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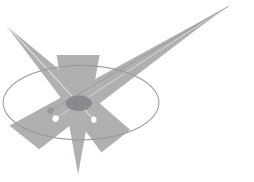

Original Paper

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Postoperative adjuvant chemoradiotherapy in patients with rectal cancer. Prognostic factors for locoregional control and survival

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Marcin Hetnał[ABCDEF], **Krzysztof Małecki**[ABCDF], **Stanisław Korzeniowski**[ADF]

Department of Radiation Oncology, Centre of Oncology, Kraków, Poland

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Summary

Aim The aim of this study is to assess the results of postoperative radiochemotherapy in pts with rectal cancer, factors influencing prognosis with regard to causes of failure and treatment tolerance.

Materials/Methods Between 1993 and 2002, 178 pts with Dukes stage B or C rectal cancer received postoperative chemoradiotherapy. Median age was 62; 110 patients were males, 68 were females. Median follow-up time was 45 months. Sixty-nine patients had stage B and 109 had stage C disease. Main endpoints of the analysis were locoregional recurrence-free survival (LRRFS), disease-free survival (DFS) and overall survival (OS). Kaplan-Meier method was used to calculate survival rates. Univariate and multivariate analyses of prognostic factors were performed using log rank test and Cox's proportional hazard method.

Results The 5-year LRRFS was 73%, DFS was 61% and OS was 65%. Lymph node involvement and method of resection (AR favoured) were the only independent prognostic factors for LRRFS. Lymph node involvement, in particular when four or more were involved, was the independent prognostic factor for DFS. For OS, the independent prognostic factors were infiltration of the pararectal fatty tissue, lymph node involvement in particular when four or more were involved, and total number of chemotherapy cycles (at least six favoured). Radiation therapy was well tolerated in 45% of patients. The most common early reactions were diarrhoea, nausea/vomiting and leucopoenia.

Neither SER (start of any treatment to the end of radiotherapy) nor total treatment time appeared to be of prognostic significance in this group of patients.

Conclusions Involvement of lymph nodes and method of resection were the only independent prognostic factors for LRRFS. Prognostic factors for OS were infiltration of the pararectal fatty tissue, lymph node metastases, four or more involved lymph nodes, and total number of chemotherapy cycles.

Key words **rectal cancer • chemoradiotherapy • adjuvant • prognostic factors**

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Author's address: Marcin Hetnał, Klinika Radioterapii, Oddział B, Centrum Onkologii O/Kraków, Garncarska 11 Str., 31-115 Kraków, Poland, e-mail: m.hetnal@hta.pl

Background

In Poland there are approximately 4700 new cases of rectal cancer registered each year (2685 in males, 2032 in females) and the disease represents the seventh and eighth most common site of cancer among males and females respectively. Approximately 1200 males and 1000 females die of rectal cancer annually. The treatment of colorectal cancer is now multidisciplinary and guided by precise staging and histopathology. Postoperative chemoradiotherapy has been the standard management for stage B and C patients with adenocarcinoma of the rectum with the objective of decreasing local recurrence rate and improving overall survival, as shown in several randomised controlled trials. Results of two randomised controlled trials [1,2] led to a National Institutes of Health Consensus Conference recommendation that patients with stage B or C rectal cancer should be treated with postoperative chemioradiotherapy [3]. The protocol of postoperative treatment of rectal cancer patients, consisting of postoperative adjuvant chemotherapy (6 cycles of 5-FU) and radiotherapy according to NCI, was introduced at the Centre of Oncology in Kraków in 1992.

Aim

The aim of this paper is an assessment of results of adjuvant chemoradiotherapy in patients with rectal cancer with respect to prognostic factors, causes of treatment failures and treatment tolerance.

Materials and Methods

Retrospective analysis was performed in a group of 178 patients after resection (R0 or R1) of adenocarcinoma of the rectum with Dukes stage B or C. All patients had to be older than 18 and younger than 80.

All patients received adjuvant chemoradiotherapy. Characteristics of patients are shown in Table 1.

Anterior resection was performed in 93 pts and abdominoperineal resection in 85 pts. Only 30% (50/178) of patients were operated at the Institute of Oncology in Kraków; the majority of them had undergone resection in surgical departments of general hospitals (123/178). Abdominoperineal resection was performed when rectal cancer was localized proximal to the anal verge, so anterior radical resection with curative intent was impossible to perform. All patients were referred for postoperative chemoradiotherapy.

Table 1. Characteristics of patients.

Characteristics	n	%
Age		
Median	62	
Range	32–80	
Sex		
Female	68	38.0%
Male	110	62.0%
Stage (Dukes, Astler-Coller)		
B	69	39.0%
C	109	61.0%
Type of resection		
Abdominoperineal resection	93	52.0%
Anterior resection	85	48.0%
Completeness of operation		
R0	168	94.3%
R1	9	5.1%
R2	1	0.6%
Histological grade		
G1	33	18.5%
G2	90	50.6%
G3	6	3.4%
Not known	49	27.5%

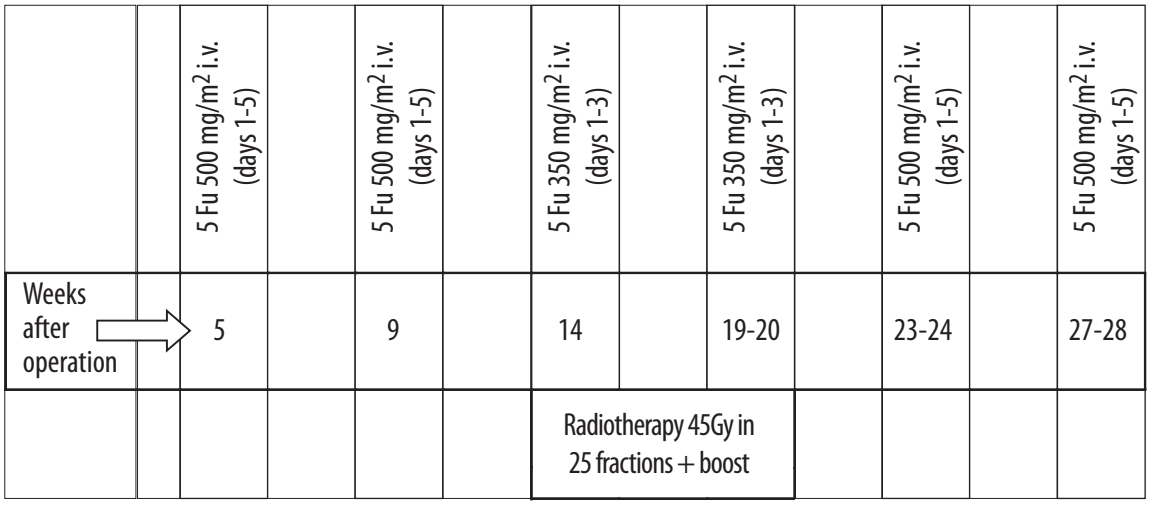

Figure 1. Chemoradiotherapy regiment according to NCI.

Patients were treated with two (1st and 2nd cycle) initial four-week cycles of infusion of fluorouracil (5-FU) and folinic acid (FA) (5-FU 500 mg per square metre, FA 20 mg per square metre; on days 1 to 5), folinic acid, followed by radiation therapy and concomitant FUFA treatment (5-FU 350 mg per square metre, FA 20mg per square metre; first (3rd cycle) and last three days (4th cycle) of radiation), followed by last two four-week cycles of infusion of fluorouracil (5-FU) and folinic acid (FA) (5-FU 500 mg per square metre, FA 20 mg per square mete; on days 1 to 5) (Figure 1).

Radiation was delivered with 6MV linear accelerator or with Cobalt-60 unit. Four-field "box" techniques were used to include the tumour bed and pelvic nodes (opposed anteroposterior-posteroanterior and opposed lateral fields) and 118 (66%) patients received boost dose to the tumour bed using the two-field technique.

More than half of the patients (57%) were treated strictly according to the protocol. There were some protocol violations. Number of chemotherapy cycles ranged from 3 to 8 (median 5.8). Median time from operation to the end of radiotherapy (SER) was 7 months (range 3–11). The main reason (25%) for delay was late referral to the Centre of Oncology and radiation therapy waiting list. Median radiation dose was 5040cGy (4500cGy in 25 fraction and boost 540cGy in 3 fraction). It was impossible to localize the tumour bed during radiotherapy planning in a minority of patients (36%) so they did not receive a radiation boost.

Among 178 patients undergoing postoperative irradiation, 1 (0.5%) failed to complete treatment due to side effects of diarrhoea and vomiting. In 33/178 patients (18.5%) time of radiation was prolonged to more than 6 weeks. The main causes of extension were machine breakdown, conservation jobs (16 patients), and other breaks in work, e.g. holidays (11 patients).

Statistical methods

Main endpoints of the analysis were locoregional recurrence-free survival (LRRFS), disease-free survival (DFS) and overall survival (OS) rates.

Survival was measured from resection to the date of death or lost to follow-up. Time to progression was measured from the date of resection to the date of local or distant progression. Local failure was defined as failure occurring inside the pelvis (and/or perineum) and distant failure as any site of failure outside the pelvis.

SER was measured from the date of operation to the end of radiotherapy.

Kaplan-Meier method was used to calculate survival rates. Univariate and multivariate analyses of prognostic factors were performed using log rank and Cox's proportional hazard method. In the course of analyses of prognostic factors clinical factors (sex, age, stage, grade, nodal status, etc) and treatment factors (method of resection, completeness, radiation dose, boost, total number of

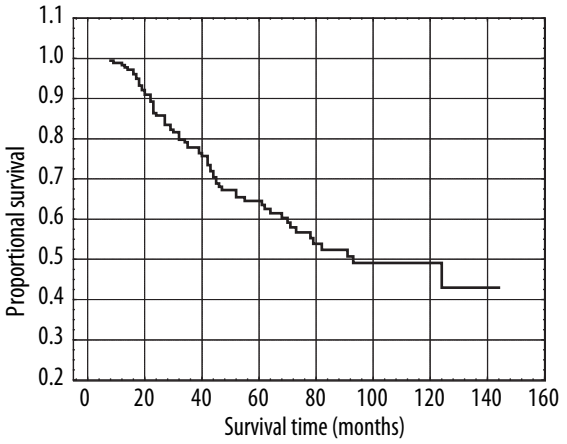

Figure 2. Overall survival (OS) for all 178 patients.

chemotherapy cycles, SER, total treatment time, year of start of treatment) were compared.

Results

Survival

After a median follow-up of 45 months (range 8–144), we observed 53 cancer related deaths, 15 pts died from other reasons and 110 were alive in January 2005 (including 95 disease-free patients).

The 5-year LRRFS rate and DFS rate were 73% and 61% respectively. The 5-year OS rate was 65% (Figure 2). The 5-year OS were 77% for Dukes B stage and 57% for Dukes C stage.

In the course of the univariate analysis (Table 2) we found that Dukes stage, type of operation, SER, and year of start of treatment had a significant impact on LRRFS.

The following prognostic factors influenced DFS: Dukes stage, type of operation, extracapsular extension of the lymph node metastases, infiltration of the pararectal fatty tissue, four or more involved lymph nodes.

Dukes stage, differentiation of the tumour, infiltration of the pararectal fatty tissue, four or more involved lymph nodes, six or more received cycles of chemotherapy were statistically significant prognostic factors for OS.

The risk of locoregional recurrence after anterior resection was less than half of the risk in patients after abdominoperineal resection (Table 3).

In the multivariate analysis, the following prognostic factors had a statistically significant impact on recurrence: Dukes C stage, four or more involved lymph nodes, which had more than twice as high risk of recurrence compared to, respectively, Dukes B patients and one to three involved lymph nodes (Table 4).

For OS (Table 5), the independent prognostic factors were infiltration of the pararectal fatty tissue, involvement of lymph nodes, in particular four or more involved lymph nodes, and total number of chemotherapy cycles (at least six favoured).

Analysis of failure

During follow-up, recurrence of malignancy was observed in 65 patients (37%). In 36 (20%) patients distant failure was observed. In 21 cases (58%) distant failure was located in the liver; in 13 (36%) it was found in the lungs. Median time to distant recurrence was 18 months (6–76).

The main cause of failure were locoregional recurrences (42/178–24%). The most common site of locoregional recurrence was the pelvis (32/42–76%), perineal region (8/42–19%) and pelvic lymph nodes (7/42–17%). Median time to local recurrence was 19 months (3–61).

In 13 (7%) patients both distant and locoregional failures were observed.

Treatment tolerance

Treatment was well tolerated by 80 patients (45%); 98 (55%) noticed at least one early complication. The most common complications of both chemotherapy and radiotherapy were diarrhoea (63/178), nausea/vomiting (26/178), leucopoenia (13/178), and early skin reactions (13/178). There was one serious (grade III/IV) side effect: thrombocytopoenia. Severities of the reactions are shown in Table 6.

Discussion

Surgery still remains the principle method of treatment of rectal cancer. In 1982 a new technique was developed based on adequate en bloc clearance of the rectal mesentery, including its blood supply and lymphatic drainage – Total Mesorectal Excision (TME). Local recurrence rates following TME approximate 6.6% from published series, accounting for more than 5,000 patients [4].

Table 2. Univariate analysis of prognostic factors (significant bolded).

Prognostic factors	Number of pts.	%	5 year LRFS%	5 year DFS%	5 year OS%
Total group	178	100%	73%	61%	65%
Sex					
Female	68	38%	70%	60%	62%
Male	110	62%	75%	61%	67%
Age					
>60 y.	100	56%	72%	60%	60%
<60 y.	78	44%	74%	62%	68%
Histological grade					
G1	33	18.5%	68%	50%	66%
G2	90	50.6%	70%	61%	60%
G3	6	3.4%	100%	0%	0% p=0.012
Not known	49	27.5%	79%	72%	75%
Stage (Dukes. Astler-Coller)					
B	68	38%	83%	75%	77%
C	110	62%	64% p=0.012	53% p=0.0006	57% p=0.009
Type of resection					
Anterior resection	93	52%	84%	71%	74%
Abdominoperineal resection	85	48%	59% p=0.002	51% p=0.014	55%
Completeness of operation					
R0	168	94%	58%	48%	80%
R1	9	5.5%	74%	62%	64%
R2	1	0.5%			
Tumour invasion through rectal wall					
whole	172	97%	72%	60%	63%
partial	6	3%	83%	83%	100%
Infiltration of the pararectal fatty tissue					
yes	128	72%	69%	57%	60%
no	50	28%	81%	70% p=0.049	76% p=0.001
Number of involved lymph nodes					
0	68	38.2%			77%
1–3	76	42.7%	69%	60%	68%
≥4	34	19.1%	57%	35% p=0.023	32% p=0.0012
Extracapsular extension of the lymph node metastases					
no	160	90%	75%	64%	66%
yes	18	10%	54%	35% p=0.007	48% p=0.051

Table 2. Continued. Univariate analysis of prognostic factors (significant bolded).

Prognostic factors	Number of pts.	%	5 year LRFS%	5 year DFS%	5 year OS%
Total number of chemotherapy cycles					
1–5	38	21.3%	66%	52%	47%
≥6	140	78.6%	74%	63%	69% p=0.047
Total treatment time (months)					
Less than 6.5	85	47.8%	70	61%	63%
More than 6.5	93	52.2%	72%	61%	66%
SER (months)					
<5	60	33.7%	63%	56%	65%
≥5	118	66.3%	78% p=0.03	64%	64%
Year of start of treatment					
1992–2000	128	72%	72.7%*	78%*	61%
2001–2002	50	28%	88.4%* p=0.046	61%%*	78%
Radiation dose					
<4600	33	19%	83%	71%	66%
≥4600	145	81%	71%	60%	64%
Radiation boost					
yes	118	66%	69%	66%	61%
no	60	36%	78%	70%	71%

* 4 year survival.

Table 3. 5 years multivariate analysis of prognostic factors for LRFS.

Variable	Relative risk	P-value
Anterior resection vs abdominoperineal resection	0.4	0.007
Dukes C vs Dukes B	2.15	0.036

Table 4. 5 years multivariate analysis of prognostic factors for DFS.

Variable	Relative risk	P-value
Dukes C vs Dukes B	2.58	0.001
Four or more vs less than four involved lymph nodes	2.03	0.02

Table 5. 5 years multivariate analysis of prognostic factors for OS.

Variable	Relative risk	P-value
Dukes C vs Dukes B	1.87	0.024
Four or more vs less than four involved lymph nodes	2.23	0.006
Infiltration of the pararectal fatty tissue vs no infiltration	2.54	0.007
Total number of chemotherapy cycles (six and more vs less than six)	0.51	0.015

Table 6. Treatment early complications (number of patients).

Complication	EORTC/RTOG scale		
	I	II	III/IV
Diarrhoea	45	19	0
Nausea/vomiting	20	6	0
Leucopoenia	9	4	0
Early skin reaction	6	7	0
Thrombocytopoenia	1	0	1

The protocol of postoperative treatment of B and C stage rectal cancer according to NCI was introduced in the Centre of Oncology in Kraków in 1992. It was known (GITS [1] and Mayo/NCCTG [2]) that surgery and postoperative combined modality treatment (radiochemotherapy) had reduced local recurrence rates and improved overall survival compared with surgery alone or surgery with postoperative radiotherapy. Both earlier trials were randomised. In GITS (227 patients) there was a significant improvement in survival in patients who received postoperative chemoradiotherapy compared with the surgery-alone control arm (54% vs. 27%, p=0.005). In the Mayo/ NCCTG trial (204 participants) patients who received postoperative chemoradiotherapy had a significant decrease in local failure (14% vs. 25%, p=0.036), distant failure (29% vs. 46%, p=0.011) and an increase in 5-year disease-free survival (63% vs. 42%, p=0.0016) and overall survival (57% vs. 48%, p=0.025) compared with postoperative radiotherapy alone. Later trials also showed that postoperative chemoradiotherapy reduces local failure rate and improves overall survival compared with surgery alone and reduces local failure rate compared with postoperative chemotherapy alone [5,6]. Moreover, Intergroup 86-47-51 trial has demonstrated a 10% improved overall survival with the use of continuous-infusion 5-FU during the course of radiation therapy compared with bolus 5-FU [7]. Our results show comparable overall and disease-free survival to Tveit trial [5] results.

Local failure rates after postoperative radiotherapy in the reported studies were between 11 and 21%. Our result – 24% were evaluated by dividing locoregional failure observed and the total number of patients. Moreover, locoregional failure rate is higher than distant failure rate (20%). Our surprising results could be caused by the fact that TME (Total Mesorectal Excision) was introduced to the hospitals in the late nineties.

Involvement of lymph nodes was an independent prognostic factor for LRRFS, DFS and OS [8]. It is well known that patients with positive lymph nodes (especially more than 4) have higher both distant and local failure rates [9].

Also the method of resection (favouring AR) (which is also an independent prognostic factor in our series) can significantly affect outcome [10,11]. The poor prognosis of patients with an APR is ascribed to the resection plane of the operation leading to a higher frequency of margin involvement by the tumour and perforation with this surgical technique.

Patients who started treatment later than in 2000 have fewer recurrences than those treated earlier (univariate analysis). That could be explained by the fact of improvement of training of the staff in the use of medical (especially surgical) technologies (learning curve).

Neither SER (start of any treatment and the end of radiotherapy as defined by Bentzen) nor total treatment time appeared to be of prognostic significance in this group of patients. A trial which compared the use of "early" radiotherapy (concomitantly with 1st and 2nd cycle of chemotherapy) with "late" radiotherapy (concomitantly with 3rd and 4th cycle of chemotherapy) showed significantly prolonged DFS [10] in the "early" radiotherapy group. In our series, patients ended radiotherapy later than in that trial, which could have worsened the results.

We also reported paradoxical results, which were not confirmed in multivariate analysis: LRFS and DFS were better in patients who received less than 4600cGy or who finished radiotherapy later than 5 months after surgery than respectively in patients who received more than 4600cGy or finished radiotherapy within 5 months after surgery. These results, which are not confirmed in other publications, could be ascribed to chance only.

More than half of the total number of patients noticed at least one early complication. The frequency of the most common early complications of both chemotherapy and radiotherapy, i.e. diarrhoea, nausea/vomiting, leucopenia and early skin reactions, is lower than in the reported trials [1,2,5,6,12].

Since publication of the Swedish Rectal Cancer Trial [13], which was the first randomised controlled trial to show survival benefit for patients irradiated preoperatively in comparison with surgery alone, many encouraging results have been reported [14]. Neoadjuvant radiotherapy decreases the relative risk of a local failure by 50–70% (postoperative by 30–40%) [15]. Nowadays preoperative radiotherapy or radiochemotherapy is a dominant option in the treatment of Dukes B and C rectal cancer. Nevertheless, many patients are still referred to radiotherapy/chemotherapy departments after surgery.

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