Preoperative radiotherapy for locally advanced rectal cancer and prognostic factors influencing outcome

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Received November 14, 2005

The aim of presented study was to evaluate the impact of different factors on survival, local recurrence and development of metastatic disease in patients with rectal cancer treated with preoperative radiotherapy or 5-fluorouracil (5-FU) based concurrent chemoradiation. Retrospective clinical evaluation was performed in 165 patients (33% women and 67% men) with locally advanced rectal adenocarcinoma treated with preoperative radiotherapy or chemoradiotherapy in the period January 1998 – March 2003. Tumor extent was evaluated by CT and/or MRI and/or TRUS examination and tumor biopsy was performed during colonoscopy. The median follow up is 21 month. All patients received preoperative external beam radiation to primary tumor, adjacent lymphnodes and presacral region. Computed tomography localisation of target volume was used for 3D radiotherapy treatment planning. Accelerated short term regimen (25 Gy/5 fraction/1 week) was performed in 14% of patients especially in year 1998–2000 and normofractionated regimen (40–50 Gy/20–25 fractions/4–5 weeks) was performed in 86% of patients. Chemoradiotherapy with 5-FU was carried out in 22% of patients.

Radical resection underwent 85% of patients, inoperable tumor persisted in 7% and distant metastases were detected peroperatively in 8%. The 2-year overall survival (OS) was 84% and 5-year OS was 60% following radical resection. The important prognostic factors affecting survival were postradiotherapy determined pathological staging ($p=0.005$), postradiotherapy tumor grade ($p<0.001$) and the presence of angioinvasion and/or perineural spread ($p=0.023$). Prognostic factors for disease-free survival were identical with those for OS. Higher local recurrence rate was associated in preradiotherapy tumor staged T4 ($p=0.048$) and in presence of angioinvasion and/or perineural spread (0.049). Age, tumor location, histological grade before radiotherapy and tumor downstaging were not statistically significant for survival and/or for local recurrence rate.

The best survival rates were obtained in patients with postradiotherapy grade 1 tumors (5-years survival 100%), tumors without angioinvasion and perineural spread (5-years survival 65%) and in patients who obtained complete remission after preoperative radiotherapy (5-years survival 86%).

Key words: rectal carcinoma, preoperative chemoradiotherapy, prognostic factors

Rectal cancer is one of the most common malignant diseases in industrialized regions. A number of 2,081 new cases is diagnosed in Czech Republic each year and 1,175 patients die from this disease, which is the highest incidence and death rate in the world for both sexes. Surgery with total mesorectal excision (TME) is the milestone of the treatment for rectal cancer. The benefit of adjuvant radiotherapy with or without chemotherapy has been proved in clinical trials and since that has been established as standard part of the multimodal treatment approach for rectal cancer. In the 1980s two clinical trials showed a local control and survival advantage with combination of radiation and chemotherapy (5-FU) in the adjuvant setting [1, 2]. The timing of radiotherapy is still under discussion, nevertheless there is an increasing trend of delivering concomitant chemoradiotherapy in preoperative setting with the aim not only to improve a local control but also to prolonge survival.

In our nonradomized retrospective study we tried to identify factors which correlate with the disease free interval, patient survival, local recurrence and/or occurence of metastatic disease in patient with locally advanced rectal carcinoma.

Material and methods

Retrospective clinical study was performed to evaluate 165 patients (33% women and 67% men) with locally advanced rectal adenocarcinoma treated between January 1998 and March 2003 with preoperative radiotherapy or chemoradiotherapy.

All patients had stage II or III and have a performance status 0–2 (WHO) with median age of 60 years (20–81 years). The extent of the tumor was evaluated by CT and/or MRI and/or TRUS examination and tumor biopsy was performed at colonoscopy. All patients received preoperative external beam radiation to primary tumor, adjacent lymph nodes and presacral region. Computer tomography localisation of target volume was used for 3D radiotherapy treatment planning. Patients were treated using linear accelerator (photons, energy 6.18 MV) with irregularly shaped three-field or four-field technique. Accelerated short term regimen (25 Gy/5 fraction/1 week) was performed in 14% of patients especially in year 1998–2000 and normofractionated regimen (40–50 Gy/20–25 fractions/4–5 weeks) was performed in 86% of patients. The patients (22%) with concurrent chemoradiotherapy received 5-FU continuous infusion 225–30 mg/m^2 from Monday to Thursday during the course of radiation. Anterior resection or abdominoperineal excision was perfomed either one week after the short term regimen of radiotherapy or one month after the normo-fractionated course. The surgical specimens were examined by local pathologist for histopatologic grade, angioinvasion, perineural spread as well as all lymph nodes of the specimen. The median follow up is 21 month.

Statistical analysis. Eleven different factors were studied to evaluate their impact on patient survival, disease-free survival, local recurrence and development of metastatic disease after treatment. The studied factors were age, duration of symptoms, tumor distance of the anal verge, preoperative stage (T or N) and postoperative stage, downstaging, preoperative histology, postoperative postradiotherapy histology, the presence or absence of perineural spread and/or angioinvasion, the possibility to undergo radical surgery. In the case of local recurrence statistical analyses was done only for those patients who underwent radical operation and consequently only eleven factors were studied.

Univariate and multivariate statistical analyses methods were employed to point out factors having influence on time dependence of patient survival, patient disease free survival, local recurrence and occurrence of metastases after the treatment. Univariate analysis was performed using Kaplan-Meier statistics with log rank test. Multivariate analysis was performed with the Cox proportional hazards model using forward stepwise (conditional likelihood ratio) method. Analyses were performed with the statistical software SPSS version 10.0. Variables with significant p-values ($p<0.050$) at least in one of two actuarial analyses were considered possible important factors for the event.

Results

Radical resection underwent 85% of patients, inoperable tumor persisted in 6% and distant metastases were detected peroperatively in 8%. The overall survival (OS) rate of 2-years is 84% and of 5-years 60% following radical resection. The important prognostic factors affecting overall survival (OS) are postradiotherapy determined pathological stage ($p=0.005$), (Fig. 1), postradiotherapy assessed tumor grade ($p<0.001$) (Fig. 2) and angioinvasion and/or perineural spread ($p=0.023$) (Fig. 3). Patients, who did not undergo radical surgery had also significantly shorter OS (Fig. 4). Other studied factors were not statistically significant for patient survival. Overview of p-values is given in the Table 1.

Prognostic factors affecting disease-free survival (DFS) were identical with those for OS (Fig. 5). Higher local recurrence rate was associated in preradiotherapy assessed T4 tumor ($p=0.048$) (Fig. 6) and in presence of angioinvasion and/or perineural spread (0.049) (Fig. 7). No statistically significant association was found according to age, tumor location, histology grading from biopsy before radiotherapy and tumor downstaging for survival and for the local recurrence rate.

Ocurrence of metastases was significantly more often in patients with higher grade of postoperation stage TN (Fig. 8), higher grade of postoperation histology, patients with perineural spread and/or angioinvasion, with non radical operation. Other studied factors were not statistically significant for occurrence of metastases. Overview of p-values is given in the Table 1.

Discussion

In this trial we studied different factors which could influence the survival rate and local recurrence rate in patients treated with preoperative chemoradiotherapy for locally advanced rectal cancer. We observed the best survival rate in patients with tumors grade 1 assessed after radiotherapy (5-year survival 100%), in tumors without angioinvasion and perineural spread (5-year survival 65%) and in patients who achieved complete remission after preoperative radiotherapy (5-year survival 86%).

Local recurrence after neoadjuvant or adjuvant treatment is the main issue in rectal cancer.

There are some studies which confirmed the benefit of preoperative radiotherapy. A meta-analysis published in 2000 [3] included 14 randomised clinical trials comparing preoperative radiotherapy plus surgery with surgery alone in patients with resectable histologically proven adenocarcinoma without metastatic disease. The combined modality significantly reduced the 5-year overall mortality rate, cancer related mortality and local recurrence. Another meta-analysis published in Lancet [4] compared in 28 randomized trials the outcome of surgery for rectal cancer with preoperative or postoperative radiotherapy with those of surgery alone. The

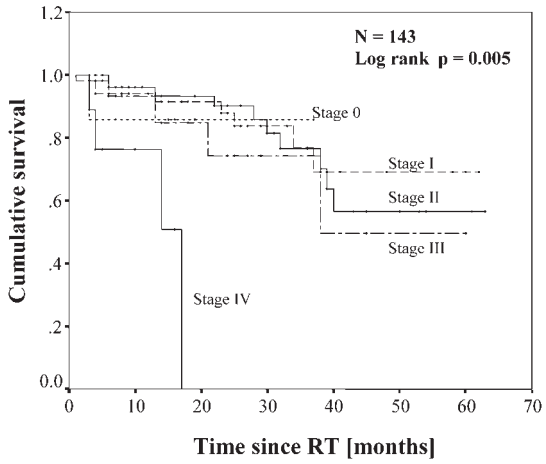


Figure 1. Kaplan-Meier survival curves in different postoperative stages T, N.

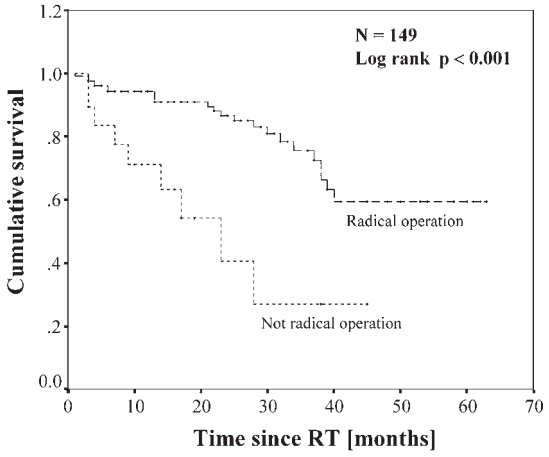


Figure 4. Kaplan-Meier survival curves for radical operation.

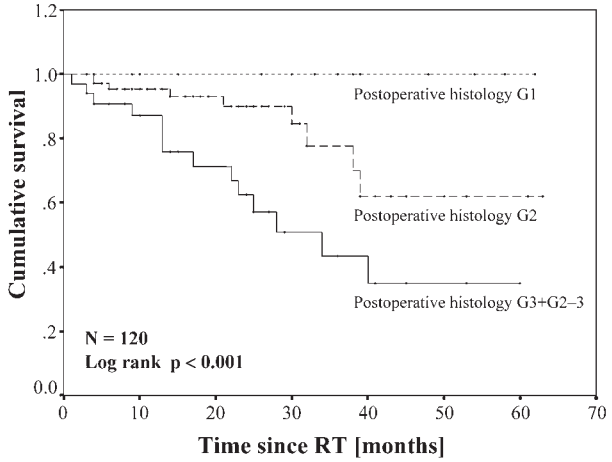


Figure 2. Kaplan-Meier survival curves for different postoperative histology.

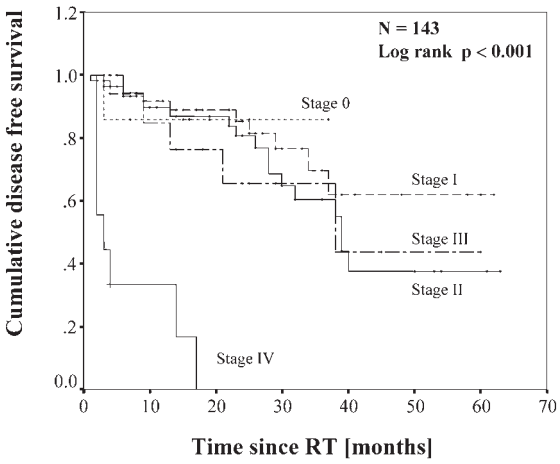


Figure 5. Kaplan-Meier disease free survival curves in different postoperative stages T, N.

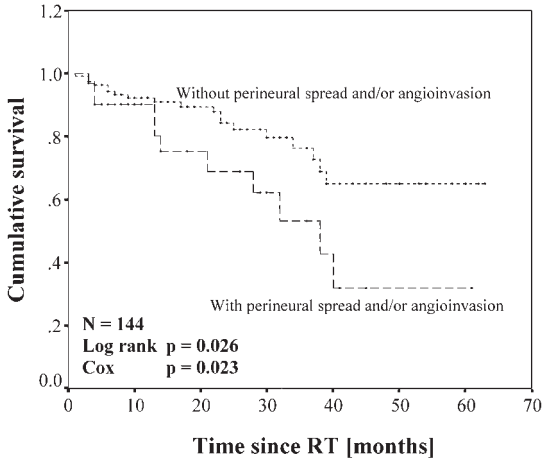


Figure 1. Kaplan-Meier survival curves in different postoperative stages T, N.

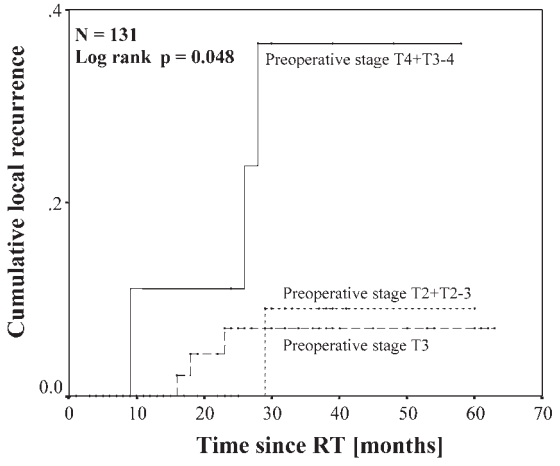


Figure 6. Kaplan-Meier curves for cumulative local recurrence in different preoperative stages T.

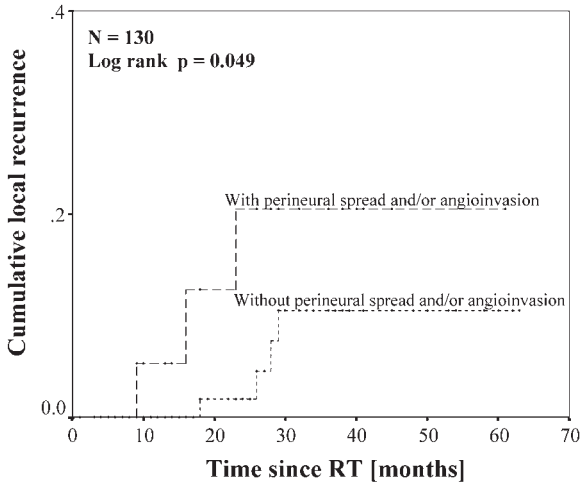
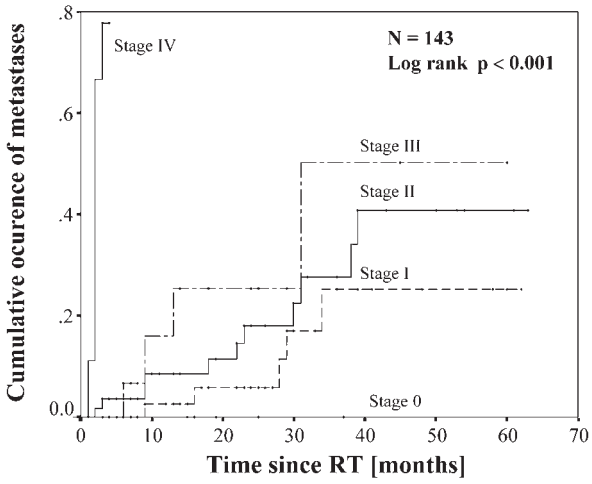


Figure 7. Kaplan-Meier curves for cumulative local recurrence for perineural spread and/or angioinvasion.



Surgical intervention	
radical surgery R0	85.0%
non radical surgery R1	0.5%
non radical surgery R2	0.5%
persisted locally inoperable	6.0%
inoperable for distant metastases	7.5%
refused surgery	0.5%

Figure 8. Kaplan-Meier curves for cumulative ocurrence of metastases in different postoperative stages.

preoperative surgery reduced risk of local recurrence and death of cancer. The overal survival was moderately improved by the use of preoperative radiotherapy. Swedish Rectal Cancer Trial I [5] included 849 patients randomised to receive 25 Gy during 5 to 7 days before surgery or to undergo surgery alone. The time to local recurrence or distant metastases was significantly prolonged in the irradiated group.

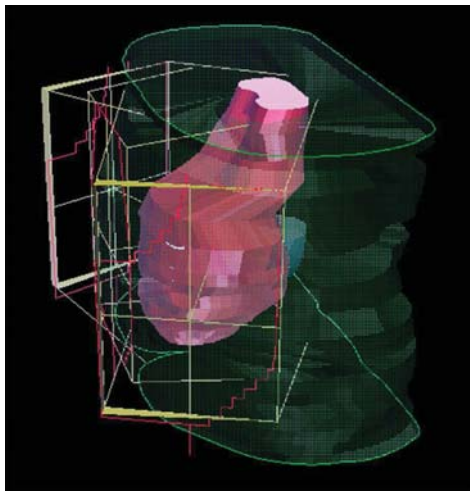


Figure 9. 3D reconstruction of PTV, 3-fields technique used, multileaf-colimator shaped fields.

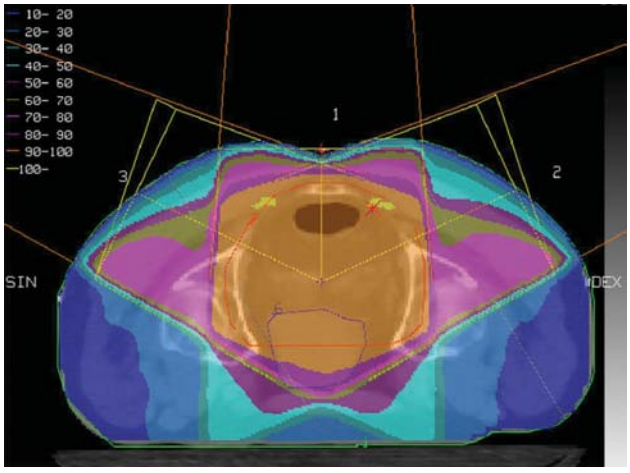


Figure 10. CT imaging of the PTV in locally advanced rectal cancer, treatment plan using direct posterior and posterior oblique fields).

There were no differences with regard to frequency of distant metastases or overall survival.

The second Swedish Rectal Cancer Trial [6] randomly assigned 1168 patients to undergo preoperative irradiation (25 Gy delivered in five fractions in one week) followed by surgery within one week or to have surgery alone. The results of this study showed an improvement of survival and reduction of local recurrence among patients who uderwent preoperative irradiation.

Lyon trial [7] randomized 201 patients to evaluate the optimal interval between preoperative radiotherapy and surgery. The study demonstrated increased tumor downstaging for longer interval between preoperative irradiation and surgery with no effect on toxicity.

The TME is established as a gold standard in the surgical treatment of rectal cancer. The randomized study performed

Table 1. Summary of statistical analysis of results. Factors having significant influence on studied events are indicated and significant p-values are listed for both univariate and multivariate analysis. Univariate analyses was performed using Kaplan-Meier statistic with log rank test. Multivariate analyses was performed with the Cox proportional hazards model using forward stepwise (conditional likelihood ratio) method. Local recurrence was analyzed only for those patients who underwent radical operation. Factors that were significant for both univariate and multivariate analysis are highlighted by gray.

	Survival	Disease free survival	Local reoccurrence	Occurrence of metastases
Age	X	X	X	X
Duration of symptoms	X	X	X	X
Distance of tumor bottom end	X	X	X	X
Preoperative stage T	X	p = 0.049 (Log rank)	p = 0.048 (Log rank)	X
Preoperative stage N	X	X	X	X
Postoperative stage T N	p = 0.005 (Log rank)	p < 0.001 (Log rank)	X	p < 0.001 (Log rank)
Downstaging	X	X	X	X
Preoperative histology	X	X	X	X
Postoperative histology	p < 0.001 (Log rank)	p = 0.039 (Cox) p = 0.003 (Log rank)	X	p = 0.037 (Log rank)
Perineural spread and/or angioinvasion	p = 0.023 (Cox) p = 0.026 (Log rank)	p = 0.016 (Log rank)	p = 0.049 (Log rank)	p = 0.005 (Log rank)
Radical operation	p < 0.001 (Log rank)	p = 0.002 (Cox) p < 0.001 (Log rank)	X	p = 0.002 (Cox) p < 0.001 (Log rank)
Operated at different centers	X	X	X	X

by MARIJNEN et al [8] evaluated the effect of TME surgery with and without preoperative radiotherapy (5x5 Gy). She concluded that the preoperative irradiation did not lead to downstaging, she only demonstrated a decrease in tumor size and in a total number of examined lymph nodes. Another study performed by a Dutch group observed a reduction of local recurrence rate in patients with preoperative radiotherapy [9]. The standardized TME with complete removal of mesorectum remains one of the most important factors influencing local recurrence in rectal carcinoma.

The results of randomized trial performed by Medical Research Council Rectal Cancer Working Party [10] including 279 patients provided futher evidence that preoperative radiotherapy can reduced the rate of local recurrence of rectal cancer in patients with locally advanced disease but without any effect on overall survival.

Another goal of preoperative treatment is to increase the number of sphincter-sparing operation. This was confirmed by two studies. ONAITIS [11] analyzed 141 patients with locally advanced rectal cancer after concomitant chemoradiotherapy with 5-FU. The number of sphincter-preserving surgery increased after combination treatment from 20% to 76% but without increasing overall survival and decreasing local recurrence rate. Authors from M.D. ANDERSON [12] observed an increase use of sphincter-preserving surgery in patients with preoperative chemoradiation. But both were retrospective nonrandomized analysis.

5-fluorouracil (5-FU) is a standard part of the concurrent chemoradiotherapy treatment. There were some trends to improve the efficacy of the monotherapy of 5-FU with other drugs. The results of Intergroup trial did not show any advantage of leucovorin- or levamisol over bolus 5-FU regimens [13].

Some trials phase one and two were published with concomitant radiochemotherapy using other drugs then 5-fluorouracil. The French group from Lyon [14] published data with oxaliplatin and continuous 5-fluorouracil and leucovorin in preoperative setting concurrently with irradiation. An objective clinical response was seen in 75% patients and sphincter-sparing surgery was possible in 26 patients from 40. The results of concurrent administration of capecitabine and oxaliplatin with preoperative radiotherapy were published by RÖDEL [15]. The results are very encouraging and this combination will be evaluated in phase III trials.

Conclusion

Postoperatively (postradiotherapy) evaluated stage, postoperative (postradiotherapy) tumor grading, vessels and perineural invasion were the most important prognostic factors influencing patients survival in our study.

Several clinical trials demonstrated the important role of concomitant preoperative radiochemotherapy with fluorouracil followed by surgery for the local control in locally advanced operable rectal cancer but till now we are still missing data improving the overal survival.

Based on data from different clinical studies, prognostically the most favorable tumors are T1-2N+ or T3N0 disease. Condition sine qua non for the treatment for rectal cancer is the performance of TME by trained surgeon and a well established communication with pathologist, who analyzes

the specimens by the method by QUIERKE et al [16] and identifies at least 12 to 14 nodes to confirm the N0 status. Considering these two factors we can obviously improve the results of the treatment for rectal cancer.

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