Original article

Karolina Osowiecka[1], Anna Sugajska[2, 3], Maciej Biernacki[4, 5], Sergiusz Nawrocki[2, 3], Monika Rucińska[2]

[1]Department of Psychology and Sociology of Health and Public Health, University of Warmia and Mazury in Olsztyn, Poland
[2]Department of Oncology, *Collegium Medicum*, University of Warmia and Mazury in Olsztyn, Poland
[3]Department of Radiotherapy, Hospital SP ZOZ MSWiA with Warmia and Mazury Oncology Centre in Olsztyn, Poland
[4]Department of Surgery, *Collegium Medicum*, University of Warmia and Mazury in Olsztyn, Poland
[5]Department of General Surgery, Hospital SP ZOZ MSWiA with Warmia and Mazury Oncology Centre in Olsztyn, Poland

Risk of reoperation for anastomotic leakage after anterior resection of rectal cancer after neoadjuvant therapy

Abstract

Background: Rectal cancer patients require a multidisciplinary approach. In the case of locally advanced rectal cancer standard treatment includes neoadjuvant radiotherapy or chemoradiotherapy. Neoadjuvant treatment could cause postoperative complications, but there is no clear evidence of an association between anastomotic leakage and the preoperative treatment of rectal cancer. This study aimed to investigate the frequency of anastomotic leakage followed by the need for reoperation and to find predictive factors for reoperation in rectal cancer patients after neoadjuvant therapy.

Patients and methods: One hundred and ten consecutive patients (median age: 65 years) with locally advanced operable rectal cancer, Clinical Stages II and III, were treated with neoadjuvant radiotherapy or chemoradiotherapy (72% were treated with short radiotherapy only, 3% with short radiotherapy and subsequent chemotherapy, 25% with long radiotherapy plus concomitant chemotherapy) and then anterior rectal resection with total mesorectal excision in the Regional Oncological Centre between January 2014 and December 2016.

Results: The reoperation for anastomotic leakage was done in 17% of patients, 8 days (median) after primary surgery. In multivariate analysis reoperation for anastomotic leakage was significantly frequent in older patients ($p = 0.03$) and upper tumours ($p = 0.04$).

Conclusions: Almost one-fifth of rectum cancer patients after preoperative radio- or chemoradiotherapy in the present study series required reoperation due to anastomotic leakage. The study findings are limited by its small sample size and retrospective character.

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Key words: anastomotic leakage, neoadjuvant treatment, rectum cancer, reoperation, mesorectal excision

Address for correspondence:
Karolina Osowiecka
Department of Psychology and Sociology of Health and Public Health, University of Warmia and Mazury in Olsztyn, Warszawska 30 St., 10–082 Olsztyn, Poland
e-mail: karolina.osowiecka@uwm.edu.pl

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Introduction

The incidence of rectal cancer in Poland accounts for 4.1% of all reported cancers in men and 2.7% in women. In 2017, the number of newly diagnosed cases of rectum cancer in Poland was over 3500 [1]. Most cases occur among men between 50 and 80 years old and in women over 70 years old. For patients diagnosed and treated in the years 2000–2007 in Poland, the five-year overall survival is 37%; in the European population, the average survival rate is 48% [2].

Rectal cancer patients require a multidisciplinary approach. Standards of rectal cancer treatment have been introduced over the last two decades [3–5]. Surgery is still the primary rectal cancer treatment. The total mesorectal excision (TME) technique has significantly reduced the risk of local recurrence in locally advanced rectal cancer — from about 25% to 10% [6–9]. However, in the case of locally advanced rectal cancer, standard treatment includes neoadjuvant radiotherapy and chemoradiotherapy [6, 10]. Preoperative radiotherapy has resulted in decreasing the risk of local recurrence by up to 4–5%, without a significant overall survival benefit [9, 11]. The indication for preoperative radiotherapy in locally advanced rectal cancer is cT3 or cN1–2 [5]. Concerning postoperative radiotherapy, preoperative treatment significantly reduces toxicity and prevents local recurrence [12]. There are two main patterns of preoperative treatment for operable rectal cancer [13]. Preoperative radiotherapy alone may be administered in a short cycle delivered over 5 days, to a total dose of 25 Gy (in 5 fractions), followed by surgery within a week. The second option is neoadjuvant chemoradiotherapy (concomitant or sequential) followed by surgery within 4–6 weeks [14]. However, neoadjuvant treatment may cause some tissue disturbances such as oedema, blood supply disorders, fibrosis, and even necrosis. This could cause some postoperative complications, such as anastomotic leakage, and a need for reoperation.

Anastomotic leakage is the most important postoperative complication after rectal cancer resection. This complication prolongs hospitalization and could cause an increase in the risk of postoperative mortality to 6–22% [15–17]. Anastomotic leakage led to a significant increase in 90-day mortality, especially in the elderly [18]. It appears that anastomotic leakage could be associated with local recurrence, the need for a permanent stoma, and a worse prognosis [17, 19, 20]. Wang et al. [21] in a meta-analysis showed that anastomotic leakage was associated with a significantly higher rate of local recurrence and decreased overall survival and cancer-specific survival without impacting distant metastases. There is no clear evidence of an association between anastomotic leakage and neoadjuvant treatment of rectal cancer in the available literature. This retrospective study aimed to determine the incidence of anastomotic leakage followed by the need for reoperation and to find the predictive factors of reoperation in rectal cancer patients treated with neoadjuvant radiotherapy or chemoradiotherapy.

Patients and methods

A retrospective analysis was carried out on 110 consecutive patients with locally advanced operable rectal cancer treated with neoadjuvant radiotherapy or chemoradiotherapy and then anterior rectal resection with total mesorectal excision — complete removal of the rectum, together with the surrounding mesorectum lymphovascular fatty tissue (mesorectum) — in the Regional Oncological Centre between January 2014 and December 2016. The list of patients was generated from the hospital's electronic database. The clinical data were collected from the medical documentation of each patient — partly from the electronic database and partly from paper records (histopathological reports and protocols of surgery) by investigators (a surgeon and oncologists). The variables that could be associated with rectal reoperation and time to reoperation for anastomotic leakage (sex, age, tumour localization, pT stage, pN stage, preoperative stoma, extent of resection, circumferential resection margin, and administered radiotherapy or radio-chemotherapy) were analysed. The missing data were not included in the analysis of individual factors. Ethical approval for this study was not required due to the retrospective analysis of the data.

Statistics

Descriptive statistics were used for the characteristic group. Uni- and multivariable predictors of reoperation were estimated through logistic regression analysis. Univariate variables with $p < 0.25$ were included in the multivariable model. The time to reoperation was measured from the date of surgery to the date of reoperation for anastomotic leakage. A p-value < 0.05 was considered statistically significant. The analysis was performed using TIBCO Software Inc. (2017). Statistica (data analysis software system), version 13. http://statistica.io.

Results

One hundred and ten consecutive patients (71 males and 39 females, age: 42–89 years, median age: 65 years) with histologically confirmed locally advanced rectal adenocarcinoma treated in Regional Onco-

logical Centre between January 2014 and December 2016 were analysed. All patients received neoadjuvant treatment: 79 patients (72%) were treated with short radiotherapy only (25 Gy in 5 fractions), 4 patients (3%) with short radiotherapy (25 Gy in 5 fractions) with subsequent chemotherapy, and 27 patients (25%) with long radiotherapy to a total dose 50.4 Gy in 28 fractions, with concomitant chemotherapy. Clinical stages of cancer were II and III (cT3-4N0M0 or cT1-4N1-2M0) according to the TNM/AJCC 2002 classification [22]. About 50% of patients had tumour localization ≥ 6 cm from the anus. In the case of 11 patients (10%), it was necessary to use a stoma before oncological treatment.

Pathological confirmation of rectum cancer after the operation was done in all subjects, but in the case of 7 patients (6%), it was carcinoma *in situ*. Most tumours were classified as pT3 (64%). In the case of 63 patients (57%), there were no metastases in lymph nodes. Primary complete radical resection of the tumour was done in 87 patients (79%). In some cases, it was possible to expand the operation margin. Finally, operation R0 was performed in 96 patients (87%) (Table 1).

The reoperation for anastomotic leakage was done in 19 out of 110 patients (17%). The time interval between primary surgery and reoperation ranged from 2 to 30 days (median: 8 days). Reoperation for anastomotic leakage was more frequent in males, older patients, those with a tumour localized ≥ 6 cm from the anus, and those with pN (+), but the differences were not statistically significant. In univariate analysis, only four factors met the inclusion criteria in the multivariate regression model ($p < 0.25$). In multivariate analysis, reoperation was significantly frequent in older patients — age ≤ 65 *vs.* > 65 years (OR: 3.80; 95% CI: 1.13–12.73, $p = 0.03$) — and in patients with upper tumour — tumour localization < 6 *vs.* ≥ 6 cm (OR: 3.42; 95% CI: 1.05–11.08, $p = 0.04$) (Table 2, Fig. 1).

Table 1. Patient and treatment characteristics

		N	%
No. of patients		110	100
Sex			
	Males	71	65
	Females	39	35
Age [years]		Median: 65; range: 42–89	
	≤ 65	56	51
	> 65	54	49
Tumour localization [cm]		Median: 5; range: 0–15	
	< 6	57	52
	≥ 6	53	48
pT status			
	In situ	7	6
	T1	0	0
	T2	25	23
	T3	70	64
	T4	8	7
pN status			
	N0	63	57
	N1	29	27
	N2	18	16
Preoperative stoma			
	Yes	11	10
	No	99	90
Primary resection margin			
Negative		87	79
Positive		23	21
	Radial	9	8
	Proximal	1	1
	Distal	8	7
	Distal-radial	2	2
	Unknown	3	3
Finally extent of resection			
	R0	96	87
	R1	10	9
	R2	1	1
	No data	3	3
Neoadjuvant treatment			
	Short radiotherapy	79	72
	Short radiotherapy plus chemotherapy	4	3
	Long radiochemotherapy	27	25

Discussion

In the literature, the authors reported 3–17.0% clinical anastomotic leakage after rectal cancer resection [20, 23–26]. In the present study series, the reoperation for anastomotic leakage was done in 17% of rectum cancer patients after neoadjuvant treatment, 8 days (median) after primer operation. Anastomotic leakage typically becomes clinically apparent in 5–8 days post-operation [15, 23, 27]. In some studies, the risk of anastomotic leakage was higher in patients receiving pre-operative radiotherapy [16, 28, 29]. Eriksen et al. [16] observed anastomotic leakage in

Table 2. Uni- and multivariate analysis of the distribution of reoperation for anastomotic leakage

		Univariate analysis			Multivariate analysis		
Variable		OR	(95% CI)	p-value	OR	(95% CI)	p-value
Sex	Females	1.00	Reference		1.00	Reference	
	Males	2.34	(0.72–7.64)	0.16	2.96	(0.81–10.79)	0.10
Age	≤ 65	1.00	Reference		1.00	Reference	
	> 65	2.00	(0.72–5.54)	0.18	3.80	(1.13–12.73)	0.03
Tumour localization [cm]	< 6	1.00	Reference		1.00	Reference	
	≥ 6	2.76	(0.97–7.91)	0.06	3.42	(1.05–11.08)	0.04
pT status	*In situ*	1.00	Reference				
	T2	0.63	(0.09–4.22)	0.63		–	
	T3–4	0.46	(0.08–2.62)	0.38		–	
pN status	N (–)	1.00	Reference				
	N (+)	1.62	(0.60–4.38)	0.34		–	
Preoperative stoma	Yes	1.00	Reference				
	No	0.93	(0.19–4.71)	0.93		–	
Primary circumferential resection margin	Positive	1.00	Reference		1.00	Reference	
	Negative	4.28	(0.53–34.37)	0.17	5.51	(0.64–47.53)	0.12
Finally extent of resection	R0	1.00	Reference				
	R 1–2	0.0	(0.0–0.0)	1.00		–	
Chemotherapy	Yes	1.00	Reference				
	No	1.12	(0.37–3.43)	0.84		–	
Radiotherapy	Long	1.00	Reference				
	Short	1.27	(0.38–4.21)	0.70		–	

OR — odds ratio; CI — confidence interval

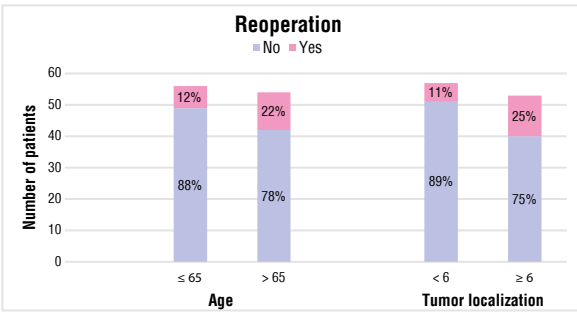

Figure 1. The ratio of rectal cancer patients reoperated to non-reoperated for anastomotic leakage depending on tumour localization and patients' age ($p < 0.05$)

23.7% of patients after neoadjuvant radiotherapy and in 11.3% of patients without radiotherapy. Sparreboom et al. [30] based on data from the Dutch ColoRectal Audit showed that the incidence of anastomotic leakage was significantly higher in patients who underwent surgery in a short interval (< 4 days) after short-term radiotherapy alone (10.1% *vs.* 7.2%). A study by Kerr et al. [31] reported that shortening the interval between the completion of neoadjuvant chemoradiotherapy and surgery resulted in an increased percentage of anastomotic leakage. However, a meta-analysis found no effect of neoadjuvant therapy for rectal cancer on the incidence of postoperative anastomotic leakage [32]. In addition, the interval to surgery after preoperative radiotherapy (short- or long-course, with or without chemotherapy) was not associated with an increased rate of postoperative anastomotic leakage [32]. The study patients included only those with preoperative treatment, so the authors could not compare patients treated preoperatively or not. No differences were observed in the incidence of anastomotic leakage depending on the type of neoadjuvant treatment.

Clinical stage is one factor correlated with anastomotic leakage after rectal cancer removal [16, 33].

Patients with more advanced tumours classified as T4 had a 2.4 times higher risk of anastomotic leakage compared to ≤ T3 [16]. There was no association between T stage and anastomotic leakage in the study series, but in only 8 patients (7%), the tumour was classified as T4. Instead, a correlation was found between stage N and the rate of anastomotic leakage in the present study. Patients with lymph node invasion significantly frequently underwent reoperation due to anastomotic leakage.

Some authors mentioned that the independent risk factor for anastomotic leakage is a low anastomotic level: 4–6 cm or less from the anal verge [16, 24, 33–35]. In the present analysis, reoperation was more often done in cases localized higher than 6 cm. This finding may be accidental and related to relatively small subgroups of patients. However, Akiyoshi et al. [36] showed, also in a small group comprising 87 rectal cancer patients after laparoscopic TME, that the independent predictive factor for overall postoperative morbidity and anastomotic leakage was a longer tumour distance from the anal verge.

In a multivariate analysis, the risk of anastomotic leakage was significantly higher in males [16, 23, 30, 33, 37]. These study results are similar. Reoperation for anastomotic leakage was more frequent in males, but the differences were not statistically significant, possibly due to small subgroups. One of the probable reasons for this is the narrow male pelvis, which makes visualization during operation more difficult. Patient age is a controversial factor — in one analysis, anastomotic leakage appeared more often in younger patients [37]; in another, it was more common in older patients [23]. In the present study, in multivariate analysis, reoperation was significantly frequent in patients aged > 65 years. This could be related to beta error due to a small number of patients in subgroups.

Hoshino et al. [33] used the data of 936 patients that had been prospectively collected by the Japanese Society for Colon and Rectal Cancer and identified the most relevant combination of predictors for anastomotic leakage: male sex, low serum albumin level, the proximity of the tumour to the anal verge, large tumour size, and simultaneous resection of other organs. On this basis, they created a nomogram for precise prediction of anastomotic leakage after low anterior resection for rectal cancer. The authors concluded that preoperative therapy was considered to be a potential risk factor for anastomotic leakage, but neoadjuvant treatment was not identified in this study to be related to more frequent anastomotic leakage because of the small number of patients who received preoperative therapies [33].

Conclusions

The reoperation due to anastomotic leakage after preoperative radio- or chemoradiotherapy in this study series concerned almost one-fifth of rectum cancer patients. In the present study, older age and a high location of the tumour were related to anastomotic leakage and the need for reoperation. However, the study was limited by its small sample size and retrospective design. Anastomotic leakage is associated with a local recurrence and harms the overall survival of rectal cancer patients. Therefore, special attention should be paid to all possible factors increasing the risk of anastomotic leakage, and the resulting findings should be employed by all attempts to decrease the incidence of anastomotic leakage.

Declaration of conflict of interests

The authors declare that there is no conflict of interest.

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