ORIGINAL ARTICLE

Long term oncological outcomes for laparoscopic versus open surgery for rectal cancer – A population-based nationwide noninferiority study

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Abstract

Aim: The aim of this work was to compare the 5-year overall survival in a national cohort of patients undergoing curative abdominal resection for rectal cancer by laparoscopic (LAP) or open (OPEN) surgery.

Method: All patients diagnosed with clinical Stage I–III rectal cancer and who underwent LAP or OPEN abdominal curative surgery in Sweden between 2010 and 2016 were retrieved from the Swedish Colorectal Cancer Registry. A noninferiority study design was employed with a statistical power of 90%, a one-side type I error of 2.5% and a noninferiority margin of 2%. The analyses were performed as intention-to-treat and the relationship between surgical technique and overall mortality within 5 years was analysed. Multilevel regression models with the patients matched by propensity scores adjusted for patient- and tumour-related variables were used.

Results: A total of 8410 Stage I–III cancer patients were included. This group underwent 2094 LAP (24.9%) and 6316 OPEN (75.1%) procedures and were followed until 31 December 2020. Multivariable Cox regression demonstrated that 5-year overall survival was higher in the LAP group [hazard ratio (HR) 0.877; 95% CI 0.775–0.993]. [Correction added on 21 November 2022, after first online publication: In the preceding sentence, the CI value for LAP group has been corrected from "0.877" to "0.775" in this version.] The outcome was similar when multiple imputation and propensity score matching were employed. When cT4 patients were excluded there was no difference (HR 0.885; 95% CI 0.790–1.033). At 5-years' follow-up local recurrence was not different, at 2.9% for the LAP group and 3.6% for the OPEN group ($p = 0.075$), while metastatic disease was more frequent in the OPEN group (19.6% compared with 15.6% for LAP; $p < 0.001$).

Conclusion: This study demonstrated that the LAP technique was not inferior to OPEN surgery with regard to overall 5-year survival. These results support the use of laparoscopic surgery.

KEYWORDS
laparoscopy, minimally invasive surgery, multiple imputation, noninferiority, oncological outcome, population based, propensity score, rectal cancer, survival

INTRODUCTION

Despite the development of various neoadjuvant treatment modalities surgery remains the cornerstone of curative treatment for rectal cancer; this represents one of the most technically demanding colorectal procedures. Several studies, including randomized clinical trials (RCTs), have demonstrated that laparoscopic surgery (LAP) for rectal cancer, compared with open surgery (OPEN), improves short-term outcomes such as postoperative pain, recovery and quality of life [1–6]. For colon cancer, RCTs have demonstrated similar long-term oncological outcomes for LAP compared with OPEN [7–9]. Regarding rectal cancer, one RCT with local recurrence as the primary endpoint demonstrated similar rates of local recurrence, disease-free and overall survival [10]. However, in recent years, two RCTs could not demonstrate noninferiority for LAP with regard to short-term results [11, 12], but when presenting long-term results one trial found no difference[13] and one questioned the oncological safety of LAP [14]. A number of observational studies, RCTs and meta-analyses comparing LAP and OPEN for rectal cancer do support the long-term oncological safety of the minimally invasive approach [10, 15–19]. In Sweden, LAP for rectal cancer was infrequent a decade ago, with only 7% of all rectal cancer resections being performed laparoscopically in 2010. Thereafter LAP increased steadily, accompanied by a moderate centralization of rectal cancer surgery, and reached 72% of procedures in 2020 [20]. However, no systematic population-based quality control has been undertaken regarding long-term oncological outcome. The aim of this study was to assess long-term oncological results in patients undergoing curative abdominal rectal cancer resection surgery, comparing LAP and OPEN techniques with a noninferiority study design, based on a nationwide cohort comprising all patients treated with curative surgery during a 7-year period.

METHOD

The study population included all patients diagnosed with clinical Stage I–III rectal cancer (cTNM I–III) between 1 January 2010 and 31 December 2016 and who underwent curative abdominal resection surgery. Patients were followed until 31 December 2020 (see flow chart in Figure 1). Patient data were obtained from the Swedish Colorectal Cancer Registry (SCRCR) [21]. The SCRCR is a nationwide registry in which registration is mandatory, and nearly all rectal cancers diagnosed in Sweden since 1995 have been included. The SCRCR has a coverage of approximately 99%, and has been validated on several occasions, most recently in 2018 [22], with a high degree of accuracy. The definition of rectal cancer in the SCRCR is an adenocarcinoma with the lower brim of the tumour ≤15 cm above the anal verge, as measured with a rigid sigmoidoscope. This study included the abdominal rectal cancer procedures of anterior resection (AR), abdominoperineal resection (APR) and Hartmann's procedure (HA). Local procedures such as transanal endoscopic microsurgery, conventional transanal resection and endoscopic excisions were not included. Urgent or unplanned rectal resections were not included (<0.5% in the SCRCR). Patients with adenomas including severe dysplasia were

What does this paper add to the literature?

In this cohort of patients from an entire nation undergoing curative abdominal rectal cancer surgery, laparoscopic and open technique were compared on an intention to treat basis. In order to mimic a randomized setting, a non-inferiority design was employed and the study population permitted a low non inferiority margin of 2%. The present study demonstrated that laparoscopic was not inferior to open technique regarding overall survival at 5 years. In Multivariabable Cox regression analysis overall survival was higher in laproscopy when cT4 was included but not when cT4 was excluded. Converted patients had a slightly worse outcome.

not included, nor were patients with Stage IV cancer diagnosed preoperatively or within 30 days of index surgery. Robotically assisted laparoscopy has been registered in the SCRCR since 2014 but in the present study conventional laparoscopy and robotically assisted laparoscopy are analysed as one group (LAP). Analysis was made on an intention-to-treat basis, and all converted cases were analysed in the LAP group. To assess conversion as a potential risk factor, converted cases were also analysed as a subgroup and compared with OPEN [23]. Local recurrence was defined as any tumour growth located within the pelvis and confirmed by imaging or histology. Systemic recurrence was defined as any malignant spread outside the pelvis.

Study hypothesis and statistical considerations

In the present study the exposure was surgical technique, i.e. LAP compared with OPEN, and the main outcome measure was overall survival at 5 years. The hypothesis of this study was that LAP would not be inferior to OPEN, thus having a lower 5-year survival rate, and for this reason a noninferiority study design was employed [24, 25]. The observed survival in all Swedish patients undergoing abdominal operation for Stage I–III rectal cancer between 2010 and 2015 was retrieved from the SCRCR through the Swedish Regional Cancer Center (RCC) website [26]. Based on the observed 5-year overall survival of 75% in the OPEN group and 79% in the LAP group, a 2% (<5% of 75%) noninferiority margin was chosen because a relative decrease of <5% in 5-year overall survival can be arbitrarily considered as not inferior to the comparator. To demonstrate noninferiority with a noninferiority margin of 2%, a statistical power of 90% and a one-side type I error of 2.5%, the required sample sizes for the LAP and OPEN groups were 742 and 1852, respectively. The actual sizes in the current study are 6316 and 2094, respectively. The analysis of long-term outcomes was based on variables related to patient demography, preoperative clinical TNM assessment (cTNM), neoadjuvant treatment, the different surgical procedures employed and year of surgery. It was hypothesized that clinical T4 (cT4) and
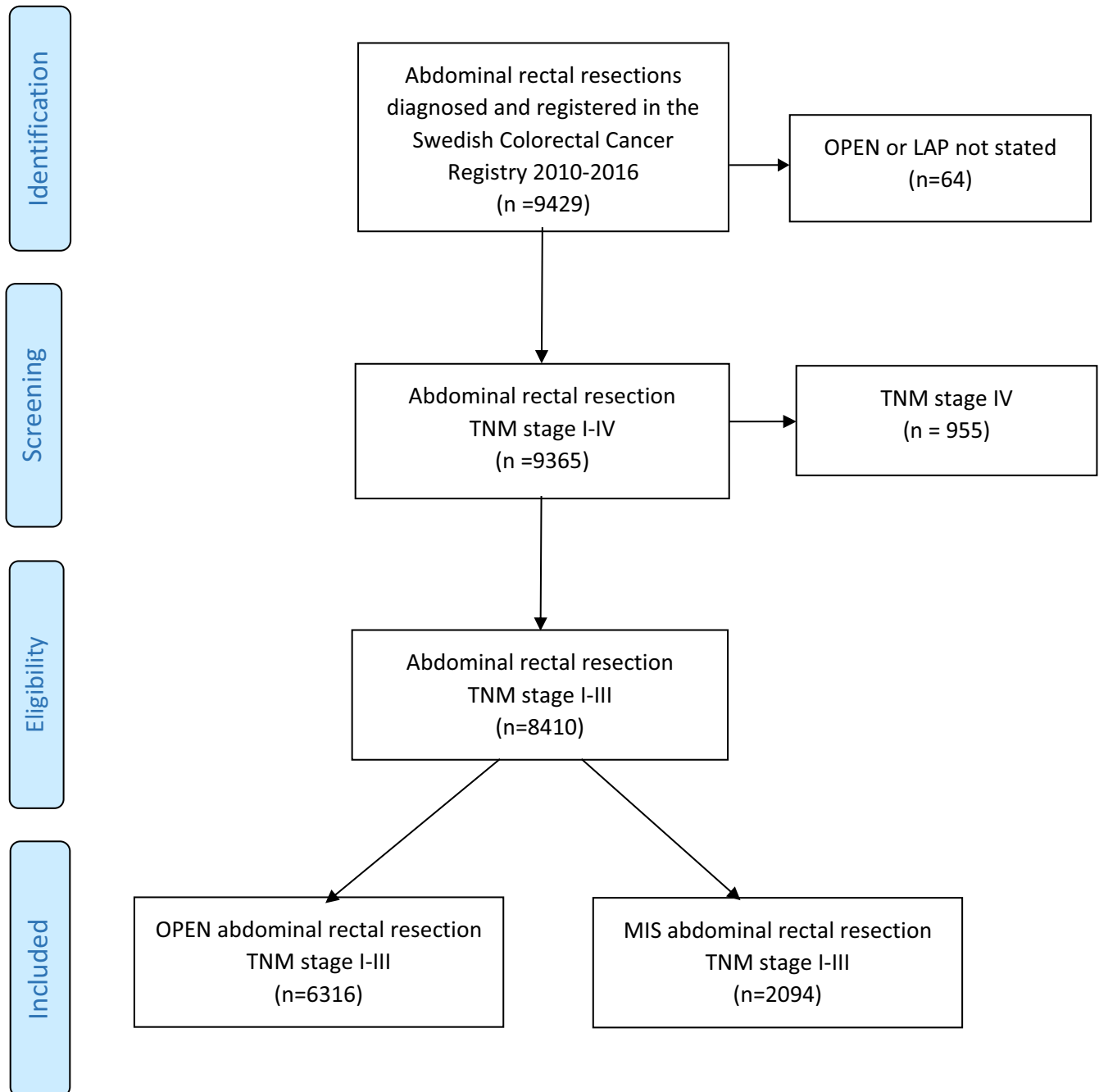
FIGURE 1 Study flow chart

American Society of Anesthesiologists (ASA) class 4 may have represented relative contraindications for LAP, and a decision to perform a subanalysis based on this presumption was made. Variables related to the pathology report are presented but not included in the statistical analysis regarding long-term results.

Statistical analysis

Results are presented as counts and percentages for categorical variables, and median and quartile range (Q1, Q3) for continuous variables, employing the chi-square test, the Wilcoxon rank sum test or the Kruskal–Wallis test as appropriate. Kaplan–Meier curves were used to illustrate all-cause and cancer stage-specific mortalities. Patients who died or emigrated during follow-up were censored. The relationship between surgical technique (LAP or OPEN) and postoperative mortality was analysed using multilevel survival regression models with the patients matched by propensity score [27], adjusted for age, sex, body mass index (BMI), ASA classification, clinical cancer stage (cTNM), neoadjuvant treatment, level of the tumour, type of surgical procedure (AR, APR, HA) and year of surgery. The propensity scores for receiving OPEN or LAP were

estimated using the logistic regression model [28] with age, sex, BMI, ASA classification, cTNM, neoadjuvant treatment, level of the tumour, type of surgical procedure (AR, APR, HA) and year of surgery. The proportional hazards assumption was examined based on the scaled Schoenfeld residuals and no violation was found. The relative risks for mortality of the LAP group and covariates are reported as hazard ratio (HR) with 95% confidence interval (CI). In one set of statistical models missing values were imputed using multiple imputation methods and the results from five imputed datasets were synthesized according to Rubin's rules [29]. The results from regression analyses are presented with a two-sided p-value, which if less than 0.05 was considered statistically significant. All analyses were performed using the statistical software Stata 16.1 (StataCorp). Permission was obtained from the ethical committee of the Uppsala–Örebro health care region (Dnr 2018/129 and Dnr 2019–01787).

RESULTS

Patient demography

A total of 8410 patients were diagnosed with clinical Stage I–III rectal cancer and subsequently underwent curative abdominal rectal resection, either AR, APR or HA. Of the included patients 24.9% (2094/8410) underwent LAP and 75.1% (6316/8410) OPEN. The proportion undergoing LAP increased from 7.3% in 2010 to 49.8% in 2016, and the conversion rate decreased from 20.5% in 2010 to 12.0% in 2016 (Figure 2). The proportion of women increased in the LAP group (43.6% compared with 38.5% in OPEN). An ASA score ≥3 was more frequent in the OPEN group (24.9% compared with 20.8% in the LAP group). BMI was slightly higher in the OPEN group (median 25.6 kg/m^2 compared with 25.2 kg/m^2 in the LAP group). Tumour level was a median of 8 cm in both groups, with 56.5% in OPEN and 56.2% in LAP being clinical cancer Stage III. cT4 was more common in the OPEN than the LAP group (17.7% and 11.0%,
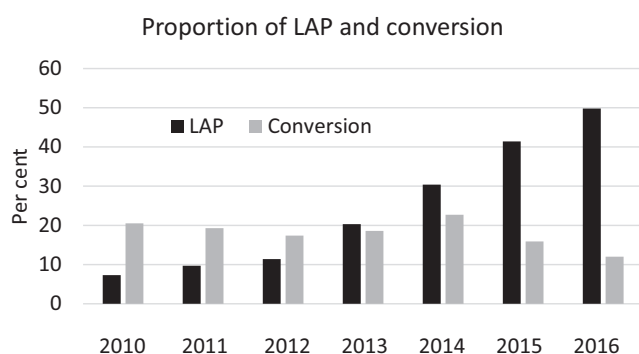
respectively). A tendency for a higher proportion of laparoscopic APR in cT4 was seen, as well as a lower proportion of laparoscopic HA in all cT stages (Table S2). cN1–2 stage was slightly higher in the LAP than the OPEN group (53.5% and 51.4%, respectively). Any type of neoadjuvant treatment was more common in the OPEN group (68.0%) than the LAP group (62.5%) (Table 1).

Surgical outcomes

In the LAP group the proportions of AR, APR and HA were 53.3%, 40.2% and 6.5%, respectively, compared with 51.4%, 36.7% and 12.0% in the OPEN group. The distal resection margin (in AR and HA) was a median of 35 mm in the LAP group and 39 mm in the OPEN group, while the circumferential resection margin was a median of 10 mm in both groups (Table S1).

Pathological short-term outcomes and adjuvant therapy

The median lymph node yield was 17 in both groups. R0 resection was obtained in 96.2% of cases in the LAP group and 94.4% in the OPEN group. Regarding the tumour characteristics in the pathology report, pN1 was comparable between the groups (24.8% in LAP compared with 24.9% in OPEN), while pN2 was less common in LAP (10.0%) than in OPEN (12.3%). High-grade cancer was also less frequently found in the LAP group (10.8%) compared with the OPEN group (13.6%). Adjuvant therapy was given to 27.4% in the LAP group and 31.3% in the OPEN group (Table S1).

Long-term outcomes

The HR for the LAP group compared with the OPEN group, based on patients with preoperatively known cTNM ($n = 7773$) and analysed with the conventional Cox regression model ($n = 7440$) was 0.877 (95% CI 0.775–0.993), with Cox regression and multiple imputation ($n = 7773$) it was 0.877 (95% CI 0.777–0.990) and with Cox regression, multiple imputation and propensity score matching ($n = 7378$) it was 0.827 (95% CI 0.702–0.973). Similar models were analysed for patients with known cTNM and in addition comprising multiple imputation for those patients with unknown cTNM ($n = 8467$), with similar outcomes (Table 2a,b). Another two analyses were performed based on patients with (1) known cTNM ($n = 6118$) and (2) known cTNM with multiple imputation for those patients with unknown cTNM ($n = 6588$), respectively, but with the exclusion of all patients preoperatively assessed as cT4, unknown cT or ASA 4. With this restriction, the outcome was not statistically different: with Cox regression and multiple imputation ($n = 6588$) HR = 0.904 (95% CI 0.790–1.036) and with Cox regression, multiple imputation and propensity score matching ($n = 6319$) HR = 0.900 (95% CI 0.783–1.033) (Table 2c).

FIGURE 2 Proportion of laparoscopy (LAP) procedures including converted cases and conversion rate in abdominal rectal cancer surgery in Sweden during each year of the study period from 2010 to 2016.

	OPEN (n = 6316)	LAP (n = 2094)	p-value
Age (years), median (Q1;Q3)	69 (62;76)	70 (62,76)	0.527[a]
Women	2431 (38.5%)	913 (43.6%)	<0.001
Men	3885 (61.5%)	1181 (56.4%)	
BMI (kg/m^2)			
Median (Q1;Q3)	25.6 (23.1;28.4)	25.2 (23.1;27.9)	0.005[a]
Missing	185	30	
ASA class			
1	1195 (19.1%)	473 (22.7%)	<0.001[b]
2	3504 (56.0%)	1180 (56.6%)	
3	1491 (23.8%)	414 (19.9%)	
4	71 (1.1%)	18 (0.9%)	
Missing	56	9	
Tumour			
Height (cm) (Q1;Q3)	8 (5;11)	8 (5;12)	0.59[a]
Missing	78	19	
Clinical T stage			
cT1–2	1562 (25.0%)	644 (30.9%)	<0.001[b]
cT3	3317 (53.0%)	1143 (54.8%)	
cT4	1107 (17.7%)	230 (11.0%)	
cTX	272 (4.3%)	68 (3.3%)	
Missing	58	9	
Clinical N stage			
cN0	2654 (42.1%)	919 (43.9%)	0.002[b]
cN1–2	3237 (51.4%)	1120 (53.5%)	
cNX	412 (6.5%)	53 (2.5%)	
Missing	13	2	
Preop. MDT			
Yes	6144 (97.3%)	2076 (99,1%)	<0.001
No	172 (2.7%)	18 (0.9%)	
Neoadjuvant therapy			
No neoadjuvant therapy	2020 (32.0%)	787 (37.5%)	0.049[b]
Radiotherapy only	2938 (46.5%)	1015 (48.5%)	
Chemoradiotherapy	1356 (21.5%)	292 (14.0%)	
Type of procedure			
Anterior resection	3244 (51.4%)	1117 (53.3%)	<0.001[b]
With defunctioning stoma	2644/3244 (81.5%)	823/1117 (73.7%)	<0.001[c]
Abdominoperineal resection	2317 (36.7%)	841 (40.2%)	
Hartmann's procedure	755 (12.0%)	136 (6.5%)	

TABLE 1 Demographic data in patients with Stage I–III disease undergoing abdominal resection for rectal cancer in Sweden 2010 to 2016

Note: Comparison between open (OPEN) and laparoscopic (LAP) surgery. Chi-square test if not otherwise indicated.

Missing cases (*n*) denoted when applicable.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; MDT, multidisciplinary team conference.

[a]Wilcoxon rank sum test.

[b]Kruskal–Wallis test.

[c]Denotes comparison between anterior resection with or without a defunctioning stoma at index surgery (chi-square test).

TABLE 2 Overall 5-year survival in patients undergoing laparoscopic (LAP) compared with open (OPEN) curative abdominal resection for rectal cancer: (a) with preoperatively known cTNM 1–3 (n = 7773); (b) with preoperatively known cTNM 1–3 with imputation for missing cTNM (n = 8467); (c) with preoperatively known cTNM 1–3. Patients with cT4, cT = unknown and American Society of Anesthesiologists class 4 are excluded (n = 6588)

	HR (95% confidence interval)	p-value
(a)		
Model 1: conventional Cox model (n = 7440; 333 patients were excluded due to missing values)	0.877 (0.775–0.993)	0.038
Model 2: Cox model with multiple imputation (n = 7773)	0.877 (0.777–0.990)	0.034
Model 3: Cox model with multiple imputation and propensity score matching (n = 7378; 395 patients were excluded from the analysis because no matched patients could be found)	0.827 (0.702–0.973)	0.022
(b)		
Model 1: conventional Cox model (n = 7440; 333 patients were excluded due to missing values)	0.877 (0.775–0.993)	0.038
Model 2: Cox model with multiple imputation (n = 8467)	0.873 (0.777–0.982)	0.024
Model 3: Cox model with multiple imputation and propensity score matching (n = 8024; 443 patients were excluded from the analysis because no matched patients could be found)	0.876 (0.776–0.988)	0.031
(c)		
Model 1: conventional Cox model (n = 6118; 470 patients were excluded due to missing values)	0.885 (0.770–1.018)	0.087
Model 2: Cox model with multiple imputation (n = 6588)	0.904 (0.790–1.036)	0.147
Model 3: Cox model with multiple imputation and propensity score matching (n = 6319; 269 patients were excluded from the analysis because no matched patients could be found)	0.900 (0.783–1.033)	0.134

Overall survival, local recurrence and metastatic disease

Overall survival is depicted in Figure 3A–D. Local recurrence was diagnosed in 2.9% in the LAP group and 3.6% in the OPEN group (p = 0.139). Distant metastatic disease was diagnosed in 15.6% in the LAP group and 19.6% in the OPEN group (p < 0.001) (Figure 4A–B).

Conversion to open surgery

In a subanalysis, LAP patients who underwent conversion to open surgery were compared with the OPEN group. A significantly increased HR for the converted patients compared with the OPEN group was found; for the conventional Cox regression model (n = 5808) the HR was 1.256 (95% CI 1.004–1.570). Additional statistical models were analysed and they yielded comparable and statistically significant results, albeit with the lower border of the CI not far from 1 (for details see Tables 3a,b and S3a–c).

DISCUSSION

This nationwide study comparing all patients diagnosed with cTNM I–III rectal cancer and undergoing curative abdominal resection with LAP or OPEN surgery in Sweden during a 7-year period, and including a 5-year follow-up, demonstrated that LAP was not inferior to OPEN. Moreover, although not designed to show this, our study found that patients in the LAP group had better overall 5-year survival, but this could not be seen for cTNM Stages II and III in subgroup analysis. One explanation for this could be the more advanced

tumour stage, and if patients with cT4 cancer were excluded the statistically significant difference for 5-year overall survival disappeared. Another explanation could be that the risk for developing metastatic disease within 5 years was significantly lower in the LAP group, a finding previously rarely described and which merits consideration. Another finding of interest which raises some concern was that in a subgroup analysis converted LAP patients had a slight but statistically significant worse long-term outcome than OPEN patients, in contrast to a recent meta-analysis which did not demonstrate differences regarding long-term outcomes [30].

These findings represent population-based real life rectal cancer treatment on a nationwide basis, although some considerations are necessary with regard to the prerequisites of such registry-based data. The fact that data are collected prospectively but analysed retrospectively is a strength as well as a shortcoming. The ideal way to investigate a novel surgical technique such as laparoscopic rectal cancer surgery would be by a RCT, and LAP for rectal cancer has been the subject of some RCTs, both with regard to short- and long-term outcomes. The COLOR II and COREAN trials, both RCTs with a noninferiority design, compared LAP with OPEN surgery. COLOR II had local recurrence as primary endpoint and demonstrated similar rates of local recurrence, disease-free and overall survival, while COREAN found no difference with regard to disease-free survival at 3 years [10, 16]. Two other RCTs with a noninferiority design, the ACOSOG [11] and the ALaCaRT [12] trials, compared the short-term outcomes of LAP and OPEN rectal cancer surgery by assessing a composite pathological outcome, and neither trial could demonstrate noninferiority for LAP. When these trials recently presented long-term results, in the form of a secondary endpoint, namely 2 years' follow-up, for which the statistical power calculation was not intended, the ACOSOG
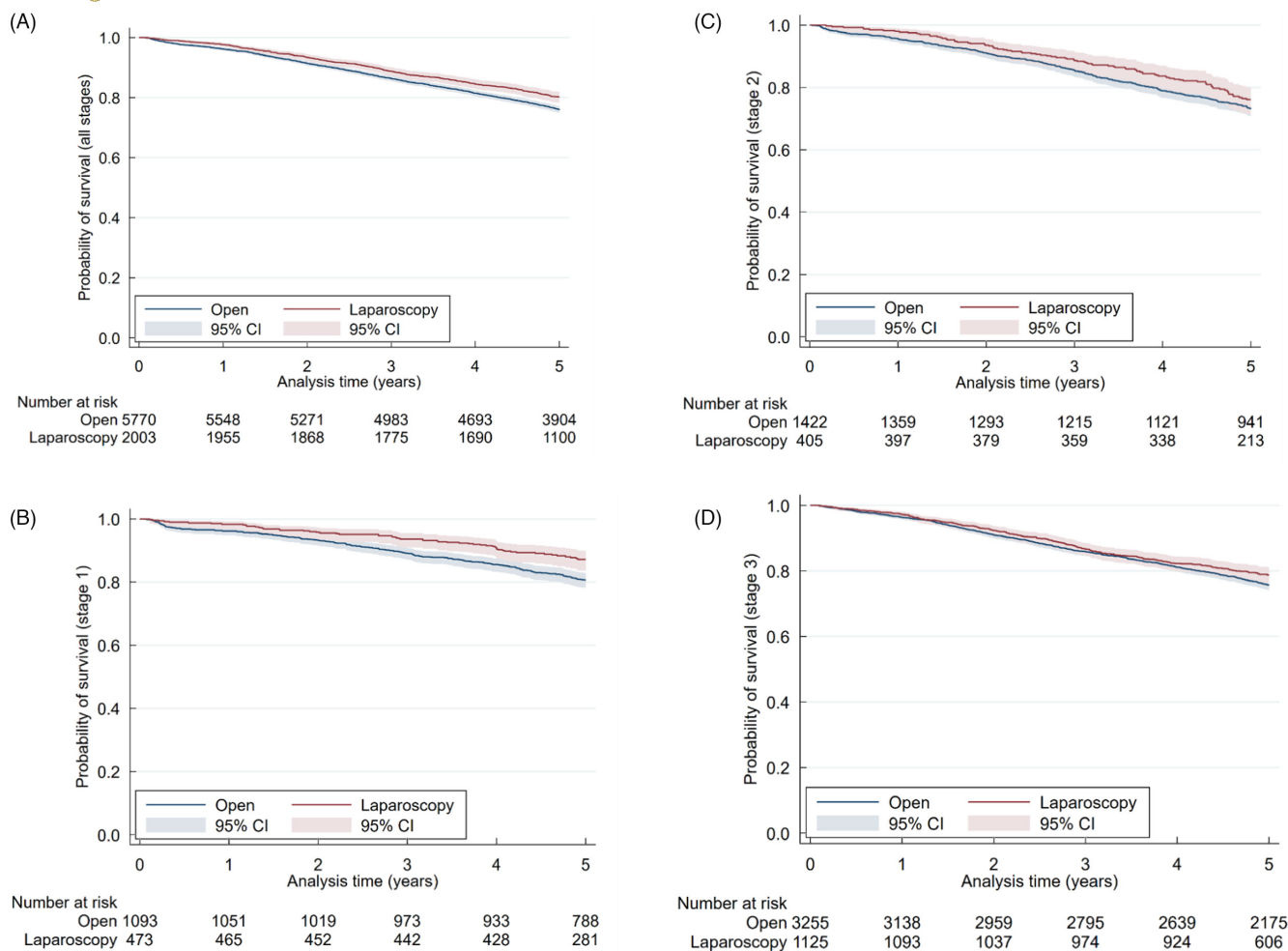
FIGURE 3 (A) Five-year overall survival in rectal cancer patients with preoperatively known cTNM Stage I–III cancer undergoing curative laparoscopic or open abdominal resection surgery (Kaplan–Meier curve). (B) Five-year overall survival in rectal cancer patients with preoperatively known cTNM cancer Stage I undergoing curative laparoscopic or open abdominal resection surgery (Kaplan–Meier curve). (C) Five-year overall survival in rectal cancer patients with preoperatively known cTNM Stage II cancer undergoing curative laparoscopic or open abdominal resection surgery (Kaplan–Meier curve). (D) Five-year overall survival in rectal cancer patients with preoperatively known cTNM Stage III cancer undergoing curative laparoscopic or open abdominal resection surgery (Kaplan–Meier curve).

trial found no difference while the ALaCaRT trial questioned the oncological safety of LAP [13, 14].

Some large observational studies have investigated LAP versus OPEN surgery. Draeger et al. [31] compared LAP and OPEN in a regional German registry-based cohort comprising more than 1500 rectal cancer patients operated on from 2004 to 2013, and found that overall survival and cancer-specific survival was higher in the LAP group. In a registry-based study from Spain, Manchon-Walsh et al. [32] also compared more than 1500 rectal cancer patients undergoing LAP or OPEN surgery during 2011–2012 using propensity score matching, and found that LAP patients had better overall and cancer-specific survival as well as fewer local recurrences.

The present study has several strengths. The first is the population-based setting comprising a large number of patients from an entire nation. The second is the high degree of completeness of data from the Swedish Colorectal Cancer Registry

(SCRCR), including a follow-up of 5 years for nearly all patients with very few lost to follow-up. Thirdly, the noninferiority hypothesis, used in randomized trials but rarely in observational studies, in our study with a relatively small non-inferiority margin was chosen to demonstrate the possibility of LAP not being inferior to OPEN. We deem it a strength that LAP was found noninferior compared with OPEN in this nationwide cohort. Fourthly, the data were analysed using different methods, and the results for the primary outcomes were consistent, which indicates the robustness of the findings. This study also has some limitations. First, there are those associated with registry-based investigations in which residual confounding cannot be completely ruled out. One example of this is that the registry does not provide any information regarding the indication for choosing LAP or OPEN surgery for individual patients. Thus, some degree of selection bias cannot be ruled out. Examples of such patient selection were in fact seen since patients in the OPEN group represented a higher proportion
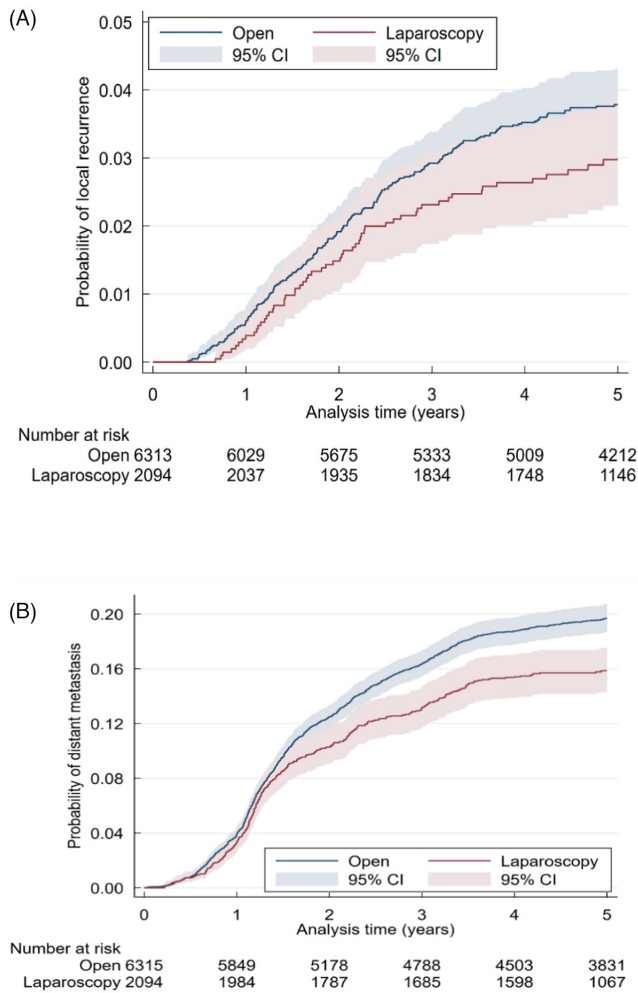
FIGURE 4 (A) Local recurrence within 5 years of follow-up in rectal cancer patients with Stage I–III cancer undergoing curative laparoscopic or open abdominal resection surgery (unadjusted data; Kaplan–Meier curve). (B) Metastatic disease within 5 years of follow-up in rectal cancer patients with Stage I–III cancer undergoing curative laparoscopic or open abdominal resection surgery (unadjusted data; Kaplan–Meier curve).

of ASA class ≥ 3 and an increased proportion of cT4 and more frequently were given neoadjuvant therapy.

The proportion of LAP procedures increased substantially over time during the study period, from 7.3% in 2010 to 49.8% in 2016. Despite this major change in surgical strategy, patient demography was in general very comparable between LAP and OPEN groups. Although clinical Stage III cancer was equally represented in both groups, it is noteworthy that patients in the OPEN group were to a higher extent selected for neoadjuvant therapy, indicating that tumour biology may have been considered potentially more threatening for those patients. This finding is in line with a larger proportion of p/ypN2 and p/yp high-grade cancer in the OPEN group, although there was no difference in the total lymph node yield. In the present study, all patients from an entire nation were included and therefore reflect real life curative rectal cancer surgery.

One finding of importance, although suspected, was that cT4 was less frequent in the LAP group. This indicates that the surgical teams had a preference for selecting OPEN surgery when operating on cT4 patients. However, cT4 comprises cT4a, intra-abdominal cT4b and extra-abdominal cT4b (overgrowth on the levators), the first two of which may influence the choice of LAP or OPEN but the latter probably not. Moreover, available registry data did not permit distinction between cT4a and cT4b. To our knowledge, no RCT has included cT4 tumours, and we deem that the most relevant comparison comprises exclusion of all cT4 patients, partly also because they may represent the most locally advanced cases; by doing so, there was no statistically significant difference in overall 5-year survival between LAP and OPEN groups in our cohort.

In conclusion, this nationwide population-based study did not demonstrate inferiority for curative laparoscopic rectal cancer surgery, which confirmed the study hypothesis. Taking into consideration the well-established short-term advantages of laparoscopic surgery, the results from this study support the use of a minimally invasive technique as standard procedure for abdominal resection for rectal cancer in routine clinical practice.

TABLE 3 Overall 5-year survival in patients undergoing laparoscopic surgery (LAP) with conversion (nonconverted LAP excluded) compared with (a) open (OPEN) curative abdominal resection for rectal cancer with preoperatively known cTNM 1–3 (n = 6049). HR (CI 95%) and (b) OPEN curative abdominal resection for rectal cancer with preoperatively known cTNM 1–3. All cT4, cT = unknown and American Society of Anesthesiologists class 4 are excluded (n = 4849)

	HR (95% confidence interval)	p-value
(a)		
Model 1: conventional Cox model (n = 5808; 241 patients were excluded due to missing values)	1.256 (1.004–1.570)	0.046
Model 2: Cox model with multiple imputation (n = 6049)	1.306 (1.052–1.621)	0.016
Model 3: Cox model with multiple imputation and propensity score matching (n = 5620; 429 patients were excluded from the analysis because no matched patients could be found)	1.266 (1.012–1.584)	0.039
(b)		
Model 1: conventional Cox model (n = 4688; 1611 patients were excluded due to missing values)	1.279 (1.001–1.633)	0.049
Model 2: Cox model with multiple imputation (n = 4849)	1.315 (1.036–1.671)	0.025
Model 3: Cox model with multiple imputation and propensity score matching (n = 4605; 244 patients were excluded from the analysis because no matched patients could be found)	1.273 (0.996–1.626)	0.054

AUTHOR CONTRIBUTIONS

Conception or design of work: KDJ, PM. Acquisition: PM. Analysis: KDJ, YC, PM. Interpretation of data: KDJ, YC, JP, EA, PM. Drafting: KDJ, YC, PM. Critical revision for intellectual content: KDJ, YC, JP, EA, PM.

CONFLICT OF INTEREST

The author(s) declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS APPROVAL

Permission was obtained from the ethical committee of the Uppsala–Örebro health care region (Dnr 2018/129 and Dnr 2019–01787).

PATIENT CONSENT

Was not required for this retrospective data research.

CLINICAL TRIAL REGISTRATION

Not needed for this study.

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SUPPORTING INFORMATION

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

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