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Oncologic outcome and recurrence rate following anastomotic leakage after curative resection for colorectal cancer

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ABSTRACT

Introduction: Anastomotic leakage is one of the most severe early complications after colorectal surgery, and it is associated with a high reoperation rate-, and increased in short-term morbidity and mortality rates. It remains unclear whether anastomotic leakage is associated with poor oncologic outcomes. The aim of this study was to determine the impacts of anastomotic leakage on long-term oncologic outcomes, disease-free survival and overall mortality in patients who underwent curative surgery for colorectal cancer.

Methods: This single-centre, retrospective, observational cohort study included patients who underwent curative surgery for colorectal cancer between 2005 and 2015 and who had a primary anastomosis. Survival- and multivariate cox regression analyses were performed to adjust for confounding.

Results: A total of 1984 patients had a primary anastomosis after surgery. The overall incidence of anastomotic leakage was 7.5%; 19 patients were excluded because they were lost to follow-up. Of the remaining 1965 patients, 41 (2.1%) developed local recurrence associated with anastomotic leakage [adjusted hazard ratio (HR) = 2.25; 95% confidence interval (CI) 1.14–5.29; P = 0.03]. Distant recurrence developed in 291(14.8%) patients with no association with anastomotic leakage [adjusted HR = 1.30 (95% CI: 0.85–1.97) P = 0.23]. Anastomotic leakage was associated with increased long-term mortality [adjusted HR = 1.69 (95% CI 1.32–2.18) P < 0.01]. Five year disease-free survival was significantly decreased in patients with anastomotic leakage, (log rank test P < 0.01).

Conclusion: Anastomotic leakage was significantly associated with increased rates of local recurrence, disease free-survival and overall mortality. Associations of anastomotic leakage with distant recurrence was not found.

1. Introduction

Anastomotic leakage (AL) is one of the most severe early complications after colorectal surgery. AL is associated with a high reoperation rate, increases in the severity of short-term morbidity and mortality rates, poor functional outcomes and higher healthcare costs [1–7]. Incidence rates of AL vary from 0.5 to 34% but are dependent on several factors, such as tumour location (colon or rectum), type of operation, and patient characteristics [4,8–10]. Another explanation for the broad range of reported cases of AL is the wide variability in the definition of AL. Some articles only included patients with symptomatic AL, whereas other authors also included asymptomatic AL, the diagnosis of which was based on radiologic findings. Because of the recent increase in sphincter preserving surgery for rectal cancer, the likelihood of AL will increase as well, and patients with a low anastomosis have a higher risk of leakage [11–14]. In general, AL is related to poor prognosis. In the literature, there have been conflicting studies of the oncologic outcomes and long-term mortality in patients with AL after curative surgery for colorectal carcinoma (CRC). Several studies have reported increased rates of local tumour recurrence [15–23], while other studies have not [24–30]. The relation with the occurrence of distant metastases has also been studied. In these studies, contradictory results have been found [9,21,22,30–32]. It remains unclear whether AL is associated with poor oncologic outcomes. The aim of this study was to determine the impact of AL on local recurrence and distant recurrence rates, -disease-free survival and overall mortality in patients who underwent curative

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surgery for CRC.

2. Materials and methods

2.1. Database and definitions

This was a single-centre retrospective observational study with data on eleven years of colorectal surgeries. We retrospectively reviewed all of the patients who were treated between January 2005 and December 2015. Data regarding patients between 2005 and 2010 were prospectively collected by the surgical team. Data from patients who underwent surgery in our hospital because of colorectal cancer between 2011 and 2015 were retrieved at the National Cancer Registration centre (Integraal Kanker Centrum Nederland, IKNL). Medical and demographic data were ascertained from medical charts. Data regarding surgery included the location of the tumour within the colon and/or rectum, type of resection that was performed and surgical approach (open or laparoscopic surgery). Laparoscopic surgery also included robotic surgery. Pathology results were classified according to The TNM classification, 5th edition [33]. Postoperative data consisted of surgical complications, including anastomotic leakage, oncologic outcomes and postoperative mortality. Anastomotic leakage was defined as communication between the intra- and extraluminal compartments, determined by clinical evidence and/or confirmed by radiologic imaging. Clinical evidence was based on symptomatic anastomotic leaks, defined by the presence of peritonitis or fever (temperature greater than 38.5 °C), or the discharge of pus or faeces from the abdominal drain. Clinical and/or biochemical suspicion (increased leucocytes and C-reactive protein (CRP)) of anastomotic leakage led to early CT assessment. Additionally, anastomotic dehiscences with leakage into the peritoneum or pelvic cavity, leakage from the efferent or afferent limb and anastomotic abscesses were also considered as anastomotic leakage. Asymptomatic anastomotic leakage was considered when leakage was assessed on CT-scan, without any relevant clinical symptoms or laboratory examination findings during the postoperative course. The oncological outcome measures were local recurrence, distant recurrence, disease free survival and overall survival. All patients with recurrent disease were confirmed histologically whenever possible, or otherwise by diagnostic imaging or surgery. Local recurrence was defined as recurrent tumour growth intraabdominally or within the pelvic cavity. Other tumour recurrence events were categorized as distant recurrence, including peritoneal metastasis/carcinomatosis. Disease-free survival was defined as the period from the date of curative surgery to the date of detection of local recurrence and/or distant recurrence, date of last follow-up or death. Overall survival was defined as the time from the date of curative surgery to the date of death or last follow-up. Date of death was confirmed using the social security numbers of patients in the Dutch Municipal Personal Records Database (Gemeentelijkebasisadministratie persoonsgegevens, GBA with their software program CompeT&TEindhoven). The follow-up strategies for patients with and without anastomotic leakage were identical. Most of the patients had a follow-up interval by the surgeon of three months during the first year and every six months thereafter. Each follow-up visit included a physical examination, measurement of the serum carcinoembryonic antigen (CEA), ultrasound of the abdomen and chest X-ray. Chest CT, abdominopelvic CT, or positron emission tomography (PET) were performed when there was high suspicion of recurrence of disease on routine imaging studies with or without increased CEA levels.

2.2. Inclusion and exclusion criteria

Patients were included if they underwent colorectal surgery for a colorectal tumour between 2005 and 2015. Patients with appendix carcinomas or pseudomyxoma peritonei (PMP) were excluded. Patients who underwent palliative surgical procedures were also excluded. Surgical procedures with permanent colostomy or no primary anastomosis were excluded as well (Hartmann procedure, abdominoperineal resection (APR) or transanal endoscopic microsurgery (TEM)).

2.3. Ethical approval

For ethical approval, we consulted the national institutional review board Medical Research Ethics Committees United (MEC-U). Referring to this study (reference number W17.073) confirmation was received that the Medical Research Involving Human Subject Act (WMO) does not apply; therefore, official approval of this study by the MEC-U was not required under the WMO. We also consulted the institutional review board of the Amphia Hospital (AMOA) and it confirmed that no formal written waiver for the need of ethics approval was required, because of the retrospective design of the study.

2.4. Statistics

The Kolmogorov-Smirnov test was used to define whether data was normally distributed. Data are reported as means and SDs for normally distributed data and medians and interquartile ranges (IQRs) for non normally distributed data. We used the $\chi 2$ test to compare dichotomous variables. Overall survival and disease free survival analyses were performed with Kaplan-Meier curves between anastomotic leakage and no anastomotic leakage. The log-rank test was used to test outcomes between these two groups. Cox proportional hazard models were used to estimate the independent effects of covariates on oncologic outcomes and overall mortality measured by the adjusted hazard ratio (HR) with a 95% confidence interval (CI). Variables that were statistically significant in the univariate Cox regression and/or had clinical relevance were included in the multivariate analysis. A two sided P-value less than 0.05 was used to indicate statistical significance. All of the data analyses were performed with the IBM SPSS statistics software program, version 24.

3. Results

A total of 2703 patients underwent surgery for CRC between 2005 and 2015 in this cohort.After exclusion, 1984 patients were eligible (73.4%) (Fig. 1). The overall incidence of AL was 148 out of 1984 patients (7.5%). Nineteen patients were lost to follow-up because of emigration orfollow-up in another hospital. A total of 1965 patients were included for the analysis. The median age was 70.0 years old (IQR 62–77), and the median follow-up time was 4.1 years (IQR 2.0–6.4) years). The patient and clinical characteristics are shown in Table 1.

3.1. Disease recurrence

The overall local recurrence rate was 2.1% (41 of 1965) and the overall distant recurrence ratewas 14.8% (291 of 1965). The incidence of local recurrence at the end of follow-up was significantly higher in the AL group compared to the no AL group (4.7% vs. 1.9%, P = 0.019). However, there was no significant difference in the incidence of distant recurrence at the end of follow-up in the AL group (17.6% vs. 14.6%, P = 0.326, Table 2). Local and distant recurrences were diagnosed in twenty patients (1.0%), three patients in the AL group and seventeen patients in the no AL group. The median time to diagnosis of local recurrence was 1.1 years (IQR 0.7–2.1 years). The median time to diagnosis of distant recurrence was 1.1 year (IQR 0.6–2.2 years). No significant difference was found in the median time to local recurrence in the anastomotic leakage group compared to the group without anastomotic leakage (1.1 years (IQR 0.7–1.8) vs. 1.0 year (IQR -0.7–2.3), P = 0.86). Likewise, no significant difference was found in the median time to distant recurrence in the anastomotic leakage group compared to the group without anastomotic leakage (0.5 year (IQR 0–1.1) vs. 0.4 year (IQR 0–1.4) P = 0.73). In the univariate analyses, Al was