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Risk of acute anastomotic leakage after preoperative radiotherapy in rectal cancer

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ABSTRACT

Objective: To evaluate the preoperative radiotherapy and its role in anastomotic leakage.
Methods: A total of 327 patients who had an anterior resection (AR) in elective surgery for a rectal carcinoma were selected and operated in our clinic of surgery during the period from 2003 to 2015. Among them, 135 patients had a low anterior resection (LAR) and the other 192 had an AR. This is a retrospective study. *Chi*-squared test was used to evaluate statistical differences and the $P < 0.05$ was considered statistically significant.
Results: A total of 126 patients had radiotherapy before surgery, and 50 of them had a LAR. In the other 201 patients, surgery was the first treatment modality, and 83 of them had a LAR. We had an overall anastomotic leakage of 7.95% or 26% patients. Anastomotic leakage was found in 14 patients with LAR, 9 of which had radiotherapy before surgery. From the 12 patients with AR who had an anastomotic leakage, 6 of them had radiotherapy before surgery.
Conclusions: Radiotherapy may affect anastomotic healing and increase the risk of leakage. This risk is higher in low anterior anastomoses where a protective stoma may be considered. A better evaluation and support for patients with preoperative radiotherapy is needed in order to diminish the concomitant risk factors as much as possible.

1. Introduction

Anastomotic leakage is the main concern following the surgery for rectal cancer. After dealing with the total mesorectum excision, the surgeon must be aware of this life-threating early complication which is often asymptomatic and associated with an increased morbidity, mortality and local recurrence[1,2]. Numerous studies have considered a lot of factors influencing negatively in anastomotic healing, which increases the rate of leakage in colorectal anastomosis[3,4]. Some of the most discussed factors are the level and stage of tumor, the distance of tumor from anus, impaired wound healing by different origins (immunosuppression, diabetes, anemia, *etc*.), bowel preparation, male gender, *etc*[3,4]. Different studies show that there is an increased risk in low anterior resections (LAR) and coloanal anastomoses ranging from almost 1% to over 22%[5,6].

Preoperative radiotherapy and chemotherapy are accused to increase the leakage rate as well. Current consensus of National Comprehensive Cancer Network is that all rectal carcinomas staged as IIB, III or IV according to TNM stage (classification of malignant tumor, according to Union for International Cancer Control) should be treated by a multimodal approach. In these cases, radiotherapy and chemotherapy should precede surgery, as a downstage is achieved resulting in a better surgical approach[7–9]. Some authors find that radiotherapy does not improve the overall survival rate after rectal cancer resection and may constitute a significant overtreatment for many patients[7].

The main concern to discuss is the increased anastomotic leakage in patients who were treated with radiotherapy before surgery[10]. There are many controversial reports on this issue. May be because of the multiple associated factors, sometimes they are difficult to determine. It is difficult to conclude that radiotherapy is an independent risk factor for anastomotic leakage after anterior resection (AR) or other concomitant factors may influence. Many studies show the role of radiotherapy in increasing early postoperative complications, where anastomotic leakage is the main concern[11,12]. Others have not shown such relation[13,14].

The new era of radiotherapy, where the linear accelerator (LINAC) is replacing conventional cobalt therapy, is giving a better result. The overall toxicity and the regional tissue collateral effects are reduced. This leads to a more suitable surgical approach after radiotherapy, probably with lower risk for anastomotic leakage.

It should be always aware, because this complication may present its clinical signs only later after surgery, even in patients

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classified as low risk. Sometimes the situation may precipitate, indicating an emergent response to treat pelvic sepsis through a defunctioning stoma and extensive drainage. Sometimes the symptoms may be minimal or absent and the evidence may present much later only in contrast imaging, showing signs of a perianastomotic or cavity abscess[15].

The aim of this study was to evaluate the role of preoperative radiotherapy in increasing the risk of anastomotic leakage.

2. Materials and methods

A total of 327 patients who had an AR in elective surgery for a rectal carcinoma were selected and 126 of them had a course of radiotherapy followed by the surgery within 1 week. All patients aged from 40 to 65 years were selected with normal blood count preoperatively and total mesorectal excision to minimize the influence of other risk factors to this study. All the patients having an elective AR with curative intention for preoperative confirmed rectal adenocarcinoma were operated in the third Clinic of Surgery at Mother Teresa Hospital from January 2003 to December 2015. Patients who had a palliative surgery, intraperitoneal dissemination and other organ metastases were excluded. Remnant and recurrent rectal cancer were excluded as well.

All the operated patients had a careful preoperative examination starting with patients' history (history of previous tumors, neoadjuvant therapy and surgery), blood tests, tumor markers, *etc*. Full colonoscopy was performed for every patient followed by biopsy samples to locate the tumor and perform histopathological examination. Preoperative staging was based on radiological data collected from abdominal CT with oral and venous contrast. Other examinations were used to clarify tumor invasion or metastases, as trans-rectal ultrasound, abdominal ultrasound, chest X-rays or CT, *etc*.

Patients who had postoperative clinical signs of anastomotic leakage, fever, purulent content or stools from drainage, abdominal distension and compromised intestinal transit, had an emergent abdominal ultrasound and blood tests followed by abdominal CT. Patients with confirmed signs of anastomotic leakage were followed up with conservative therapy (liquids, antibiotics, parenteral feeding) during a short period in which the necessity of a decompressive stoma was evaluated.

Out of the 126 patients who had radiotherapy before surgery, 83 were treated with cobalt therapy and the other 43 patients were treated with intensity modulated radiation therapy (IMRT) through LINAC. The operated patients were divided into three groups depending on the first treatment modality and the control group was the one with no preoperative radiotherapy.

Statistical analysis was performed using *Chi*-square test to compare the risk of anastomotic leakage among the groups. $P < 0.05$ was considered statistically significant.

The study protocol was performed according to the Helsinki declaration and approved by Komiteti i Etikes Mjeksore (Medical Ethics Commettee which approved the investigations). Informed written consent was obtained from Medical Ethics Committee.

3. Results

A total of 327 patients who had an AR in elective surgery for a rectal carcinoma were selected, in which 133 had a LAR and the other 194 had an AR. One hundred and twenty-six patients had radiotherapy before surgery and 50 of them had a LAR. In the other 201 patients, surgery was the first treatment modality, 83 of which had a LAR. We had an overall anastomotic leakage in 7.95% or 26 patients. The anastomotic leakage was found in 14 patients with LAR, 9 of which had radiotherapy before surgery. From the 12 patients with AR who had an anastomotic leakage, 6 had radiotherapy before surgery. The demographic data were shown in Table 1.

Table 1
Demographic data of patients with and without preoperative chemo-radio therapy (CRT).

Patients data		CRT (n = 126)		No CRT (n = 201)	
Sex	Male	67	20.5%	104	32.0%
	Female	59	18.0%	97	29.5%
Mean age (years)		58.9		58.7	
Average ASA score		2.6		2.4	
Rectal cancer	Stage I (n = 54)	0	0.0%	54	16.5%
TNM stage	Stage II (n = 92)	9	2.8%	83	25.4%
	Stage III (n = 116)	64	19.6%	52	15.9%
	Stage IV (n = 65)	53	16.1%	12	3.7%
Surgical procedure	AR	76		118	
	LAR	50		83	

ASA: American Society of Anesthesiologists physical classification system; TNM: Classification of malignant tumor, according to Union for International Cancer Control.

The nine patients of stage II who had CRT before surgery were considered IIB preparatory. The reason why some of the patients of stage IV did not have CRT before surgery was preoperative mistaken downstage or leakage of consent by their side.

All the 327 patients were divided into three groups (Group 1: no radiotherapy; Group 2: cobalt therapy; Group 3: LINAC) depending on the use of preoperative radiotherapy. Also for each group, the number of patients were shown with anastomotic leakage depending on the surgical procedure they had and the data were shown in Table 2.

Table 2
Anastomotic leakage in the three groups.

Group	Operation	Patients	Anastomotic leakage
Group 1 (n = 201)	AR	118	6
	LAR	83	5
Group 2 (n = 84)	AR	51	5
	LAR	33	7
Group 3 (n = 42)	AR	25	1
	LAR	17	2

Groups 2 and 3 were compared with the first group for anastomotic leakage and the data were given in Table 3.

Table 3
Group comparison for anastomose leakage.

Comparison between groups		*Chi*-squared value	P
Group 2 *vs*. Group 1		6.202	0.012761
Group 3 *vs*. Group 1		0.178	0.673098
Group 2 *vs*. Group 1	AR	1.303	0.253666
	LAR	5.873	0.015375
Group 3 *vs*. Group 1	AR	0.052	0.819619
	LAR	0.714	0.398119

$P < 0.05$ was considered statistically significant.

As shown in Table 3, the difference was significant for the patients treated with preoperative cobalt radiotherapy (Group 2 *vs*. Group 1), especially for those who had a LAR. The patients treated with IMRT through LINAC did not have a significant difference as compared with the control group.

4. Discussion

The major concern of a surgeon in elective surgery for rectal carcinoma is the anastomotic healing following LAR. The consequences of its failure are associated with serious morbidity and mortality and may require an urgent surgical procedure. There are many factors that influence in this complication. Some depend on surgery and some did not. Even a meticulous procedure with no vascularity impairment and tension-free anastomotic construction may not be sufficient. Preoperative factors related to or not to the patient may affect healing biology. There is a large list of these factors like low blood protein, leucopenia, anemia and other patient conditions that affects the healing process. Anastomotic leakage itself is generally diagnosed at the late stage after surgery and often is asymptomatic[5,15]. This leads to an increased risk for local infection and sepsis that often require a permanent stoma as the ultimate solution[16].

Deciding if a protective stoma is necessary or not requires a very accurate evaluation of every known risk factor, as well as the psychological problems of patients, which is associated to the stoma and their management. It is important to inform every patient undergoing this kind of surgery for the risk of complications despite the location and stage of tumor. Every patient has the potential possibility to develop a complication with all the consequences[11].

Physiopathology of this condition is clear. Early findings following radiotherapy show mucosal hyperemia and acute tissue edema. In the later stage, obliterating endarteritis and fibrosis impair rectal compliance and tissue oxygenation[17]. All these alterations affect anastomotic healing. The aim of this study was to evaluate radiotherapy as a risk factor for the anastomotic leakage. It is important to decide which cases we should perform the defunctioning stoma to avoid an urgent operation. Previous studies have shown that the risk for anastomotic leakage is reduced by the use of defunctioning stoma[18,19]. Others do not embrace this theory. Calculating complications related to stoma itself and the necessity of another operation[20], the surgeon should chose these cases with prudence.

In this study, the authors tried to exclude patients with other known risk factors to have the possibility of a more accurate evaluation as much as they could. For this purpose, the authors grouped and compared patients depending on surgical procedure they had (AR or LAR) to minimize the influence of this factor in conclusions as well (Tables 2 and 3). In the previous studies[21], no advantage of defunctioning stoma on anastomotic leakage was found, hence it is not considered in this study.

Anastomotic leakage associated to neoadjuvant therapy varies in different studies up to 10%–20%. Replacement of cobalt therapy with IMRT through LINAC has diminished lateral effects of radiotherapy, like toxicity and extensive fibrosis. This promises better surgical approach and results. In this study, the significant difference was not found regarding to the anastomotic leakage among the patients treated with preoperative radiotherapy and those who did not had a preoperative radiotherapy (Table 3). This means that preoperative IMRT may not be considered for a defunctioning stoma, unless there are concomitant risk factors. Otherwise, conventional radiotherapy through cobalt will increase the risk of anastomotic leakage (Table 3). Also, it is considered that radiotherapy through cobalt predisposes to an extensive fibrosis of the treated area, which for sure is unpleasant to the operatory surgeon. Counting the toxicity of the procedure itself as well, it might be considered the defunctioning stoma after resecting the tumor, especially when performing a LAR (Table 3).

Finally, it should be aware that a small number of patients treated with IMRT make the further investigation more than necessary. Also, several data may be missed as they were collected retrospectively leading to lack of evidence for the exclusion criteria mentioned above.

To draw the conclusion, patients undergoing an AR for rectal carcinoma after radiotherapy should be considered for a defunctioning stoma, if they have a LAR, radiotherapy through cobalt, or any other concomitant risk factor. IMRT through LINAC alone should not be considered as an important risk factor for anastomotic leakage.

Conflict of interest statement

The authors report no conflict of interest.

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