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ORIGINAL ARTICLE

Short-term preoperative radiotherapy in locally advanced rectal cancer does not increase postoperative complications and improves the rate of sphincter-preserving surgery

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Summary

Purpose: *The Swedish Rectal Cancer Trial (SRCT) demonstrated that a short term regimen of high-dose preoperative radiotherapy (RT) (5×5 Gy) not only reduces the risk for local recurrence, but also improves the overall survival rate. However, an increase in postoperative mortality and morbidity has also been observed. We, therefore, evaluated the early postoperative complications in patients treated with neoadjuvant RT for locally advanced rectal adenocarcinoma.*

Patients and methods: *Between 2000 and 2004, 85 patients with locally advanced rectal tumors were treated in our institution. Preoperative staging was based on computed tomography (CT) scan and, in several cases, with endorectal ultrasonography. There were 55 men and 30 women, with a median age of 68 years. Patients were retrospectively divided into two groups: group A, which included 40 patients receiving preoperative RT (25 Gy in 5 fractions), followed by surgery within one week, and group B, which included 45 patients with rectal cancer undergoing surgery immediately after diagnosis. Both groups were homogeneous regarding age, gender and preoperative stage of disease. The two groups were compared for both technical difficulties during operation and rate of postoperative complications.*

Results: *No postoperative deaths were recorded in either group. In group A, complete pathologic response was observed in 6 (15%) patients and microscopic residual cancer was found in 8 (20%). Low anterior resection (LAR) with total mesorectal excision (TME) was performed in all group A patients, whereas 8 patients in group B underwent abdominoperineal resection (APR) ($p < 0.05$). Diverting stoma was performed in 7 patients of group A; this was closed 3-6 months later in all cases. Postoperative morbidity was not statistically significant between the two groups (40% versus 39%). The rate of postoperative hemorrhage, pelvic or abdominal wound infection, acute urinary infection and delayed ileus was similar. The percentage of major anastomotic leak was also similar in both groups (5 versus 6.6%).*

Conclusion: *Short-term preoperative RT in locally advanced rectal cancer does not increase postoperative complications and improves the rate of sphincter-preserving surgery.*

Key words: neoadjuvant treatment, radiotherapy, rectal cancer

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Introduction

In the treatment of rectal cancer, local recurrence is a major problem, occurring in 15-45% of rectal cancer patients [1,2]. Local recurrence causes severe disabling symptoms and is difficult to treat. The occurrence of a locoregional relapse substantially influences the overall prognosis. Evaluation of recent data demonstrated that the 5-year overall survival rate after curative surgery was 85% for patients without local recurrence, whereas, it dropped to 23% for pa-

tients with local relapse [3]. The risk of local relapse is clearly related to the depth of tumor extension through the bowel wall and the presence or absence of nodal involvement. A retrospective analysis of more than 770 patients with rectal cancer, operated during the last decade at the Department of Surgery in the University of Erlangen, Germany [4], demonstrated an overall local recurrence rate of 14% and an overall 5-year survival rate of 71.2% after curative surgery without adjuvant RT (Table 1). Local control and survival were excellent in stage I disease, but decreased markedly with more extensive tumor penetration (> pT3a/b) and nodal involvement. While it is clear from these data that patients with stage I disease do not generally require adjuvant treatment after curative surgery, and that those with multiple lymph node involvement (stage III) urgently do, it is less clear whether all patients with stage T3N0 rectal cancer will benefit from adjuvant RT. It has been demonstrated, however, that the extent of tumor invasion into perirectal fat, as well as other anatomic and biologic determinants like lymphatic, vascular or neural invasion, tumor grade, integrity of the radial resection margin and location of the tumor in the upper, middle or lower rectum, can substantially influence the risk for local recurrences [5]. As of this, with the exception of the subset of patients showing histologically favorable T3N0 rectal cancer with minimal invasion into the perirectal tissue (pT3a/b), the vast majority of patients with stage II disease would significantly benefit from adjuvant treatment [5].

To reduce local recurrence rates after curative surgery, adjuvant RT has been administered to patients either preoperatively or postoperatively. In a large Swedish trial, short-term preoperative RT resulted in better local control than postoperative RT (local recurrences 13 *versus* 22%) [6]. All trials with short-term preoperative RT showed lower local recurrence rates in the RT arm [7,8]. Results of the SRCT even showed an improved overall survival with the short-term regimen of 5 doses of 5 Gy compared with surgery alone, with 58% 5-year survival in the irradiated group *versus* 48% in the non-irradiated group [9].

The present study was undertaken to assess the postoperative complications of the short-term preoperative RT in patients with locally advanced rectal cancer who underwent TME surgery and to address the influence of 5 doses of 5 Gy on sphincter-preservation.

Table 1. 5-year local failure rates and 5-year overall survival rates after curative surgery (R0) alone according to tumor stage and perirectal invasion depth [4]

	5-year local failure (%)	*5-year overall survival (%)*
All patients (n=776)	14.0	71.2
UICC Stage I		
pT1 pN0 (n=60)	1.7	94.9
pT2 pN0 (n=145)	6.5	87.9
UICC Stage II		
pT3a/b pN0 (n=128)	4.4	87.8
pT3c pN0 (n=60)	14.8	74.5
pT3d pN0 (n=43)	18.0	67.2
pT4 pN0 (n=20)	10.6	63.5
UICC Stage III		
pT1-4 pN1 (n=183)	18.3	66.8
pT1-4 pN2 (n=137)	32.3	35.0

pT3a-d = perirectal tumor invasion depth <1 mm (a), >1-5 mm (b), >5-15 mm (c), >15 mm (d)

Patients and methods

Study population

From January 2000 to August 2004, 85 patients suffering from locally advanced rectal adenocarcinoma were surgically treated in our department. As ongoing interest in neoadjuvant RT was evident, some patients received preoperative RT followed by standardized TME surgery within one week and some others underwent TME surgery alone. Patients treated had a biopsy confirmation of rectal adenocarcinoma, resectable and locally advanced tumors (T3-4N0, T1-4N1-2) as judged by clinical examination, abdominal CT scan and endorectal ultrasound, tumors with the inferior margin within 15 cm of the anal verge, and no hereditary colorectal cancer syndrome. Distant metastases had to be excluded by chest x-ray and ultrasound or CT scan of the liver. Patients in whom another malignancy had been previously diagnosed were not included in this retrospective study.

Preoperative radiotherapy

Group A patients submitted to photon beam preoperative RT received a total dose of 20 Gy in 5 fractions during 5 consecutive days, using linear accelerator of ≥ 6 MV energy. The prescribed dose was specified according to International Commission on Radiation Units and Measurements 50 guidelines [10]. The clinical target volume included the primary tumor and the mesentery with vascular supply, containing the perirectal, presacral, and the internal iliac nodes (up to the L5/S1 junction). The recommended upper border was at the level of L5/S1. RT was delivered with a three-portal technique.

Shielding of the lordotic area at the dorsum of the sacrum was included. The protocol recommended a treatment time from Monday to Friday, with surgery performed within the following week.

Surgery

All patients underwent surgery according to the TME principle, as advocated by Heald [11]. Surgery was performed by especially trained surgical oncologists of the same department, following the same technical guidelines.

Postoperative complications

All postoperative complications were taken into account, and the following definitions were used. Anastomotic leaks included those clinically apparent, those determined on contrast enema after suspicion, and those necessitating reintervention. An abscess around the anastomosis was recorded as leakage. Because it was difficult to discriminate between perineal dehiscence and perineal wound infection, these complications were recorded as perineal wound complications. Hospital death was defined as any death occurring during the first admission, whereas postoperative mortality was defined as any death occurring during the first 30 days after the operation.

Statistics

All data were entered in a database and analyzed with the SPSS package (SPSS, Inc, Chicago, IL). Mann-Whitney tests were used to compare quantitative and ordered variables, and Student's t tests were used to analyze differences in normally distributed data between the two groups. A p-value of 0.05 or less was considered statistically significant.

Results

Of the 85 patients with locally advanced rectal tumors enrolled in the study, 55 were men and 30 women. Their median age was 68 years (range 25-89). Patients were retrospectively divided into two treatment groups: group A included 40 patients who underwent short-term preoperative RT (25 Gy in 5 fractions) followed by surgery within one week. Group B included 45 patients undergoing surgical treatment immediately after diagnosis. The two groups were equally balanced in respect to age, gender, tumor level inferior margin and preoperative stage of the disease (Table 2).

Table 2. Clinical and pathological characteristics

	Group A (RT^+) (n=40) Patients, n (%)	*Group B (RT^-) (n=45) Patients, n (%)*
Age (years)		
Median	68	66
Range	25-89	27-88
Gender		
Male	26 (65)	28 (63)
Female	14 (35)	17 (37)
Tumor level inferior margin (cm)		
0-5	12 (30)	14 (32)
5-10	18 (45)	19 (43)
10-15	10 (25)	12 (25)
TNM stage		
II	24 (60)	25 (56)
III	16 (40)	20 (44)

No hospital death or postoperative mortality was recorded in either group. In group A complete pathologic response was observed in 6 (15%) patients and microscopic residual cancer was found in 8 (20%) patients.

In all cases, LAR with colorectal or coloanal anastomosis was initially intended to be accomplished. LAR with TME was performed in all group A patients, with preservation of the sphincter mechanism. In contrast, 8 patients from group B had to undergo APR combined with TME (17.7%, $p < 0.05$).

More group A patients underwent a temporary diverting stoma at the time of TME surgery (7 patients)

Table 3. Type of surgery performed and postoperative complications

	Group A (RT^+) (n=40) Patients, n (%)	*Group B (RT^-) (n=45) Patients, n (%)*	*p-value*
LAR+TME	40 (100)	37 (82.3)	NS
APR+TME	0 (0)	8 (17.7)	<0.05
Hemorrhage	1 (3)	1 (3)	NS
Sepsis	2 (5)	3 (6)	NS
Wound hematoma	1 (3)	2 (4)	NS
Wound infection	3 (7)	2 (4)	NS
Wound dehiscence	3 (7)	3 (6)	NS
Urinary infection	2 (5)	3 (6)	NS
Ileus	2 (5)	2 (4)	NS
Anastomotic leak	2 (5)	3 (6)	NS
Any complication	16 (40)	19 (39)	NS

LAR: low anterior resection, TME: total mesorectal excision, APR: abdominoperineal resection, NS: nonsignificant

than group B patients (3 patients) (17 *versus* 6%; $p < 0.05$). Diverting stoma was closed 3-6 months after surgery, in all cases.

Postoperative morbidity showed no statistically significant difference between the two groups (40 *versus* 39%). In addition, no difference was found between the two treatment arms in respect to postoperative hemorrhage, wound hematoma, sepsis/fever, wound infection, wound dehiscence, urinary infection, ileus or major anastomotic leak (Table 3).

Discussion

Among the potential advantages of the preoperative RT approach are downstaging and downsizing effects that possibly enhance curative surgery in locally advanced rectal cancer and sphincter preservation in low-lying rectal tumors. Moreover, neoadjuvant therapy may be advantageous in resectable rectal cancer as sterilization of the tumor cells prior to surgery may reduce the risk of tumor cell spillage during surgery. The small bowel in an unviolated abdomen will be mobile and less likely to be within a pelvic radiation portal, the irradiated volume does not require coverage of the perineum, as in the cases after ABR, and there is no irradiation of the anastomotic region. Thus, preoperative RT may cause less acute and late toxicity and more patients will receive full-dose RT [12]. In addition, a certain dose of irradiation seems to be more effective when given preoperative RT delivery, compared with postoperatively, most probably due to the fact that oxygen tension within the tumor may be higher prior to surgical compromise of the regional blood flow. This may improve the radiosensitivity of the tumor by decreasing the more radioresistant hypoxic fraction. A major concern for preoperative RT is that patients with early-stage tumors or disseminated disease will often receive unnecessary treatment. Moreover, neoadjuvant treatment usually postpones definitive surgery considerably and may also be associated with increased morbidity. For these reasons, an intensive short-course RT with large fractions, e.g. 5×5 Gy, for one week followed by surgery within the following week, seems to be an attractive option. Due to short overall treatment time, early operation, low costs and patients convenience, the concept of the one-week preoperative radiation therapy has been adopted in many institutions dealing with resectable rectal cancer. However, some radio- and tumor-biological shortcomings have also prompted criticism: first of all, since surgery is performed only one week after the completion of RT, significant tumor shrinkage ("downstaging") is very unlikely and a major goal of preoperative treatment, the preservation of the sphincter, is less likely to be achieved [13].

The high single dose (5 Gy) used in the Swedish concept has been criticized for inducing more acute and late toxicity. Moreover, although postoperative mortality might not be increased after preoperative short-course RT, provided more sophisticated multiple-field radiation techniques are used, an analysis of the current Dutch TME trial indicated an increased infection rate, higher blood loss during operation and an increased rate of perineal wound healing complications after short-term preoperative RT (5×5 Gy) [14-16]. Recent data also indicated that there is a substantial change in bowel function (median bowel frequency, incontinence for loose stools, urgency etc.) after high-dose preoperative RT in the long term [17], thus emphasizing the need for further optimizing radiation techniques and for identifying the risk groups for local failures to avoid substantial overtreatment.

The results of this study, dealing with a relatively small but solid population, suggest that short-term preoperative RT does not complicate the postoperative course of radical TME surgery for the treatment of locally advanced rectal cancer. In addition, preoperative RT significantly improved the rate of sphincter-preserving surgery, as shown by the increased number of LAR *versus* APR among irradiated patients. The latter should be attributed to the significant "downstaging" and "downsizing" effect seen in 15-20% of patients treated with neoadjuvant RT. Similar objective results for potential pathologic response were reported by other investigators [18]. Given the known rate of inadequacy of preoperative staging procedures, however, and the low statistical power of the study, these latter results should be considered with caution and should only indicate a possible trend towards sphincter-preservation after neoadjuvant RT [18]. In contrast to our favorable results, the mortality rate in the Stockholm I trial with 5 doses of 5 Gy was 8% in the RT^+ group *versus* 2% in the RT^- group [19]. In the Imperial Cancer Research Fund trial, in which patients were treated with three doses of 5 Gy, these percentages were 12 *versus* 7%, respectively [7]. The difference was mainly due to an increase in cardiovascular deaths in patients older than 75 years. Therefore, patients older than 80 years were excluded from the Stockholm II trial and SRCT, with consequent optimization of the mortality rates [20]. Another explanation for those initial poor results is possibly the suboptimal treatment technique. In these trials, the treatment was administered by two opposed fields, which increased the volume treated with 25 Gy considerably. In the SCRT trial, 48 patients were treated with a two-portal technique, and those patients showed

a higher mortality rate than the patients treated with three or four portals [21]. Our results demonstrate that the introduction of radical surgery after preoperative RT does not lead to an increase in the postoperative mortality rate, as long as at least three portals of radiation are used.

The relatively high incidence of postoperative complications seen in our study (40%) might be explained by the great effort taken to meticulously register all possible complications. Similar complication rates were reported in larger prospective studies [15,20].

Anastomotic leakage is a major clinical problem in rectal or anal anastomoses. In the present report, the number of patients with clinical anastomotic leakage was 5 (6%). The reported clinical leakage rate after LAR varies from 3 to 11% in different studies [22,23]. It has been also shown that a diverting stoma is an important measure in reducing the complications of anastomotic leakage [24]. After TME surgery, more serious anastomotic leakage has been reported as compared with conventional surgery [24]. This increase can be partly explained by the removal of the pain-sensitive peritoneum, which prevents early detection of anastomotic failure [25].

In the present study, no difference in clinical leakage rates between group A and group B patients was observed, which is in agreement with previous reports about preoperative RT [8,26,27]. This might have been the result of the increased use of a diverting stoma in RT^+ patients. The performance of a temporary diverting colostomy or ileostomy, in case there is any doubt about the quality of the anastomosis, should be strongly recommended.

Although results are difficult to compare because of the various definitions for wound infection, hematoma or dehiscence, a two-fold increase is generally reported after RT [8,19,21,27]. The absence of significant difference in wound complication rate observed in our study could be attributed to the relatively small number of the patients enrolled, the optimization of the three-portal radiation system and the meticulous surgical technique used.

In conclusion, short-term preoperative RT in locally advanced rectal cancer is a safe approach, does not increase postoperative mortality and morbidity and significantly improves the rate of sphincter-preserving surgery.

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