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Original contributions

Postoperative radiotherapy combined with 5-fluorouracil in patients with rectal cancer

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Introduction. The aim of the study was to evaluate the results of postoperative radiotherapy combined with 5-fluorouracil in patients with rectal cancer, with particular reference to tolerance of treatment.
Material and methods. The study group included 64 patients treated between the years 1991 and 1995 at the Department of Oncology and Radiotherapy, Medical University of Gdańsk. All patients received postoperative irradiation to the pelvis. Treatment schedule included two parallel opposite fields, a total dose of 45 Gy in 23–25 fractions, and concomitant 5-fluorouracil chemotherapy during the first three and the last three days of irradiation.
Results. Median follow-up for the entire group was 37 months (11–60 months). Major early complications included diarrhoea (58%), leucopoenia (33%), nausea and vomiting (16%), dysuria (6%) and anaemia (5%). In total, acute side effects occurred in 43 patients (67%,) in 18 of them (28%) reaching grade 3–5. One patient died due to postradiation ileus and 3 patients did not complete treatment due to exacerbation of side effects and/or deterioration of their performance status. Late complications, mainly from bowels and urinary bladder, occurred in 22 patients (34%) and in 7 of them (11%) were severe. The actuarial five year survival in the entire group was 54%. Local recurrence occurred in 15 patients (23%) and distant metastases in 18 patients (28%).
Conclusion. Our method of postoperative radiochemotherapy in rectal cancer was accompanied by a large number of acute and late complications and did not secure satisfactory local control. Literature data demonstrates that better tolerance of treatment may be achieved with the use of special techniques, which decrease small bowel volume in the irradiation field. There are also strong arguments in favour of replacing postoperative irradiation by preoperative radiotherapy.

Pooperacyjna radioterapia skojarzona z 5-fluorouracylem u chorych na raka odbytnicy

Wstęp. Celem pracy była ocena odległych wyników leczenia uzupełniającego z udziałem radioterapii skojarzonej z 5-fluorouracylem, ze szczególnym uwzględnieniem tolerancji leczenia, u chorych po radykalnym zabiegu operacyjnym z powodu raka odbytnicy.
Materiał i metody. Przedmiotem oceny było 64 chorych leczonych w Klinice Onkologii i Radioterapii Akademii Medycznej w Gdańsku w latach 1991–1995. Wszyscy chorzy po zabiegu operacyjnym otrzymali uzupełniające napromienianie na okolicę miednicy małej techniką 2 pól przeciwstawnych do dawki całkowitej 45 Gy w 23–25 frakcjach, skojarzone z podawaniem 5-fluorouracylu przez trzy pierwsze i trzy ostatnie dni napromieniania.
Wyniki. Mediana czasu obserwacji dla całej grupy wynosiła 37 miesięcy (11–60 miesięcy). Głównymi wczesnymi powikłaniami w czasie leczenia były biegunki (58%), leukopenia (33%), nudności i wymioty (16%), objawy dyzuryczne (6%) i niedokrwistość (5%). Do ostrych powikłań doszło ogółem u 43 chorych (67%), w tym u 18 (28%) miały one charakter ciężki (stopień 3–5). Jedna chora zmarła w następstwie niedrożności, a troje kolejnych chorych nie ukończyło leczenia z powodu nasilonych objawów niepożądanych lub pogorszenia stanu ogólnego. Późne powikłania, przede wszystkim w obrębie jelit i dróg moczowych, wystąpiły ogółem u 22 chorych (34%), w tym u 7 (11%) – w stopniu ciężkim. Oszacowane pięcioletnie przeżycie w badanej grupie wynosiło 54%. Do wznowy miejscowej doszło u 15 chorych (23%), natomiast przerzuty odległe wystąpiły u 18 chorych (28%).
Podsumowanie. Stosowana przez nas metoda pooperacyjnego leczenia raka odbytnicy jest związana z dużym ryzykiem wczesnych i późnych powikłań oraz niezadowalającym odsetkiem wyleczeń miejscowych. Dane z piśmiennictwa wskazu-

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ją, że tolerancję leczenia można poprawić stosując techniki zmniejszające objętość jelita cienkiego w polu napromieniania. Szereg argumentów uzasadnia także celowość zastąpienia napromieniania pooperacyjnego napromienianiem przedoperacyjnym.

Key words: rectal cancer, postoperative radiochemotherapy
Słowa kluczowe: rak odbytnicy, pooperacyjna radiochemioterapia

Carcinoma of the rectum is one of the most common malignancies in Poland, estimated to afflict some 4500 persons every year [1]. Radical surgery is considered to be standard management of this malignancy.

Prognosis for the patients who undergo radical resection depends mostly on the stage according to Dukes' classification or its modifications. Results of treatment in patients with early stages of rectal carcinoma are satisfactory, but in more advanced cases (Dukes' stage B and C) local recurrence occurs in 35-50% of patients [2, 3]. The tendency to develop local recurrence of rectal cancer is determined by the characteristic anatomical features of this organ such as: lack of serosa in its lower, extraperitoneal fragment and close vicinity of other pelvic organs, which limits resectability of tumor with safe margins of healthy tissues [3]. Local recurrence of rectal cancer not only shortens overall survival, but also worsens the quality of life.

Therefore different forms of combined treatment have been investigated in patients with a high risk of recurrence for nearly 30 years. Results of extensive, randomised clinical trials have proven that in this group of patients postoperative radiotherapy combined with chemotherapy results in a 10-20% reduction of local recurrence risk and prolongs overall survival [4–6]. On this basis American National Institute of Health recommended this form of combined treatment as a routine procedure in locally advanced rectal cancer in 1990 [7]. The above recommendations where introduced in the Department of Oncology and Radiotherapy of the Medical University of Gdańsk in 1991. The aim of this publication is to present our results of combined treatment in patients with advanced rectal cancer.

Material and methods

Between 1991–1995, 64 patients received adjuvant treatment in the Department of Oncology and Radiotherapy in Gdańsk after potentially curative resection of rectal cancer (Tab. I). Adjuvant radiochemotherapy was administrated to all patients with tumour located in the rectum or sigmo-rectal juncture. Dukes' stage B and C was diagnosed in 33 and 31 patients respectively. In most patients there was no precise information concerning the distance between inferior edge of the tumour and the anal verge, therefore the above localisation of tumour was the only accepted anatomical criterion to implement adjuvant treatment. All patients underwent radical surgical procedure: 37 according to Miles' method, 26 to Dixon's and 1 to Hartmann's. Patients were referred to adjuvant treatment along with generally accepted rules. Low performance score (3 or 4), advanced age and other individual risk factors were relative contraindications to radiotherapy, but such situations were exceptional. Average age in the group was 61 years (range: 31–77 years).

Tab. I. Patients' characteristics

Sex	Females	33 (52%)
	Males	31 (48%)
Age	<40	3 (5%)
	41-50	9 (14%)
	51-60	9 (14%)
	61-70	33 (52%)
	>71	10 (15%)
Dukes' stage	B	33 (52%)
	C	31 (48%)
Grade	G1	36 (56%)
	G2	24 (38%)
	G3	4 (6%)
Type of surgery	APR (Miles)	37 (57%)
	AR (Dixon)	26 (41%)
	Hartmann	1 (2%)
Time from surgery to radiotherapy	<6 weeks	32 (50%)
	6-12 weeks	28 (44%)
	>12 weeks	4 (6%)
Radiotherapy dose	<45 Gy	56 (88%)
	>45 Gy	8 (12%)

Predominant pathological grades were G1 and G2. In 32 patients the time between surgery and the onset of radiotherapy was shorter than 6 weeks, in 28 patients it was between 6 and 12 weeks and in four patients it was longer than 12 weeks (median 54 days, range 19–109 days). Patients received pelvic radiation therapy delivered by a cobalt-60 machine or linear accelerator with photon energy of 9 MeV. Two AP-PA parallel opposed field technique was used. The superior border of the radiation field was above the fifth lumbar vertebral body, and the inferior field margin was below the obturator foramina. The lateral borders were 1.5 cm lateral to the widest bony margin of the true pelvic sidewalls. Most of the patients were treated to a total dose of 45 Gy calculated to the encompassing isodose in 23–25 fractions (range between 16 and 57 Gy), i.e. 47.6 Gy to the reference ICRU point (half of IPD). Fraction dose was between 1.8 and 1.96 Gy. The dose of 450 mg/m^2 of 5-fluorouracil was administrated during the first three and the last three fractions of radiotherapy. During the period covered by this analysis patients did not receive chemotherapy neither before nor after the course of radiotherapy. Median follow-up was 37 months (range 11–60 months). The following factors were included in the survival analysis: type of surgery, pathological grade, stage according to Dukes' classification, number of involved lymph nodes, encompassing dose, maximal dose, fraction dose, breaks in radiotherapy, chemotherapy schedule and dose of 5-fluorouracil. Treatment side effects were evaluated according to WHO classification. Overall and local recurrence-free survivals were assessed with the Kaplan-Meier method. Log-rank test was used to compare survival curves. Multivariate analysis was performed by Cox proportional hazard model. Appropriate hazard ratios and their 95% confidence intervals were reported for significant variables in final multivariate model. Hypothesis testing was based on commonly accepted level of type I error, $\alpha=0.05$.

Tab. II. Acute toxicity

Toxicity grade in WHO scale	1	2	3	4	5	Total number of patients (%)
Diarrhoea	6	17	14	-	-	37 (58%)
Leucopoenia	13	7	1	-	-	21 (33%)
Nausea and vomiting	6	3	1	-	-	10 (16%)
Anaemia	3	-	-	-	-	3 (5%)
Bowel obstruction	-	-	-	3	1	4 (6%)
Dysuria	4	-	-	-	-	4 (6%)
Total* (%)	8 (13%)	17 (27%)	14 (22%)	3 (5%)	1 (1%)	43 (67%)

* in a number of patients several acute reactions were observed

Results

Early complications of radiotherapy

Early radiotherapy complications were observed in 43 patients (67%, Tab. II). Grade 1–2 and grade 3–5 toxicity occurred in 40% and 28% of patients, respectively. The most frequent were gastrointestinal complications: diarrhoea occurred in 37 cases, and nausea and vomiting – in 10 patients. Leukopoenia and anaemia were recorded in 21 and 3 patients, respectively and urinary symptoms – in 4 patients. One patient experienced fatal complications: during radiation treatment (after a dose of 36 Gy), intestinal obstruction developed and was the cause of death, despite adequate surgical management. Three patients did not comply with the prescribed treatment – one due to intestinal obstruction requiring surgical intervention, one due to protractive diarrhoea, and one due to consent withdrawal. Two other patients diagnosed with obstruction during radiotherapy completed their treatment after resolution of symptoms. Full chemotherapy dose (given in the first three and the last three days of radiotherapy) was administered to 47 patients, the remaining patients were not able to comply with chemotherapy given in the last three days due to early radiotherapy toxicity.

Late complications of radiotherapy

Late radiotherapy complications were observed in 22 out of 64 patients (34%). Most of the complications (19%) were related to gastrointestinal toxicity (Tab. III). Diarrhoea of less than five stools in 24 hours (grade 1) was observed in 11 patients, and in 1 patient grade 2 was recorded (more than five stools/24 hours). Six patients experienced intestinal obstruction requiring surgical intervention. No patient died due to obstruction. In one patient, recto-vaginal fistula developed and was treated surgically.

Tab. III. Late toxicity

Toxicity grade in WHO grade	1	2	3	4	Total
Intestinal complications	11	1	6	1	19 (30%)
Dysuria	3	2	-	-	5 (8%)
Total*	13	2	6	1	22 (34%)

*in a number of patients several late reactions were observed

This patient died three months after surgery due to tumour recurrence. Mild urinary symptoms – frequent or painful voiding – were observed in five patients and resolved after typical symptomatic treatment.

Overall survival

Five-year actuarial survival probability was 54% (Fig. 1). In univariate analysis, Dixon type of surgery and 5-

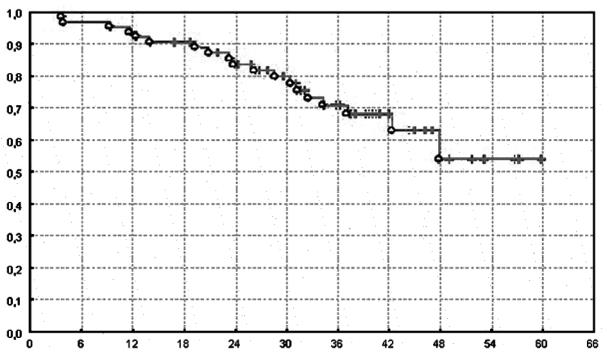

Fig. 1. Overall survival

-fluorouracil dose (full dose vs chemotherapy given in first three days only) were associated with better survivals. (p=0.03 and 0.04, respectively). Only the former variable retained significance in multivariate model (p=0.03, Tab. IV). Out of 37 patients who had undergone abdomino-perineal surgery, 16 died (43%), whereas in the group of anterior-abdominal approach (26 patients), there were three deaths (12%, Fig. 2; the

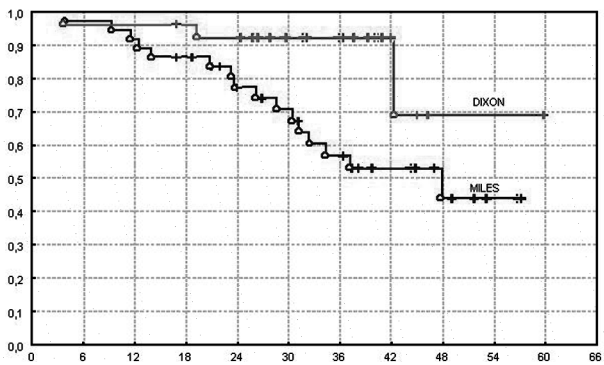

Fig. 2. Overall survival according to type of surgery

Tab. IV. Univariate and multivariate analysis of overall survival

Variable	Univariate analysis, p	Multivariate analysis – initial model, p	Multivariate analysis – final model, p – hazard ratio, HR (95% confidence interval)
Gender	0.98	0.52	
Age	0.38	0.41	
Type of surgery [a]	0.03	0.01	0.03; HR = 0.26 (0.08-0.90)
Stage[b]	0.30	0.18	
Grade[c]	0.60	0.77	
Nodal involvement	0.33	0.31	
Time from surgery to RT	0.72	0.66	
Minimal RT dose	0.89	0.31	
Maximal RT dose	0.47	0.25	
Dose per fraction	0.77	0.24	
Radiotherapy delay	0.73	0.30	
Chemotherapy[d]	0.94	0.86	
5-FU Dose	0.04	0.09	

[a] – Miles vs Dixon
[b] – B2 vs C
[c] – G1 vs G2 vs G3
[d] – according to treatment plan (day 1, 2, 3, 23, 24, 25 of RT) vs no

only patient treated with Hartmann procedure was excluded from the analysis). Both in the univariate (p=0.30) and the multivariate analysis (p=0.18 – initial model), stage did not appear to influence survival significantly.

Treatment failures

Local recurrence was observed in 15 patients (23%). Mean time to recurrence was 20 months (range: 4–31, fig. 3). Higher radiotherapy dose was associated with better recurrence-free survival in univariate analysis (p=0.046 for dose at minimal target dose and p=0.06 for maximal target dose, Tab. V). Eleven out of 37 patients (30%) treated, with Miles' resection experienced a relapse, as compared with 4 out of 26 patients (15%) treated with Dixon's type of surgery (p=0.09). Probability of local recurrence-free survival according to the type of surgery is shown in Fig. 4 (the only patient treated with Hartmann procedure was excluded from the analysis). In the multivariate model, both radiotherapy dose and type of surgery appeared to be significant prognostic factors for local relapse-free survival (p<0.01 and p=0.039, respectively, Tab. V).

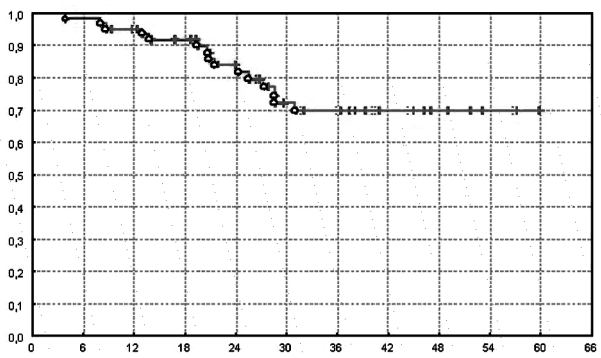

Fig. 3. Local relapse-free survival

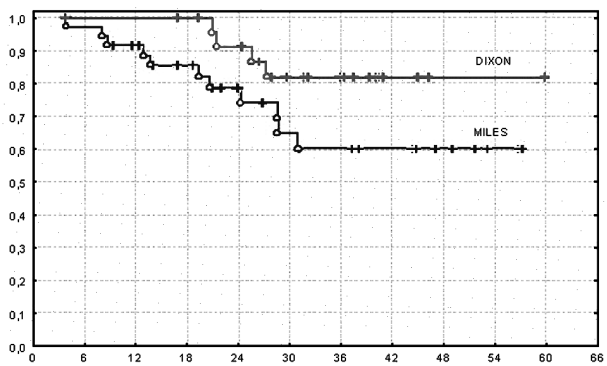

Fig. 4. Local relapse-free survival according to type of surgery

Out of 64 patients, disease dissemination was observed in 18 (28%). Mean time from the date of surgery to diagnosis of metastatic spread was 16 months (range: 3–39). Liver (14 patients), lung (2 patients) and bone (2 patients) were the sites of distant recurrence. In one case metastatic disease was found both in liver and paraaortic lymph nodes. No significant variable determining distant relapse-free survival was found in respective univariate or multivariate models.

Discussion

Combined radiochemotherapy after radical surgical resection is considered a standard treatment in patients with rectal cancer of stage B and C. This policy is based on the results of extensive randomised clinical trials in which patients received adjuvant pelvic irradiation combined with simultaneous chemotherapy [4–6]. The regimen used in these trials included semustine and 5-fluorouracil given before and/or after radiotherapy. The following studies showed that semustine neither improved the results of treatment nor was well tolerated and the administration of this drug was abandoned [8]. Currently preope-

Tab. V. Local relapse-free survival

Variable	Univariate analysis, p	Multivariate analysis - initial model, p p	Multivariate analysis - final model, p - hazard ratio, HR (95% confidence interval)
Gender	0.45	0.82	
Age	0.78	0.98	
Type of surgery[a]	0.09	0.044	0.039; HR=0.29 (0.09-0.94)
Stage[b]	0.67	0.29	
Grade[c]	0.51	0.90	
Nodal involvement	0.55	0.64	
Time from surgery to radiotherapy	0.37	0.50	
Minimal RT dose	0.046	0.94	0.009; HR=0.98 (0.96 - 0.99)
Maximal RT dose	0.06	0.65	
Dose per fraction	0.55	0.53	
Radiotherapy delay	0.12	0.17	
Chemotherapy[d]	0.99	0.95	
5-FU dose	0.48	0.72	

[a] - Miles vs Dixon
[b] - B2 vs C
[c] - G1 vs G2 vs G3
[d] - according to treatment plan (day 1, 2, 3, 23, 24, 25 of RT) vs no chemotherapy on day 23, 24, 25

rative radiotherapy is preferred by many authors. The question whether this method is better than postoperative radiation and whether preoperative combined radiochemotherapy is better than preoperative radiotherapy alone has been addressed in the ongoing 4-arm EORTC trial number 22921. Recent introduction of total mesorectal resection technique resulted in considerable decrease of local recurrences [9, 10]. With this technique local control is so satisfactory that some authors question the need of any adjuvant treatment. This issue is the subject of a randomised trial which has begun recently in Holland. In our series 5-fluorouracil was administrated only during the first and the last three days of radiotherapy. Nowadays, chemotherapy is also given routinely before and after radiotherapy, according to the recommendations of American National Institute of Health.

Local recurrence was observed in 15 of 64 patients (23%) in our group, considerably more often than in the mentioned above GITSG and NCCTG trials (11% and 14% of patients respectively). Also in other studies the recurrence rate was usually lower than in our study. It is stressed that the radicality of surgery is the most important therapeutic factor determining local control [3]. Therefore, a relatively high recurrence rate observed in our patients may be caused by the fact that they were operated in centres characterised by a varied experience in rectal cancer treatment. Other factors determining higher recurrence rate include: greater depth of tumour invasion and the infiltration of the periintestinal fatty tissue [11], greater lymph node involvement, higher pathological grade and lower performance status [3]. Surgical skills, especially in total mesorectal resection and presence of cancer cells in a radial margin, are supposed to be another important factors influencing local recurrence [10, 12]. In our series multivariate analysis has shown that the type of surgery and dose of radiation were the only independent factors associated with local control. In our group, the frequency of local recurrences in patients who had abdomino-perineal resection was doubled, as compared with those who had abdominal anterior resection. This difference was statistically significant in the multivariate analysis. The type of surgical resection is closely determined by tumour location in the rectum, so it appears that its more inferior location indicates poorer prognosis. Worse outcome of Miles' procedure was also demonstrated in GITSG and NCCTG trials. In the former Miles' procedure was connected with significantly shorter time to recurrence and in the latter it had substantial influence on survival. However, in some studies the results of treatment were comparable after both types of operation, or even better after Miles' procedure [12-14]. The radiation dose was another factor influencing the results of treatment in our group. Since in only eight patients the radiation dose exceeded 45 Gy, the importance of this factor has to be judged with great caution despite its high statistical significance.

Due to the retrospective type of our study and since not all patients were followed-up in oncological centres, it appeared impossible to determine the total number of perineal recurrences. This question seems to be particularly relevant, because the inferior border of the irradiation field lay below the obturator foramina, therefore it did not encompass the perineum. Some authors recommend a routine irradiation of this region, even though such an extended field is connected with higher risk of radiation side effects.

Distant metastases were detected in 18 of our patients (28%). In GITSG and NCCTG trials dissemination occurred in 26% and 29% respectively; significantly more often in cases of deep intestinal infiltration and positive lymph nodes. In our group, probably due to a small number of patients, these relations were not confirmed in multivariate analysis.

Actuarial five – year survival was observed in 54% of our patients, similarly to the outcome in the mentioned above trials (respectively 57% and 53%). The type of sur-

gery was the only factor influencing survivals. The higher was the stage the shorter was the survival, but the difference did not reach statistical significance. Tumour advancement is a substantial prognostic factor in most publications. The lack of its significance in our group may result from its small size, understaging of Dukes' stage C, or incomplete resection. The analysed group of patients came from different, often small regional departments, where accurate staging was not always possible. Surgery protocols and pathological reports frequently did not include the number of excised and examined lymph nodes.

Combined adjuvant treatment of rectal cancer is often accompanied by a high risk of complications [2, 15]. In our study acute toxicity affected 67% of patients and in 28% it reached a high grade (3-5). The rates and types of acute toxicity were similar to those reported by other authors using the same treatment. Despite a high intensity of complications, 94% of patients completed radiotherapy and 73% received a planned course of chemotherapy. Acute and late toxicity of adjuvant treatment of rectal cancer mainly affects the alimentary tract. Diarrhoea was the most frequent toxicity caused by irradiation, and was the result of a substantial volume of small intestine moving to the small pelvis after rectal resection [16,17]. The risk of radiation intestinal injury in postoperative reactions may be decreased by a replacement of the small intestine from the irradiated pelvis [18]. Customised blocking, modern multiple field techniques, computer 3-dimentional treatment planning and special therapeutic tables – "belly boards" – are used to accomplish this aim [19]. Radiotherapy in the prone position with a full urinary bladder is also a simple method of limiting the risk of complications [19]. Protection of intestines is also possible by using radioprotectors such as sucralfate [20]. Routine evaluation of individual small intestine volume in the radiation field has been conducted in our department for some years. It allows for a modification of the field margins in selected cases. The results of this study and other publications encouraged us to modify our technique of radiotherapy. Nowadays we employ a four field technique, prone patient position and customised blocking in all cases. We are awaiting the effects of these modifications.

In recent years preoperative radiotherapy in rectal cancer patients attracts special interest. Good tolerance of treatment and also a chance to decrease the size of tumor, which enables its resection and often allows a sphincter preservation are advantages of this method [21, 22]. Preoperative radiotherapy gives an opportunity to decrease the irradiated healthy tissue volume, makes treatment planning easier, allows to avoid the risk of postsurgical tissue hypoxia and decreases the risk of tumour dissemination during the surgical procedure [22]. The disadvantages of this method are: a higher risk of radiation complications which make the operation more difficult, and tumor progression during radiotherapy in case of its primary radioresistance [22]. Results of clinical trials performed so far prove that preoperative radiotherapy prolongs survival in comparison with surgery alone and is more effective in preventing local recurrences than postoperative radiotherapy [23-25].

In conclusion, the outcome of postoperative radiochemotherapy applied in our department was unsatisfactory in terms of both locoregional control and treatment – induced toxicity. Currently there is an increasing use of preoperative radiotherapy. This method has been used in our department for some years, at the onset as part of a prospective randomised clinical trial conducted by EORTC, and recently also in a trial co-ordinated by the Institute of Oncology in Warsaw. With a more common use of total mesorectal excision in Poland further significant improvement of treatment results may be expected.

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