

Neoadjuvant radio-chemotherapy prolongs healing of anastomotic leakage after rectal resection treated with endoscopic vacuum therapy

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Abstract

Background: Neoadjuvant radiochemotherapy (nRCT) is an important component in the treatment of advanced rectal cancer. Endoscopic vacuum therapy (EVT) has become the treatment of choice for anastomotic leakage after rectal resection in many institutions in Germany. Published case series report on average success and stoma reversal rates of more than 80%. However, so far, there is no distinct report on the potential influence of nRCT on EVT.

Methods: A total of 11 patients treated with EVT for anastomotic leakage after nRCT and rectal resection were retrospectively compared with a cohort of eight patients with rectal anastomotic leakage without neoadjuvant treatment. Primary endpoints were death, treatment success, and long-term preservation of intestinal continuity. Secondary endpoint was the duration of treatment. Statistical analysis was performed using Statistical Package for Social Science (SPSS) version 23.0.

Results: There was no difference in mortality (0%), success rate (90.9% versus 100%, $p=0.381$), or long-term preservation of continuity (63.6% versus 62.5%, $p=0.960$). After nRCT, patients showed a significant longer duration of EVT (31.1 days versus 15.9 days, $p=0.040$) which was associated with a significantly higher number of sponge applications (9.6 versus 5.0, $p=0.042$).

Conclusions: In our analysis, EVT showed success in over 90% of patients with anastomotic leakage after rectal resection for colorectal cancer, regardless of neoadjuvant treatment. However, in case of anastomotic leakage, nRCT seems to be associated with the need for a significant longer duration of EVT.

Keywords: anastomotic leakage, EVT, neoadjuvant therapy, rectal resection

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Introduction

Radiochemotherapy (RCT) is an important component in treating patients with advanced rectal cancer, and, a neoadjuvant treatment has been shown to be superior to an adjuvant therapy. Previously, we and other working groups have shown that neoadjuvant RCT (nRCT) leads to improved cancer-related survival and disease-free survival on the one hand, but also to more

complications and potentially impaired function on the other.^{1–3}

Endoscopic vacuum therapy (EVT) has become the treatment of choice for anastomotic leaks after rectal resections in various institutions. Suction and drainage *via* an open-pored polyurethane sponge decrease bacterial contamination, secretion, and local edema. At the same time,

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perfusion and granulation are promoted.⁴ The first larger patient series for intracorporal use of vacuum therapy was published by Weidenhagen and colleagues.⁵ In the current analysis, we aimed to investigate the impact of a neoadjuvant treatment on EVT for anastomotic leakage after rectal resection for colorectal cancer.

Patients and methods

All patients were treated at Rostock University Medical Center. A total of 19 patients were treated with EVT for anastomotic leakage after rectal resection for cancer. All patients were operated between November 2007 and March 2015. Patient characteristics, cancer, and treatment parameters were collected from charts or during follow up visits. Characteristics are depicted in Table 1.

Death, treatment success, and long-term preservation of intestinal continuity were the primary endpoints of this analysis. Treatment success was defined as healing of the anastomotic leak. Long-term preservation of intestinal continuity was defined as the absence of a stoma after 18 months.

Outcome of patients treated with EVT after nRCT was compared with a control group that had received EVT without previous nRCT. There was an indication for nRCT for all patients with rectal cancer in the lower and middle rectum with a local cancer stage T3/4 or positive lymph nodes or both. The term rectum carcinoma was applied to adenocarcinomas located at a distance from 0 to 16 cm from the anal verge, measured by rectoscopy. According to German guidelines,⁶ the rectum is divided into the lower (0–<6 cm), middle (6–<12 cm) or upper (12–16 cm) rectum. Patients received an intensified nRCT,⁶ including a daily intake of Capecitabine with a single dose between 1000 and 1650 mg/m² combined with weekly applications of irinotecan (40 mg/m²) or oxaliplatin, and local radiation 5 days a week with a single dose of 1.8 Gy adding up to 55.8 Gy.

EVT

EVT was performed as published previously.⁷ The commercially available system Endo-Sponge (B. BRAUN®, Melsungen, Germany) was used in all patients receiving EVT. If there was an indication for EVT, flexible endoscopic examination and lavage were conducted. Sponges were cut accordingly to the size of the cavity and installed

via an overtube as described previously.⁷ Sponges were changed every 3 days. For all results, percentages or arithmetic means are presented if not otherwise specified.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Science (SPSS) version 23.0. Statistical analysis included Pearson's Chi-square test (Fisher's exact test) or *t* test. A *p*-value of <0.05 was considered as statistically significant.

Results

Patient characteristics are shown in Table 1. Both groups were comparable in general characteristics. All patients in the neoadjuvant group had rectal cancer, whereas around one-third of patients in the control group had sigmoid cancer. However, there was no significant difference in the tumor distance from the anal verge between the two groups. The average tumor distance from the anal verge in both groups was 6.5 cm, 5.8 cm in the nRCT group, and 7.4 cm in the control group (*p*=0.288). Age, gender, comorbidities, American Society of Anesthesiologists (ASA) score, and Union for International Cancer Control (UICC) stage were within the expected range without any significant differences between both groups.

Table 2 shows the results of EVT according to administering neoadjuvant RCT. EVT showed success in over 90% of patients with anastomotic leakage after rectal resection for colorectal cancer, regardless of neoadjuvant treatment. There was no difference in mortality (0%), success rate (90.9% versus 100%; *p*=0.381), or long-term preservation of continuity (63.6% versus 62.5%, *p*=0.960). The mean duration until closing of the ileostomy was 10.2 months (±5.1). Between both groups, there was no significant difference in the time interval until the reversal of the ileostoma (8.4 months in the nRCT group versus 12.8 months without nRCT; *p*=0.148). Patients after nRCT showed a significantly longer duration of EVT (31.1 d versus 15.9 d; *p*=0.040), which was associated with a significant higher number of endoscopic sessions and sponge applications (9.6 versus 5.0; *p*=0.042).

Discussion

EVT has become the treatment of choice for anastomotic leaks of the lower GI tract in various

Table 1. Biological data and comorbidity in the study and control groups.

	All patients % (n = 19)	EVT after nRCT % (n = 11)	EVT without RCT % (n = 8)	p-value
Gender ratio (f:m)	1:8.5	1:10	1:7	0.811
Age (mean), (years)	64.5	66.1	62.4	0.587
Comorbidity	100	100	100	
Pulmonary	31.6	27.3	37.5	0.636
Cardiovascular	52.6	45.5	62.5	0.463
Renal	5.3	0	12.5	0.228
Diabetes	21.1	18.2	25.0	0.719
Hypertension	52.6	54.5	50.0	0.845
Others	84.2	90.9	75.0	0.348
ASA score (mean)	2.26	2.36	2.13	0.268
Cancer location				0.058
Rectum	84.2	100	62.5	
Colon sigmoideum	15.8	0	37.5	
Mean tumor distance from anal verge (cm) (range)	6.5 (2–11)	5.8 (2–10)	7.4 (4–11)	0.288
BMI	27.6	27.7	27.5	0.930
UICC (cancer only)				0.547
0	0	0	0	
I	36.8	36.4	37.5	
II	26.3	18.2	37.5	
III	26.3	27.3	25.0	
IV	10.5	18.2	0	

ASA, American Society of Anesthesiologists; BMI, body mass index; EVT, endoscopic vacuum therapy; nRCT, neoadjuvant radiochemotherapy; RCT, radiochemotherapy; UICC, Union for International Cancer Control.

institutions. So far, the relationship between EVT and neoadjuvant treatment for colorectal cancer has not been the subject of a clinical investigation. Therefore, we aimed to analyze our patients treated with EVT after rectal and sigmoid cancer resection with and without a previous neoadjuvant treatment.

In our study, there was no difference in treatment success, long-term preservation of continuity, or time until ileostomy closure, although we found a

significantly prolonged course of the healing process after neoadjuvant treatment. This finding might have important clinical implications for the management and treatment of these patients.

Radiation and chemotherapy lead to an impairment not only of cancer cells but also of the surrounding tissue. This is the reason for the higher incidence of anastomotic leaks and higher complication rate in these patients. Growth factors play an important role in the process of wound

Table 2. EVT treated patients with or without nRCT.

	All patients %	EVT after nRCT %	EVT without RCT %	p-value
Patients (n)	19	11	8	
Sponge placement				0.493
Intracavitary	57.9	63.6	50.0	
Luminal	5.3	0	12.5	
Both	31.6	27.3	37.5	
Sacral cavity	5.3	9.1	0	
Death	0	0	0	
Successful treatment	94.7	90.9	100.0	0.381
Long term preservation of continuity	63.2	63.6	62.5	0.960
Number of sponges needed	7.7	9.6	5.0	0.042
Length of treatment (days)	24.7	31.1	15.9	0.040
Time until closing of protective ileostomy (months)	10.2	8.4	12.8	0.148
EVT, endoscopic vacuum therapy; nRCT, neoadjuvant radiochemotherapy; RCT, radiochemotherapy.				

healing, and might be downregulated after nRCT,⁸ which could explain the prolonged wound healing. Nonetheless, EVT was successful in more than 90% of neoadjuvant-treated patients, which underscores the efficacy of this method. However, the significantly prolonged treatment duration reflects the alterations in the indirectly pretreated tissue.

In the literature, there is not much data regarding wound healing after nRCT and rectal resection. Bullard and colleagues have shown that preoperative radiation therapy doubles the rate of perineal wound complications after rectum extirpation.⁹ Also, there is no data reporting the impact of neoadjuvant treatment on the duration of wound healing.

Horisberger and colleagues revealed a relationship between tumor response to intensified neoadjuvant therapy and major postoperative complications.¹⁰ The rate of anastomotic leakages was 25.9% in the group with a major response compared with 0% in the group with a minor response to the neoadjuvant treatment. The authors suggest that collagen deposition, the depressing effect on the blood cells, and other essential elements of wound healing, as well as an

irritation of the bowel mucosa, might have influenced the results of the study.

Similarly, Thorgersen and colleagues identified a good response to nRCT, abdominoperineal resection (APR), age, and operative blood loss to be risk factors for surgical site infections.¹¹ Both studies imply that a good response to the neoadjuvant treatment is unfortunately accompanied by an increase in complications, such as anastomotic leaks and prolonged wound healing.

Limitations of this analysis include the small number of patients and the retrospective design of the study. Furthermore, all patients in the neoadjuvant group had rectal cancer, whereas about one-third of patients in the control group had sigmoid cancer. However, there was no significant difference in the tumor distance from the anal verge between the two groups. Despite these limitations, our findings might have important clinical implications. Before initializing EVT, patients should be informed about a likely prolonged healing process after nRCT, and timely EVT can be planned in an ambulatory setting in order to reduce health care expenditure and to accelerate patient rehabilitation.

Conclusion

In our analysis, EVT showed success in over 90% of patients with anastomotic leakage after rectal resection for colorectal cancer, regardless of neoadjuvant treatment. However, in the case of anastomotic leakage, nRCT seems to be associated with the need for a significantly longer duration of EVT.

Author contributions

LS and FK conceived the study, collected patient data, and drafted the manuscript. LS performed the statistical analysis. NW, FS, MG, and EK critically revised the manuscript for important intellectual content.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate

Local ethics committee (Rostock University) ruled that no formal ethics approval was required in this study. Written informed consent forms about the procedures were obtained from all patients.

Consent for publication

Not applicable.

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