative. This procedure is however associated with higher morbidity and cancer recurrence rate.² Although traditionally performed through an open approach, growing evidence suggests that minimally invasive APR could reduce morbidity with acceptable oncologic results.³ Laparoscopic APR is technically very demanding; the long rigid instruments are often insufficient in the narrow pelvic space. A robotic approach could overcome these limitations and has gained popularity in rectal cancer surgery over the past

decade.⁴ Its current role is not yet defined because of lack of evidence, but available data suggest that it may be of significant help for difficult pelvic dissections, especially in anatomically challenging and obese patients.⁵⁻⁷ Ng et al published the first description of hybrid robotic APR in 2007,⁸ with laparoscopic colonic mobilization and robotic rectal dissection. Descriptions of fully robotic⁹ and single-port robotic procedures¹⁰ were published thereafter. A recent retrospective analysis of the National Inpatient Sample database (Healthcare Cost and Utilization Project, United States) showed that robotic APR may reduce conversion rate and hemorrhagic complications, but significantly increases in-hospital costs compared with open and laparoscopic APR.¹¹ These data, however, are pulled from a nationwide database and thus provide few details about surgical technique, intraoperative outcomes, and pathological results. Analyzing retrospectively 21 robotic APR compared with

open APR, Kim et al¹² showed improved oncologic outcomes in the robotic group. Eftaiha et al¹³ found similar results comparing retrospectively 22 robotic APR with laparoscopic cases. Small number of patients limit these studies, but large sample size is difficult to obtain for such a highly specialized procedure.

When choosing robotic assistance for APR, the surgeon can decide between a hybrid laparoscopic-robotic (HAPR) or totally robotic approach (RAPR). HAPR are often preferred in early robotic experience. The RAPR however, by improving workflow and ergonomics, may lead to more efficient and potentially cheaper procedures. Decreasing operative time and abdominal wall manipulations could reduce surgical trauma, thus improving postoperative outcomes and reducing recovery time. These outcomes improvements as well as the reduced number of instruments needed as compared with hybrid approach may optimize cost-efficiency, which is always of interest in robotic surgery. Data comparing hybrid and totally robotic procedures in general, and especially in the field of rectal surgery, are scarce.

The purpose of this study is to explore outcomes of robotic abdominoperineal resection in a large cohort of patients and determine whether RAPR or HAPR approach should be favored in further development of this technique.

2 | MATERIAL AND METHODS

2.1 | Study design and participants

We conducted a retrospective analysis of patients who underwent robotic APR in six US centers between November 2008 and March 2016 for low to ultra-low rectal cancers (less than 7 cm from anal verge) or anal canal cancers requiring APR due to tumor specifics or patient related issues (sphincter involvement, pre-existing incontinence or poor sphincter function, comorbidities, and age). Seven surgeons trained in colorectal surgery or surgical oncology of various robotic experience were involved. All consecutive cancer patients who underwent robotic APR during this period were included.

2.2 | Technique

Abdominoperineal resection using either totally robotic or hybrid approach were performed as per the surgeon's personal preference. Both robotic systems (Si or Xi DaVinci surgical system (Intuitive Surgical Inc Sunnyvale, CA) were used depending on availability at the different institutions. In HAPR, the left colon mobilization and ligation of inferior mesenteric artery were performed laparoscopically, and the robotic system was docked only for the rectal dissection. In the RAPR approach, the abdominal part of the procedure was also performed robotically. Figure 1 shows standard trocars placement for RAPR using the Xi system. Surgical approach (hybrid or totally robotic), and surgical technique and position for perineal part of procedure (prone vs lithotomy) were chosen depending on surgeon's preference and experience. A total mesorectal excision was attempted in all cases. The levator muscles were divided

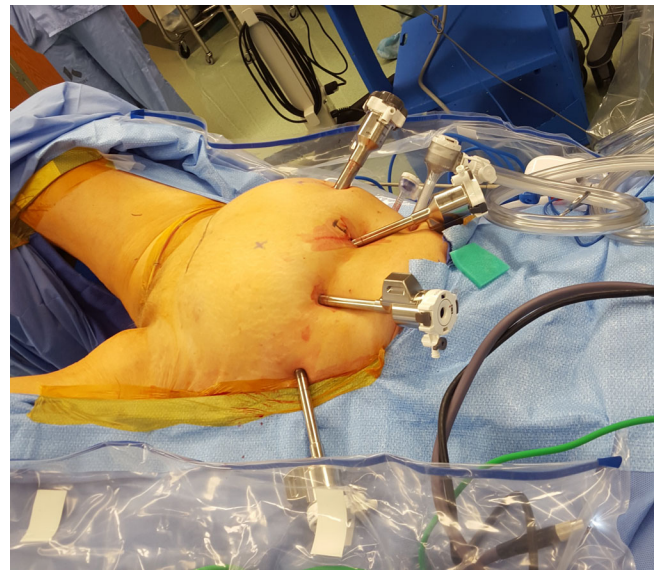


FIGURE 1 standard trocars positioning for totally robotic APR using Xi system

either transabdominally using the robot, or from below during the perineal part of the procedure. Standard or cylindrical APR resection was chosen depending on preoperative imaging and tumor involvement of the pelvic floor. Closure of the perineal defect included primary closure, placement of mesh or muscle-flaps. The stomas were performed in a standard fashion, without any prophylactic mesh reinforcement.

2.3 | Data collection

Patients' demographics and comorbidities, tumor stage, tumor type, and any neoadjuvant treatment received were recorded. Surgical technique data included surgical approach (HAPR vs RAPR), as well as position and technique of perineal dissection. Surgeons' experience was classified according to their volume of robotic APR. Surgeons who had performed less than 10 robotic APRs were considered low volume, surgeons with more the 10 cases high volume surgeons.

Surgical outcomes were recorded intraoperatively (operative time, conversion, complication, transfusion) and postoperatively (complications at 30 days, survival and local recurrence, length of follow-up, readmission rate at 30 days and reoperation rate at 30 and 60 days). Pathological outcomes included tumor size and location, tumor staging according to the eighth edition of American Joint Committee on Cancer (AJCC) staging manual,¹⁴ completeness of mesorectum, positivity of circumferential resection margins (CRM), specimen perforation, and lymph nodes status.

2.4 | Ethical statement

All procedures were in accordance with ethical standards of institutional and national research committee and with the 1964 Helsinki



Declaration and its later amendments or comparable ethical standards. This is a retrospective analysis and all data used in this manuscript were obtained from an institutional-quality database. There are no patient identifiers included in the publicly available data, and thus, patient consent and institutional review board are not required.

2.5 | Statistics

Statistical analysis was carried with Stata 15.0 software (Stata Corp, College Station, TX). *P* value lower than .05 was considered statistically significant. Continuous data were analyzed using Student *t* test or the Mann-Whitney test when data were not normally distributed. Binary and categorical data were analyzed using chi-squared test or the Fisher exact test when expected effects were lower than 5. Considering the retrospective nature of these data and potential confounding factors, outcomes of interest identified in univariable analysis were tested using multivariable linear and logistic regression analysis.

Multivariable model for intraoperative outcomes and pathological results included type of approach (RAPR or HAPR), obesity (defined by body mass index [BMI] of more than 30 kg/m²), previous abdominal surgery, surgeon's experience, intraoperative complication, and eventual additional procedure.

Multivariable model for postoperative outcomes included type of approach (RAPR or HAPR), age (older than or younger than 75 years old), obesity (defined by BMI of more than 30 kg/m²), previous abdominal surgery, surgeon's experience, intraoperative complication, eventual additional procedure, overall comorbidities, and length of follow-up (more than or less than 24 months).

3 | RESULTS

In total, 125 patients were included, 48 in HAPR group and 77 in RAPR group. Seven surgeons in six US hospitals participated in this study, three of them considered high volume surgeons in terms of robotic APR experience who accounted for 95.8% of HAPR and 77.9% of RAPR. Patients' demographics and comorbidities were not statistically different among groups, except significantly more previous abdominal surgery in RAPR patients (66.2% vs 41.7%, *P* = .007), and higher rates of hypertension (58.4% vs 35.4%, *P* = .012). Other patients' and tumors' characteristics at baseline are described in Table 1.

Regarding surgical technique, prone position for the perineal resection was only used in 10.4% of patients of the RAPR group (*P* = .021). Cylindrical perineal resection was significantly more frequent in RAPR group (45.5% vs 4.17%, *P* < .001), as well as trans-abdominal division of levator muscles (61.0% vs 6.2%, *P* < .001). Additional procedures were not statistically different among groups (*P* = .373). Lysis of adhesions, vaginal wall resection and reconstruction, gracilis or rectus flap were the most frequently performed additional procedures. Other surgical technique details were not statistically different and can be found in Table 2.

TABLE 1 Patients' characteristics at time of surgery

Parameter	Hybrid APR (n = 48)	Robotic APR (n = 77)	<i>P</i> value
Age (years), mean (SD)	62.5 (12.0)	61.2 (11.0)	.269
Gender			.081
Male, n (%)	36 (75)	46 (59.7)	
Female, n (%)	12 (25)	31 (40.3)	
Body mass index (kg/m ²), mean (SD)	28.3 (6.0)	27.2 (6.9)	.173
Previous intra-abdominal surgery, n (%)			.007
No	28 (58.3)	26 (33.8)	
Yes	20 (41.7)	51 (66.2)	
Co-morbidities, n (%)			
Obesity	18 (37.5)	18 (23.4)	.090
Coronary Artery Disease	8 (16.7)	5 (6.5)	.070
Hypertension	17 (35.4)	45 (58.4)	.012
Diabetes	10 (20.8)	9 (11.7)	.166
Overall	29 (60.4)	59 (76.6)	.054
Surgeons' experience, n (%)			.007
Low volume	2 (4.2)	17 (22.1)	
High volume	46 (95.8)	60 (77.9)	
Tumor type, n(%)			
Rectal adenocarcinoma	40 (85.1)	64 (83.1)	.770
Recurrent rectal adenocarcinoma	4 (8.5)	2 (2.6)	.137
Rectal squamous cell cancer	1 (2.1)	9 (11.7)	.088
Anal adenocarcinoma	1 (2.1)	0 (0)	.379
Ulcerative colitis with multifocal signet cell cancer	0 (0)	1 (0)	1.0
Melanoma	0 (0)	1 (0)	1.0
Gastro-intestinal stromal tumor (GIST)	1 (2.1)	0 (0)	.379
Neoadjuvant treatment, n(%)			.807
Yes	43 (89.6)	70 (90.9)	
No	5 (10.4)	7 (9.1)	

Significant reduction of operative time was observed in the RAPR group (266.9 ± 107.8 min vs 318.9 ± 75.1 min, *P* = .001) (Table 3). Rate of conversion was 2.6% in the RAPR group and 6.4% in the HAPR group (*P* = .371). Intraoperative complication rate was similar between groups (15.6% in RAPR vs 16.7% in HAPR, respectively), however specimen perforation was almost twice more frequent in the HAPR group (12.5%) as compared with the RAPR group (6.5%) (*P* = .332).

Mean tumor size was 1 cm higher in RAPR group (*P* = .093) and tumors were almost 1 cm closer from anal verge in this group (*P* = .006) (Table 3). Pathological staging was comparable between groups. CRM involvement was found in 18.75% of HAPR patients and 14.29% of RAPR patients (*P* = .508).

**TABLE 2** Surgical technique and intra-operative outcomes

Parameter	Hybrid APR (n = 48)	Robotic APR (n = 77)	P value
Perineal resection position, n (%)			.021
Lithotomy	48 (100)	69 (89.6)	
Prone	0 (0)	8 (10.4)	
Perineal resection, n (%)			<.001
Cylindrical	2 (4.2)	35 (45.5)	
Standard	46 (95.8)	42 (54.6)	
Closure of perineal defect, n (%)			.516
Primary	46 (95.8)	69 (89.6)	
Flap	2 (4.2)	5 (6.5)	
Mesh	0 (0)	1 (1.3)	
Flap and mesh	0 (0)	2 (2.6)	
Division of levator muscle, n (%)			<.001
Below	45 (93.8)	30 (39.0)	
Transabdominal	3 (6.2)	47 (61.0)	
Additional procedure, n (%)	20 (41.7)	26 (33.8)	.373
Operating time (min), mean (SD)	318.9 (75.1)	266.9 (107.8)	.001
Conversion, n (%)			
Overall	3 (6.3)	2 (2.6)	.371
To open surgery	2 (4.2)	2 (2.6)	.638
To hand assisted laparoscopy	1 (2.1)	0 (0)	.384
Intraoperative complications, n (%)			
Overall	8 (16.7)	12 (15.6)	.872
Bleeding	3 (6.3)	6 (7.8)	1.000
Require transfusion	4 (8.3)	9 (11.7)	.550
Specimen perforation	6 (12.5)	5 (6.5)	.332
Urethral injury	0 (0)	3 (3.9)	.285

Similarly, completeness of mesorectal resection was not statistically different between groups. Mean number of lymph nodes retrieved in both groups were above recommendations from AJCC (12 lymph nodes), although significantly more lymph nodes were retrieved in the HAPR group (20.71 ± 16.13 vs 15.14 ± 11.27 , $P = .020$).

Home discharge was significantly more frequent after RAPR than after HAPR (91.18% vs 66.67%, $P = .001$). In-hospital length of stay, perineal wound complications, pelvic abscess rate, readmission, and reoperation within 30 days were slightly improved in the RAPR group, although not statistically significant (Table 4). Readmissions within 30 days were for wound infections or pelvic abscess (four in each group), dehydration or deconditioning (one of each in each group) and small bowel obstruction (SBO) (four in the HAPR group and two in the RAPR group). In the HAPR group, three patients needed reoperation for SBO and one for wound debridement. In the RAPR group, one patient needed percutaneous

TABLE 3 Pathology findings

Parameter	Hybrid APR (n = 48)	Robotic APR (n = 77)	P value
Tumor size (cm), mean (SD)	2.75 (2.0)	3.26 (1.9)	.093
Distance from anal verge (cm), mean (SD)	4.13 (0.3)	3.28 (0.2)	.006
Pathological staging, (%)			.288
0	5 (10.4)	13 (16.9)	
1	14 (29.2)	17 (22.1)	
2a	11 (22.9)	19 (24.7)	
2b	0 (0)	0 (0)	
2c	0 (0)	6 (7.8)	
3a	4 (8.3)	3 (3.9)	
3b	7 (14.6)	11 (14.3)	
3c	3 (6.3)	1 (1.3)	
4	4 (8.3)	7 (9.1)	
Resection, (%)			.576
0	39 (81.3)	67 (87.0)	
1	8 (16.7)	9 (11.7)	
2	1 (2.1)	1 (1.3)	
Circumferential margin involvement, (%)			.508
Negative	39 (81.3)	66 (85.7)	
Positive	9 (18.8)	11 (14.3)	
Mesorectal resection quality, (%)			.650
Complete	21 (43.8)	35 (45.5)	
Near complete	9 (18.8)	9 (11.7)	
Incomplete	6 (12.5)	14 (18.2)	
Missing data	12 (25.0)	19 (24.7)	
Specimen perforation, (%)			.332
Yes	6 (12.5)	5 (6.5)	
No	42 (87.5)	72 (93.5)	
Lymph nodes retrieved (number), mean (SD)	20.71 (16.1)	15.14 (11.3)	.020

endoscopic gastrostomy (PEG) for re-alimentation, two needed reoperation for SBO, one for flap debridement and one for excision of positive margins.

At long-term follow-up, parastomal hernia rate was lower after RAPR (9.86% vs 3.71%, $P = .001$); although length of follow-up was significantly lower in this group (14.38 ± 13.77 months vs 25.58 ± 17.15 months, $P < .001$).

After multivariate linear regression, reduction of operative time in the RAPR group remained statistically significant (coefficient -69.87 min, $P < .001$), independently from two confirmed confounding factors: surgeons' experience (coefficient -135.32 min, $P < .001$) and additional concomitant procedure (coefficient $+46.32$ min, $P = .003$). Other variables integrated in the multivariate

**TABLE 4** Post-operative outcomes

Parameter	Hybrid APR (n = 48)	Robotic APR (n = 77)	P value
Patients with stay on ICU, n (%)	6 (12.50)	11 (14.29)	.777
Post-operative wound complications 30 days, n (%)			
Minor wound	15 (31.25)	21 (27.27)	.663
Major wound	4 (8.33)	12 (15.58)	.283
Pelvic abscess	6 (12.50)	3 (3.90)	.085
Other post-operative complications 30 days (eg, urinary, respiratory, ileus, kidney failure), n (%)	19 (39.58)	19 (24.68)	.078
Length of hospital stay, days (SD)	6.43 (3.87)	5.92 (4.11)	.247
Type of discharge, n (%)			.001
Home	26 (66.67)	62 (91.18)	
Rehabilitation	13 (33.33)	6 (8.82)	
Re-admissions within 30 d, n (%)	10 (20.83)	8 (10.39)	.106
Re-operations within 30 d, n (%)	4 (8.33)	5 (6.49)	.732
Re-operations within 60 d, n (%)	2 (4.26)	2 (2.60)	.634
Length of post-operative follow-up, months (SD)	25.58 (17.15)	14.38 (13.77)	<.001
Parastomal hernia, n (%)	15 (35.71)	7 (9.86)	.001

model did not reach statistical significance (obesity, previous abdominal surgery and intraoperative complication) (Appendix S1).

Parastomal hernia rate remained significantly lower in the RAPR group after multivariate logistic regression (OR 0.13, $P = .002$) (Appendix S2). The only statistically significant confounding factor was additional procedure (OR 0.13, $P = .002$). Age older than 75 years and high-volume surgeon also approached statistical significance (respectively OR 4.37, $P = .057$ and OR 0.21, $P = .084$).

RAPR patients in the multivariate model also less needed rehabilitation at discharge (OR 0.16, $P = .006$) independently from patient-related variables or surgeon's experience (Appendix S3). As such, intraoperative complication was the only confounding factor almost reaching statistical significance (OR 4.25, $P = .051$).

4 | DISCUSSION

In this cohort, RAPR appeared to be feasible and safe.

With comparable oncologic outcomes, RAPR led to significant reduction of OR time and parastomal hernia rate as compared to hybrid approach.

In an oncologic point of view, the main issues of APR are CRM involvement and specimen perforation, as these are thought to be

responsible for high cancer recurrence rate after APR. Moreover, recent analysis of the United States National Cancer Database showed a significant increase in positive surgical margins for colon and rectal cancer between 1998 and 2012.¹⁵ CRM involvement in our cohort was 18.75% in the HAPR group and 14.29% in the RAPR group ($P = .508$). This difference, although not statistically significant, may be related to more frequent extra-levator resections in the RAPR group (45.5% vs 4.2% in HAPR group, $P < .001$). Results in both groups, however, showed low CRM involvement as compared with existing literature. In a large Swedish national registry-based observational cohort study, Prytz et al found CRM involvement in 28% of cases after standard APR and 29% after extra-levator APR (727 patients analyzed).¹⁶ Other European results also show high rate of CRM involvement. Analyzing 300 APR from 11 European centers, West et al found 49.6% CRM involvement with standard APR, but significant reduction to 20.3% with extra-levator APR ($P < .001$).¹⁷ Similarly, West et al described intraoperative specimen perforation (IOP) rate of 28.2% after standard APR and 8.2% after extra-levator APR ($P < .001$). In our cohort, IOP rate was 12.50% in the HAPR group and 6.49% in the RAPR group ($P = .332$).

Our results are consistent with findings from Kim et al^{12,18} who compared outcomes from 40 robotic APR to 78 open APR and found a reduction from 14% to 3% of CRM involvement in the robotic group; although under statistical significance limit ($P = .057$) because of small number of events.

These findings demonstrate appropriate pathologic-oncologic results of robotic APR. This could indicate a trend towards improvement of oncologic outcomes but must be interpreted with caution because of limitations of retrospective design. Considering prospective studies, ROLAAR trial¹⁹ randomized laparoscopic and robotic rectal resections for cancer. In this study, 234 patients were included in the laparoscopic group of which 42 APR, and 237 patients were included in the robotic group of which 43 APR. No significant oncologic benefit of robotic approach was found for rectal cancer in general, but no subgroup analysis of the APR patients was run. Main outcome of ROLAAR trial, rate of conversion to open surgery, showed small nonsignificant reduction of conversion rate in robotic group (8.1%) vs laparoscopic group (12.2%, $P = .160$). According to authors, however, surgeons performing procedures in this study were expert laparoscopic rectal surgeons, but still in their learning phase of robotic approach. Comparatively, in the present study, very low conversion rates were found, especially in RAPR (2.6%). Robotic surgery may thus help to reduce conversion rate during APR. This assumption is supported by recent meta-analysis from Prete et al for rectal cancer surgery in general.²⁰ COLOR II trial showed that minimally invasive colorectal procedures lead to less surgical trauma and functional complications.²¹ Reducing conversion rate in rectal cancer surgery may thus be a major advantage of robotic approaches.

Operative time, however, was identified as a major pitfall of this approach in the meta-analysis of Prete et al. Strategies to improve this specific outcome are thus needed, such as the totally robotic APR.

Data comparing hybrid and totally robotic approach for rectal cancer treatment are scarce. In early robotic experience, hybrid



procedures are usually performed. Depending on surgeon volume, the technique will often move to totally robotic procedures rather than keeping a hybrid approach. Although using laparoscopy for easier parts of robotic procedures is thought to save some time, our data suggest that time spared by performing colonic mobilization laparoscopically in hybrid approach may be not so important and may not compensate time lost in setup modifications. As such, mean operative time was almost 40 minutes shorter with RAPR. After multivariate analysis, decreased operative time remains statistically significant, regardless of obvious confounding factors (surgeon's experience, obesity, and additional procedure) and the fact that 10.4% of RAPR patients were turned into prone position during the procedure vs none in HAPR group. Thus, transition to totally robotic approach tends to improve surgical workflow and operative time independently from other time consuming factors, as it has been described previously in other procedures such as bariatric surgery.²²

Outcomes such as in-hospital length of stay, minor wound complications, pelvic abscess rate, readmission and reoperation within 30 days suggest tendency towards reduced surgical trauma after RAPR, although no conclusion can be made as these results were not statistically significant. Lower parastomal hernia rate observed in RAPR group, even after multivariate adjustment including length of follow-up, also suggests reduced parietal trauma as there was no difference in terms of stoma hernia prevention in both groups; but this result must obviously be interpreted with caution as the physiologic explanation remains disputable. Home discharge was significantly improved in RAPR groups, both after univariate and multivariate analysis, and was not related with traditional factors such as age or comorbidities. These findings may of course be related to shorter procedures in RAPR group, as shorter operative time are known to improve such outcomes.²³ Another hypothesis could be related to abdominal wall stress during procedure. Robotic systems may allow reduced parietal trauma compared with long rigid laparoscopic instruments, as articulated tips of robotic instruments limit leverage forces applied on abdominal wall. This concept has been described in studies comparing laparoscopic and robotic approach for hysterectomy,²⁴⁻²⁶ where trocars placements are very similar to those of APR. Thus, limiting abdominal wall tensions, totally robotic procedures may theoretically improve functional outcomes as compared with hybrid procedures.

Conclusions must be careful because of obvious study shortcomings. Although interesting results were found compared with existing literature, no direct comparison can be made between this robotic cohort and standard open or laparoscopic approaches. Retrospective nature of data implies inherent biases that limit significance and generalization of findings. Authors concede strong interest in robotic surgery, which may alter their interpretation.

Conversely, sample size for such highly specialized procedure is worth noting and adds to study validity. Results compared with existing literature are encouraging, especially considering various robotic experience and daily practice of participating surgeons. Furthermore, this study adds some new data to orientate technical choice between hybrid and totally robotic procedures in rectal cancer surgery.

5 | CONCLUSION

In this cohort of robotic APR, totally robotic approach is safe, feasible, and leads to significant reduction of OR time and possibly reduced surgical trauma as characterized by fewer parastomal hernias and fewer need for rehabilitation at discharge. No significant difference in terms of oncological outcomes or other complications were found. Thus, when deciding of robotic approach for APR, totally robotic approach seems advisable. In addition, global oncologic and functional results from this cohort as compared to existing literature show robotic APR to be promising technique to improve low rectal cancer care. These findings have yet to be confirmed by further prospective studies.

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Dr. Hellan has nothing to disclose.

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ENDNOTES

Note. Model $\chi^2 = 25.16$, $P = .003$. Pseudo $R^2 = 0.23$.

Note. Model $\chi^2 = 23.41$, $P = .005$. Pseudo $R^2 = 0.23$.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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