

EPIDEMIOLOGICAL STUDY

Influence of neoadjuvant treatment of rectal carcinoma on operability and incidence of distant metastases

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Abstract: In the Czech Republic, rectal carcinoma does not only represent a medical problem, but also a socio-economic one. At our department, we treated totally 266 patients with rectal carcinoma in the years 1998 through 2006. Among our patients, neoadjuvant treatment led to a reduction in size of the tumour in 37.6 %, in 50.8 % the size did not change. In T3 tumours, the reduction in size was observed in 36.7 % of the patients and did not change in 56 %; in T4 tumours, the reduction in size was observed in 60% of the patients. In 88 % of the patients who underwent the operation, no residual tumour was found, in 9 % of patients, a residual tumour was detected. In 19 % of the patients, a local recurrence of the tumour was detected. A statistically significant relationship was proved between the appearance of the metastatic disease and the presence of angioinvasion and the size of the primary tumour according to the Duke's classification (Tab. 1, Fig. 4, Ref. 20). Full Text in PDF www.elis.sk.
Key words: rectal carcinoma, neoadjuvant treatment, chemo-radiotherapy before surgery, angioinvasion.

In the Czech Republic, the incidence rate of rectal carcinoma has recently reached 20.7 per 100 000 population and mortality rate has reached 10.1 per 100 000 population (data from the year 2007). The incidence increases steeply from 50 years of age. The Czech Republic is ranked among the countries with the highest incidence of this disease. According to the latest Czech population data from the year 2007, the proportions of the stages of rectal carcinoma is as follows: stage I. 22.9 %, stage II 20.4 %, stage III 24.1 %, stage IV 21.7 % and 10.9 % of newly diagnosed cases are unstaged mostly due to objective reasons, like a very advanced disease, early death, patient's refusal of anti-tumour therapy, generally poor health status of a patient, etc..

Surgical approach is the basis of therapy for the clinical stages II and III. In contrary to the early stage I, enough evidence from clinical studies has been collected over the last decade to support a treatment strategy combining chemotherapy and radiotherapy for the stages II and III. These studies were inspired by the frequent appearance of local relapses but also distant metastases in patients treated solely surgically. The results of these studies had clearly shown that a combined therapeutic approach leads to a significantly lower incidence of relapses (1–4).

The goal of our retrospective analysis is to ascertain the effect of neoadjuvant treatment on the reduction of size of the primary

tumour, achieving operability and affecting the incidence of early generalization of the disease.

Patients and methods

In the period 1998–2006, we treated at our department totally 266 patients diagnosed with rectal carcinoma. 102 of the patients were females, with the median age of 64 years (ranging 29–89 years); 164 were males with the median age of 60 years (ranging 26–84 years) (Fig. 1). 6 % of the tumours were of the stage T2, 82 % stage T3 and 11 % stage T4; in 1 % of the patients the tumour stage was undeterminable. The proportion of the clinical stages I, II, III, and IV were 5.6 %, 72.2 %, 14.7 %, and 2.3 % respectively, in 5.3 % of the patients, the clinical stage was undeterminable. 42 % of the tumours were localized less than 5cm from the anus. 244 patients (92 %) underwent a surgical procedure, of which 38 % underwent neoadjuvant chemo-radiotherapy, 54 % only radiotherapy. 52.8 % of the patients in the age group younger than 50 years underwent a simultaneous neoadjuvant chemo-radiotherapy, as compared to merely 12.3 % of the patients of 70 years or more. Concomitant chemo-radiotherapy was given to 41 % of the patients with a T3 tumour and to 33 % with a T4 tumour. 53 % of patients with a T3 tumour and 37 % of patients with a T4 tumour underwent radiotherapy without chemotherapy. The majority of the patients were treated with a concomitant regime with 5-fluorouracil (bolus or continual application) or capecitabine administered orally.

Statistical analyses

Standard rank summary statistics were used to describe the primary data, i.e. median, min/max values and 5th–95th percentile range. The non-parametric Mann–Whitney U test based on com-

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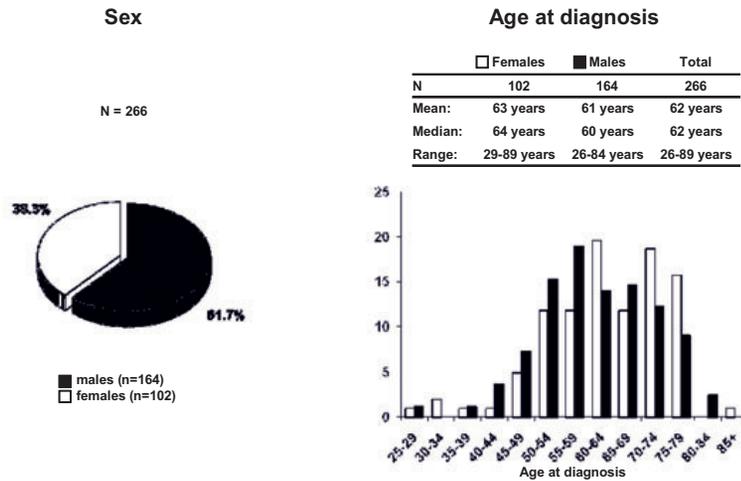


Fig. 1. Patient's sex and age.

parison of median values was applied to test differences between the compared variants in continuous variables. The maximum likelihood χ^2 test was applied to test the differences between the variants in categorical variables. Correlation between parameters was tested using the Spearman's rank correlation coefficient. Survival outcomes were assessed using the standard Kaplan–Meier curves. The value $p=0.05$ was taken as cut-off for a statistical significance in all applied tests.

Results

Of the patients who underwent neoadjuvant treatment, a total 37.6 % had a reduction in size of the tumour, 50.8 % had no change and only 2.6 % had a progression of the primary tumour. Primary tumours of size T3 had a reduction in size in 36.7 % and

no change in size in 56 %, for T4 tumours it was 60 % and 10 % respectively; in the remaining 30 % it was not possible to evaluate the change in size (Fig. 2). 8.3 % of the patients were inoperable after the neoadjuvant treatment. There were 7.2 % of inoperable patients following neoadjuvant radiotherapy, and 9.7 % following the combined radio-chemotherapy. The median age of the inoperable patients was 65 years (ranging 47–82 years). Inoperability rose with age, and the median age was 71years among women and 64 years among men.

The most frequent type of surgical procedure was a resection of the rectum in 54.5 % of the patients followed by an abdomino-perineal resection in 37.7 %. Three patients underwent a protective colostomy, in 2 cases liver metastases were also resected during the operation, and in 1 patient a wedge resection of the urinary bladder was also performed. 69.3 % of the operated patients were

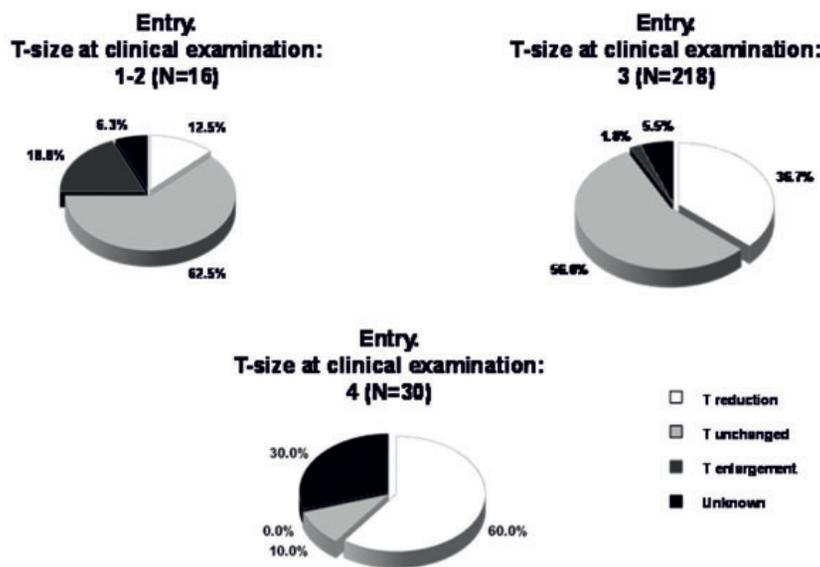


Fig. 2. Reduction of primary tumor our after neoadjuvant therapy.

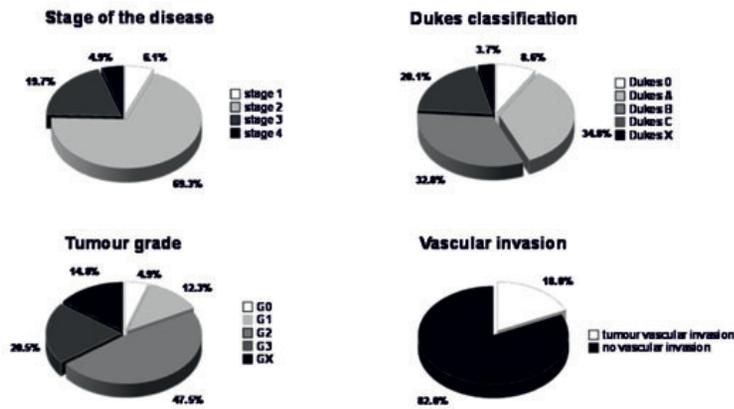


Fig. 3. Characteristics of patients undergoing surgery (n=244).

Relationship of number of examined and positive lymph nodes in patients undergoing surgery

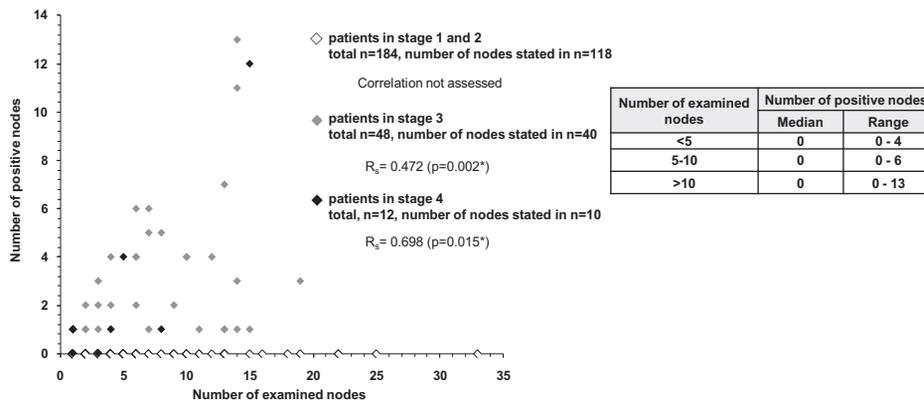


Fig. 4. Characteristics of patients undergoing surgery.

in the clinical stage II, 20 % in the stage III and 5 % in the stage IV. The histopathologic grading was determined as grade 1 in 12.3 %, grade 2 in 47.5 %, grade 3 in 20.5 %, and grade 4 in 14.8 %. Angioinvasion was observed in 18 % of the operated patients (Fig. 3). In a total of 88 % of the operated patients, no residual tumour was found, as compared to merely 9 % of patients where a residual tumor was still present. All 244 patients had their lymph nodes examined, but only in 168 cases we have the reports of the number of examined lymph nodes and positive lymph nodes. A statistically significant correlation between the number of examined lymph nodes and the number of lymph nodes containing a metastasis in the clinical stages III and IV was observed ($p<0.05$) (Fig. 4). We detected a local recurrence of the tumour in 17.2 % of the patients. The majority of cases of local recurrences were detected in patients in the clinical stage IV – 75 % of the patients, followed by 19 % in stage III and 13 % in stages I and II together ($p<0.001$). The appearance of distant metastases with a median time of 15 months since the end of treatment was noted in 19 % of the patients. The metastases were detected predominantly in the patients who were inoperable – 27.3 %, of whom 15.7 % underwent neoadjuvant chemo-radiotherapy and in 20.4 % who underwent

only neoadjuvant radiotherapy. A statistically significant relationship was determined between the appearance of metastatic disease and the presence of angioinvasion and the size of the tumour according to Duke’s classification. The characteristics of patients with metastatic disease are summarized in the Table 1.

Discussion

In our retrospective analysis, we tried to evaluate the effects of neoadjuvant therapeutic approach in patients with rectal carcinoma who were treated at our department with standard treatment modalities and procedures.

A radical surgical operation with the resection of the primary tumour and a total mesorectal excision is the primary curative treatment modality for a locally advanced rectal carcinoma. The choice of solely surgical treatment leads to a 25–40 % risk of developing a local recurrence (5, 6). Data from large randomized clinical studies have proven the benefits of preoperative treatment. Results of “The German Rectal Study Group” study have lead to the implementation of neoadjuvant chemo-radiotherapy of T3 and T4 tumours into the guidelines (3). This treatment modality has lead to the

Tab. 1. Appearance of metastases after treatment.

Factor		N	Metastases after therapy	p1
Sex	female	102	19.6%	0.887
	male	164	18.9%	
Age at diagnosis	< 50 years	36	16.7%	0.262
	50–60 years	86	15.1%	
	60–70 years	79	17.7%	
	> 70 years	65	27.7%	
Stage	stage 1+2	196	16.3%	0.158
	stage 3	52	26.9%	
	stage 4	18	27.8%	
T	T 1+2	16	18.8%	0.816
	T 3	218	18.3%	
	T 4	30	23.3%	
N	N 0+1	210	17.6%	0.359
	N > 1	42	23.8%	
M	M 0	259	19.3%	0.869
	M 1	6	16.7%	
Tumour location	> 5 cm from anal orifice	153	17.0%	0.279
	up to 5 cm from anal orifice	112	22.3%	
Therapy	RT + CHT + surgery	102	15.7%	0.400
	RT + surgery	142	20.4%	
	inoperable	22	27.3%	
Duke classification	Dukes 0	21	0.0%	0.002*
	Dukes A	85	14.1%	
	Dukes B	80	18.8%	
	Dukes C	50	32.0%	
Grade	grade 0+1	42	11.9%	0.179
	grade 2	116	19.0%	
	grade 3+4	52	26.9%	
Vascular invasion	occured	200	15.5%	0.017*
	not occured	44	31.8%	

shrinkage of the primary tumour and to the down-staging of the disease (7). On the other hand, there is no general consensus as to the treatment of T3 tumours without lymphadenopathy. It seems that in the case of patients undergoing a radical surgical procedure with clean edges and a sufficient number of lymph nodes examined (that is 12), the addition of radiotherapy into the combined neoadjuvant treatment is superfluous. This point of view is supported by the results of the German study with rectal carcinoma patients. In the group of patients pre-operatively diagnosed with a T3 tumour with negative lymph nodes, who underwent the operation without any neoadjuvant treatment were in fact in the stage pT1 to pT2. Some consider neoadjuvant treatment in this group of patients as superfluous. On the contrary, the Italian study of 42 patients who underwent neoadjuvant concomitant chemo-radiotherapy suggested that there was a possible benefit of this therapeutic approach in patients in the stage II (8). The most frequent stage in our group of 266 patients was T3 – 82 %, of whom 41 % underwent neoadjuvant chemo-radiotherapy and merely 3.6 % were found to be inoperable. In 36.7 % of cases, we achieved down-staging of the tumour, in T4 tumours positive effects of neoadjuvant treatment were observed in 60 % of the patients. Regression of the tumour following adjuvant chemotherapy was proven to be a significant prognostic marker (7). One of the aims of neoadjuvant treatment is

the avoidance of having to perform an abdominoperitoneal resection and to lower the incidence of local recurrences. According to a recently published survey, the frequency of this operation currently ranges from 10 % to 67 % (9). In our group, a resection of the rectum prevailed in 54.5 % and abdominoperitoneal resection with the necessity of permanent colectomy was performed in 37.7 % of the patients. The criteria of a radical resection were met in 88 % of the operations. As far as operability was concerned, similar effects were achieved for T3 and T4 tumours, irrespectively of whether simple radiotherapy or concomitant radio-chemotherapy was used. Even among the inoperable patients, the chosen neoadjuvant treatment did not differ. This group comprised primarily of older patients and female patients (the median age of women was 71 years, in men 64 years). We based the choice of the treatment modality predominantly on the performance status of the patient and his co-morbidities. The majority of our patients were treated with neoadjuvant chemotherapy consisting of 5-fluorouracil or capecitabine, only 5 of our patients with metastatic disease underwent concomitant chemotherapy with FOLFOX. The importance of adding oxaliplatin into the neoadjuvant treatment is supported by the study ACCORD 12/405, which compared concomitant chemo-radiotherapy comprising capecitabine against to the same treatment supplemented with oxaliplatin. The results did not prove any significant advantage of the combined chemotherapy and recommended capecitabine as “merits investigation” for T3 and T4 tumours (10). Attempts to increase the outcome of combined neoadjuvant chemo-radiotherapy have lead to numerous phase 2 studies with tumour targeted drugs. The results of the Italian study, which combined cetuximab and 5-fluorouracil with radiotherapy, have shown an acceptable toxicity, but surprisingly a low percentage of pathological responses (11). Two American studies had evaluated the effects of bevacizumab in combination with capecitabine or 5-fluorouracil. Both of these studies have proven the safety and tolerability of these combined neoadjuvant therapies and have recommended these combinations for further clinical studies with the emphasis on long term toxicity, finding biomarkers as predictors of response to treatment, post-operational course and the overall survival rate (12, 13).

Achieving a complete pathological remission seems to be a significant prognostic factor mainly in patients in clinical stage III and influences the choice of a further treatment modality (14). Currently, there is no general consensus concerning the necessity of adjuvant therapy after neoadjuvant treatment (15, 16); and this fact increases the importance of examining a sufficient number of lymph nodes as a part of the pathological staging. Lymph nodes were examined in the majority of our patients, but only in 168 cases we had exact numbers of examined and affected lymph nodes. We have proven a significant correlation between the number of examined lymph nodes and the number of lymph nodes containing metastases in the clinical stages III and IV among our patients. Affected lymph nodes were predominantly in the mesorectum, 5.7 % in T1 tumours, 20 % in T2 tumours, 65 % in T3 tumours, and 78 % in T4 tumours (17). The presence of lymph nodes containing metastases after the treatment with adjuvant radiotherapy is a significant negative prognostic factor. The persistence of metastases within the lymph nodes is

connected with a higher cancer mortality rate and is a marker of a more aggressive tumour behavior with the need of further adjuvant systemic treatment (18). Among our patients, we have observed a relatively higher rate of local recurrences following neoadjuvant treatment, 19 % in stage III and 13 % in the stages I and II, which probably correlated with an insufficient number of examined lymph nodes and thus an inappropriate treatment regime. Local recurrences following neoadjuvant treatment in combination with modern surgical approaches including a total mesorectal excision had the rate of approximately 10 % (19, 20). The presence of angioinvasion, a negative prognostic factor, statistically significantly correlated with a more frequent rate of developing a metastatic disease. The systemic contribution of neoadjuvant chemo-radiotherapy probably lowered the incidence of distant metastases to the rate of 15.7 % as compared to 20.4 % of patients who merely underwent neoadjuvant radiotherapy without further adjuvant post-operative treatment.

Our treatment strategy of locally advanced rectal carcinoma was identical with the standards of other European centres specializing in the treatment of rectal carcinoma. Conditions in everyday setting with numerous co morbidities of the patients, their treatment preferences and often hardly accessible early staging examinations can significantly influence our decisions, but also the outcomes of the treatment as compared to clinical studies.

Despite the generally accepted standard treatment approach to pre-operative treatment of locally advanced rectal carcinoma, there are many unanswered questions. What is the optimal combination of cytostatic treatment and its combination with systemic targeted treatment? What is the optimal dose of radiotherapy and fractionation? There are controversies concerning chemo-radiotherapy in early T3 tumours with total mesorectal excision and genetic predictive and prognostic markers.

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Received May 2, 2011.
Accepted January 12, 2013.