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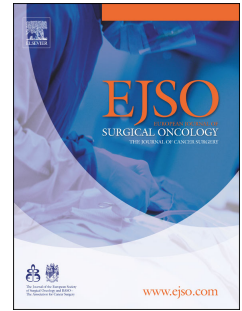


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Original Article**Anastomotic leakage after colon cancer surgery: a predictor of significant morbidity and hospital mortality, and diminished tumour-free survival**

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Abstract**Aim**

The objective of this study was to find out the effects of anastomotic leakage (AL) following resection of colon cancer upon perioperative outcome and long-term oncological result.

Patients and methods

Using the data base of a country-wide quality assurance study “Quality Assurance in Primary Colorectal Carcinoma” we analysed the data from the complete sub-population of 844 patients who had AL after resection of colon cancer. These were compared with corresponding data from 27 427 similar patients without AL. Hospital mortality, AL-associated post-operative morbidity and long-term outcome were investigated.

Results

Hospital mortality after AL was 18.6%, compared with 2.6% for patients without AI. AL-related secondary complications occurred in 62.7% cases, while patients without AL had a corresponding rate of 19.9%. Those with AL had a poorer long-term oncological result, with a five-year survival rate of 51.0% ($p < 0.001$) and a five-year tumour-free survival rate of 63.0% (compare 74.6% without AL; $p < 0.001$).

Conclusions

Post-operative AL after resection of colon cancer is associated with significant morbidity and hospital mortality rates and a greater risk of a poor oncological outcome.

Keywords: Colonic neoplasm – Colon surgery – Anastomotic leakage – Postoperative complications – Survival analysis

Introduction

In spite of recent developments in diagnosis, treatment and surgical technique, the problem of anastomotic leakage (AL) remains a major one. It is encountered frequently in routine surgical practice, and it is associated with an increase in early post-operative mortality [1, 2, 3, 4]. For colorectal cancer, there are indications that AL worsens the long-term oncological result [5, 6, 7]. However, until now a corresponding tendency has not been demonstrated for colon carcinoma [8, 9].

The objective of this research was to find out the peri-operative effects of AL in a large, multicentric analysis of a representative patient population. In addition, the influence of AL upon the long-term oncological result was investigated.

Methods

- Study -

In the German multicentric study “Qualitätssicherung Kolon/Rektumkarzinome (Primärtumor)” (Quality Assurance in Primary Colorectal Carcinoma), data for patients with colorectal carcinoma were acquired prospectively by the An-Institut für Qualitätssicherung in der operativen Medizin at the University of Magdeburg. Data acquisition took place over a period of five years, from January 1st 2000 to December 31st 2004. These data represent the state of treatment of these patients in routine clinical practice, and they cover the entire spectrum of hospital types in Germany. A total of 346 institutions providing treatment at all levels took part in the study. The individual data were recorded on a standardised questionnaire at each participating hospital. This questionnaire comprises 68 questions to record the important aspects of peri-operative management of the patient: demographic characteristics, pre- and post-operative tumour status, tumour location, details of the operation and peri-operative treatment, pathological findings, hospital mortality the patient's status at discharge from hospital, and further treatment planned. The completed questionnaires were subjected to final checking by the hospital's local representative with responsibility for the study. Additionally, the data were also checked for completeness in an annual cross-check between the patients registered in the study and those registered at the hospitals, and plausibility checks were conducted by comparing the study data with the operation reports and patient narratives.

The study was conducted in accordance with the Declaration of Helsinki. Participation in the study was voluntary, and data were recorded anonymously. This was a purely observational study and thus had no influence upon the methods or the course of treatment. For this reason, a vote of the ethics committee was not required. All the patients gave written consent to the acquisition and anonymised evaluation of their data.

- Analysis -

The present analysis covered the set of patients who received an anastomosis after resection of colon carcinoma, i.e. – by definition – all carcinomas between the ileocaecal valve and a point 16 cm above the anal verge. The criterion for distinction between this and rectal carcinoma was provided by measurement of the distance between the lower edge of the tumour and the anal verge with a rigid rectoscope. An AL was recorded if any of the following criteria were met: (i) surgical procedure (relaparotomy performed), (ii) radiological

results (computer-aided tomography or X-ray with contrast medium) or (iii) evidence from an autopsy.

Long-term outcome data were obtained with the help of a second questionnaire completed either by the patient's general practitioner or by the hospital at which the operation had taken place. A second questionnaire was completed by the patient's own doctor or, where appropriate, by the hospital; this include last contact with the patient, life status or cause of death (tumour-related, tumour-independent), any local recurrence, any distal metastasis, and as appropriate the time of recurrence and the method of detection (biopsy, endoscopy, imaging). In addition, information about the current tumour status was recorded (tumour-free, locally recurrent, distant metastases) and in cases of recurrence the time and method of detection (biopsy, endoscopy, imaging). The acquisition of follow-up data by the general practitioner was performed only with the written consent of the patient; a breakdown of patients according to their granting (or withholding) consent to the follow-up observation showed that those who withheld consent did not differ significantly from those who gave it, in respect of demographic variables (sex, body height and weight, age, body mass index or UICC (Union Internationale Contre le Cancer) tumour stage.

The set of patients with AL was investigated for the risk of development of AL-associated general or operation-specific secondary complications and for long-term outcome; this population was then compared with the patients without AL.

- *Statistics* -

The data were entered into an ACCESS data base and were evaluated with the statistical programme suite SPSS 12.0 (SPSS Inc., Chicago, IL, USA). For the descriptive statistics, frequency testing was performed for the various categorical variables. Differences among the variables in two-dimensional contingency tables were investigated by using the χ^2 test. Differences between groups were considered significant if a two-sided test yielded a *p* value below 0.05. Continuous variables, such as patient's age, were tested by using the robust *t* test. The analyses of overall and tumour-free survival were performed by the Kaplan–Meier method, and survival curves were compared by the log-rank test. The significance threshold for the appearance of a type-1 error was set at 5%.

Results

The study population included a total of 28 271 patients treated for colon cancer by resection with anastomosis. Of these, 3.0% ($n = 844$) developed an AL.

▪ *Post-operative course of disease*

- *Hospital mortality*

Hospital mortality was 18.6% (157 of 844) for patients with AL and only 2.6% (700 of 27 427). The risk of death for patients with an AL was thus 7.2 times higher than for those without this complication.

- *Morbidity*

Of the patients with AL, 62.7% (529 / 844) developed secondary complications. The complication rate was 19.9% (5 479 / 27 424) for patient without AL. Tables 1 and 2 show the frequencies of various kinds of general and operation-specific complications encountered.

- *Hospital stay*

The duration of stay in hospital was 2.3 times greater for patients with AL, and had a greater scatter (standard deviation, SD) than for those without it (Table 2).

- *Recommendation for adjuvant chemotherapy at time of discharge*

In the AL group, adjuvant chemotherapy in stage UICC III was less frequently recommended at time of discharge: 73.4% of patients in stage III without AL ($N=5\ 959 / 8\ 118$), but only 60.3% of patients with AL ($N=140 / 232$), had a recommendation for adjuvant chemotherapy ($p < 0.001$). Within the study it was not possible to determine whether chemotherapy was actually administered.

▪ *Long-term oncological outcome*

- *Follow up*

Follow-up information was available for 74.4% of the patients with AL (628 / 844) and for 77.6% of those without AL (21 296 / 27 427). The mean follow-up period was 23 months.

- *Overall survival, tumour-free survival*

The presence of AL was associated with a poorer long-term oncological outcome. The probability of 5-year overall survival was 51.0% in the group with AL, compared with 67.3% in the group without AL ($p < 0.001$; Figure 1). The worse long-term oncological outcome of

the patients with AL was not only due to peri-operative mortality: even the probability of 5-year tumour-free survival was 63.0% in the group with AL and was thus clearly lower than that in the group without AL, 74.6% ($p < 0.001$; Figure 2).

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Discussion

This study included 844 cases of AL and thus contains a body of data of sufficient size to yield a differentiated analysis of the effects of AL upon the peri-operative result and the oncological outcome.

- Peri-operative result -

Patients with AL have a substantial hospital mortality rate and a high rate of morbidity associated with the AL. The results of the present study showed an increase in hospital mortality by a factor of 7.2 in comparison with patients who did not have AL (hospital mortality with AL, 18.6%; without AL, 2.6%). This is in agreement with published results. McArdle et al. have reported a 30-day mortality for AL patients 16%, compared with 3.9% without AL [6], and Branagan et al. found corresponding rates as high as 29% and 4.3% [8]. Other groups, too, report a high early mortality associated with AL [2, 3]; furthermore, the removal of an anastomosis following an anastomotic leak often results in a 'permanent' stoma [4].

In many cases, an AL is the origin of further post-operative complication, above all those involving sepsis. This is clear if the frequencies of general and operation-specific complications in AL patients are compared with the corresponding rates found among patients without AL (Tables 1 and 2). In association with AL, pneumonia was 3.4 times, non-pneumonia pulmonary complications were 4.8 times, cardiac complications 3.4 times, renal complications 7.7 times and multi-organ failure was as much as 14.5 times more frequent than in its absence. Sepsis was more frequent by a factor of 23.7, wound infection 5.1, abscesses 18, enterocutaneous fistula 46, peritonitis 65.3 and complete rupture of the operation wound 7.2. Accordingly, the duration of post-operative hospital stay after the appearance of an AL was prolonged by a factor of 2.3. Some instances of documented enterocutaneous fistula without reported AL can be explained by assuming either that this was not a consequence of AL, but of some other intestinal injury, or that it was a consequence of delayed post-operative AL – which can occasionally occur [10] – or of unrecognised AL.

- Long-term result -

A substantial body of data is available on the long-term oncological outcome of rectal carcinoma. These show that AL has a negative influence upon long-term survival and is furthermore associated with an elevated rate of local recurrence and distant metastases [5, 7, 8, 9, 11]. Numerous groups have analysed the overall population of colorectal-carcinoma

patients. McArdle et al. investigated the long-term course of disease in a large ($N = 2235$) multicentric historical study of patients with colon and rectal carcinomas. The 5-year survival rate was 42% with and 66.9% without AL [6]. For the relatively long interval from 1971 to 1991, Walker et al. analysed 1722 patients with colon and rectal carcinomas at a single centre in Australia, where the AL rate was 5.1%. Among patients with AL, the overall five-year survival rate was 44.3%, compared with 64.0% for patients without AL [7].

There are only few data in the literature on the influence of AL upon the long-term oncological outcome for colon carcinoma, and such data as there are refer to small patient cohorts [8, 9]. After analysing 1201 patients with an AL rate of 2.6% ($n = 31$), Branagan et al. reported finding no influence of AL after colon resection (if rectal carcinoma is considered separately) on the rate of local recurrence or on five-year overall survival [8]. A Japanese group described a similar finding after assessing the comparatively small patient population at their (single) centre; their analysis included only 12 cases of AL after colon resection [9].

According to the results present here, the presence of an AL is associated with a substantially poorer long-term oncological course of disease than is found in its absence. This is seen immediately in the five-year overall survival (51.0% with AL and 67.3% without it). The initial sharp drop in the survival curve (Figure 1) is striking; this is due principally to the higher rates of post-operative mortality among patients with AL. However, the probability of five-year tumour-free survival is also significantly worse for patients with AL (63.0%, compared with 74.6% without AL), even when the peri-operative mortality associated with the operation itself is excluded from the analysis (Figure 2).

The causes of the poorer prognosis for patient with AL are not clear. In a highly detailed multivariate analysis of risk factors for anastomotic leakage following bowel resections for colon cancer already published by our group [12] it was shown that neither tumour-related factors (TNM stage, tumour grade) nor the patient's age is associated with an increase in the risk of AL, so that these factors are also not responsible for this effect. In the same study we found an increased risk of AL following resection of left-sided lesions. However, this factor does not provide a suitable explanation. Our group compared left- and right-side colon cancers using the same database, and found only a marginal difference in 5-year disease-free survival rate (74% and 73% respectively) [13]. Our data provide suggest that there may be an association with the lower rate of adjuvant therapy in the AL group. We found that adjuvant chemotherapy in UICC stage III was less frequently recommended in the AL group at the time of discharge for patients without AL (73.4%) than for those with AL (60.3%). A similar

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explanation was offered by Jung *et al.* [11]. This chemotherapy effect might be due to post-operative morbidity. Another reason could be the association with higher cardiac and hepatic comorbidity for the AL group, described recently by our study group [12]. Walker *et al.* [7] opined that the adverse impact of anastomotic leakage on long-term survival may be attributed not only to a reflection of the high post-operative morbidity associated with the development of intra-abdominal sepsis but also to an unknown inflammation-related immunological process that might enhance cancer recurrence. However, it is also possible that leaks occur as a consequence of other conditions, not detected in the data of the present study, that are themselves precursors of a poor outcome, making leakage prognostic rather than causative.

- *Conclusion* -

Our results show that post-operative AL is less frequent after resection of colon carcinoma than after corresponding rectal resection, but that it can also lead to significant morbidity and hospital mortality, thus worsening the long-term oncological outcome.

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Conflict of interest

None of the authors of this paper has any financial relationship that could lead, or have led, to a conflict of interest in connection with this work. The authors are employees of the respective institutions to which they are affiliated.

Authors' contributions

All authors contributed to the design of the study. Data were acquired by RK, IG and HL. The analysis was performed by US, RK, HL. The manuscript was drafted by RK, PM, IG and HL; the complete version was prepared by RK. All authors provided revisions where necessary, and all approved the final version.

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Tables**Table 1:** General post-operative complications

Complication	Without AL <i>N</i> = 844	With AL <i>N</i> = 27 427	<i>p</i>
Pulmonary complications (pleural effusion, atelectasis) n (%)	951 (3.5)	142 (16.8)	<0.001
Pneumonia n (%)	1056 (3.9)	113 (13.4)	<0.001
Cardiac complications n (%)	1161 (4.2)	118 (14.0)	<0.001
Thrombosis n (%)	111 (0.4)	15 (1.8)	<0.001
Pulmonary embolism (%)	128 (0.5)	5 (0.6)	0.603
Renal complications n (%)	340 (1.2)	78 (9.2)	<0.001
Urinary-tract infection n (%)	1584 (5.8)	67 (7.9)	0.009
Multi-organ failure n (%)	315 (1.1)	134 (15.9)	<0.001

Table 2: Specific post-operative complications and duration of hospitalisation

Complication	Without AL <i>N</i> = 844	With AL <i>N</i> = 27 427	<i>p</i>
Post-operative haemorrhage n (%)	246 (0.9)	16 (1.9)	0.009
Sepsis n (%)	153 (0.6)	120 (14.2)	<0.001
Obstruction n (%)	220 (0.8)	25 (3.0)	<0.001
Wound infection n (%)	791 (2.9)	15 (14.7)	<0.001
Abscess n (%)	128 (0.5)	76 (9.0)	<0.001
Enterocutaneous fistula n (%)	52 (0.2)	78 (9.2)	<0.001
Peritonitis n (%)	93 (0.3)	165 (19.6)	<0.001
Rupture of operation wound n (%)	321 (1.2)	73 (8.6)	<0.001
Duration of hospital stay [days] mean ± SD	15.6 ± 7.7	35.3 ± 22.5	0.009

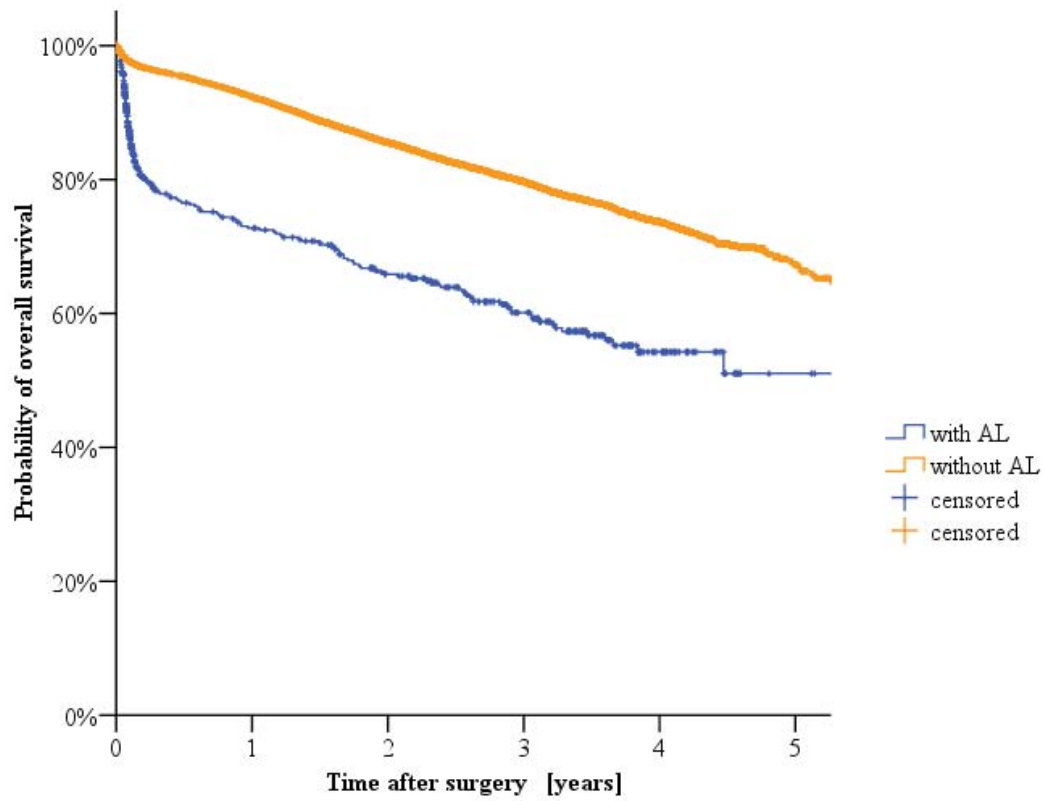
Figures

Figure 1. Comparison of the probability of overall survival of up to five years for patients with and without AL (log-rank test: $p < 0.001$)

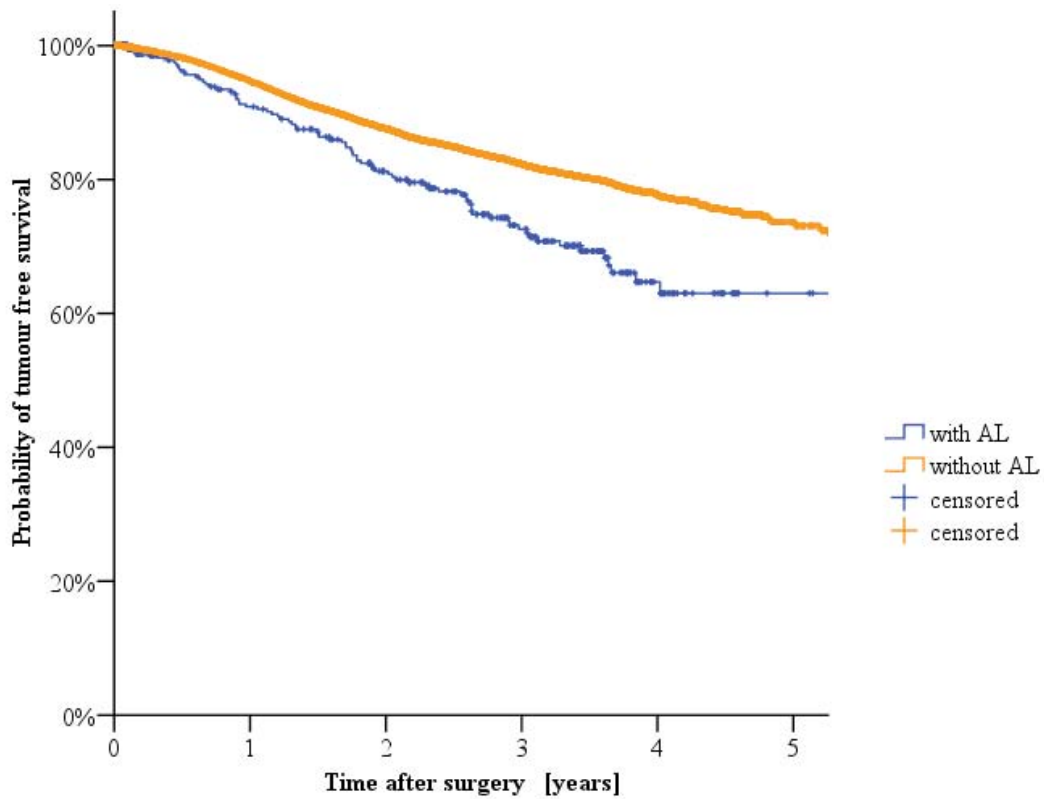


Figure 2. Comparison of the probability of tumour-free survival of up to five years for patients with and without AL (log-rank test: $p < 0.001$).