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Laparoscopic versus open surgery for locally advanced rectal cancer: five-year survival outcomes in a large, multicenter, propensity score matched cohort study

Running title: Long-term survival lower rectal cancer

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Data analysis and interpretation: DN, KH, AS, and S.Morita

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Keywords: Rectal neoplasm; Laparoscopy; Recurrence; Repeat surgery.

Abstract

Background: There is a paucity of evidence pertaining to long-term survival outcomes of laparoscopic versus open surgery for locally advanced rectal cancer.

Objective: This study aimed to evaluate the long-term survival outcomes of laparoscopic surgery for locally advanced rectal cancer and to investigate the recurrence pattern.

Design: This was a prospective analysis of a registered cohort.

Settings: This study was conducted at 69 institutions across Japan.

Patients: A total of 1500 patients with clinical stage II–III rectal cancer located below the peritoneal reflection between January 2010 and December 2011 were included. After propensity score matching, all eligible patients, including the matched patients registered in 2014, were prospectively followed up.

Main Outcome Measures: Five-year relapse-free survival was the primary outcome.

Results: The median follow-up period was 5.6 years. Among the 964 matched patients, the 5-year relapse-free survival was 65.1% in the open group versus 63.5% in the laparoscopic group (hazard ratio 1.04; $p = 0.71$). Distant recurrences at rare sites, that were more frequently observed in the laparoscopic group, were significantly less salvaged (adjusted odds ratio 0.74; $p = 0.045$). Post-recurrence 5-year overall survival was significantly better in patients who underwent salvage surgery than those who did not; 55.3% vs. 29.5% for patients with initial local recurrence ($p = 0.03$) and 64.4% vs. 30.7% for patients with distant recurrence alone ($p < 0.001$).

Limitations: Potential heterogeneity and influence of unknown confounding.

Conclusions: Five-year follow-up data demonstrated that laparoscopic surgery for locally advanced rectal cancer was safely performed in terms of long-term prognosis. In addition, salvage surgery for recurrent lesions was associated with prolonged post-recurrence survival,

both in patients with local and distant recurrence. However, recurrence at rare sites may require further investigation.

Introduction

Over the past three decades, advances in surgical techniques, like total mesorectal excision in combination with multidisciplinary therapies, have helped improve the outcomes of patients with rectal cancer; the local recurrence (LR) rates have decreased from 20–30% to approximately 10% over this period.[1-6] Recent years have witnessed increasing popularity of laparoscopic rectal cancer surgery owing to its advantages, including rapid recovery, fewer complications, and better anatomical characterization of the pelvis.[7, 8] Several randomized controlled trials and observational studies have investigated the short- and mid-term outcomes of laparoscopic surgery for locally advanced rectal cancer (LARC).[9-17] The COLOR II trial (n = 1044) demonstrated the non-inferiority of laparoscopic surgery with respect to 3-year locoregional recurrence rate;[9] similarly, the COREAN trial (n = 340) demonstrated the non-inferiority of laparoscopic surgery with respect to 3-year relapse-free survival.[10] However, there is a paucity of evidence regarding the long-term prognosis.

The recurrence pattern and the subsequent treatment can affect the long-term survival outcomes of patients who develop recurrence after rectal cancer surgery. Distant recurrence (DR) is a leading cause of death after surgery for rectal cancer;[18] the reported DR rates after surgery range from 20% to 35%.[3-6, 19] In a recent study based on a population-based tumor registry, the LR rate was approximately 10%;[20] this pattern of recurrence is often associated with pelvic pain and diminished quality of life.[21] Salvage surgery for LR typically requires extended resection. In a recent series of patients with locally recurrent rectal cancer, complete resection of LR was found to prolong post-recurrence cancer-specific survival.[22] However, in another study of patients with LARC who received preoperative chemoradiotherapy, salvage surgery for LR did not prolong post-recurrence survival, whereas salvage surgery for lung or liver metastases did prolong survival.[23] Thus, there is no conclusive evidence pertaining to outcomes of salvage surgery for recurrent LARC. Additionally, the effect of the surgical

approach for the primary surgery on the subsequent salvage surgery after disease recurrence is not well characterized.

Here, we conducted a prospective follow-up study of 964 propensity score-matched patients with LARC[17] and assessed the long-term prognosis after laparoscopic surgery for LARC; additionally, we investigated the patterns of disease recurrence.

Materials & Methods

Study design and participants

This was a multicenter cohort study across 69 institutions affiliated with the Japanese Society of Laparoscopic Colorectal Surgery. We previously reported short- and mid-term outcomes of laparoscopic versus open surgery for LARC patients using the propensity score matching method,[17] which showed fewer postoperative complications in the laparoscopic group. Here, we assessed the long-term outcomes of these patients over a follow-up period of 5 years. After the previous study was completed in 2014, the matched patients were registered and followed up prospectively. The study population included patients with clinical stage II/III, pathologically proven, low rectal cancer (below the peritoneal reflection) who underwent surgery with curative intent between January 2010 and December 2011.[17] The open and the laparoscopic procedures were performed contemporaneously, and the decision about surgical approach was at the discretion of the surgeon and the institution. Patient data were collected using a clinical report form. This study was approved by the Institutional Review Board of Kyoto University and all the participating centers (UMIN registration number: 000026789). An opt-out was employed to obtain consent in accordance with the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects.[24]

Definition of recurrence

LR was defined as a tumor regrowth within the pelvis or pelvic wound and classified into 6 areas: anterior wall; posterior wall; left and right (lateral) wall; anastomotic site; and perineal wound. DR was classified according to the organ involved: lung, liver, peritoneum, extra-regional lymph nodes, and other rare sites. We assessed the first recurrence site for each patient and classified the patients into two groups: patients with DR alone; and patients with LR. Patients who had concomitant LR and DR were deemed as patients with LR.

Statistical analysis

Categorical variables are presented as frequencies and percentages and between-group differences assessed using the Chi-squared test. Continuous variables are presented as mean ± standard deviation and between-group differences assessed using the *t*-test. Variables with skewed distribution are presented as median and interquartile range (IQR) and analyzed using Mann-Whitney test, unless otherwise stated. Relapse-free survival (RFS), overall survival (OS), local recurrence rate (LRR), distant recurrence rate (DRR), and post-recurrence survival were estimated using the Kaplan–Meier method; between-group differences with respect to survival outcomes were assessed using the log-rank test. RFS was calculated from the date of surgery to the date of the first recurrence or death from any cause. OS was calculated from the date of surgery to the date of death from any cause. LRR was calculated from the date of surgery to the date of LR regardless of DR, with death being censored. DRR was calculated from the date of surgery to the date of DR regardless of LR, with death being censored. Post-recurrence survival was calculated from the date of clinically and/or radiologically confirmed recurrence to the date of death from any cause. For assessment of LRR, subsequent LRs following DRs were included.

As previously reported,[17] propensity score was calculated to adjust for confounding by indication[25] using the following 8 preoperative variables: age, body mass index, sex, history

of abdominal surgery, tumor distance from anal verge, clinical tumor depth, clinical node involvement, and preoperative therapy. The caliper width was designated as 0.2 of the standard deviation of the propensity score logit. The primary endpoint of this study was the 5-year RFS of the matched cohorts, including patients with macroscopically incomplete (i.e., R2) resection. To assess the recurrence pattern and treatment, R2 patients were excluded from the recurrence pattern analyses. Hazard ratios between groups for RFS, OS, LRR, and DRR were calculated using a Cox proportional hazard model. Logistic regression analysis was used to identify factors associated with the implementation of salvage surgery for recurrent disease. Factors associated with LRR were investigated using a multivariable Cox proportional hazard model. In a sensitivity analysis, OS was assessed with a mixed-effects model to account for institutional heterogeneity. All statistical analyses were performed using R version 3.4.4 (R-project 2018).[26] All p values were two-sided, and $p < 0.05$ was considered indicative of statistical significance. The article was prepared in accordance with the STROBE statement.[27]

Results

Study population

Among the 1500 eligible patients (Table S1), a total of 964 patients were matched in a 1:1 ratio using propensity scores (Fig. S1). After retrieving long-term survival data, the median follow-up period was 5.6 years (IQR, 3.8–6.5 years). The patient demographics are presented in Table 1. Lateral lymph node dissection (LLND) was significantly more frequently performed in the open group (286 of 482 [59%]) than in the laparoscopic group (121 of 482 [25%]) ($p < 0.001$). The number of patients with R2 resection in the open and laparoscopic groups was nine and one, respectively.

Long-term prognosis

The 5-year RFS was 65.1% (95% confidence interval [CI], 60.8–69.5) in the open group and 63.5% (95% CI 59.2–68.1) in the laparoscopic group (hazard ratio [HR] 1.04, 95% CI 0.84–1.28; $p = 0.71$) (Fig. 1A). The 5-year OS was 83.1% (95% CI 79.7–86.5) in the open group and 79.5% (95% CI 75.8–83.4) in the laparoscopy group (HR 1.23, 95% CI 0.93–1.62; $p = 0.15$) (Fig. 1B). In the mixed-effects model, the HR for OS was 1.16 (95% CI 0.86–1.57; $p = 0.33$). The proportion of patients who died without disease recurrence in the open and laparoscopic groups was 6.0% (29 of 482) and 6.8% (33 of 482), respectively.

Recurrence pattern

Fig. 2 shows the details of recurrence and salvage patterns in each group. After excluding 10 patients with R2 resection, 134 and 149 patients in the open and laparoscopic groups, respectively, developed recurrence ($p = 0.37$) among the remaining 954 patients; 102 of whom (10.7%) developed LR while 205 of whom (21.5%) developed DR (including 24 patients [2.5%] with concomitant local and distant recurrence). The most frequent site of DR was lung (n = 120; 59%), followed by liver (n = 62; 30%), extra-regional lymph nodes (n = 22; 11%), peritoneum (n = 10; 5%), and other rare sites (n = 15), including brain, bone, adrenal gland, pancreas, mediastinum, muscle, and pericardium. The laparoscopic group had a significantly higher number of recurrent cases at rare sites ($p = 0.007$). The most frequent site of LR was lateral (n = 48; 47%) followed by posterior (n = 35; 36%), anastomosis (n = 16; 17%), anterior (n = 11; 12%), and perineal wound (n = 2; 2%) (Fig. 3). The 5-year LRR in the open and laparoscopic groups were 10.8% (95% CI 7.9–13.7) and 12.5% (95% CI 9.3–15.5), respectively (HR 1.10, 95% CI 0.76–1.60; $p = 0.62$) (Fig. S2A); this included 9 patients who subsequently developed LR after DR (7 in the open group and 2 in laparoscopic group). In the multivariable Cox hazards model, LRR was significantly associated with LLND (adjusted HR 0.46, 95% CI 0.28–0.75; $p = 0.002$), pathological T4 tumor (adjusted HR 2.51, 95% CI 1.53–

4.14; p = 0.0003), preoperative chemotherapy (adjusted HR 2.61, 95% CI 1.37–4.99; p = 0.004), and sphincter preservation (adjusted HR 0.62, 95% CI 0.42–0.92; p = 0.02), whereas it was not significantly associated with laparoscopic surgery (adjusted HR 1.00, 95% CI 0.66–1.51; p = 1.00) or preoperative chemoradiotherapy (adjusted HR 1.07, 95% CI 0.69–1.67; p = 0.76) (Table S2). The 5-year DRRs in the open and laparoscopic groups were 21.2% (95% CI 17.3–25.0) and 23.4% (95% CI 19.4–27.2), respectively (HR 1.12, 95% CI 0.85–1.47; p = 0.43) (Fig. S2B).

Surgical intervention after recurrence

Overall, salvage surgery was performed in 110 (39%) of the 283 patients with disease recurrence (Fig. 2). The rate of salvage surgery in the open group was 44% (59/134) and that in the laparoscopic group was 34% (51/149); the difference was 9.8% (95% CI −1.5–21; p = 0.09). Multivisceral distant metastases were observed in 18 (10%) of 181 patients with DR alone. Of these, 7 of 88 patients in the open group (8.0%) had multivisceral recurrence, 2 of whom were salvaged. In the laparoscopic group, 11 of 93 patients (11.8%) had multivisceral recurrence, of whom 3 were salvaged. Among those five patients salvaged, four had concomitant liver and lung metastases.

On multivariable analysis (Table 2), the surgical approach for the primary surgery did not significantly affect the implementation of salvage surgery in patients with DR alone (odds ratio [OR] 0.91, 95% CI 0.79–1.06; p = 0.22); in addition, metastases in organs other than lung, liver, peritoneum, and extra-regional lymph nodes were significantly less salvaged (OR 0.74, 95% CI 0.55–0.99; p = 0.045). Regarding salvage surgery for patients with LR, the surgical approach for the primary surgery was not significantly associated with the implementation of salvage surgery (OR 0.95, 95% CI 0.31–3.01; p = 0.93). Preoperative chemotherapy was associated with the implementation of salvage surgery in patients with LR

(OR 4.79, 95% CI 1.18–21.6; $p = 0.03$).

Post-recurrence survival

Among patients with recurrence, salvage surgery was significantly associated with prolonged post-recurrence survival both in patients with LR and patients with DR alone (Fig. 4). The post-recurrence 5-year OS rate was significantly greater in patients whose LR was surgically resected as compared to patients whose LR was not resected: 55.3% (95% CI 38.3–80.0) versus 29.5% (95% CI 18.7–46.3) ($p = 0.03$). In terms of DR, the post-recurrence 5-year survival rate was 64.4% (95% CI 53.3–77.9) in patients who underwent salvage surgery and 30.7% (95% CI 21.5–44.0) in patients who did not undergo salvage surgery ($p < 0.001$).

Discussion

Here, we investigated the long-term prognosis of LARC over 5 years in a Japanese cohort. To our knowledge, this is the largest cohort of LARC with the longest follow-up period. There are two major findings of our study. First, the 5-year RFS after laparoscopic surgery was similar to that after open surgery. Second, salvage surgery, not only for DR but also for LR, was associated with the prolonged post-recurrence survival.

Several randomized trials that compared the outcomes of laparoscopic with those of open surgery for LARC found no major differences with respect to 2- or 3-year disease-free survival, which were >70% in both groups.[9, 10, 13, 15] The 3-year RFS in our previous study was similar to these trials.[17] In the present study, there were no significant between-group differences in the 5-year RFS and frequency of recurrence. These findings support the safety of laparoscopic surgery on long-term prognosis. Meanwhile, the survival curves of OS gradually diverged after 3 to 4 years of observation; the between-group difference with respect to 5-year OS was 4 percentage points, although not statistically significant. One

possible explanation of this finding is the difference in the rate of salvage surgery for recurrent lesions. In our registered sample, the proportion of salvage surgery was approximately 10% higher in the open group, although the between-group difference was not significant. The 10% difference may have had an impact on the OS rate in the late phase. A possible interpretation is that salvage surgery might not have been indicated in some patients of the laparoscopic group because the proportion of multivisceral distant recurrences was higher (approximately 4%). Furthermore, we postulate that the difference in salvage rate is attributable partly to the heterogeneity among institutions with regard to treatment policies after recurrence and hospital case volume. The sensitivity analysis for OS suggested that heterogeneity among institutions was possible. However, this heterogeneity is unlikely to have had an influence on the 5-year RFS, which therefore justifies the use of laparoscopic surgery as a useful option.

Regarding the sites of recurrence, the laparoscopic group had more cases of DR at rare sites, such as the brain, bone, and pancreas; this may have been associated with approximately a 10% less salvage rate in the laparoscopic group. In the present study, 8 out of 15 patients with recurrence at rare sites had simultaneous recurrence at multiple sites; this is a possible explanation for less frequent implementation of salvage surgery. However, the patient number was too small to clarify this. The reason for more DR cases at rare sites in the laparoscopic group is unknown. Rare site recurrences, when detected, might be accompanied by latent and silent lung metastasis.[28, 29] It is still unclear whether distant recurrences at common sites are more latent and silent in the laparoscopic group because of other mechanisms, whether the detection might be skewed between the groups, or whether the laparoscopic surgery may directly influence the frequency of rare site recurrences. Further studies are required to investigate the factors and mechanisms that influence recurrence at rare sites.

In the present study, salvage surgery for LR significantly prolonged the post-recurrence

survival, with 55% of the patients expected to survive 5 years after recurrence; this highlights the value of salvage surgery. However, this finding does not concur with the finding of a recently published single-center study[23] that analyzed 27 patients with LR and reported that salvage surgery for LR was not associated with prolonged post-recurrence survival in patients who underwent neoadjuvant chemoradiotherapy. In that study, all participants received neoadjuvant chemoradiotherapy, and curative salvage resection resulted in approximately 40% 5-year post-recurrence survival, which was almost the same as that of patients who received palliative treatment. In our registered sample, only 35% of patients received neoadjuvant therapy; this may explain the incongruence of the results. Meanwhile, our results are consistent with those obtained from patients who underwent surgery for locally recurrent rectal cancer at five centers, wherein complete resection for locally recurrent cancer prolonged the post-recurrence cancer-specific survival.[22] Notably, our study demonstrated prolonged post-recurrence survival after curative resection in a large, multicenter setting, whereas a few studies that have previously reported similar results were conducted at single cancer centers.[21, 30, 31] Taken together, our results encourage salvage surgery for patients with LR who are in a feasible situation.

Preoperative chemotherapy was associated with the implementation of salvage surgery among patients with LR in this study; chemotherapy may offer advantages in implementation of salvage surgery. However, this result did not take the frequency of LR into account, which may differ from that of chemoradiotherapy or no treatment, and thus, should be carefully interpreted.

Although the 5-year LRR in the present study was not significantly different between the open and laparoscopic groups, these rates were slightly higher than those in previous trials. In the ALaCaRT trial, the 2-year LRR in the laparoscopic and open groups were 5.4% and 3.1%, respectively (the 5-year LRR has not been published).[13] COLOR II trial also demonstrated

low LRR at 3 years (5.0% in both the open and laparoscopic group).[9] Several reasons may explain the difference. The present study included patients with clinical T4 tumors, whereas the trials mentioned above excluded such patients. Moreover, the present study included more patients with lower rectal tumors than these trials; all patients in the present study had tumors below the peritoneal reflection, and the mean distance from the anal verge to tumor was 4.5 cm. Of note, patients with low rectal cancer who were included in the ALaCaRT trial and COLOR II trial comprised only 30% of the participants. Considering these, the slightly higher LRRs in the present study may have reflected tumor depth and location.

Some limitations of the current study should be considered while interpreting the results. First, although we performed propensity score analysis to minimize the effect of confounding by indication, the retrospective enrollment may have introduced an element of selection bias; moreover, the effect of unmeasured or unknown confounders on our results cannot be ruled out. Second, information about secondary distant metastases that may affect the OS, and details of the operative procedures for salvage surgery were not available in our data. Third, heterogeneity among the participating hospitals (such as differences in treatment policy and hospital case volume) may have affected our results. Fourth, because of the retrospective nature of this study, the quality of TME was not assessed. However, our study has the following strengths: First, this was a large study exclusively focused on patients with low rectal cancer (located below the peritoneal reflection). Second, although the patient enrollment was retrospective in the previous study, the enrolled patients were followed up prospectively, with a total follow-up of more than 5 years. Third, this is one of the few studies that evaluated post-recurrence survival and revealed the value of salvage surgery.

Conclusions

In this nationwide multicenter study, laparoscopic surgery for LARC was found to be safe in

terms of long-term prognosis compared with open surgery; additionally, salvage surgery was significantly associated with the prolonged post-recurrence survival. However, our results should be interpreted with caution because of possible heterogeneity with respect to post-recurrence treatment. Further studies are required to investigate factors and mechanisms of metastases at rare sites. Long-term outcomes and recurrence patterns in previously conducted randomized trials are being awaited.

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References

1. Marsh PJ, James RD, Schofield PF. Adjuvant preoperative radiotherapy for locally advanced rectal carcinoma. Results of a prospective, randomized trial. *Dis Colon Rectum*. 1994;37:1205-1214.
2. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol*. 2005;23:5644-5650.
3. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol*. 2012;30:1926-1933.
4. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Eng J Med*. 2006;355:1114-1123.
5. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg*. 2007;246:693-701.
6. Ogura A, Konishi T, Cunningham C, et al. Neoadjuvant (chemo)radiotherapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: results of the multicenter lateral node study of patients with low cT3/4 rectal cancer. *J Clin Oncol*. 2019;37:33-43.
7. Sakai Y, Nomura A, Masumori K, Kawamura J, Nagayama S. Recent interpretations of Denonvilliers' fascia and the lateral ligament of the rectum. *Asian J Endosc Surg*. 2009;2:8-12.
8. Inomata M, Shiroshita H, Uchida H, et al. Current status of endoscopic surgery in Japan: The 14th National Survey of Endoscopic Surgery by the Japan Society for Endoscopic Surgery. *Asian J Endosc Surg*. 2020;13:7-18.

9. Bonjer HJ, Deijen CL, Haglind E. A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Eng J Med*. 2015;373:1324-1332.
10. Jeong SY, Park JW, Nam BH, et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. *Lancet Oncol*. 2014;15:767-774.
11. Kang SB, Park JW, Jeong SY, et al. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. *Lancet Oncol*. 2010;11:637-645.
12. Stevenson AR, Solomon MJ, Lumley JW, et al. Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer: the ALaCaRT randomized clinical trial. *JAMA.* 2015;314:1356-1363.
13. Stevenson ARL, Solomon MJ, Brown CSB, et al. Disease-free survival and local recurrence after laparoscopic-assisted resection or open resection for rectal cancer: The Australasian Laparoscopic Cancer of the Rectum Randomized Clinical Trial. *Ann Surg.* 2019;269:596-602.
14. Fleshman J, Branda M, Sargent DJ, et al. Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes: the ACOSOG Z6051 randomized clinical trial. *JAMA*. 2015;314:1346-1355.
15. Fleshman J, Branda ME, Sargent DJ, et al. Disease-free survival and local recurrence for laparoscopic resection compared with open resection of stage II to III rectal cancer: follow-up results of the ACOSOG Z6051 randomized controlled trial. *Ann Surg*. 2019;269:589-595.
16. van der Pas MH, Haglind E, Cuesta MA, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *Lancet*

Oncol. 2013;14:210-218.

17. Hida K, Okamura R, Sakai Y, et al. Open versus laparoscopic surgery for advanced low rectal cancer: a large, multicenter, propensity score matched cohort study in Japan. *Ann Surg*. 2018;268:318-324.
18. Franke AJ, Parekh H, Starr JS, Tan SA, Iqbal A, George TJ, Jr. Total neoadjuvant therapy: a shifting paradigm in locally advanced rectal cancer management. *Clin Colorectal Cancer.* 2018;17:1-12.
19. Oki E, Murata A, Yoshida K, et al. A randomized phase III trial comparing S-1 versus UFT as adjuvant chemotherapy for stage II/III rectal cancer (JFMC35-C1: ACTS-RC). *Ann Oncol*. 2016;27:1266-1272.
20. Kodeda K, Derwinger K, Gustavsson B, Nordgren S. Local recurrence of rectal cancer: a population-based cohort study of diagnosis, treatment and outcome. *Colorectal Dis*. 2012;14:e230-e237.
21. You YN, Habiba H, Chang GJ, Rodriguez-bigas MA, Skibber JM. Prognostic value of quality of life and pain in patients with locally recurrent rectal cancer. *Ann Surg Oncol*. 2011;18:989-996.
22. Harris CA, Solomon MJ, Heriot AG, et al. The outcomes and patterns of treatment failure after surgery for locally recurrent rectal cancer. *Ann Surg*. 2016;264:323-329.
23. Ikoma N, You YN, Bednarski BK, et al. Impact of recurrence and salvage surgery on survival after multidisciplinary treatment of rectal cancer. *J Clin Oncol*. 2017;35:2631-2638.
24. Japanese Ministry of Health, Labor, and Welfare. Ethical Guidelines for Medical and Health Research Involving Human Subjects (in Japanese). https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000166072.pdf. Published 29 May 2017. Accessed 29 July, 2020.

25. Kyriacou DN, Lewis RJ. Confounding by Indication in Clinical Research. *JAMA*. 2016;316:1818-1819.
26. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, 2018. Vienna, Austria.
27. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology.* 2007;18:805-835.
28. Katayama A, Mafune K, Makuuchi M. Adrenalectomy for solitary adrenal metastasis from colorectal carcinoma. *Jap J Clin Oncol*. 2000;30:414-416.
29. Murakami S, Terakado M, Hashimoto T, Tsuji Y, Okubo K, Hirayama R. Adrenal metastasis from rectal cancer: report of a case. *Surg Today*. 2003;33:126-130.
30. Hahnloser D, Nelson H, Gunderson LL, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. *Ann Surg.* 2003;237:502-508.
31. Miner TJ, Jaques DP, Paty PB, Guillem JG, Wong WD. Symptom control in patients with locally recurrent rectal cancer. *Ann Surg Oncol.* 2003;10:72-79.

Figure legends

Figure 1. Kaplan–Meier curves for A) relapse-free survival and B) overall survival in the matched cohort.

Open, open surgery; Lap, laparoscopic surgery; CI, confidence interval

Figure 2. Patient flow diagram of recurrence pattern and salvage surgery. The number of recurrences did not tally due to overlapping elements.

†Other sites include the brain, bone, pericardium, mediastinum, muscle, adrenal gland, and pancreas. * $p = 0.007$.

DR, distant recurrence; LR, local recurrence

Figure 3. This plot visualizes synchronous disease recurrence as a matrix in which the rows represent the metastatic sites and the columns represent their overlaps. In the rows, the bars show the number of recurrences (separately for distant and local sites). In the columns, the bars show the number of patients who had the same pattern of recurrence: The most frequent pattern was lung metastasis alone (33% [93 of 283]); the most frequent overlapping pattern was synchronous lung and liver metastasis (2% [6 of 283]).

ERLN, extra-regional lymph node; DR, distant recurrence; LR, local recurrence

Figure 4. Kaplan–Meier curves for post-recurrence survival of A) patients with local recurrence and B) patients with distant recurrence only, compared between patients with or without salvage surgery.

Figure S1: Patient flow diagram of registered patients. Modified from Hida (2018).[17]

Figure S2. Kaplan–Meier curves for A) local recurrence rate and B) distant recurrence rate in the matched cohort.

Open, open surgery; Lap, laparoscopic surgery; CI, confidence interval

Table1. Characteristics of registered patients

Characteristics	Open (n = 482)	Laparoscopic (n = 482)	*P* value
Age, years, mean (SD)	63.5 (11.0)	63.4 (13.1)	0.89
Female, n (%)	147 (30.5)	155 (32.2)	0.58
BMI, kg/m^2, mean (SD)	22.4 (3.5)	22.5 (3.6)	0.77
ASA-PS ≥3, n (%)	27 (5.6)	24 (5.0)	0.67
Distance from anal verge, cm, mean (SD)	4.6 (2.2)	4.6 (2.4)	0.68
CEA ≥5 ng/ml, n (%)	199 (41.3)	196 (40.7)	0.84
cT stage, n (%)			0.31
cT1/2	49 (10.2)	38 (7.9)	
cT3	365 (75.7)	384 (79.7)	
cT4	68 (14.1)	60 (12.4)	
cN+, n (%)	279 (57.9)	271 (56.2)	0.65
Preoperative treatment, n (%)	167 (34.6)	169 (35.1)	0.60
(chemo) radiotherapy	119	149	
chemotherapy	48	20	

Abbreviations: SD, standard deviation; BMI, body mass index; CEA, carcinoembryonic antigen. Modified from Hida (2018).[17]

Table 2. Multivariable logistic regression for salvage surgery

	Factors	Odds Ratio (95% CI)	*P* value
Local	Laparoscopic surgery	0.95 (0.31 to 3.01)	0.93
	LLND	1.27 (0.35 to 4.61)	0.71
	Preoperative (chemo)radiotherapy	1.11 (0.34 to 3.50)	0.86
	Preoperative chemotherapy	4.79 (1.18 to 21.6)	0.03
	Simultaneous distant metastases	0.47 (0.12 to 1.44)	0.24
	Lateral recurrence	0.42 (0.13 to 1.26)	0.13
	Anastomotic site recurrence	2.32 (0.65 to 8.56)	0.20
Distant	Laparoscopic surgery	0.91 (0.79 to 1.06)	0.22
	Adjuvant chemotherapy	1.09 (0.94 to 1.26)	0.25
	Liver metastasis	1.02 (0.80 to 1.29)	0.89
	Lung metastasis	0.88 (0.69 to 1.11)	0.27
	Peritoneal metastasis	0.88 (0.60 to 1.29)	0.51
	Extra-regional LN metastasis	0.76 (0.57 to 1.02)	0.07
	Other distant metastasis *	0.74 (0.55 to 0.99)	0.045

Abbreviations: LLND, lateral lymph node dissection; LN, lymph node.

*Other distant metastasis included brain, bone, adrenal gland, pancreas, mediastinum, muscle, and pericardium.

Figure1

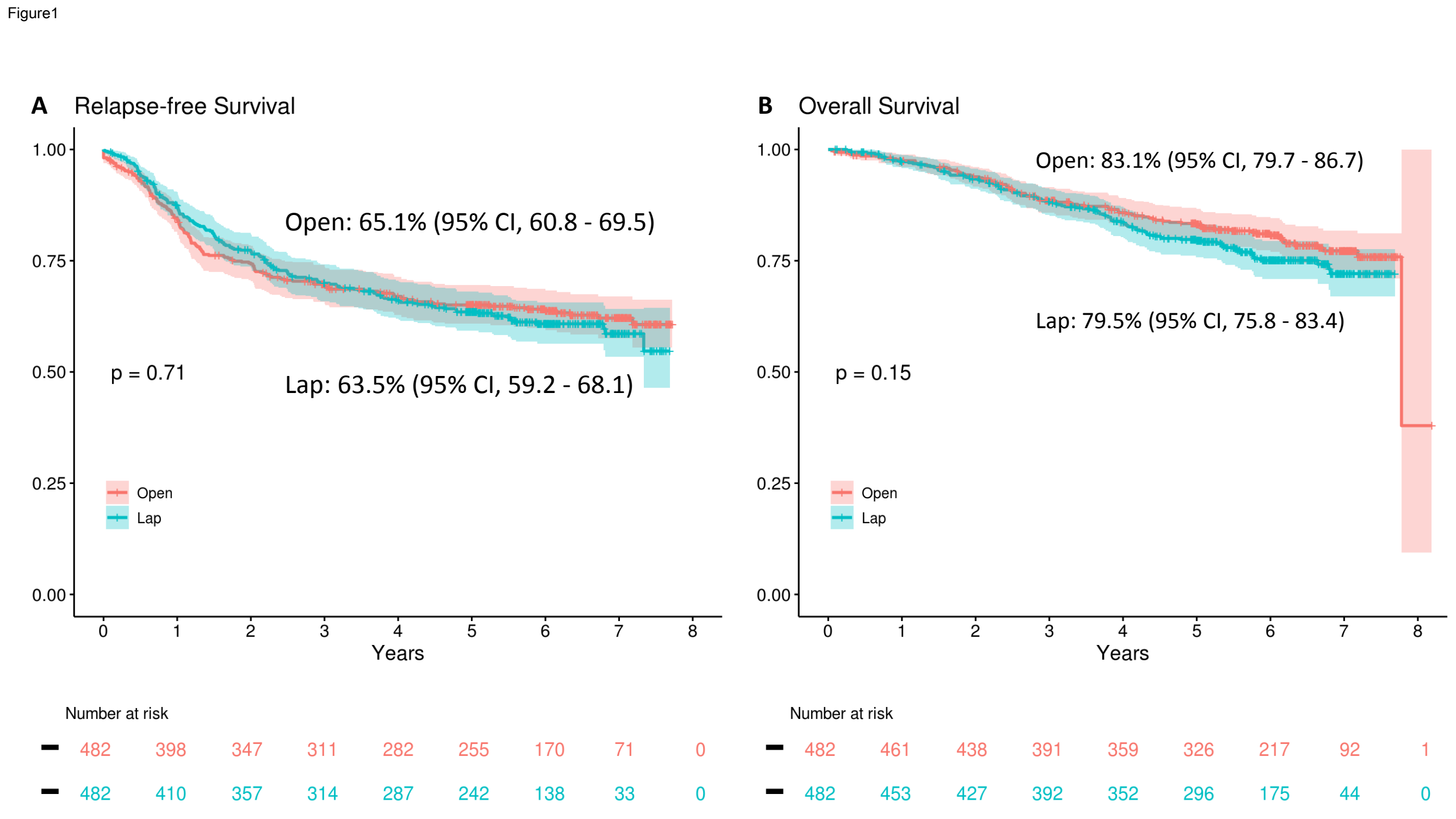

A Relapse-free Survival
1.00
0.75
0.50
0.25
0.00
Open: 65.1% (95% CI, 60.8 - 69.5)
p = 0.71
Lap: 63.5% (95% CI, 59.2 - 68.1)
Open
Lap
0 1 2 3 4 5 6 7 8
Years
Number at risk
Open 482 398 347 311 282 255 170 71 0
Lap 482 410 357 314 287 242 138 33 0
B Overall Survival
1.00
0.75
0.50
0.25
0.00
Open: 83.1% (95% CI, 79.7 - 86.7)
Lap: 79.5% (95% CI, 75.8 - 83.4)
p = 0.15
Open
Lap
0 1 2 3 4 5 6 7 8
Years
Number at risk
Open 482 461 438 391 359 326 217 92 1
Lap 482 453 427 392 352 296 175 44 0

Figure2

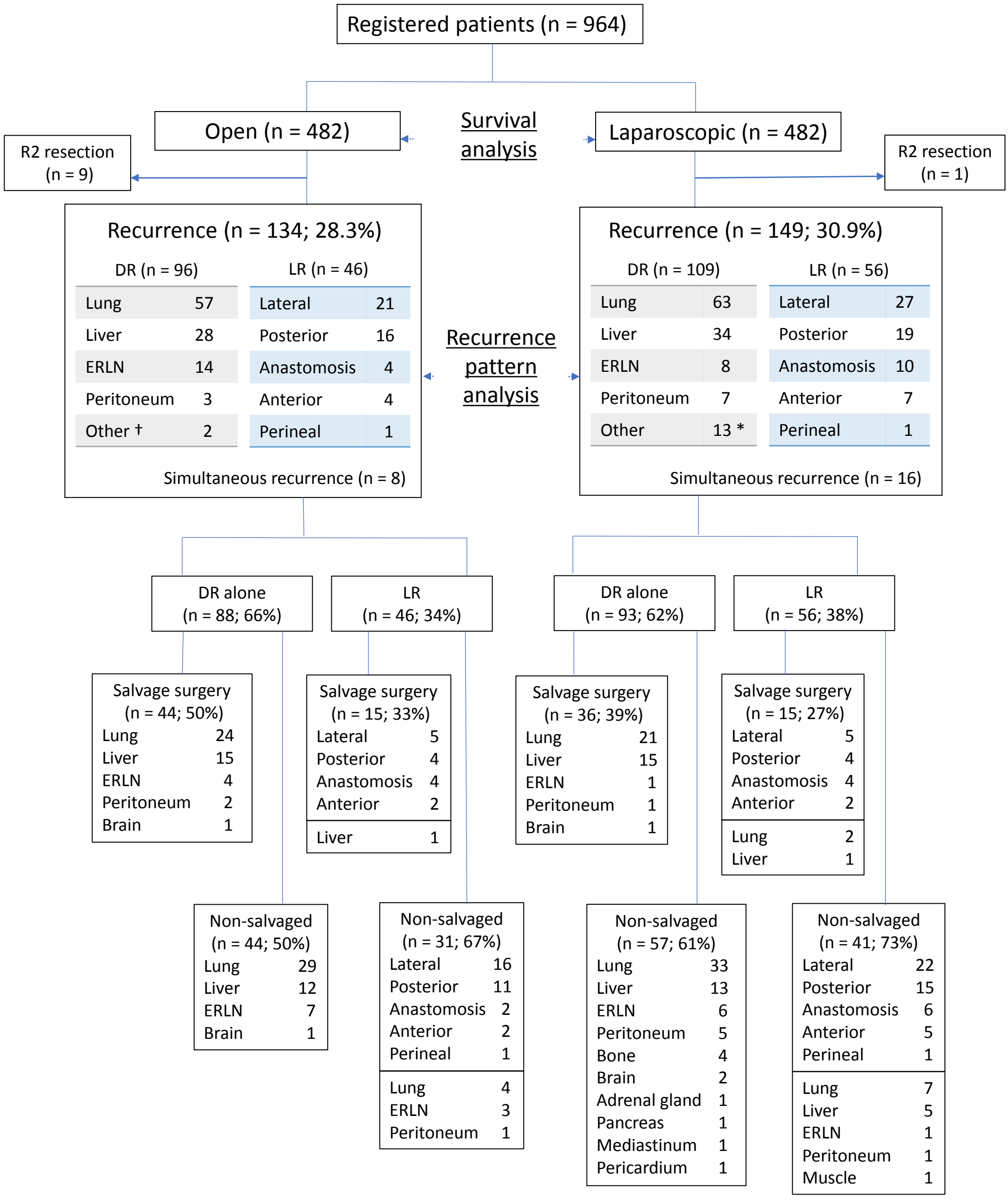
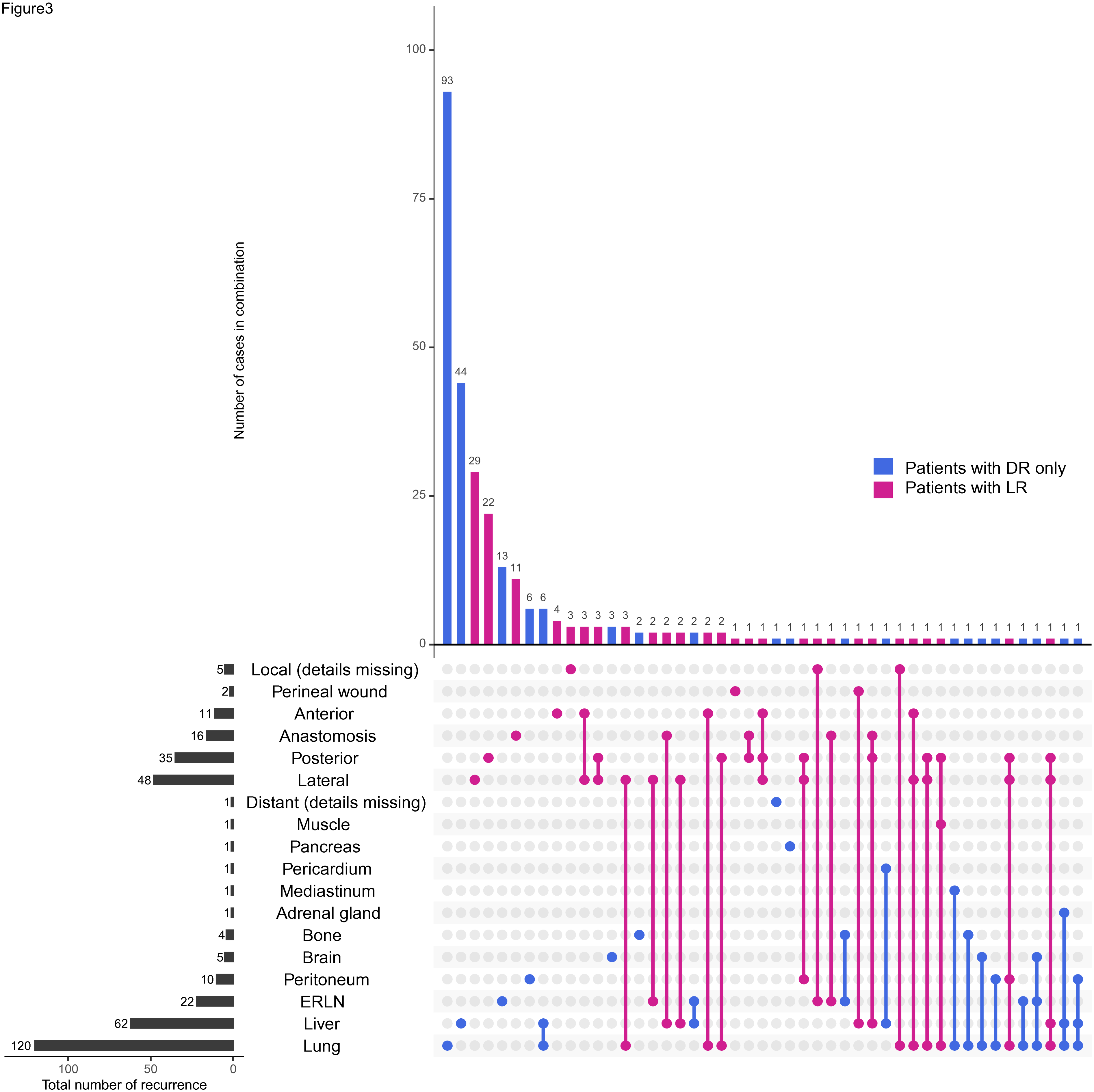
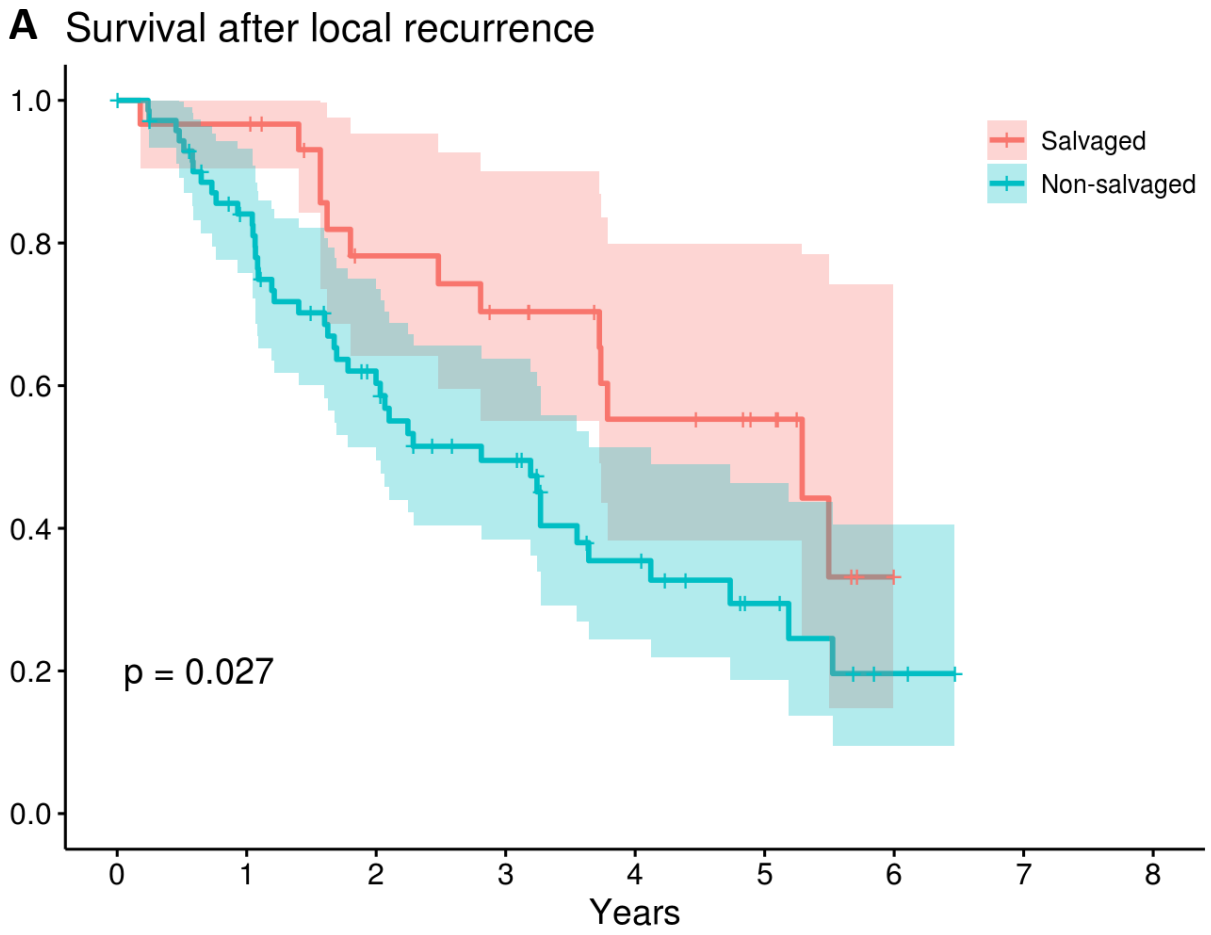

Registered patients (n = 964)
Open (n = 482)
Survival analysis
Laparoscopic (n = 482)
R2 resection (n = 9)
R2 resection (n = 1)
Recurrence (n = 134; 28.3%)
DR (n = 96)
Lung 57
Liver 28
ERLN 14
Peritoneum 3
Other † 2
LR (n = 46)
Lateral 21
Posterior 16
Anastomosis 4
Anterior 4
Perineal 1
Simultaneous recurrence (n = 8)
Recurrence pattern analysis
Recurrence (n = 149; 30.9%)
DR (n = 109)
Lung 63
Liver 34
ERLN 8
Peritoneum 7
Other 13 *
LR (n = 56)
Lateral 27
Posterior 19
Anastomosis 10
Anterior 7
Perineal 1
Simultaneous recurrence (n = 16)
DR alone (n = 88; 66%)
LR (n = 46; 34%)
DR alone (n = 93; 62%)
LR (n = 56; 38%)
Salvage surgery (n = 44; 50%)
Lung 24
Liver 15
ERLN 4
Peritoneum 2
Brain 1
Salvage surgery (n = 15; 33%)
Lateral 5
Posterior 4
Anastomosis 4
Anterior 2
Liver 1
Salvage surgery (n = 36; 39%)
Lung 21
Liver 15
ERLN 1
Peritoneum 1
Brain 1
Salvage surgery (n = 15; 27%)
Lateral 5
Posterior 4
Anastomosis 4
Anterior 2
Lung 2
Liver 1
Non-salvaged (n = 44; 50%)
Lung 29
Liver 12
ERLN 7
Brain 1
Non-salvaged (n = 31; 67%)
Lateral 16
Posterior 11
Anastomosis 2
Anterior 2
Perineal 1
Lung 4
ERLN 3
Peritoneum 1
Non-salvaged (n = 57; 61%)
Lung 33
Liver 13
ERLN 6
Peritoneum 5
Bone 4
Brain 2
Adrenal gland 1
Pancreas 1
Mediastinum 1
Pericardium 1
Non-salvaged (n = 41; 73%)
Lateral 22
Posterior 15
Anastomosis 6
Anterior 5
Perineal 1
Lung 7
Liver 5
ERLN 1
Peritoneum 1
Muscle 1

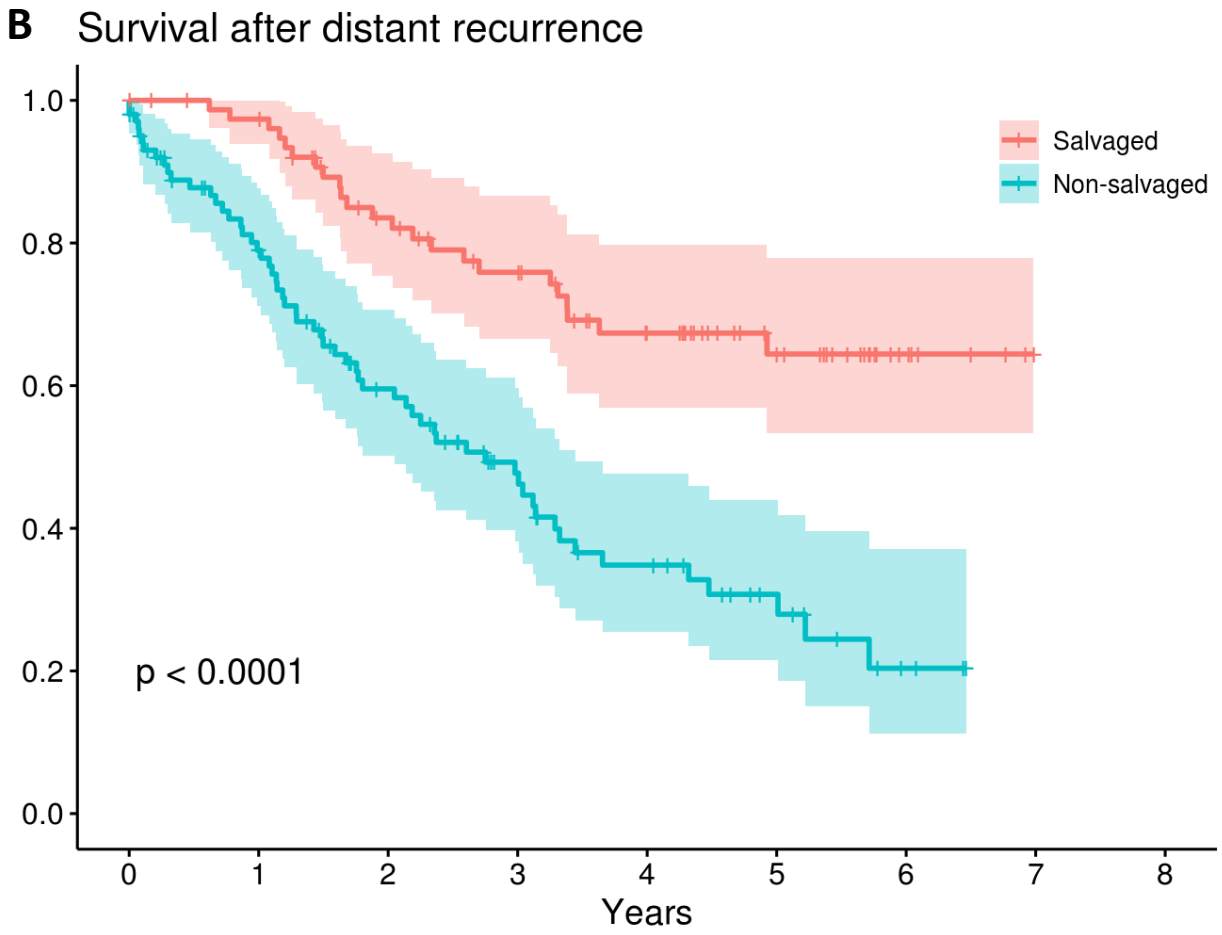
Figure3



Number of cases in combination
100
75
50
25
0
93
44
29
22
13
11
6
6
4
3
3
3
3
3
2
2
2
2
2
2
2
1
Patients with DR only
Patients with LR
Local (details missing)
Perineal wound
Anterior
Anastomosis
Posterior
Lateral
Distant (details missing)
Muscle
Pancreas
Pericardium
Mediastinum
Adrenal gland
Bone
Brain
Peritoneum
ERLN
Liver
Lung
5
2
11
16
35
48
1
1
1
1
1
1
4
5
10
22
62
120
100
50
0
Total number of recurrence

Figure4





Number at risk

Salvaged	30	29	20	17	11	8	0	0	0
Non-salvaged	72	55	35	25	14	7	2	0	0

Number at risk

Salvaged	79	74	57	48	35	22	7	0	0
Non-salvaged	102	71	48	31	20	11	3	0	0

Table S1. Characteristics of original cohort

Characteristics	Open (n = 926)	Laparoscopic (n = 574)	*P* value
Age, years, mean (SD)	63.8 (11.1)	63.3 (12.8)	0.38
Female, n (%)	282 (30.5)	183 (31.9)	0.57
BMI, kg/m^2, mean (SD)	22.2 (3.5)	22.6 (3.6)	0.03
ASA-PS ≥3, n (%)	60 (6.5)	25 (4.4)	0.09
Distance from anal verge, cm, mean (SD)	4.4 (2.2)	4.6 (2.3)	0.02
CEA ≥5 ng/ml, n (%)	410 (44.6)	221 (38.9)	0.03
cT stage, n (%)			<0.001
cT1/2	51 (5.5)	62 (10.8)	
cT3	673 (72.7)	449 (78.4)	
cT4	202 (21.8)	62 (10.8)	
cN+, n (%)	596 (64.5)	326 (56.9)	0.003
Preoperative treatment, n (%)	193 (20.8)	231 (40.2)	<0.001
(chemo) radiotherapy	134	210	
chemotherapy	59	21	

Abbreviations: SD, standard deviation; BMI, body mass index; CEA, carcinoembryonic antigen. Modified from Hida (2018).[17]

Table S2. Result of Cox regression for local recurrence rate

Factor		Hazard ratio (95%CI)	*P* value
Approach	Open	Ref	
	Laparoscopy	1.00 (0.66 to 1.51)	1.00
Lateral lymph node dissection	Not performed	Ref	
	Performed	0.46 (0.28 to 0.75)	0.002
Sphincter preservation	Not preserved	Ref	
	Preserved	0.62 (0.42 to 0.92)	0.02
Adjuvant chemotherapy	Not performed	Ref	
	Performed	0.89 (0.57 to 1.40)	0.62
Nodal status	(y)pN0	Ref	
	(y)pN1	1.67 (0.98 to 2.83)	0.06
	(y)pN2	3.82 (2.18 to 6.68)	0.00003
	(y)pN3	5.09 (2.53 to 10.22)	0.00005
Tumor depth	≤ (y)pT3	Ref	
	(y)pT4	2.51 (1.53 to 4.14)	0.0003
Neoadjuvant therapy	Not performed	Ref	
	Chemoradiotherapy	1.07 (0.69 to 1.67)	0.76
	Chemotherapy	2.61 (1.37 to 4.99)	0.004

	Radiotherapy	1.62 (0.50 to 5.25)	0.42

Fig. S1

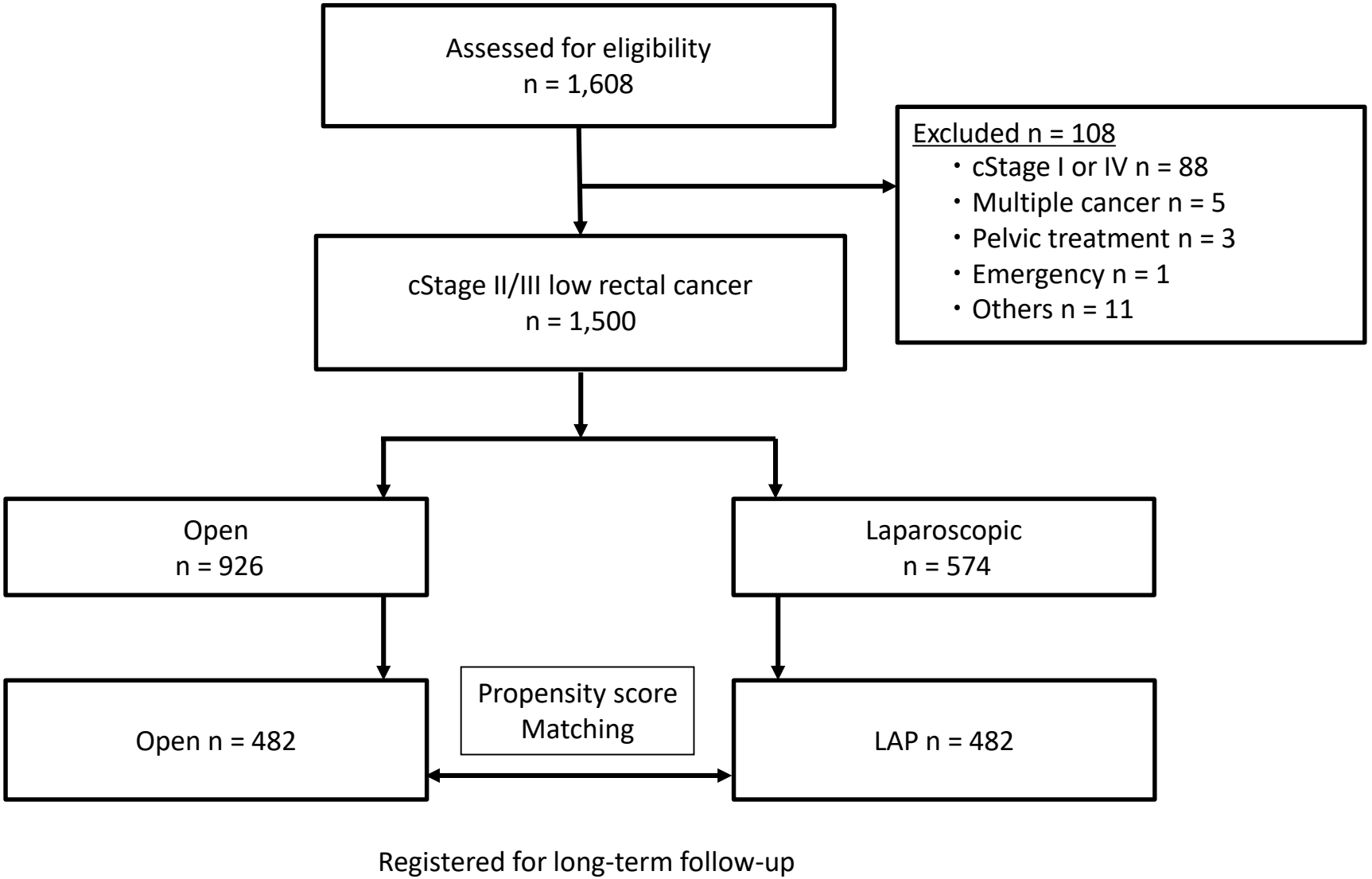
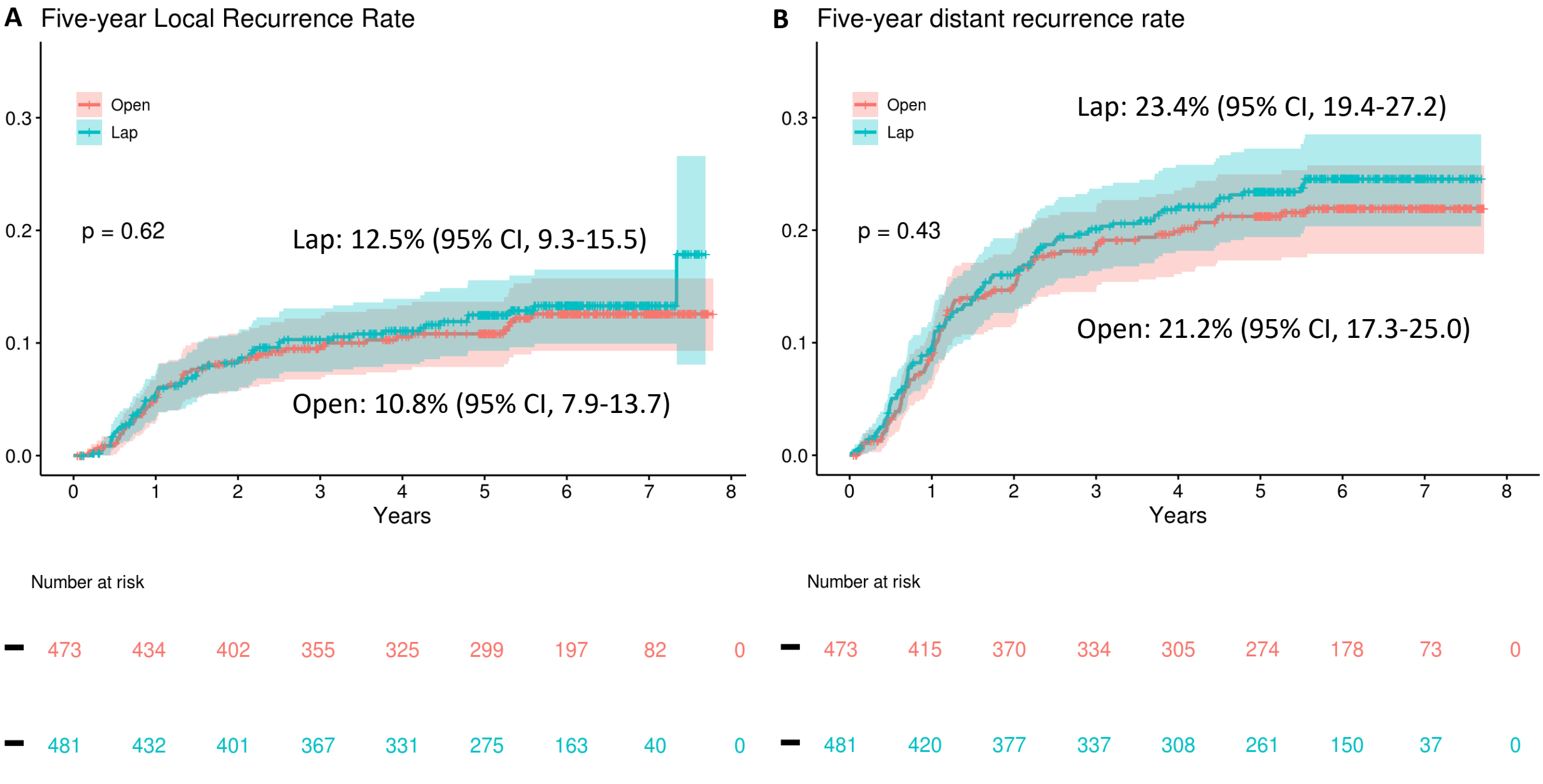

Assessed for eligibility
n = 1,608
Excluded n = 108
・cStage I or IV n = 88
・Multiple cancer n = 5
・Pelvic treatment n = 3
・Emergency n = 1
・Others n = 11
cStage II/III low rectal cancer
n = 1,500
Open
n = 926
Laparoscopic
n = 574
Propensity score
Matching
Open n = 482
LAP n = 482
Registered for long-term follow-up

Fig. S2


A Five-year Local Recurrence Rate
Open
Lap
p = 0.62
Lap: 12.5% (95% CI, 9.3-15.5)
Open: 10.8% (95% CI, 7.9-13.7)
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8
Years
Number at risk
473 434 402 355 325 299 197 82 0
481 432 401 367 331 275 163 40 0
B Five-year distant recurrence rate
Open
Lap
p = 0.43
Lap: 23.4% (95% CI, 19.4-27.2)
Open: 21.2% (95% CI, 17.3-25.0)
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8
Years
Number at risk
473 415 370 334 305 274 178 73 0
481 420 377 337 308 261 150 37 0