A propensity-score-matched analysis of laparoscopic vs 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 vs open surgery for resection of rectal cancer, using unselected data from the public healthcare system of Catalonia (Spain).

**Methods** This was a multicentre retrospective cohort study of all patients who had surgery with curative intent for primary rectal cancer at Catalanian public hospitals from 2011 to 2012. We obtained follow-up data for up to 5 years. To minimize the 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 2 years and death at 2 and 5 years.

**Results** Of 1513 patients with Stage I–III rectal cancer, 933 (61.7%) had 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 2 years [hazard ratio (HR) 0.65, 95% CI 0.48, 0.87; \( P = 0.004 \)] and 5 years (HR 0.61, 95% CI 0.5, 0.75; \( P < 0.001 \)) and of local relapse at 2 years (HR 0.44, 95% CI 0.27, 0.72; \( P = 0.001 \)) showed laparoscopy to be an independent protective factor compared with open surgery.

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

**Keywords** Rectal cancer, laparoscopy, population-based, propensity-score analysis, surgery

**What does this paper add to the literature?** The oncological risk/benefit trade-off for laparoscopy in rectal cancer is controversial. We compare laparoscopic vs 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.

Introduction

Surgery is the main treatment 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 further to improve surgical management in patients with rectal cancer [6–8]. 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 2011–2012 clinical cohort with rectal cancer included information on laparoscopic surgery.

The aim of the present study was to compare process and outcome indicators of laparoscopic vs open surgery for surgical treatment of rectal cancer, using unselected data from the public healthcare system of Catalonia at 2 and 5 years after surgery.

**Method**

We conducted a multicentre retrospective cohort study of all initial presentations of rectal cancer patients who were treated surgically with curative intent in the public hospitals of Catalonia in 2011 and 2012, and followed up until 2017 to measure 5-year survival. We excluded all patients who had a tumour located outside the rectum (>15 cm from the anal margin), patients who had premalignant disease and patients who did not receive surgery for their primary tumour during the study period. We also excluded patients who had 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 a previous audit, involving trained external auditors; the methods are described in detail elsewhere [19]. The Clinical Research Ethics Committee of Bellvitge University Hospital approved this study.

The main variable in the study was the surgical approach (laparoscopic vs open surgery). Comparisons between the two groups followed the intention-to-treat principle by including converted cases 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 Catalan hospital discharge minimum dataset from 2003 to date of admission for surgery, adding the information to each patient’s records. This dataset was processed through the ASEDAT software for cancer registry automation, which allowed data extraction [21]. Excluding all types of solid tumours and metastases, comorbidities were categorized according to the number of conditions affecting the patient at the time of surgery (none, 1, 2+, unknown) [22].

Tumours were classified according to the distance between the tumour 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 (tumour 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 5 years, until February 2017. Locoregional recurrence was defined as any tumour located within the pelvis, either in isolation 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’s t test. Death rates were calculated at 5-year 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; tumour location; hospital admission; neoadjuvant treatment; multidisciplinary team meeting; comorbidities; and clinical T (cT) and N (cN) staging. The rest of the analysis was

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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. Analyses were carried out through the statistical package R (cran.r-project.org).

Results
We included 1513 patients who had surgery for Stage I–III rectal cancer during the study period. The surgical approach was laparoscopic in 938 (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 had open surgery with laparoscopy (including conversions to open surgery), and we then compared the patients receiving open surgery with the conversion subgroup alone. The approach was unknown in 39 cases, which we excluded in PSM and subsequently for the rest of the statistical analysis. After applying the PSM strategy (2:1), 842 laparoscopy and conversion patients were matched to 517 open surgery patients (Fig. S1). Variables showing group imbalance after PSM were ASA, comorbidities and cN (Fig. S2).

The type of treatment and pathological results are shown in Table 2. The rates of first relapse and crude mortality by surgical approach are shown in Table 3.

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 2 years [hazard ratio (HR) 0.65, 95% CI 0.48, 0.87] and 5 years (HR 0.61, 95% CI 0.50, 0.75; Table 2) as well as for locoregional relapse at 2 years (HR 0.44, 95% CI 0.27, 0.72).

Discussion
This study describes the characteristics of laparoscopic surgery in rectal cancer in Catalonia (Spain) and its benefits for locoregional recurrence and mortality compared with open surgery. There are few other 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 2 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. 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 3 years after index surgery [15,16]. However, a subgroup analysis in the COLOR II trial found significantly lower 3-year locoregional recurrence in patients with low 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 of 12.9 percentage points; 95% CI 2.2, 23.6). Lacy et al. [24] reported similar findings in patients who underwent laparoscopic resection of Stage III colon cancers.

A pooled analysis of three RCTs comparing long-term oncological outcomes of laparoscopic vs open surgery for rectal cancer found no difference 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 with 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 this population-based study.

In contrast, our results are inconsistent with those reported in the ACOSOG and the ALaCaRT studies, two recent multicentre RCTs that compared laparoscopic with open surgery in rectal cancer, assessing a composite pathological outcome (quality of the mesorectal specimen, the completeness of tumour-free circumferential and distal resection margins) [26,27]. Both trials showed a higher success rate for open surgery; nevertheless, the validity of the composite end-
Table 1 Baseline characteristics by surgical approach (overall series and propensity score matching).

|                          | Overall series | Propensity-score-matched pairs |
|--------------------------|----------------|-------------------------------|
|                          | LS + CONV      | Open surgery                  | CONV                      | Unknown                  | LS + CONV      | Open surgery                  |
|                          | (n = 933)      | (n = 541)                     | (n = 123)                 | (n = 39)                 | (n = 842)      | (n = 517)                     |
|                          |                |                               |                           |                          |                |                               |
| Sex                      |                |                               |                           |                          |                |                               |
| Male                     | 601 (64.4)     | 348 (64.3)                    | 87 (70.7)                 | 25 (64.1)                | 0.972          | 0.177                         |
| 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)              | 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                         |
| 61–70                    | 262 (28.1)     | 148 (27.4)                    | 42 (34.1)                 | 11 (28.2)                | 236 (28.0)     | 142 (27.5)                    |
| 71–80                    | 305 (32.1)     | 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                        | 2 (0.21)       | 0                             |
| ASA                      |                |                               |                           |                          |                |                               |
| ASA I                    | 65 (7)         | 18 (3.3)                      | 10 (8.1)                  | 0                        | < 0.001        | 0.011                         |
| 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 (1.9)                  | 64 (7.6)       | 37 (7.2)                      |
| Tumour location          |                |                               |                           |                          |                |                               |
| Distal rectum (0–6 cm)   | 322 (34.5)     | 167 (30.9)                    | 39 (31.7)                 | 13 (33.3)                | 0.258          | 0.051                         |
| 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                         |
| 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                         |
| 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                         |
| 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                         |
| 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                         |
| 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                         |
| 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)                    |
point has not yet been demonstrated, and the trialists did not take the non-inferiority margin into account in the clinical interpretation of their findings. No differences for recurrence or overall survival at 2 years have been identified [28].

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 rectal resection in terms of overall survival, disease-free survival or local recurrence at 3-year follow-up [29]. Further analysis confirmed the absence of difference at 5 years [30]. 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 2 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 CRMs, in contrast to 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 the 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 definitively been established, several preclinical and clinical studies have provided supporting evidence that soluble factors released by the inflammatory response might facilitate the survival and growth of residual tumour cells in their course 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 trait [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. [9] 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 non-radical resection in the laparoscopic surgery group. To our knowledge, there are only two other published population-based studies on the same topic with long-term follow-up [12,13]. Both obtained better long-term results in the laparoscopic group compared with 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. [12] reported that those in the laparoscopic group had better cancer-specific survival outcomes than the open surgery group (5-year mortality rate 27.3 vs 29.3; adjusted HR 0.71, 95% CI 0.51, 1.00). Draeger et al. [13] also analysed the long-term results of a population-based study in rectal cancer patients treated with open surgery vs laparoscopy in a southern German region (n = 1507). After 5 years, 80.4% of laparoscopy patients were still alive compared with 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.
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

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

|                      | LS + CONV (n = 842) | Open surgery (n = 517) | Total (n = 1359) | \( P^\dagger \) |
|----------------------|---------------------|------------------------|------------------|----------------|
| Hospital stay (days)*| 11.4 (13.8)         | 13.3 (11.6)            | 12.1 (13.0)      | **0.008**\‡ |
| 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)         |                |
| Quality of mesorectal excision (pathology report) | | | | |
| Complete             | 590 (70.1)          | 351 (67.9)             | 941 (69.2)       | 0.012          |
| Nearly complete      | 71 (8.4)            | 29 (5.6)               | 100 (7.4)        |                |
| 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          |
| \( \geq 12 \)        | 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. *Mean (SD).
\( \dagger \) \( \chi^2 \) test.
\( \ddagger \) \( t \) test.
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 with the low-risk patients selected for RCTs. McCloskey et al. [37] proposed this explanation in their case-matched cohort study on laparoscopic vs open colectomy in high-risk veteran patients, reporting the safety of laparoscopy, despite the common perception that laparoscopy is contraindicated in this group. A similar process could have occurred in Catalonia with rectal cancer, since we observed some selection bias favouring 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.

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

As expected, our data do not show any impact on metastases, which is consistent with curative surgery and its role in multidisciplinary treatment.

Postoperative morbidity in our study was significantly lower in the patients receiving 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. There may be variability in recording this complication and in defining intra-abdominal infection. Previous research has 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

| Table 3 Comparison of first relapse and mortality crude rates by procedure. |
|---------------------------------------------------------------|
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| **Table 3** Comparison of first relapse and mortality crude rates by procedure. |
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| **Table 4 Multivariate Cox regression analysis of laparoscopy (LS+CONV) in rectal cancer surgery.** |
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|                                                                 |
| **Table 4 Multivariate Cox regression analysis of laparoscopy (LS+CONV) in rectal cancer surgery.** |
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|                                                                 |
| CI, confidence interval; LR, locoregional relapse ± synchronic metastasis; MTS, metastasis. Reference value: open surgery. |
|                                                                 |
| *Adjusted model by ASA, number of comorbidities and cN. |
|                                                                 |
|                                                                 |
| 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 with the low-risk patients selected for RCTs. McCloskey et al. [37] proposed this explanation in their case-matched cohort study on laparoscopic vs open colectomy in high-risk veteran patients, reporting the safety of laparoscopy, despite the common perception that laparoscopy is contraindicated in this group. A similar process could have occurred in Catalonia with rectal cancer, since we observed some selection bias favouring 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. The conversion rate observed in the present study (13.2%) is similar to that seen in the population-based study by de Neree et al. [20] and the meta-analysis by Arezzo et al. [11], and it is lower than that reported in a Spanish prospective non-randomized study [38]. Compared with open surgery, our results did not show any association between conversion and mortality or recurrence, in line with the results published by de Neree et al. [20]. As expected, our data do not show any impact on metastases, which is consistent with curative surgery and its role in multidisciplinary treatment. Postoperative morbidity in our study was significantly lower in the patients receiving 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. There may be variability in recording this complication and in defining intra-abdominal infection. Previous research has 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 1 month after surgery in the laparoscopy group is less than half that of the open surgery group. It is likely that the negative impact on long-term outcome is driven primarily by severe postoperative infections [40].

The reason for selecting 2011 and 2012 as the study period was to enable the assessment of mortality at 5 years. However, it is worth noting that this period was 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 outcome indicators in a clinical audit of all patients with rectal cancer treated in the Catalonian public system; centres that performed fewer than 11 operations annually obtained worse clinical results compared with those that handled more than 30 cases per annum [19]. The patients included in our study were operated mostly in centres authorized to perform curative surgery for rectal cancer, fulfilling the criteria of minimum volume and adequate quality.

The strengths of our study include a large population-based cohort of rectal cancer patients and an external audit by trained data managers, but it also has some limitations. First, 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 amongst the study population. Another limitation is that it is retrospective. We addressed this 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. Another potential limitation was that the follow-up of locoregional recurrence was just 2 years; however, more than 70% of recurrences appear during this time [41], and the better 5-year survival results in the laparoscopy group support a lower locoregional recurrence rate beyond 2 years.

With regard to PSM, this method matches only the variables introduced — 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 collected. In our case, the PSM included the variables we believe to be the most significant before surgery: sex; age; ASA physical status; tumour 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. We did not collect individual surgeon data; instead, data were collected by hospital. Further research into this 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 receiving 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. 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 also now been standardized in Catalonia.

**Conclusion**

In unselected patients, laparoscopy has a lower risk for locoregional recurrence and long-term mortality than open surgery.

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

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**Conflicts of interest**

The authors have no conflicts of interest to disclose.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Density distributions of PSM.

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