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A propensity score-matched analysis of laparoscopic versus open surgery for rectal cancer in a population-based study

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Abstract:	Aim: The oncological risk/benefit trade-off for laparoscopy in rectal cancer is controversial. Our aim was to compare laparoscopic versus open surgery for resection of rectal cancer, using real-world data from the public healthcare system of Catalonia (Spain). Methods: Multicentre retrospective cohort study of all non-metastatic patients who underwent surgery with a curative intent for primary rectal cancer at Catalonian public hospitals in 2011-2012. We obtained data on

	vital status for up to five years. To minimise differences between the two groups we performed propensity score matching on baseline patient characteristics. We used multivariate Cox proportional hazards regression analyses to assess locoregional relapse at two years and death at two and five years. Results: Of 1513 patients with stage I to III rectal cancer, 933 (61.7%) underwent laparoscopy (conversion rate: 13.2%). After applying our propensity score matching strategy (2:1), 842 laparoscopy patients were matched to 517 open surgery patients. Multivariate Cox analysis of death at two years (hazard ratio [HR] 0.65; 95% confidence interval [CI] 0.48, 0.87; p=0.004) and five years (HR 0.61; 95% CI 0.5, 0.75. p <0.001) and of local relapse at two years (HR 0.44; 95% CI 0.27, 0.72; p=0.001) showed laparoscopy to be an independent protective factor compared to open surgery. Conclusions: Laparoscopy results in lower locoregional relapse and long-term mortality in rectal cancer in real-world conditions with all-risk patient groups included. Studies using long-term follow-up of cohorts and real-world data can provide information on clinically relevant outcomes to supplement randomized controlled trials.

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Original article

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ABTRACT

Aim: The oncological risk/benefit trade-off for laparoscopy in rectal cancer is controversial. Our aim was to compare laparoscopic versus open surgery for resection of rectal cancer, using real-world data from the public healthcare system of Catalonia (Spain).

Methods: Multicentre retrospective cohort study of all non-metastatic patients who underwent surgery with a curative intent for primary rectal cancer at Catalonian public hospitals in 2011-2012. We obtained data on vital status for up to five years. To minimise differences between the two groups we performed propensity score matching on baseline patient characteristics. We used multivariate Cox proportional hazards regression analyses to assess locoregional relapse at two years and death at two and five years.

Results: Of 1513 patients with stage I to III rectal cancer, 933 (61.7%) underwent laparoscopy (conversion rate: 13.2%). After applying our propensity score matching strategy (2:1), 842 laparoscopy patients were matched to 517 open surgery patients. Multivariate Cox analysis of death at two years (hazard ratio [HR] 0.65; 95% confidence interval [CI] 0.48, 0.87; p=0.004) and five years (HR 0.61; 95% CI 0.5, 0.75. p <0.001) and of local relapse at two years (HR 0.44; 95% CI 0.27, 0.72; p=0.001) showed laparoscopy to be an independent protective factor compared to open surgery.

Conclusions: Laparoscopy results in lower locoregional relapse and long-term mortality in rectal cancer in real-world conditions with all-risk patient groups included. Studies using long-term follow-up of cohorts and real-world data can provide information on clinically relevant outcomes to supplement randomized controlled trials.

What does this paper add to the literature?

The oncological risk/benefit trade-off for laparoscopy in rectal cancer is controversial. We compare laparoscopic versus open surgery for treating primary rectal cancer, using population-based data plus propensity score analysis to improve comparability. The results provide further evidence in favour of laparoscopy as a standard surgical approach, in real-world conditions.

Introduction

Surgery is the cornerstone therapy for non-metastatic rectal cancer. In the past two decades, substantial improvements in both rectal surgery (standardization of mesorectal excision) and perioperative management (preoperative chemoradiotherapy and postoperative chemotherapy for locally advanced rectal cancer) have contributed to reducing the risk of local recurrence **[**1–3**].** Efforts have also been made to decrease the risk of postoperative morbidity and improve functional outcomes [4,5]. Minimally invasive surgical approaches including laparoscopy have been introduced to further improve surgical management in patients with rectal cancer [6–8]. In this respect, the laparoscopic approach has demonstrated clinically measurable short-term advantages in rectal cancer [9,10]. However, unlike in surgery for colon cancer, there is still controversy regarding the oncological safety of laparoscopy in rectal cancer surgery: while several trials, meta-analyses and observational studies comparing short- and long-term outcomes between laparoscopic and open surgery have supported the oncological safety of a minimally invasive approach in these patients [11–16], one recent systematic review questioned the capacity to achieve a successful resection of rectal cancer [17].

In Catalonia (Spain), the surgical treatment of rectal cancer has been centralized since 2012 in order to improve equitable access to quality multidisciplinary care. The policy of concentrating tertiary surgical activity has been accompanied by regular evaluations of rectal cancer surgery through clinical audits [18]. The 2011–12 clinical audit on rectal cancer included information on laparoscopic surgery.

The aim of the present study was to compare process and outcomes indicators of laparoscopic versus open surgery for surgical treatment of rectal cancer, using real-world data from the public healthcare system of Catalonia at two and five years' follow-up.

Methods

We conducted a multicenter retrospective cohort study of all rectal cancer patients who were surgically treated for the first time with curative intent in public hospitals of Catalonia in 2011 and 2012, followed up until 2017 for five-year survival. We excluded all patients who had a tumor located outside the rectum (> 15 cm from anal margin), patients who had preneoplastic diseases or who did not receive surgery for their primary tumor during the study period. We also excluded patients who underwent surgery with palliative intent and patients with stage IV disease at diagnosis. The methodology used for identifying cases and retrieving data was the same as with the previous audit, involving trained external auditors; the details are described in length elsewhere [19]. The Clinical Research Ethics Committee of Bellvitge University Hospital approved this study.

The main variable of interest in this the study was *surgical approach* (laparoscopic versus open surgery). Comparisons between the two groups followed the intention-to-treat principle by including converted resections in the laparoscopic group [9,15,16]. In order to determine whether conversion was a risk factor, we also performed a subgroup analysis in the conversion group [20].

We collected data on comorbidities from the Catalonian hospital discharge minimum data set from 2003 to date of admission for surgery, adding the information to each patient's records. This data set was processed through the ASEDAT software for cancer registry automation, which allowed data extraction [21]. Excluding all types of solid tumor cancer and metastases, *comorbidities* were categorized according to the number of pathologies affecting the patient at the time of surgery (none, 1, 2+, unknown)[22].

Tumors were classified according to the distance between the tumor and the anal margin and the anatomical extent of the disease (TNM Classification of Malignant Tumors, 7th edition) as recorded in the diagnostic procedures report (*tumor location, cT, cN*). The anatomical pathology report provided data on the pT (TNM 7th edition), the *mesorectal excision* (complete, almost complete or incomplete), the radial margin (positive [≤ 1 mm] or not), and the number of lymph nodes examined.

Time to last follow-up, locoregional recurrence, metastasis and death were assessed from the date of rectal excision. We performed a linkage with the central registry of the insured population of Catalonia in order to update the vital status of all participants up to five years, until February 2017. Locoregional recurrence was defined as any tumor located within the pelvis, either alone or with metastases, and confirmed histologically or by imaging. Systemic recurrence was defined as spread of the disease outside the surgical field to organs such as the liver, lungs, bones or brain.

Statistical analysis

First, we performed a descriptive analysis of the categorical variables using absolute and relative frequencies. Next, we compared the study variables by surgical approach using the Chi-squared test and Student T-test. Death rates were also calculated at five years' follow-up.

Propensity score matching

To minimize baseline differences between the open surgery group and the laparoscopy group, we undertook propensity score matching (PSM)(23), which consists of the estimated probability for a patient to be in the open surgery group based on clinical characteristics. We matched two individuals in the laparoscopic group (laparoscopy + conversion) to each individual in the open surgery group. Confounding variables used to compute the propensity score were sex; age; American Society of Anesthesiologists (ASA) physical status; tumor location; hospital admission; neoadjuvant treatment; multidisciplinary team meeting; comorbidities; and clinical T (cT) and N (cN) staging. The rest of the analysis was performed using the matched patients by surgical approach.

We identified the variables that resulted in group imbalance according to PSM by computing the standardized mean difference (< 0.1), and we included them in the subsequent Cox model as covariates. The proportionality of risks in the Cox models was verified using Schoenfeld residuals (See Supplementary material). Analyses were carried out through the statistical package R (cran.r-project.org).

Results

We included 1513 patients who underwent surgery for stage I to III rectal cancer during the study period. The surgical approach was laparoscopic in 933 (61.7%) patients; in 123 (13.2%) patients, laparoscopic surgery was converted to laparotomy.

Table 1 describes patient characteristics and therapeutic procedures by surgical approach. We first compared patients who underwent open surgery versus laparoscopy (including conversions to open surgery), and we then compared the patients receiving open surgery versus the conversion subgroup alone. Whether the approach was laparoscopic or open was unknown in 39 cases, which we excluded in PSM and consequently for the rest of the statistical analysis. After applying PSM strategy (2:1), 842 laparoscopy and conversion patients were matched to 517 open surgery patients. (See Fig. S1. Density distributions of the two groups [OS vs. LS + CONV] in Supplementary material).

Variables showing group imbalances after PSM were ASA, comorbidities and cN. (See Fig. S2 Standardized mean differences [SMD] between the two compared groups [OS vs. LS + CONV], Supplementary material).

Table 2 presents the type of treatment and pathological results.

Table 3 shows rates of first relapse and crude mortality by surgical approach.

COX models

Multivariate Cox proportional hazards regression analysis, adjusted for ASA, number of comorbidities and cN, revealed laparoscopy to be an independent protective factor for mortality at two years (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.48, 0.87) and five years (HR 0.61, 95% CI 0.50, 0.75) (**Table 4, Fig. 1**) as well as for locoregional relapse at two years (HR 0.44, 95% CI 0.27, 0.72).

Discussion

The present study describes the characteristics of laparoscopic surgery in rectal cancer in Catalonia (Spain) and its benefits for locoregional recurrence and mortality compared to open surgery. To our knowledge, there are few reports of long-term mortality results in laparoscopic surgery for rectal cancer.

With regard to the ongoing debate on the benefits of laparoscopy in rectal cancer beyond the immediate postoperative period (in our study, this technique shortened hospital stay by two days compared with open surgery), our results provide further evidence supporting its use as a standard surgical approach in rectal cancer. We observed a better prognosis in patients who received laparoscopic surgery after adjusting for the main prognostic factors of rectal cancer. In this regard, the European multi-institutional COLOR II and the COREAN randomized controlled trials (RCTs) found an oncological equivalence between laparoscopic and open rectal cancer resection in terms of locoregional recurrence and disease-free survival three years after index surgery [15,16]. However, a subgroup analysis in the COLOR II trial found significantly lower three-year locoregional recurrence in patients with lower rectal cancer undergoing laparoscopic surgery, both in the intention-to-treat and per-protocol analyses, an observation confirmed by our results [16]. Moreover, although the rates of disease-free survival were similar in patients with stage I and II rectal cancer, in patients with stage III disease, the rate of disease-free survival was 64.9% in the laparoscopic surgery group and 52.0% in the open surgery group (difference 12.9 percentage points; 95% CI, 2.2 to 23.6). Lacy et al. reported similar findings in patients who underwent laparoscopic resection of stage III colon cancers [24]. Also, a pooled analysis of 3 RCTs comparing long-term oncological outcomes of laparoscopic versus open surgery for rectal cancer found no differences in locoregional recurrence or overall survival at 10 years. However, there was a trend toward lower recurrence at 10 years in the laparoscopic group compared to the open group in patients with stage III cancer (P=0.078).[25] The results of these analyses suggest that the oncological advantage of laparoscopic surgery may only be evident in studies with a large number of patients operated by experienced surgeons. The centralization of rectal cancer surgery in Catalonia and the implementation of the laparoscopic approach for total mesorectal

excision more than 10 years ago might maximize the potential oncological benefits of minimally invasive surgery, as we have observed in the present population-based study.

In contrast, our results are inconsistent with those reported in the ACOSOG and the ALaCaRT studies, two recent multicenter RCTs that compared laparoscopic versus open surgery in rectal cancer, assessing a composite pathological outcome (quality of the mesorectal specimen, the completeness of tumor-free circumferential, and distal resection margins) [26,27]. Both trials showed a higher success rate for open surgery; nevertheless, the validity of the composite endpoint has not yet been demonstrated, and the trialists did not take the non-inferiority margin into account in the clinical interpretation of their findings. However, no differences for recurrence or overall survival at 2 years have been identified.[28] Furthermore, in the UK MRC CLASICC trial, a slightly higher, but not statistically significant, circumferential resection margin (CRM) positivity did not translate into any detectable difference between laparoscopic and open anal resection in terms of overall survival, disease-free survival, or local recurrence at three-year follow-up [29]. Further analysis confirmed the absence of difference at five years [30]. Moreover, a recent meta-analysis has demonstrated only small differences between the two approaches in terms of the quality of mesorectal excision [31]. In our study the differences detected in the completeness of the excised mesorectum are consistent with those observed in locoregional recurrence rates at two years. However, some caution is warranted when interpreting this result, as 14% of the values were missing. As in the COLOR II trial, we did not identify statistically significant differences in CRM involvement. In a recently published study, open surgery was found to be a risk factor for positive CRM, in contrast with the ALACART and ACOSOG results [32].

The lower local recurrence and long-term mortality in patients undergoing laparoscopic rectal excision cannot be explained by differences in the quality of surgery because early pathological outcomes were similar between groups. It is well known that open surgery leads to a greater inflammatory response than laparoscopy, and amplification of postoperative inflammation has been associated with poor outcomes after curative resection in patients with colorectal cancer [33]. Although no causal relationship has been

definitively established, several preclinical and clinical studies have provided direct evidence supporting that soluble factors released by the inflammatory response might facilitate the survival and growth of residual tumor cells in their path to recurrence. It is plausible that a combination of mechanisms such as increased angiogenesis [34], impaired immune function [35], and induction of an epithelial-to-mesenchymal transition traits [36] as a result of surgery-induced inflammation might be responsible for the differences observed in the long-term outcomes between open and laparoscopic surgery.

Regarding population-based studies, Kolfschoten et al. compared laparoscopic and open surgery in 7350 patients with colorectal cancer, observing a significantly lower risk of in-hospital mortality, major morbidity, prolonged hospital stay and no radical resection in the laparoscopic surgery group [9]. To our knowledge there are only two other published population-based studies on the same topic with long follow-up.[12,13] Both obtained better long-term results in the laparoscopic group compared to the open surgery group. In a population-based study from New South Wales (Australia) including 6970 surgical procedures, with a median follow-up of 6 years, Dobbins et al. reported that those in the laparoscopic group had better cancer-specific survival outcomes that the open surgery group (5-year mortality rate 27.3 vs 29.3; adjusted HR 0.71, 95% CI 0.51, 1.00). [12] Draeger et al. also analyzed the long-term results of a population-based study in rectal cancer patients treated with open surgery versus laparoscopy in a southern German region (n= 1507).[13] After 5 years, 80.4% of laparoscopy patients were still alive compared to 68.6% in the open surgery group ($p<0.001$). Laparoscopy was also associated with better local recurrence-free survival in the multivariable analysis, which is consistent with our results. Regarding overall survival, however, evidence of a benefit was weak in the multivariate model (HR 0.77, 95% CI 0.58, 1.02; $p=0.073$).

The advantage of population-based studies and their 'real-world data' is that all risk groups are included. The benefits of laparoscopy over open surgery for patient outcomes in both the present paper and in previous population-based studies might be explained by a stronger effect for laparoscopy in high-risk patients compared to the low-risk patients selected for RCTs. McCloskey et al. already proposed this explanation in their case-matched cohort study on laparoscopic versus open colectomy in high-risk veteran

patients, reporting the safety of laparoscopy despite the common perception that laparoscopy was contraindicated in this group [37]. Something similar could have happened in Catalonia with rectal cancer, since we observed some level of selection bias favoring low-risk patients for laparoscopic surgery: this group was more likely to be younger than 80 years, have fewer comorbidities, present a lower ASA and be diagnosed at an earlier disease stage.

Regarding the conversion rate observed in the present study (13.2%), it is very similar to that obtained in the population-based study by Neree et al. [20] and the meta-analysis by Arezzo et al.[11], and it is lower than the one reported in a Spanish prospective non-randomized study.[38] Compared to open surgery, our results did not show any association between conversion and mortality or recurrence (see results in the annex), in line with the results published by Neree et al.[20]

As expected, our data do not show any impact on metastasis, which is consistent with the purpose of surgery and its role in multidisciplinary treatment.

Postoperative morbidity in our study was significantly lower in the patients undergoing laparoscopy, which is in line with results reported elsewhere [9,11]. However, minimally invasive surgery was associated with a higher proportion of intra-abdominal infectious complications and reintervention. Readers should consider the possible variability in recording this complication in the clinical history and in defining intra-abdominal infection. In fact, previous research has already described inconsistent reporting of postoperative adverse events, limiting accurate comparison of rates over time and between institutions [39]. With regard to reinterventions, it is unlikely that these were caused by serious, life-threatening complications, since the mortality rate at one month after surgery in the laparoscopy group is less than half that of the open surgery group. In this sense, research has shown that the negative impact on long-term outcome is primarily driven by severe postoperative infections.[40]

The reason for selecting 2011 and 2012 as the study period was to enable the assessment of mortality at five years. However, it is worth underlining that this period fell during the initial implementation of the health policy centralizing highly specialized oncological treatments. This policy was a response to the

variability observed in the process and outcomes indicators in a clinical audit of all patients with rectal cancer operated in the Catalonian public system; centers that performed fewer than 11 operations annually obtained worse clinical results compared to those that handled more than 30 cases every year [19]. The patients included in our study were operated mostly in centers authorized to perform curative surgery for rectal cancer, fulfilling criteria of minimum volume and adequate quality.

Strengths of our study include having examined a large population-based cohort of rectal cancer patients and being based on an external audit by trained data managers, but it is also subject to some limitations. Firstly, the study is restricted to the public system. That said, the Spanish national healthcare system handles more than 85% of the patients undergoing rectal cancer surgery in Catalonia, which indicates both the high coverage of our study and the representativeness of the quality of the procedure among the study population. Another limitation is the study's retrospective nature. We addressed this aspect by equipping a trained team of professionals with purpose-designed instruments to ensure highly accurate data collection from patients' medical charts. Furthermore, hospital results were individually presented to the respective participant hospitals, prompting the feedback necessary to validate our results. In brief, data collection and assessment involved all the participating hospitals and relevant professionals in order to ensure that the data were a true reflection of clinical practice in the study period. Another potential limitation was that the follow-up of locoregional recurrence was just two years; however, this is the interval when more than 70% of recurrences appear [41], and the better five-year survival results in the laparoscopy group should support a lower locoregional recurrence rate beyond two years in this group. With regard to PSM, this method matches only the variables introduced, that is, it reduces the selection bias for these variables. However, there may be residual selection bias related to variables that were not included in the PSM, such as those that were not available because they were not collected. In our case, the PSM included the variables we believe are the most significant before surgery: sex; age; ASA physical status; tumor location; hospital admission; neoadjuvant treatment; multidisciplinary team meeting; number of comorbidities; and cT and cN staging. Variables showing group imbalances after PSM (ASA, number of comorbidities and cN) were included in the multivariate Cox proportional hazards regression analysis for adjustment. Lastly, we

cannot rule out the possibility that the differences observed between laparoscopy and open surgery are related to the expertise of the surgeon, not just the surgical technique or the patient selection criteria. However, we did not collect data by the individual surgeon but only by hospital. Further research on this point is ongoing.

The years in which the study took place do not correspond to an introductory period for laparoscopic surgery in rectal cancer in the region, since more than half of the stage I–III patients (61.7%) in the public network were already being operated with this approach. Rather, the study period fell during a transitional phase between the introduction of the technique and its widespread adoption as a standard technique. In this sense, a recent population-based study in the Netherlands saw a dramatic rise in the use of laparoscopy in rectal cancer: from 49% to 89% between 2011 and 2015, which is a higher increase than that seen in colon cancer. It is likely that this minimally invasive technique has now also been standardized in Catalonia.

Conclusion

In real-world conditions with all risk groups, laparoscopy shows lower risk for locoregional recurrence and long-term mortality than open surgery.

Studies using long-term follow-up of cohorts and real-world data can provide information on clinically relevant outcomes to supplement randomized controlled trials.

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Tables

Table 1. Baseline characteristics by surgical approach (overall series and propensity-core matching)

	Overall series						Propensity-score matched pairs	
	LS + CONV (n=933)	Open surgery (n=541)	CONV (n=123)	Unknown (n=39)	p[a,b]	p[c,b]	LS + CONV (n=842)	Open surgery (n=517)
Sex								
Male	601 (64.4)	348 (64.3)	87 (70.7)	25 (64.1)	0.972	0.177	551 (65.4)	333 (64.4)
Female	332 (35.6)	193 (35.7)	36 (29.3)	14 (35.9)			291 (34.6)	184 (35.6)
Age (years)*	68.4 (11.3)	69.9 (11.5)	68.7 (11.1)	69.8 (11.7)	0.011[d]	0.284[d]	69.2 (11.0)	69.8 (11.5)
Age								
≤ 60	246 (26.4)	121 (22.4)	30 (24.4)	11 (28.2)	0.054	0.329	202 (24.0)	118 (22.8)
61 - 70	262 (28.1)	148 (27.4)	42 (34.1)	11 (28.2)			236 (28.0)	142 (27.5)
71 - 80	305 (32.)	175 (32.3)	32 (26.0)	6 (15.4)			287 (34.1)	165 (31.9)
> 80	118 (12.6)	97 (17.9)	19 (15.4)	11 (28.2)			117 (13.9)	92 (17.8)
Unknown	2 (0.21)	0	0	0				
ASA								
ASA I	65 (7)	18 (3.3)	10 (8.1)	0	<0.001	0.011	25 (3.0)	18 (3.5)
ASA II	515 (55.2)	245 (45.3)	68 (55.3)	18 (46.2)			472 (56.0)	237 (45.8)
ASA III	265 (28.4)	213 (39.4)	37 (30.1)	13 (33.3)			264 (31.4)	201 (38.9)
ASA IV	17 (1.8)	25 (4.6)	2 (1.6)	1 (2.6)			17 (2.0)	24 (4.6)
Unknown	71 (7.6)	40 (7.4)	6 (4.9)	7 (17.9)			64 (7.6)	37 (7.2)
Tumor location								
Distal rectum (0 - 6 cm)	322 (34.5)	167 (30.9)	39 (31.7)	13 (33.3)	0.258	0.051	277 (32.9)	161 (31.1)
Middle rectum (7 - 11 cm)	398 (42.7)	253 (46.8)	45 (36.6)	18 (46.2)			378 (44.9)	243 (47.0)
Proximal rectum (12 - 15 cm)	213 (22.8)	121 (22.4)	39 (31.7)	8 (20.5)			187 (22.2)	113 (21.9)
Hospital admission								
Emergency department	8 (0.9)	29 (5.4)	1 (0.8)	1 (2.6)	<0.001	0.028	8 (1.0)	9 (1.7)
Scheduled	925 (99.1)	512 (94.6)	122 (99.2)	38 (97.4)			834 (99.0)	508 (98.3)
Neoadjuvant treatment								
Yes	585 (62.7)	320 (59.1)	69 (56.1)	22 (56.4)	0.177	0.535	524 (62.2)	310 (60.0)
No	348 (37.3)	221 (40.9)	54 (43.9)	17 (43.6)			318 (37.8)	207 (40.0)
MDT meeting								
Yes	579 (62.1)	376 (69.5)	93 (75.6)	19 (48.7)	<0.001	0.179	284 (33.7)	161 (31.1)
No	354 (37.9)	165 (30.5)	30 (24.4)	20 (51.3)			558 (66.3)	356 (68.9)
Number of comorbidities								
0 pathologies	551 (59.1)	271 (50.1)	70 (56.9)	24 (61.5)	0.001	0.042	471 (55.9)	256 (49.5)
1 pathologies	237 (25.4)	143 (26.4)	36 (29.3)	12 (30.8)			229 (27.2)	139 (26.9)
2+ pathologies	123 (13.2)	107 (19.8)	11 (8.9)	3 (7.7)			122 (14.5)	102 (19.7)
Unknown	22 (2.3)	20 (3.7)	6 (4.9)	0			20 (2.4)	20 (3.9)
cT								
T0/TiS/T1	20 (2.1)	11 (2.0)	2 (1.6)	1 (2.6)	0.142	0.228	19 (2.26)	11 (2.13)
T2	156 (16.7)	100 (18.5)	19 (15.4)	5 (12.8)			148 (17.6)	97 (18.8)
T3	580 (62.2)	319 (59.0)	67 (54.5)	25 (64.1)			516 (61.3)	308 (59.6)
T4	107 (11.5)	70 (12.9)	18 (14.6)	6 (15.4)			100 (11.9)	64 (12.4)
TX	70 (7.5)	41 (7.6)	17 (13.8)	2 (5.1)			59 (7.01)	37 (7.16)
cN								
N0	307 (32.9)	181 (33.5)	42 (34.1)	9 (23.1)	0.002	0.010	282 (33.5)	174 (33.7)
N1	329 (35.3)	152 (28.1)	39 (31.7)	14 (35.9)			281 (33.4)	149 (28.8)
N2	163 (17.5)	127 (23.5)	17 (13.8)	14 (35.9)			161 (19.1)	119 (23.0)

N+	40 (4.3)	30 (5.5)	3 (2.4)	0	37 (4.4)	28 (5.4)
NX	94 (10.1)	51 (9.4)	22 (17.9)	2 (5.1)	81 (9.6)	47 (9.1)

ASA: American Society of Anesthesiologists physical status; CONV: conversion; LS: laparoscopy; MDT: multidisciplinary team; cT; cN (TNM 7th ed.)

Values in parentheses are percentages; values are *mean(SD).

[a] Comparisons between LS+CONV versus Open Surgery.
[b] χ^2 test
[c] Comparisons between CONV versus Open surgery
[d] T-test

p-values below 0.05 (two-sided) were considered to indicate statistical significance

Table 2. Type of treatment received, pathologic results and postoperative variables by surgical approach (Propensity score matching (2:1))

		LS + CONV (n=842)	Open surgery (n=517)	Total (n=1359)	P[a]
Hospital stay (days)*		11.4 (13.8)	13.3 (11.6)	12.1 (13.0)	0.008[b]
Type of operation	Anterior resection	620 (73.6)	381 (73.7)	1001 (73.7)	0.023
	Abdominoperineal resection	203 (24.1)	111 (21.5)	314 (23.1)	
	Hartmann´s procedure	19 (2.2)	25 (4.8)	44 (3.2)	
Radicality	R0	295 (35.0)	142 (27.5)	437 (32.2)	0.011
	R1	10 (1.2)	12 (2.3)	22 (1.6)	
	R2	4 (0.5)	4 (0.8)	8 (0.6)	
	Unknown	533 (63.3)	359 (69.4)	892 (65.6)	
Quality of mesorectal excision (pathology report)	M. complete	590 (70.1)	351 (67.9)	941 (69.2)	0.012
	M. nearly complete	71 (8.4)	29 (5.6)	100 (7.4)	
	M. incomplete	83 (9.9)	48 (9.3)	131 (9.6)	
	Unknown	98 (11.6)	89 (17.2)	187 (13.8)	
pT	pTis, pT0, pT1	162 (19.2)	84 (16.2)	246 (18.1)	0.006
	pT2	232 (27.6)	146 (28.2)	378 (27.8)	
	pT3	386 (45.9)	218 (42.2)	604 (44.4)	
	pT4	50 (5.9)	57 (11.0)	107 (7.9)	
	pTX	12 (1.4)	12 (2.3)	24 (1.8)	
Circumferential resection margin (pathology report)	Negative	758 (90.0)	456 (88.2)	1214 (89.3)	0.266
	Positive	45 (5.3)	39 (7.5)	84 (6.2)	
	Not assessed	19 (2.3)	14 (2.7)	33 (2.4)	
	Unknown	20 (2.4)	8 (1.5)	28 (2.1)	
Distal margin (pathology report)	Negative	808 (96.0)	492 (95.2)	1300 (95.7)	0.863
	Positive	17 (2.0)	13 (2.5)	30 (2.2)	
	Not assessed	11 (1.3)	7 (1.3)	18 (1.3)	
	Unknown	6 (0.7)	5 (1.0)	11 (0.8)	
Proximal margin (pathology report)	Negative	815 (96.8)	503 (97.3)	1318 (97.0)	0.594
	Positive	1 (0.1)	2 (0.4)	3 (0.2)	
	Not assessed	17 (2.0)	7 (1.3)	24 (1.8)	
	Unknown	9 (1.1)	5 (1.0)	14 (1.0)	
Lymph nodes examined (pathology report)	<12	298 (35.4)	177 (34.2)	475 (35.0)	0.894
	≥12	523 (62.1)	326 (63.1)	849 (62.5)	
	Unknown	21 (2.5)	14 (2.7)	35 (2.5)	
Postoperative complication	None	506 (60.1)	299 (57.8)	805 (59.2)	0.042
	Intra-abdominal infectious complication	110 (13.1)	51 (9.9)	161 (11.9)	
	No Intra-abdominal infectious complication	226 (26.8)	167 (32.3)	393 (28.9)	
Reintervention	Yes	87 (10.3)	35 (6.8)	122 (9.0)	0.033
	No	755 (89.7)	482 (93.2)	1237 (91.0)	

Values in parentheses are percentages; values are *mean(SD).

[a] χ^2 test

[b] T-Test

Table 3. Comparison of first relapse and mortality crude rates by procedure.

	Total (n=1359)	LS + CONV (n=842)	Open surgery (n=517)	*P*[a]
Mortality at 1 month, No. (%)	28 (2.1)	11 (1.3)	17 (3.3)	0.022
Mortality at 3 months, No. (%)	39 (2.9)	15 (1.8)	24 (4.6)	0.004
Mortality at 2 years, No. (%)	181 (13.3)	91 (10.8)	90 (17.4)	0.001
Mortality at 5 years, No. (%)	373 (27.4)	191 (22.7)	182 (35.2)	<0.001
LR relapse at 2 years, No. (%)	67 (4.93)	29 (3.44)	38 (7.35)	0.002
MTS at 2 years, No. (%)	122 (8.98)	84 (9.98)	38 (7.35)	0.122

Abbreviations: CONV: converted laparoscopy; LS: laparoscopy; LR: locoregional relapse ± synchronic metastasis ; MTS: Metastasis
a $\chi 2$ test

Table 4. Multivariate Cox regression analysis of laparoscopy (LS+CONV) in rectal cancer surgery

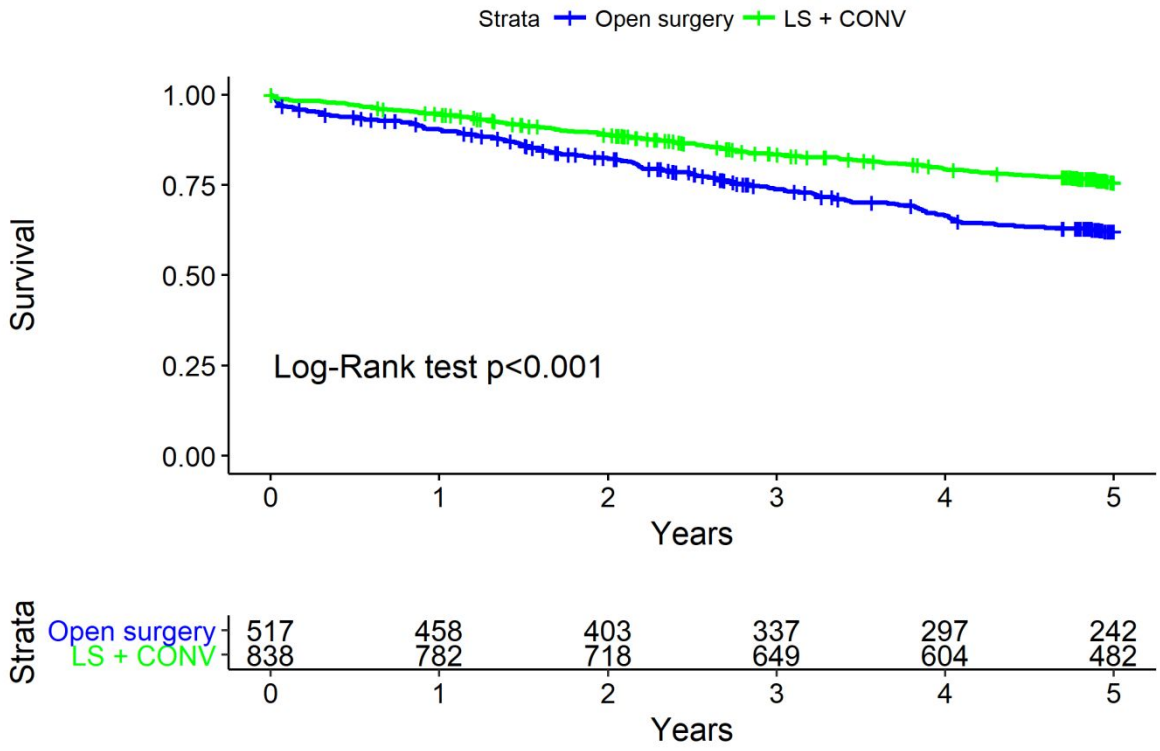
	Overall series				Propensity-score matched pairs			
	Crude model		Adjusted model[a]		Crude model		Adjusted model[a]	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Mortality at 2 years	0.52 (0.40 , 0.70)	<0.001	0.61 (0.46 , 0.82)	0.001	0.60 (0.44 , 0.80)	<0.001	0.65 (0.48 , 0.87)	0.004
Mortality at 5 years	0.54 (0.44 , 0.66)	<0.001	0.60 (0.49 , 0.73)	<0.001	0.58 (0.47 , 0.71)	<0.001	0.61 (0.5 , 0.75)	<0.00
LR relapse at 2 years	0.40 (0.25 , 0.64)	<0.001	0.43 (0.27 , 0.70)	0.001	0.44 (0.27 , 0.72)	0.001	0.44 (0.27 , 0.72)	0.001
MTS at 2 years	1.29 (0.89 , 1.86)	0.179	1.18 (0.81 , 1.72)	0.402	1.28 (0.87 , 1.88)	0.202	1.25 (0.85 , 1.84)	0.263

Abbreviations: CI: confidence interval; LR: locoregional relapse ± synchronic metastasis ; MTS: Metastasis

[a] Adjusted model by ASA, Number of comorbidities and cN

Reference value: open surgery

Figure 1. Overall survival by surgical procedure



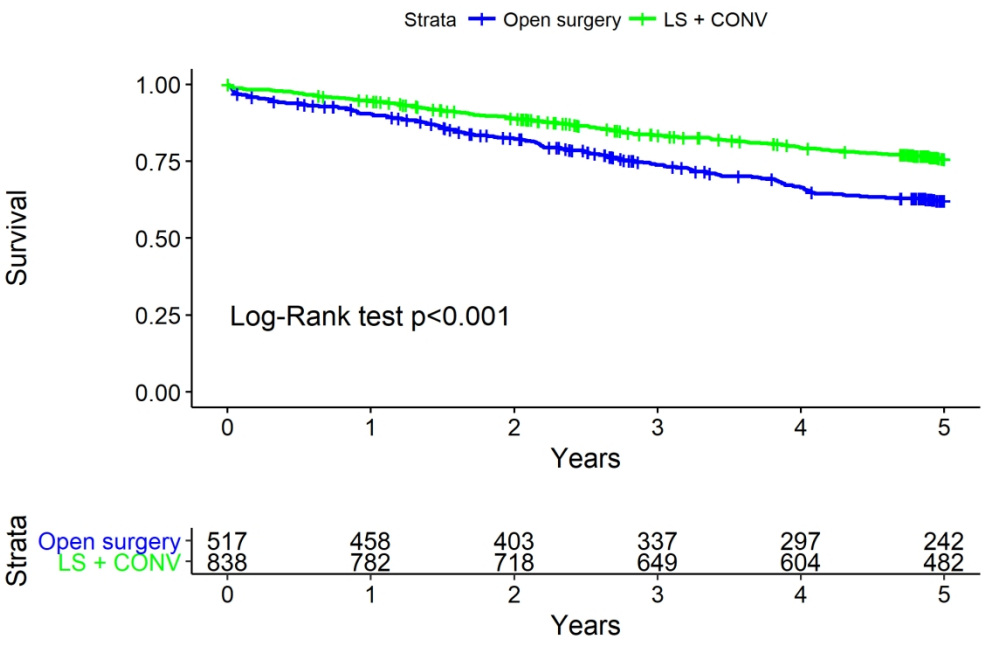


Figure 1. Overall survival by surgical procedure

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Supplementary material

Statistical analyses: Verification of proportionality of risks in COX models

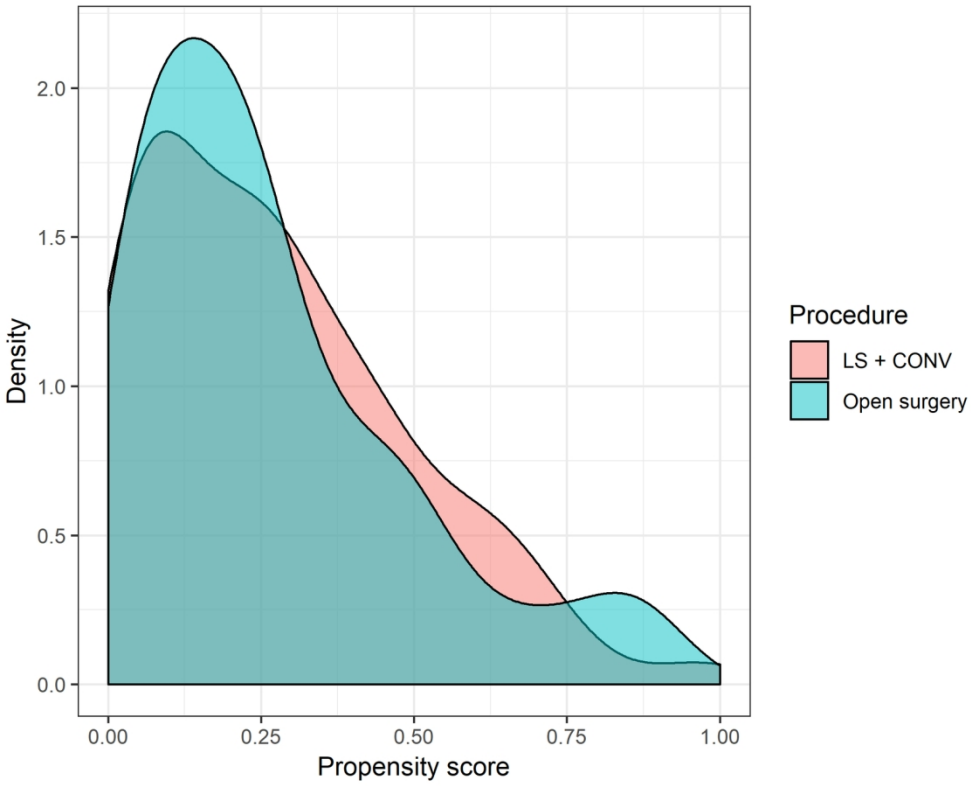
For the crude models, the test of the proportional hazards assumptions for the *surgical approach* variable yielded a chi-square value of 0.48 and a p-value of 0.488 for death at two years, a chi-square value of 0.033 and a p-value of 0.857 for death at five years, and a chi-square value of 2.048 and a p-value of 0.152 for locoregional recurrence at two years. Thus, we can assume a proportional hazards scenario in each case. For the adjusted models, the test of proportional hazards assumptions for the variable *surgical approach* yielded a chi-square value of 0.079 and a p-value of 0.779 for death at two years, a chi-square value of 0.048 and a p-value of 0.827 for death at five years, and a chi-square value of 1.706 and a p-value of 0.191 for locoregional recurrence at two years. Again, we can also assume a proportional hazards scenario in each case.

Figure S1. Density distributions of PSM

In figure S1 we can observe the density distributions of the two groups: there is a good overlap between the propensity scores of the two groups, showing that most patients can be matched. In fact, only 24 cases in the open surgery group could not be matched.

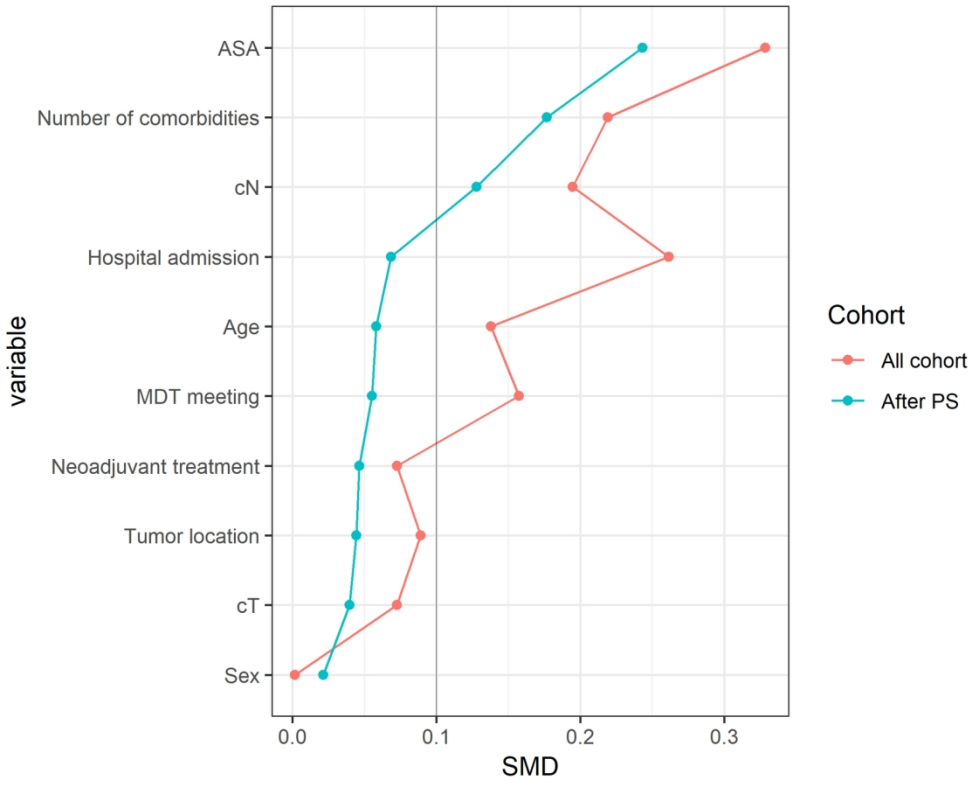
Figure S2. Standardized mean differences between open surgery and laparoscopic surgery in the whole series and after PSM.

In Figure S2 we can observe standardized mean differences (SMD) between the two compared groups (OS ; LS + CONV) with the overall series (red line) and after the PSM (blue line): imbalance has been reduced in all variables achieving an SMD of 0 to 0.1 except for the variables ASA, number of comorbidities, and cN, which still show imbalance. These three variables have been included in the multivariate Cox proportional hazards regression analysis for adjustment.



Supplementary material Figure S1. Density distributions of PSM

149x119mm (300 x 300 DPI)



Supplementary material Figure S2. Standardized mean differences between open surgery and laparoscopic surgery in the whole series and after PSM.

149x119mm (300 x 300 DPI)

	Item No	Recommendation		Page location	Comments
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Fulfilled	1-2	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Fulfilled	2	
Introduction					
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Fulfilled	3	
Objectives	3	State specific objectives, including any prespecified hypotheses	Fulfilled	4	
Methods					
Study design	4	Present key elements of study design early in the paper	Fulfilled	5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Fulfilled	5-6	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Fulfilled	5-6	
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Fulfilled	6-7	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Fulfilled	5-7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Fulfilled	5	
Bias	9	Describe any efforts to address potential sources of bias	Fulfilled	5	
Study size	10	Explain how the study size was arrived at	Fulfilled	5	This is a population-based study: "multicenter retrospective cohort study of **all** rectal cancer patients who were surgically treated for the first time with curative intent in public hospitals of Catalonia in 2011 and 2012"
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Fulfilled	5	. "The main variable of interest in this the study was surgical approach (laparoscopic versus open surgery). Comparisons between the two groups followed the intention-to-treat principle by including converted resections in the laparoscopic group[9,13,14] " . "The methodology used for identifying cases and retrieving data was the same as with the previous audit, involving trained external auditors; the details are described in length elsewhere [17] "
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Fulfilled	6-7	
		(*b*) Describe any methods used to examine subgroups and interactions	Fulfilled	6-7	
		(*c*) Explain how missing data were addressed	Fulfilled	8	Whether the approach was laparoscopic or open was unknown in 39 cases, which we excluded in PSM and consequently for the rest of the statistical
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable		
		(*e*) Describe any sensitivity analyses	Not applicable		
Results					
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fulfilled	8	
		(b) Give reasons for non-participation at each stage	Not applicable		
		(c) Consider use of a flow diagram	Not applicable		It does not seem necessary as numbers of individuals are clearly reported at each stage
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Fulfilled	Table 1	
		(b) Indicate number of participants with missing data for each variable of interest	Fulfilled	Table 1	
		(c) Summarise follow-up time (eg, average and total amount)	Fulfilled	Fig 1	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Fulfilled	Fig 1	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Fulfilled	Table 4	
		(*b*) Report category boundaries when continuous variables were categorized	Fulfilled	Table 1	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Fulfilled	Table 3 and table 4	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Fulfilled	9	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Fulfilled	9-10, 12-13	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Fulfilled	9-15	
Generalisability	21	Discuss the generalisability (external validity) of the study results	Fulfilled	13-15	
Other information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Fulfilled	1	