Journal of BUON **12:** 227-232, 2007

ORIGINAL ARTICLE

Short versus conventional preoperative radiotherapy of rectal cancer: indications

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Summary

Purpose: *Preoperative radiotherapy (RT) at high-dose short-course or at conventional fractions for rectal cancer has proven effect in increasing the tumor control. The aim of this study was to test the impact of 2 different preoperative RT schemes on local recurrence, distant metastasis and survival rates and to define the indications for each of them.*

Patients and methods: *The study included 84 patients with biopsy-proven rectal adenocarcinoma of the middle and lower third, clinically staged T2-T4, N0-2, M0. Group I patients (n=51) received a total dose of 25 Gy in 5 fractions of 5 Gy each for 5 consecutive days; operation was performed 3-5 days later. Group II patients (n=33) received a total dose of 50 Gy in 25 fractions of 2 Gy each in 5 weeks, followed by surgery after 4-5 weeks. Surgery included abdomino-perineal resection (APR) for tumors of the lower half of distal rectum, abdomino-transanal resection (ATR) for tumors of the upper half of distal rectum and anterior resection (AR) for tumors of the middle rectum.*

Results: *After a median follow-up of 53 months (range 22-84) overall survival (OS) of all patients at 4 years was 84% and the distant metastasis-free survival (DMFS) 82%. For stage II patients only, OS and DMFS was 100% in both preoperative RT groups. For stage III patients, OS in group I and II was 72% and 70%, respectively ($p > 0.05$) and DMFS 66% and 68%, respectively ($p > 0.05$). Local recurrence-free survival (LRFS) for all stages was 94% with 5×5 Gy and 25×2 Gy; for stage II only it was 100% and for stage III only 90%. However, the use of short preoperative 5×5 Gy scheme for tumors of the lower third of the rectum and sphincter-saving surgery was accompanied with higher rates of local recurrence: 11% after 5×5 Gy vs. 0% after 25×2 Gy. Partial tumor regression with 50 Gy of conventional RT was achieved in 79% of the cases. Such regression was not possible to assess for the 5×5 Gy group since surgery was performed 3-5 days after RT. No late adverse effects on normal tissues were observed with any scheme of preoperative RT.*

Conclusion: *The conventional preoperative RT with 50 Gy proved more effective for advanced rectal cancer (T4 or N2) and for sphincter-saving resections for lower-lying tumors. The short scheme 5×5 Gy is appropriate for less advanced tumors (T2-3, N0-1), therefore requiring accurate clinical staging.*

Key words: conventional irradiation, local recurrence, preoperative radiotherapy, rectal cancer, rectal surgery, short irradiation

Introduction

Rectal cancer is a frequently occurring disease with increasing incidence. Surgical treatment can achieve full disease control only in stage I. Preoperative RT, either high-dose short-course or conventionally fractionated, has proven efficacy in increasing the rate of lower sphincter-saving resections in low-located tumors and reducing the local recurrence rate after radical surgery [1,2]. Some studies have shown that the time to distant metastasis was delayed with preoperative RT [3]. A large range of doses was tested preoperatively: single fraction of 5 Gy; 20-25 Gy in 5 fractions; 45-50 Gy in 25 fractions.

The question is when to apply short and when conventional preoperative RT.

Our aim was to test the impact of 2 different preoperative RT schemes on local recurrence, distant me-

Received 14-02-2007; Accepted 28-03-2007

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tastasis and survival rates and to define the indications for each of them. To this purpose, short or conventional preoperative RT followed by radical surgery was applied to 84 patients with rectal adenocarcinoma. The results obtained after a median follow-up of 53 months are reported.

Patients and methods

Study population

The study included 84 patients with rectal cancer of the middle and lower third, clinically staged T2-T4, N0-2, M0, admitted for preoperative RT between February 1998 - January 2003. Group I patients (n=51) received a total dose of 25 Gy in 5 fractions of 5 Gy daily for 5 days, followed by surgery after 3-5 days. Group II patients (n=33) received a total dose of 50 Gy in 25 fractions of 2 Gy daily in 5 weeks, followed by surgery after 4-5 weeks. Patients had biopsy-proven adenocarcinoma. The distance from the lower tumor pole to the dentate line was determined in each patient by digital rectal examination and endoscopy and preoperative staging was based on spiral CT scan. The clinical characteristics of the 2 patient groups are shown in Table 1.

All patients were categorized as radically resected, but the lateral margins were not systematically assessed. Table 2 displays the main pathological tumor characteristics of the patients in the 2 groups. Distal rectum location and grade 2 differentiation prevailed in both groups. The cases with stage I in group II resulted from downstaging after 50 Gy of conventional RT. The percentage of stage III patients was higher in the group with short RT course. Pre-therapy clinical TN was not reported because it was determined by CT scan, a method with less accuracy regarding the exact assessment of the real local tumor spread.

Table 1. Patient characteristics (n=84)

Characteristic	*Group I* *5 fractions ×5 Gy* *n=51*	*Group II* *25 fractions ×2 Gy* *n=33*
Sex		
Males	30	20
Females	21	13
Mean age, years (range)	55.8 (43-70)	56.7 (47-67)
Surgery		
APR	15	17
ATR	18	7
AR	18	7
Hartmann	–	2

APR: abdomino-perineal resection, ATR: abdomino-transanal resection, AR: anterior resection

Response criteria

The degree of tumor regression was evaluated from the postoperative pathological findings which were compared with the approximate pretreatment CT-tumor volume.

Complete response (CR) was defined as a complete tumor regression; partial response (PR) was defined as > 30% decrease of perpendicular diameters of CT-tumor volume; stable disease (SD) was defined as absence of tumor progression or regression; progressive disease (PD) was defined as increase of tumor volume [4].

Survival definitions

OS was calculated from the first day of preoperative RT to death of any cause or end of observation. DMFS was calculated from the first day of preoperative RT to the first detection of distant metastasis or end of observation. LRFS was measured from the first day of preoperative RT to the first appearance of local recurrence or end of observation.

Statistical analysis

Data were analyzed with SPSS package (v. 1101/2001). The life-table method of Kaplan-Meier was used to calculate survival: OS, DMFS and LRFS. For com-

Table 2. Pathological tumor characteristics (n=84)

Characteristic	*Group I* *5 fractions × 5 Gy* *n=51* *n (%)*	*Group II* *25 fractions × 2 Gy* *n=33* *n (%)*
Tumor size		
pT2		9 (27)
pT3	40 (78)	16 (49)
pT4	11 (22)	8 (24)
Nodal status		
pN0	19 (37)	17 (52)
pN1	23 (45)	10 (30)
pN2	9 (18)	6 (18)
Distance from dentate line (cm)		
< 3	9 (18)	13 (40)
3-6	23 (45)	8 (24)
6-10	19 (37)	12 (36)
Grade		
1	11 (21)	4 (12)
2	34 (67)	24 (73)
3	4 (8)	3 (9)
colloid	2 (4)	2 (6)
Stage		
pI		9 (27)
pII A+B	19 (37)	8 (24)
pIII A+B+C	32 (63)	16 (49)

parison of survival curves the log-rank test was used. P-value was calculated with x^2 and $p(x^2)$ test of Pearson and with Fisher's exact test. In cases with $p<0.05$ the difference was accepted as statistically significant.

Preoperative radiotherapy

Forty-one percent of all patients were treated with conventional ^{60}Co gamma-therapy and 2D planning system. The rest of the patients were treated with Linac 18MV X-rays and 3D planning system. Patients were treated prone. Application of 3- or 4-field technique depended on the clinical target volume (CTV). The CTV in T2-3 tumors of the middle third of the rectum included the posterior half of the small pelvis: primary tumor, rectum with mesorectum, presacral and prepromontorial lymph nodes and internal iliac nodes. The CTV in tumors of the lower third of the rectum and in all tumors involving adjacent organs included the whole small pelvis and the perineum.

Surgery and chemotherapy

APR was performed to patients with very low-lying rectal cancer. ATR for sphincter-preservation was carried out in cases when the distal margin of the lower tumor pole was at a minimum of 2 cm from the dentate line [5]. AR was carried out for all tumors of the middle rectum. In all patients surgery included total mesorectal excision.

In patients with pT4 and/or pN+ (group I – 32 patients, group II –16 patients) conventional chemotherapy was prescribed postoperatively: 5-fluorouracil (5-FU) 500 mg/m^2 /day i.v. bolus, days 1-5, plus leucovorin 20 mg/m^2 /day i.v. bolus, days 1-5 every 4 weeks, for 4-6 cycles.

Follow-up

After therapy patients were regularly followed-up every 3 months in the first year, and every 6 months up to the 3rd year. Follow-up included clinical examination, serum CEA estimations, abdominal and thoracic CT scans, and endoscopy for patients with sphincter-saving surgery. Relapses were classified as local recurrence when they occurred inside the irradiated volume, or as distant metastasis when they occurred outside.

Results

Analysis of 4-year OS, DMFS and LRFS is shown in Table 3. The results of the two preoperative RT regimes did not differ significantly ($p>0.05$). For stage I and II patients in both groups the 4-year survival was 100%. In stage III patients of both groups 4-year OS was 70-72%, DMFS 66-68% and LRFS 90% ($p=1.0$). LRFS in both groups for all stages was the same: 94% with 5×5Gy and 25×2Gy ($p=1.0$; Figure 1). The comparison of the local recurrence rate for patients with low-lying tumors and low sphincter - saving resection (ATR) according to the 2 dose regimens is shown in Table 4. Due to the insufficient number of patients with preoperative RT+ATR no proper statistical evaluation was applicable. Still, it is worth noting that after conventional RT no local recurrences were observed whereas there were 2 cases with local recurrences with the short RT scheme.

The conventional irradiation of the planning target volume (PTV) was used to destroy the microscopic metastases in the regional lymph nodes and reduce the periphery of the primary tumor. To check the effective-

Table 3. Four-year survival for the two groups according to stage

Stage	*Survival*	*5 fractions × 5 Gy %*	*25 fractions × 2 Gy %*	*p-value*
	OS			
I		–	100	
II		100	100	NS
III		72	70	NS
	DMFS			
I		–	98	
II		100	100	NS
III		66	68	NS
	LRFS			
I		–	100	
II		100	100	NS
III		90	90	NS

OS: overall survival, DMFS: distant metastasis-free survival, LRFS: local recurrence-free survival, NS: non significant

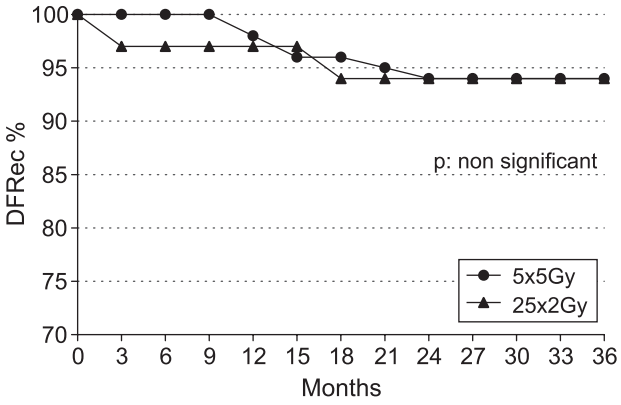

Figure 1. Local recurrence-free survival according to the 2 dose regimes.

Table 4. Local recurrence rate for patients with rectal tumors of the lower third (3-6 cm above the dentate line) and ATR according to the 2 dose regimens

Preoperative RT + ATR	*Local recurrences*	
	n	*(%)*
5×5 Gy, n=18 patients	2	(11)*
25×2 Gy, n=7 patients	0	(0)*

ATR: abdomino-transanal resection
*p-value not applicable due to small number of patients

ness of this approach we analyzed the rate of the tumor radiosensitivity and compared the rate of local recurrences depending on the degree of tumor regression in the 33 group II patients. The degree of tumor shrinkage of these patients and the rate of local recurrence according to this degree is presented in Table 5. PR was achieved in 79% and SD in 24% of the cases. All patients were radically operated. No local recurrences were observed among patients achieving PR, while in cases with SD local recurrences amounted to 28.5% (p=0.04).

During the 4-year follow-up, local recurrences appeared only in patients with absence of radiosensitivity and minimal tumor shrinkage after conventional preoperative RT.

Discussion

Surgery and RT in combination have been widely applied in rectal cancer to achieve higher locoregional control. Surgery rarely failed to remove the primary tumor but it often failed in the periphery of the pelvis. RT can kill micrometastases in the pelvis but can not destroy the sizeable primary rectal cancer. For this reason the surgery-alone treated patients have shown high local recurrence rate ranging from 20 to

Table 5. Local recurrence rate in 33 group II patients (25×2 Gy) according to the degree of tumor response

Tumor response	*n (%)*	*Local recurrence, n (%)*	*p-value*
PR	26 (79)	0 (0)	0.04
SD	7 (21)	2 (28.5)	

PR: partial response; SD: stable disease

28% [6]. Improvement of the results was achieved by introducing a new surgical technique, such as mesorectal excision, but with rather unsatisfactory results in cases with locally advanced rectal cancer [7,8]. The microscopic pelvic lymph nodes metastases, especially in cases of distal rectal tumors, are the cause of local failure [9]. The minimal dose to destroy micrometastases with RT is about 50 Gy in 5 weeks [10,11]. The main important investigations in radiobiology have shown that the short preoperative scheme 5×5 Gy in 5 days has radiobiological effect corresponding to 45-50 Gy of conventional RT, according to the linear-quadratic formula [12].

A large number of randomized trials have shown that preoperative RT can reduce locoregional recurrences from 13-20% to 6-8% [13-17]. At the same time it can slightly improve the DMFS and the OS [18,19]. Postoperative RT has no influence on the latter two parameters and, in addition, the rate of local recurrences has been reduced only when the doses were higher - at least 60 Gy [20,21].

Many randomized trials have proved the benefit of preoperative RT in rectal cancer. Some investigators emphasize the advantage of short schemes, like 5×5 Gy, independent of the degree of local tumor spread [22-24]. Other authors are supporters of the conventional RT only. They consider that the short schedules, like 5×5 Gy, result in more late toxicity compared to conventional treatment [25]. Our investigation showed that the preoperative RT is well tolerated, independent of the fraction dose, if the total radiation dose do not exceed 50 Gy. It should not be ignored the level of the technical radiological development, where the more advanced 3D determination of the target volume and the number of radiation options can minimize the proportion of the small intestine within the CTV.

The results obtained suggest that both preoperative schemes of RT have a distinct role in improving the local tumor control. These schemes slightly improve the OS. The short schedule 5×5 Gy with surgery 3 days later is attractive for both surgeons and radiation oncologists because it saves treatment time and is less expensive. This scheme represses temporary the cancer cells' mitoses and devitalizes them, but it can

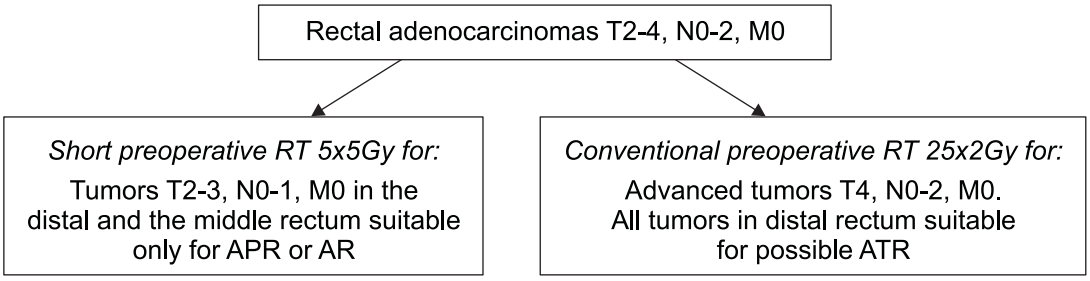

Figure 2. Indications for short and conventional preoperative radiotherapy. APR: abdomino-perineal resection, AR: anterior resection, ATR: abdomino-transanal resection.

not reduce substantially the tumor volume and sterilize the pelvic lymph nodes. Although attractive, the short scheme is appropriate for non-advanced tumors only, where surgical intervention would be possible without tumor shrinkage. For more locally advanced tumors it is very important to decrease the tumor size and sterilize the pelvic lymph nodes. The same principle can apply for low-lying rectal tumors, where the potential tumor shrinkage can make possible a sphincter-saving low resection.

The degree of tumor regression after conventional preoperative RT is closely related to the rate of local recurrences. Tumor resistance to RT could serve as a prognostic factor in the assessment of the disease's aggressiveness.

For correct assessment of the preoperative RT scheme, either short or conventional, it is indispensable to accomplish the exact determination of the tumor clinical TN stage. In our investigation the clinical TN stage was assessed by CT scan. After analysis of the results we conclude that the depth of tumor invasion into the rectal wall and perirectal fat tissues can not be determined correctly using CT scan. For this reason the clinical TN stage must be determined by endorectal ultrasound, which is more precise and a less expensive method.

In conclusion, our results suggest that short preoperative RT with 5×5 Gy, followed by surgery after 3-5 days, is more appropriate for non-advanced tumors of the middle rectum and for operable very low-lying tumors, suitable only for APR. 50 Gy of conventional RT could ensure high rates of recurrence-free survival in locally advanced tumors and could significantly increase the possibilities for lower sphincter-saving resections. In Figure 2 we suggest a simple scheme indicating the need of short or conventional preoperative RT according to the results of this study.

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