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Prognostic impact of anastomotic leakage after elective colon resection for cancer – A propensity score matched analysis of 628 patients

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ABSTRACT

Background: There is limited information regarding the impact of anastomotic leakage on oncologic outcome in exclusively colon cancer patients.

Methods: The colorectal database of the Department of Surgery of the University of Heidelberg was used to assess the impact of anastomotic leakage on oncologic outcome in patients undergoing curative resection for Stage I–III colon cancer. Risk-adjusted Cox regression analysis and propensity score methods were used to assess overall, disease-free, and relative survival.

Results: 628 patients of which 26 (4.1%) experienced anastomotic leakage were analysed. Anastomotic leakage was associated with significantly worse overall, disease-free and relative survival in univariate and multivariate analysis. The analysis after exact propensity score matching confirmed the negative impact of anastomotic leakage on overall (HR 2.62, 95% CI 1.33–5.18, $p = .011$), disease-free (HR 2.28, 95% CI 1.16–4.47, $p = .027$) and relative survival (HR 3.70, 95% CI 1.82–7.52, $p < .001$). 5-year overall survival was 51.6% (95% CI 34.5–77.2%) for patients with anastomotic leakage compared to 77.7% (95% CI 73.0–82.8%) for patients without anastomotic leakage.

Conclusions: All conceivable efforts should be made to avoid anastomotic leakage after colon resection for cancer not only to evade short-term consequences but also to allow for adequate long-term outcome.

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Introduction

In Europe, colorectal cancer represents the second most common malignancy and, after lung cancer, it is the second most frequent cause of cancer death [1,2]. Even though survival of patients with colorectal cancer increased with implementation of modern multimodal treatment strategies, the mainstay of treatment remains radical surgery.

Anastomotic leakage is the most serious complication after colorectal surgery resulting in severe impairment of quality of life [3], reoperations and higher perioperative mortality [4]. In addition to the short-term postoperative consequences, a potential negative

impact on oncological outcome has been discussed. Especially after rectal resections, several studies [5–7] and a comprehensive meta-analysis [8] identified a negative impact of anastomotic leakage on overall and disease-free survival. However, most of these retrospective studies were not able to adjust for clinically relevant factors such as quality of mesorectal resection and circumferential resection margin status, which are well known to impact survival and local recurrence rates in rectal cancer [9–11]. Although such confounding parameters, except for the principle of complete mesocolic excision, are less important in colon cancer resection, there is limited information regarding the impact of anastomotic leakage on survival in exclusively colon cancer patients. Furthermore, the prognostic relevance of anastomotic leakage is even more controversial within the few existing former studies, which report conflicting results [8].

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Thus, the objective of the present analysis was to assess the impact of anastomotic leakage on oncologic outcome in a large homogenous cohort of patients with exclusively colon cancer receiving curative resection for Stage I–III disease. To increase statistical strength and to further elaborate on the possible detrimental impact of anastomotic leakage on survival, both Cox proportional hazard regression analyses and propensity-scoring methods were applied.

Methods

In present retrospective analysis the prospectively maintained colorectal database of the Department of General, Visceral, and Transplantation Surgery of the University of Heidelberg was queried for patients undergoing colonic resection due to sporadic colon cancer between January 2001 and June 2014. Patients with stage IV disease, in-hospital or 30-day mortality, resections due to local recurrence, emergency resections, patients with inflammatory bowel disease or hereditary colorectal cancer syndromes, R1/2 or Rx resection and patients lost to follow-up were excluded from the analysis. The cohort was divided into two groups on the basis of the occurrence of anastomotic leakage.

Informed consent was acquired from all patients planned to undergo colon resection for cancer. The independent ethics committee of the University Heidelberg approved the present study. Predefined data were collected and ascertained from medical charts and registered in a prospective electronic database. Baseline data included age, gender, American Society of Anaesthesiologists (ASA) score, body mass index (BMI), type of colonic resection, American Joint Committee on Cancer (AJCC) stage, number of harvested and number of positive lymph nodes, tumor grade, CEA and CA19-9 levels. Relevant comorbidities and risk factors were also evaluated. Furthermore, the following information was assessed: surgical approach (open/laparoscopic), intensive care unit stay (yes/no; duration), adjuvant chemotherapy (yes/no).

Complications were closely monitored, including overall complications, surgical complications, anastomotic leakage, post-operative haemorrhage, intra-abdominal abscess, wound infection, reoperation, hospital readmission, pneumonia, urinary tract infection, cardiac complications, respiratory decompensation, deep vein thrombosis, pulmonary embolism and acute renal failure/dialysis.

All operations were performed or supervised by experienced colorectal surgeons and done as highly standardized procedures. In the case of a right sided tumor the venous vessels were divided at the inflow into the superior mesenteric vein, which was always identified. The corresponding arteries were transected at the same level. A mobilisation of the duodenum (Kocher manoeuvre) was not routinely performed. In patients with a carcinoma in the region of the hepatic flexure the great curvature of the stomach was freed for 10–15 cm from the right gastroepiploic arcade. In this view, the surgical concept of complete mesocolic excision representing a sharp dissection of the undamaged visceral fascia of mesocolon from the parietal fascia of peritoneum was performed in all patients [12].

Anastomotic leakage was defined as communication between the intra- and extraluminal compartments resulting from a defect in the integrity of the intestinal wall at the anastomosis diagnosed by extravasation of endoluminally administered water-soluble contrast medium at radiography or computed tomography, or proof of anastomotic leakage at reoperation. The presence of an abscess near the anastomosis was also considered as anastomotic leakage.

Regular follow-up was performed for 5-years postoperatively at the outpatient clinics of the Surgical Department or the National Center for Tumor Diseases, Heidelberg, Germany. The follow-up

was performed according to national guidelines [13]. Adjuvant chemotherapy was administered routinely to patients with node-positive disease.

Statistical analyses were performed using R statistical software (www.r-project.org). A two-sided p-value < .05 was considered statistically significant. Continuous data are expressed as means \pm standard deviation. For comparing proportions, Chi-Square statistics and for comparing continuous variables t-tests and Mann-Whitney U-tests were used as appropriate. Missing data were imputed using the random survival forest method [14].

First, bias concerning anastomotic leakage versus no leakage was assessed regarding the above mentioned baseline data. The same set of covariates including anastomotic leakage versus no leakage were then assessed as putative prognostic factors for overall, relative and disease-specific survival in unadjusted and risk-adjusted Cox regressions including a backward variable selection procedure from the full Cox regression model based on the Akaike's information criterion.

It is often difficult or even impossible to ascertain the exact cause of death, especially in retrospective cohort studies. Relative survival was shown to be a good estimate of the cancer-specific survival without the necessity to classify the exact cause of death [15]. The relative survival represents the ratio of the observed (=overall) survival of the patients with colon cancer and the expected survival, where the expected survival is the survival of a group of the general German population with similar characteristics (gender, age, calendar year of birth) than the study cohort except for the risk factor (colon cancer) analysed. The population tables regarding background mortality for relative survival analyses were obtained from the National Statistical Office [16]. The relative survival analyses were performed using the R package *relSurv* using the Pohar-Perme estimator [17]. Population mortality rates were included as time-dependent covariates (multiplicative Cox regression model) [18]. Age and gender were also included in the risk set for the multivariate relative survival analysis to allow for informative censoring, although the baseline mortality rate was already estimated according to age and gender [19].

Moreover, a propensity score analysis was performed [20–22]. We used the "Matching" R package to perform a bipartite weighting propensity score analysis [23,24].

Baseline risk of the matched patients was finally compared to assure that no major differences in observed baseline patient's characteristics persisted. The prognostic value of anastomotic leakage versus no leakage for overall, relative and disease-specific survival was finally assessed in a stratified Cox regression analysis applying the subclasses and the weights obtained by the propensity score analysis. Based on these models, adjusted survival curves and 5-year survival rates were estimated for overall and disease-specific survival. This was not possible for relative survival because the Cox regression model is not capable to simultaneously incorporate the weights for relative survival analysis and the weights obtained in the propensity score analysis.

Results

In total, 1251 patients with colon cancer underwent colon resection during the study period. Patient selection is illustrated in Fig. 1. A total number of 628 patients that underwent R0-resection for primary colon cancer (AJCC stage I–III) were analysed. Of these, 26 patients (4.1%) experienced anastomotic leakage and 602 patients (95.9%) did not develop anastomotic leakage. 23 of the 26 patients (88.5%) with anastomotic leakage underwent reoperation, whereas 3 (11.5%) were treated by antibiotic therapy only.

Mean follow-up of the cohort was 4.7 ± 3.7 years. The median age of the total cohort was 69.0 years [IQR 60.2–75.8] (anastomotic

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