Oncological Outcomes After Anastomotic Leakage After Surgery for Colon or Rectal Cancer

**Increased Risk of Local Recurrence**

**Objective:** The aim of this study was to evaluate oncological outcome for patients with and without anastomotic leakage after colon or rectal cancer surgery.

**Summary of Background Data:** The role of anastomotic leakage in oncological outcome after colorectal cancer surgery is still topic of debate and impact on follow-up and consideration for further treatment remains unclear.

**Methods:** Patients included in the international, multicenter, non-inferior, open label, randomized, controlled trials COLOR and COLOR II, comparing laparoscopic surgery for curable colon (COLOR) and rectal (COLOR II) cancer with open surgery, were analyzed. Patients operated by abdominoperineal excision were excluded. Both univariate and multivariate analyses were performed to investigate the impact of leakage on overall survival, disease-free survival, local and distant recurrences, adjusted for possible confounders.

**Primary endpoints in the COLOR and COLOR II trial were disease-free survival and local recurrence at 3-year follow-up, respectively, and secondary endpoints included anastomotic leakage rate.**

**Results:** For colon cancer, anastomotic leakage was not associated with increased percentage of local recurrence or decreased disease-free survival. For rectal cancer, an increase of local recurrences (13.3% vs 4.6%; hazard ratio 2.96; 95% confidence interval 1.38–6.34; \( P = 0.005 \)) and a decrease of disease-free survival (53.6% vs 70.9%; hazard ratio 1.67; 95% confidence interval 1.16–2.41; \( P = 0.006 \)) at 5-year follow-up were found in patients with anastomotic leakage.

**Conclusion:** Short-term morbidity, mortality, and long-term oncological outcomes are negatively influenced by the occurrence of anastomotic leakage after rectal cancer surgery. For colon cancer, no significant effect was observed; however, due to low power, no conclusions on the influence of anastomotic leakage on outcomes after colon surgery could be reached. Clinical awareness of increased risk of local recurrence after anastomotic leakage throughout the follow-up is mandatory.

**Keywords:** anastomotic leakage, colorectal cancer, colorectal surgery, locoregional recurrence, oncological outcomes, survival

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astomotic leakage is a severe complication of colorectal cancer surgery. This complication occurs in 2%–19% of patients that have undergone such surgery,† depending on tumor localization, surgical technique, and emergency surgery.‡,‡† Although the role of anastomotic leakage on short-term morbidity and mortality is well recognized,‡,‡‡ its impact on long-term oncological outcome is debated. Several studies described an association of anastomotic leakage with a higher local recurrence rate‡‡–‡‡† and decreased disease-free and overall survival,‡‡‡–‡‡†‡ but other studies have failed to recognize,‡‡–‡‡† its impact on long-term oncological outcome is debated.
to confirm this association. Many of these papers; however, did not make a distinction between patients operated for colon or rectal cancer and most studies are retrospective cohort series with varying definitions of leakage.

Knowledge on the effect of leakage on long-term oncological outcome is relevant, as it may affect patient follow-up and consideration for further treatment. To investigate this role, the data of 2 international multicenter, randomized controlled trials: COLOR29,30 and COLOR II,31,32 each incorporating over 1000 patients, were analyzed.

This study aims to evaluate the influence of anastomotic leakage on local recurrence rate, overall survival, and disease-free survival in patients who had undergone laparoscopic or open resection with curative intent for colon or rectal cancer.

METHODS

Patients

The data of patients included in the international, multicenter, randomized trials COLOR and COLOR II were used. Inclusion criteria of the COLOR trial were patients with adenocarcinoma in the caecum, ascending colon, descending colon, or sigmoid. Eligible patients were randomly assigned to open or laparoscopic surgery with stratification for hospital and type of resection. Only patients with a primary anastomosis were included in this study. Inclusion criteria of the COLOR II trial were patients suffering from adenocarcinoma of the rectum within 15 cm from the anal verge. Eligible patients were randomized in a 2:1 ratio to elective laparoscopic or open surgery with stratification for hospital, tumor location, and preoperative radiotherapy. Growth of the carcinoma in adherent structures (T4) or patients with distant metastases were excluded. Patients operated by abdominoperineal excision were excluded from this study. Primary endpoint of the COLOR trial was cancer-free survival at 3-years follow up and primary endpoint of the COLOR II trial was local recurrence at 3-years follow up. More detailed information of the COLOR and COLOR II trials concerning study design, inclusion and exclusion criteria, randomization, quality control, and follow-up can be found in earlier published articles.9,31

Ethics and Regulation

Each participating center obtained institutional ethical review board approval, according to local regulations. Patients provided written informed consent. The COLOR and COLOR II trials were registered with ClinicalTrials.gov, number NCT00387842 and NCT00297791, respectively. The sponsors had no role in the study design, data gathering, analyses, interpretation of data or writing of the reports.

Endpoints

In this study, comparison of the oncological outcome in patients with and without an anastomotic leakage after colorectal resection was performed, including the end points local recurrence, overall survival, disease-free survival, and distant recurrence. Separate analyses were performed for patients with colon cancer and rectal cancer.

Definitions

Follow-up was defined as time between primary resection of the adenocarcinoma and death or last observation. Leakage was defined as an evident dehiscence of the anastomosis or rectal stump clinically or by abdominal computed tomography-scan and/or a pelvic abscess after rectal surgery or after left sided colon surgery diagnosed within 90-days after surgery. Postoperative mortality was defined as death from index surgery up to 90-days follow-up. OS was defined as date of index surgery to date of death from any cause. DFS was defined as date from index surgery to date of a recurrence or death from any cause. For colon cancer, LR included recurrences at the site of the primary tumor, at port sites, and at wound sites. For rectal cancer, LR included pelvic recurrences. All other recurrences were considered to be distant.

Statistical Analysis

Data were analyzed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL). Differences between patients with and without leakage were analyzed with the Pearson Chi-square test or Fisher exact test, where appropriate, in case of dichotomous data. The t-test for independent samples was used to analyze continuous values between groups. Continuous values were expressed as mean ± standard deviation or median (range), depending on whether the data were normally distributed or not, respectively. Categorical data were reported as frequencies with percentages. Uni- and multivariate Cox regression analysis was performed to identify independent predictive variables for overall survival, disease free survival, local recurrence rate, and distant recurrence rate. The variables tested were age, sex, body-mass index, American Society of Anesthesiologists Physical Status Classification System (ASA classification), American Joint Committee on Cancer-tumor stage, (neo)adjuvant therapy, randomized procedure, performed procedure, conversion, positive resection margin, postoperative complications, leakage, perioperative blood transfusion for colon cancer, and tumor distance from the anal verge for rectal cancer. Variables that had shown a statistically significant association with the studied outcome in univariate analysis ($P < 0.10$) were subsequently entered into a multivariate Cox regression model. All $P$-values were 2-sided and $P < 0.05$ in multivariate analysis was considered to be statistically significant. The hazard ratio and 95% confidence interval (CI) were presented for every significant predictive variable in multivariate analysis. A power calculation was performed using PASS 15.0.5 for the COLOR cohort regarding the effect of anastomotic leakage on local recurrence. Power was calculated for a univariate Cox regression model, based on the sample size, hazard ratio, local recurrence rate, leakage rate, and a 2-sided alpha of 0.05.

RESULTS

Patient Characteristics

In the COLOR trial, 1076 patients with non-metastatic, non-T4 colon cancer were entered between March 1997 and March 2003. Eight patients received an end colostomy at index surgery and were excluded from our analysis. The remaining 1068 patients, including 27 (2.5%) patients with a leakage, were analyzed. No differences were found between the groups, comparing baseline characteristics, pathology, and operative details, as shown in Table 1, http://links.lww.com/SLA/C74. In the COLOR II trial, 1044 patients with non-metastatic, non-T4 rectal cancer were entered between January 2004 and May 2010. After excluding patients operated by abdominoperineal excision, 764 patients with an anastomosis or rectal stump were included, of which 84 patients (11.0%) had anastomotic leakage within 90-days of index surgery. Baseline characteristics, pathology, operative details, and short-term outcomes are summarized in Table 1, http://links.lww.com/SLA/C74. Preoperative radiotherapy was an independent risk factor for leakage [hazard ratio (HR) 1.81, 95% CI 1.14–2.90]. Median follow-up for patients without and with leakage was similar (Table 1, http://links.lww.com/SLA/C74).
Overall Survival
After colon cancer surgery, mortality within 90 days of index surgery was 2.1% for patients without anastomotic leakage and 14.8% for patients with leakage ($P = 0.003$, Table 1, http://links.lww.com/SLA/C74). Overall survival at 5-year follow-up was 74.4% and 58.5%, respectively. Ten variables, significant in univariate analysis, were entered into multivariate analysis. Finally, 6 variables were identified as significant predictors of overall survival at 5-year follow-up, including male sex (HR 0.74, 95% CI 0.57–0.96) age ≥70 years (HR 1.83, 95% CI 1.35–2.48), ASA-score III/IV (HR 2.52, 95% CI 1.68–3.76 and HR 14.74, 95% CI 6.07–35.81, respectively), tumor stage III (HR 2.85, 95% CI 1.96–4.13), need for intraoperative conversion (HR 2.14, 95% CI 1.42–3.22), and positive resection margin (HR 2.37, 95% CI 1.26–4.52) (Table 2, http://links.lww.com/SLA/C74).

After rectal cancer surgery, postoperative mortality was 2.1% for patients without leakage and 7.1% for patients with leakage ($P = 0.030$, Table 1, http://links.lww.com/SLA/C74). Overall survival at 5 years follow-up was 78.7% and 69.3%, respectively. Two out of 5 possible confounders remained significant: ASA-score and tumor stage II or III (HR 1.91, 95% CI 1.14–3.21 and HR 3.58, 95% CI 2.23–5.75, respectively) (Table 2, http://links.lww.com/SLA/C74). Leakage was not an independent predictor of overall survival at 5-years follow-up after colon or rectum cancer surgery (HR 1.33, 95% CI 0.58–3.02 and HR 1.39, 95% CI 0.89–2.17, respectively) (Table 2, http://links.lww.com/SLA/C74).

Disease-free Survival
After colon cancer surgery, disease-free survival was 67.6% for patients without anastomotic leakage and 50.9% for patients with leakage (Table 3, http://links.lww.com/SLA/C74, Fig. 1). Out of the 8 variables found with univariate analysis, 4 variables including ASA-score III or IV (HR 2.26, 95% CI 1.64–3.12 and HR 12.12, 95% CI 5.20–28.26, respectively), tumor stage III (HR 2.86, 95% CI 2.06–3.97), need for intraoperative conversion (HR 1.97, 95% CI 1.37–2.83) and positive resection margin (HR 2.26, 95% CI 1.23–4.15) were identified as independent predictors (Table 3, http://links.lww.com/SLA/C74). Anastomotic leakage was not a significant risk factor of decreased disease-free survival (HR 1.40, 95% CI 0.69–2.84).

After rectal cancer surgery, disease-free survival at 5 years was 70.9% for patients without and 53.6% for patients with leakage (Table 3, http://links.lww.com/SLA/C74, Fig. 1). Uni- and multivariate analysis showed that ASA-score II or III (HR 1.64, 95% CI 1.13–2.37 and HR 1.71, 95% CI 1.10–2.66, respectively), tumor stage III (HR 2.37, 95% CI 1.68–3.55), positive resection margin (HR 2.11,
95% CI 1.17–3.79), and leakage (HR 1.67; 95% CI 1.16–2.41) were independent factors for a decreased disease-free survival (Table 3, http://links.lww.com/SLA/C74).

Recurrence

After colon cancer surgery, local recurrence at 5-years follow-up was 8.4% in patients without anastomotic leakage and 15.4% in patients with leakage (Table 4, http://links.lww.com/SLA/C74, Fig. 2). Multivariate analysis identified 2 variables as significant predictors for local recurrence: tumor stage III (HR 5.20, 95% CI 2.34–11.53) and positive resection margin (HR 5.00, 95% CI 2.17–11.52). Distant recurrence rate was 15.1% respectively 16.2% (Table 5, http://links.lww.com/SLA/C74). Tumor stage II or III was the only significant variable in the analysis of distant recurrence (HR 2.14, 95% CI 1.10–4.16 and HR 6.81, 95% CI 3.64–12.76) (Table 5, http://links.lww.com/SLA/C74). Anastomotic leakage was not a significant variable for local or distant recurrence (HR 2.10, 95% CI 0.66–6.68 and HR 1.02, 95% CI 0.33–3.21, respectively).

After rectal cancer surgery, local recurrence at 5-years follow-up was 4.6% and 13.3%, respectively (Table 4, http://links.lww.com/SLA/C74, Fig. 2). Multivariate analysis showed that positive resection margin (HR 5.01, 95% CI 1.89–13.29) and anastomotic leakage (HR 2.96; 95% CI 1.38–6.34) were independent factors for local recurrence after resection for rectal cancer (Table 4, http://links.lww.com/SLA/C74). Distant recurrence was 19.6% and 25.0% (Table 5, http://links.lww.com/SLA/C74). Tumor stage III (HR 2.62, 95% CI 1.69–4.06) and positive resection margin (HR 2.59, 95% CI 1.38–4.86) were the 2 variables significant in the multivariate analysis. Anastomotic leakage was not a significant variable for distant recurrence (HR 1.21, 95% CI 0.71–2.04).

DISCUSSION

This study, analyzing the data of the COLOR and COLOR II trials, shows that anastomotic leakage after rectal cancer surgery is associated with an increased local recurrence rate and decreased disease-free survival rate at 5-year follow-up. Distant recurrences and overall survival were not significantly influenced by leakage after rectal cancer surgery. For colon cancer surgery, no significant effect of anastomotic leakage on long-term oncological outcomes was observed, presumably due to low power as a result of a relatively low leakage rate.

Strengths of this study include the randomized, multicenter design of the 2 trials included, COLOR and COLOR II, both comparing laparoscopic to open surgery. All patients received perioperative care and follow-up according to uniform study protocol.
to limit the variability in practice. Furthermore, the size of each of the trials is such that meaningful analyses could be made separately for colon and rectal cancer. Further strengths include the low rates of post randomization exclusions and the high follow-up rates. The prospective collection of data necessary for adjusted analysis are also important for the quality of these analyses. A limitation is the rather long time that has evolved since randomization and data collection, as in all probability, clinical routines may have changed over the years.

In the COLOR trial, no significant effect of leakage on oncological outcomes was observed. Although the local recurrence rate at 5-years follow-up was 8.4% in patients without anastomotic leakage and 15.4% in patients with leakage, this difference was not statistically significant. With a relatively low sample size and anastomotic leakage rate in the COLOR study (2.5%), this study was possibly underpowered to detect a true difference in outcomes. Due to this possible type II error, no conclusions on the effect of anastomotic leakage after colon surgery on long-term oncological outcomes can be drawn. In current literature results are often influenced by combining the results of patients after colon and rectal cancer resections. Of these studies, only the study by Krarup et al, using the prospective database of the Danish Colorectal Cancer Group, found a significantly higher rate of distant recurrence in patients with anastomotic leakage. Adding these results to a previously published meta-analysis by Mirnezami et al, showed that the association of increased distant recurrences was indeed significant. None of the studies showed an association between anastomotic leakage and local recurrences after colon cancer resection. Even though the COLOR trial is the largest randomized controlled trial comparing laparoscopic and open surgery for colon cancer, it was not designed and powered to investigate the difference between patients with and without anastomotic leakage. It should be mentioned that with a 1%–3% anastomotic leakage rate after colon cancer surgery, very large populations with long follow-up are mandatory for accurate evaluation. This suggestion is supported by the fact that Krarup et al, including almost 30,000 patients, indeed found significant differences in long-term oncological outcomes. We, therefore, believe that our results should be included in upcoming meta-analyses on long-term oncological outcomes after colon cancer surgery comparing patients with and without anastomotic leakage.

FIGURE 2. Local recurrence. A, Local recurrence at 5 years follow-up for patients with colon cancer; B, local recurrence at 5 years follow-up for patients with rectal cancer.

| Leakage    | 27 | 20 | 18 | 14 | 13 | 9 | 6 |
|------------|----|----|----|----|----|---|---|
| No Leakage | 1041 | 977 | 891 | 827 | 694 | 551 | 308 |
to improve the quality of such analyses, validate our results and increase the level of evidence on this matter.

In the COLOR II trial, local recurrence rate at 5-years follow-up was significantly higher in patients who had anastomotic leakage after rectal cancer surgery. Although local recurrence in patients without leakage stabilized around 5%, the percentage of patients with an anastomotic leak and a subsequent local recurrence increased to 13.3% at 5-year follow-up. These findings are in line with other studies. The most recent meta-analysis of high-quality by Lu et al also found an increased rate of local recurrence after anastomotic leakage with an odds ratio of 1.45 (95% CI 1.19–1.76, P < 0.001). Our results, from one of the largest rectal cancer trials, strengthens the findings that there is an association between anastomotic leakage and local recurrence.

To make valid comparisons with literature, clear-cut inclusion criteria and definitions are needed. One aspect is separate analysis of surgery for colon and rectal cancer. Many articles discussing outcome after anastomotic leakage combined results of these 2 groups, which makes their results difficult to interpret. Another aspect is a uniform definition of anastomotic leakage. Despite a proposal by the International Study Group of Rectal Cancer to classify anastomotic leakage after low anterior resection based on the intervention needed, a wide range of definitions is used to describe anastomotic leakage, which hampers comparison of results. Because development of presacral abscess is suggested to be an anastomotic leak, patients after a Hartmann resection were also included despite the absence of an anastomosis. Leakage of the rectal stump causing a pelvic abscess could lead to an inflammatory response similar to anastomotic leakage.

In literature various perioperative factors have been examined as possible causes of cancer recurrence after surgery. However, the mechanisms between leakage and recurrence remains to be clarified. Often the postponement of adjuvant therapy needed for stage III disease after anastomotic leakage is thought to cause worse disease free survival. However we did not find this association within the data from the COLOR study, as for stage III disease, no difference was observed in disease free survival nor local recurrence rate after leakage. For rectal cancer, as documented in the COLOR II trial, the potential bias is less obvious. A substantial percentage of the patients was included in the Netherlands. In the Dutch guidelines, adjuvant chemotherapy is not considered as standard therapy for stage III disease. One hypothesis on the mechanism by which leakage could lead to cancer recurrence is based on research on mechanisms behind peritoneal recurrence after colorectal cancer surgery. This hypothesis states that viable cancer cells may spill into the peritoneal cavity during surgery. The inflammatory response to surgical trauma could then enhance tumor cell adherence and later growth. Another explanation could be that the localized inflammatory reaction due to leakage upregulates the expression of receptors associated with adhesion of tumor cells as is shown in rat models after surgical

FIGURE 2. (Continued).
inflammatory response. This might explain the association found between anastomotic leakage and increased (intra-abdominal) recurrence rate. More research on this phenomenon, however, is needed as this hypothesis is based on the idea that the spilled tumor cells in the abdominal cavity remain vital up to the moment when anastomotic leakage occurs, which can vary between a few days to a couple of months after index surgery.

The current trial has several limitations. First, in the COLOR trial, additional power calculation revealed a 20% probability of rejecting a false null hypothesis, no effect of anastomotic leakage on local recurrence (see Supplementary Documents: power calculation, http://links.lww.com/SLA/C71). The low power, which is partly due to a low incidence of anastomotic leakage in the COLOR cohort, makes it difficult to reach significant differences. Secondly, some of the lack of effect of leak on outcome in the colon cancer analyses may relate to the relative ineffectiveness of adjuvant therapies, as the COLOR trial largely predates the era of FOLFOX adjuvant chemotherapy. Another limitation is that the type of intervention needed for the anastomotic leakage was not recorded consistently in the COLOR and COLOR II trial, therefore the relationship between severity of the anastomotic leakage and oncological impact could not be studied properly. In addition, some risk factors of anastomotic leakage that could also influence poor oncologic outcome, such as smoking history, cardiovascular disease, and prednisone use, were not registered in the COLOR and COLOR II databases and, therefore, could not be taken into account in the analyses. Nevertheless, this is one of the largest high quality data sets demonstrating the risk association of cancer recurrence after anastomotic leakage. Although these trials were not designed to investigate the effect of anastomotic leakage on oncological outcome, we believe that the high-quality data allow important comparison of these groups.

In summary, leakage was an independent risk factor influencing local recurrence and disease-free survival after rectal cancer surgery. For colon cancer, no significant effect was observed; however, due to low power, no conclusions on the influence of anastomotic leakage on outcomes after colon surgery could be reached. Based on our results, in combination with findings reported in the literature, we conclude that follow-up for patients with evidence of anastomotic leakage after rectal cancer surgery should be more frequent and should include investigations that could detect early signs of local recurrence.

Figures, http://links.lww.com/SLA/C73

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REFERENCES
1. McDermott FD, Heeney A, Kelly ME, et al. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg. 2015;102:462–479.
2. Smith JA, King PM, Lane RH, et al. Evidence of the effect of ‘specialization’ on the management, surgical outcome and survival from colorectal cancer in Wessex. Br J Surg. 2003;90:583–592.
3. Vignali A, Fazio VW, Lavery IC, et al. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. J Am Coll Surg. 1997;185:105–113.
4. Ishibest WH. Anastomotic leak in colorectal surgery: a single surgeon’s experience. ANZ J Surg. 2003;7:516–520.
5. Milewsky WJ, Joel RJ, Rege RV, et al. Treatment of anastomotic leakage following low anterior colon resection. Arch Surg. 1988;123:968–971.
6. Murrell ZA, Stamos MJ. Reoperation for anastomotic failure. Clin Colon Rectal Surg. 2006;19:213–216.
7. Platell C, Barwood N, Dorfmann G, et al. The incidence of anastomotic leaks in patients undergoing colorectal surgery. Colorectal Dis. 2007;9:71–79.
8. Akyol AM, McGregor JR, Galloway DJ, et al. Anastomotic leaks in colorectal cancer surgery: a risk factor for recurrence? Int J Colorectal Dis. 1991;6:179–183.
9. Bell SW, Walker KG, Rickard MJ, et al. Anastomotic leakage after curative anterior resection results in a higher prevalence of local recurrence. Br J Surg. 2003;90:1261–1266.
10. Brabanag G, Finnis D. Prognosis after anastomotic leakage in colorectal surgery. Dis Colon Rectum. 2005;48:1021–1026.
11. Fujita S, Teramoto T, Watanabe M, et al. Anastomotic leakage after colorectal cancer surgery: a risk factor for recurrence and poor prognosis. Jpn J Clin Oncol. 1993;23:299–302.
12. Law WL, Choi HK, Lee YM, et al. Anastomotic leakage is associated with poor long-term outcome in patients after curative colorectal resection for malignancy. J Gastrointest Surg. 2007;11:8–15.
13. Merkel S, Wang WY, Schmidt O, et al. Locoregional recurrence in patients with anastomotic leakage after anterior resection for rectal carcinoma. Colo- rectal Dis. 2003;1:154–160.
14. Mirnezami A, Mirnezami R, Chandakumarana K, et al. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leakage: systematic review and meta-analysis. Ann Surg. 2011;253:890–899.
15. Petersen S, Freiag M, Hellmich G, et al. Anastomotic leakage: impact on local recurrence and survival in surgery of colorectal cancer. Int J Colorectal Dis. 1998;13:160–163.
16. Prok H, Marusch F, Meyer F, et al. Impact of anastomotic leakage on oncological outcome after rectal cancer resection. Br J Surg. 2007;94:1548–1554.
17. Boccolla MA, Buettner PG, Rozen WM, et al. Risk factors and outcomes for anastomotic leakage in colorectal surgery: a single-institution analysis of 1576 patients. World J Surg. 2011;35:186–195.
18. Furnee EB, Aukema TS, Oosterling SJ, et al. Influence of conversion and anastomotic leakage on survival in rectal cancer surgery; retrospective cross-sectional study. J Gastrointest Surg. 2019;23:2007–2018.
19. Jung SH, Yu CS, Choi PW, et al. Risk factors and oncologic impact of anastomotic leakage after rectal cancer surgery. Dis Colon Rectum. 2008;51:902–908.
20. Kube R, Mroczykowski P, Granowski D, et al. Anastomotic leakage after colon cancer surgery: a predictor of significant morbidity and hospital mortality, and diminished tumour-free survival. Eur J Surg Oncol. 2010;36:120–124.
21. Marra E, Steffen T, Kalak N, et al. Anastomotic leakage as a risk factor for the long-term outcome after curative resection of colon cancer. Eur J Surg Oncol. 2009;35:1060–1064.
22. McArdle CS, McMillan DC, Hore DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. Br J Surg. 2008;95:1150–1154.
23. Walker KG, Bell SW, Rickard MJ, et al. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Am J Surg. 2004;240:255–259.
24. Espin E, Ciga MA, Pera M, et al. Oncological outcome following anastomotic leak in rectal surgery. Br J Surg. 2015;102:416–422.
25. Jorgsen F, Johansson R, Damber L, et al. Anastomotic leakage after rectal cancer: a risk factor for local recurrence, distant metastasis and reduced cancer-specific survival? Colorectal Dis. 2011;13:272–283.
26. Phillips RK, Hittinger R, Blesovsky L, et al. Local recurrence following ‘curative’ surgery for large bowel cancer: I. The overall picture. Br J Surg. 1984;71:12–16.
27. Sauven P, Playforth MJ, Evans M, et al. Early infective complications and late recurrent cancer in stapled colonic anastomoses. Dis Colon Rectum. 1989;32:33–35.
28. Shigagapan S, Askari A, Maitzetz G, et al. The impact of anastomotic leak and its treatment on cancer recurrence and survival following elective colorectal cancer resection. World J Surg. 2015;39:1052–1058.
29. Veldkamp R, Kruyker H, Hop WC, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol. 2005;6:477–484.
30. Buunen M, Veldkamp R, Hop WC, et al. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. Lancet Oncol. 2009;10:44–52.
31. 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.
32. Bonjer HJ, Deijen CL, Haglind E, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med*. 2015;372:1324–1332.

33. ASA. American Society of Anesthesiologists. ASA Physical Classification System. Available at: https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system. Accessed April 5, 2019.

34. AJCC. American Joint Committee on Cancer Staging Manual, 8th edition. Available at: https://cancerstaging.org/references-tools/deskreferences/Pages/default.aspx. Accessed April 5, 2019.

35. Krarup PM, Nordholm-Carstensen A, Jorgensen LN, et al. Anastomotic leak increases distant recurrence and long-term mortality after curative resection for colonic cancer: a nationwide cohort study. *Ann Surg*. 2014;259:930–938.

36. Lu ZR, Rajendran N, Lynch AC, et al. Anastomotic leaks after restorative resections for rectal cancer compromise cancer outcomes and survival. *Dis Colon Rectum*. 2016;59:236–244.

37. Rahbari NN, Weitz J, Hohenberger W, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery*. 2010;147:339–351.

38. Hiller JG, Perry NJ, Poullogiannis G, et al. Perioperative events influence cancer recurrence risk after surgery. *Nat Rev Clin Oncol*. 2018;15:205–218.

39. van den Tol PM, van Rossen EEL, van Eijck CH, et al. Reduction of peritoneal trauma by using nonsurgical gauze leads to less implantation metastasis of spilled tumor cells. *Ann Surg*. 1998;227:242–248.

40. Fermor B, Umpleby HC, Lever JV, et al. Proliferative and metastatic potential of exfoliated colorectal cancer cells. *J Natl Cancer Inst*. 1986;76:347–349.

41. Umpleby HC, Fermor B, Symes MO, et al. Viability of exfoliated colorectal carcinoma cells. *Br J Surg*. 1984;71:659–663.

42. Weese J, Ottery FD, Emoto SE. Do operations facilitate tumor growth? An experimental model in rats. *Surgery*. 1986;100:273–277.

43. Murthy SM, Goldschmidt RA, Rao LN, et al. The influence of surgical trauma on experimental metastasis. *Cancer*. 1989;64:2035–2044.

44. Oosterling SJ, van der Bij GJ, van Egmond M, et al. Surgical trauma and peritoneal recurrence of colorectal carcinoma. *Eur J Surg Oncol*. 2005;31:29–37.