Multimodal treatment of rectal cancer – evaluation of preoperative radiotherapy

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Colorectal cancer constitutes 10% of all malignant neoplasms and is the fourth most common cancer in men and the third most common cancer in women, worldwide (second most common in Poland). Unfortunately, despite large scale screening programs, changes in diet and lifestyle, colorectal cancer incidence rates for both male and female patients has increased.

The aim of the study was to analyze the influence of preoperative radiotherapy (RTH) on the survival and local recurrence rate of patients with rectal cancer, subject to surgical treatment with postoperative (adjuvant) chemotherapy (CTH).

Material and methods. The study group comprised 132 patients, including 53 females and 79 males. Patients were divided into the following groups: I – 70 patients treated by means of preoperative radiotherapy, II – 62 patients treated by means of surgery alone. Patients qualified to radiotherapy were diagnosed with stage B (39 patients) and stage C (31 patients) cancer, according to Duke’s classification (CT).

The patients received 5 Gy each day for a period of 5 days (25 Gy altogether), and underwent surgery. Postoperative pathomorphology demonstrated the following: group I comprised 39 patients with stage B and 31 patients with stage C cancer, whereas group II comprised 34 and 28 patients, respectively. Patients with stage B and C (both groups) received postoperative chemotherapy – six courses of 5-FU 435 mg/kg/d with leucovorin 20 mg/m².

Results. Kaplan-Meier’s survival analysis was applied in each group, according to the following: grade of tumor (pT), lymph node involvement (pN, pN ,'+',pN ,'-'), type of surgical resection, stage of cancer, administration of radiotherapy, and presence of local recurrence. Result analysis point to the existing correlation between radiotherapy and the five-year survival rate (p=0.031), and local recurrence (stage B: p=0.1; stage C: p=0.049).

Conclusions. Preoperative radiotherapy, considering prospective studies and our own study render hope for better prospects of treating rectal carcinoma in the future, and better 5-year survival rates. Analysis of the five-year survival rates, local recurrences, and distant complications confirmed the effectiveness and safety of preoperative radiotherapy in the treatment of rectal cancer, considering B and C patients.

Key words: rectal cancer, preoperative radiotherapy, multimodal treatment of rectal cancer

Colorectal carcinoma is one of the most common neoplasms constituting 10% of all malignant neoplasms (worldwide: fourth most common cancer in men and third in women, while in Poland- the second most common neoplasm). Unfortunately, in spite of the many screening programs, diet and lifestyle promotions the incidence of colorectal carcinoma is continuously on the rise (1). According to investigations undertaken by the IARC (International Agency for Research on Cancer 2002), in Poland, the incidence of new cases of colorectal carcinoma is 41.1 per 100 000 male patients, and 40 per 100 000 female patients. Rectal cancer is diagnosed in 35% of cases (more than 11 000 new cases every year). Thus,
the above-mentioned neoplasm deserves special attention, being described separately from colorectal carcinoma. The separation of rectal cancer from colorectal carcinomas is justified, considering different diagnostic methods, adjuvant therapy, and psychosocial aspects (stoma) (2, 3).

When diagnosing rectal cancer one should precisely determine the macroscopic and histological type of lesion, as well as “grading”.

In case of rectal tumors epithelial cell carcinomas are most often diagnosed—adenocarcinoma and mucinous adenocarcinoma (4). The incidence of the above-mentioned is estimated at more than 90% of all cases, being considered a significant problem. The presented classifications only consider the histopathological image of the tumor. However, in order to properly determine the type of lesion and plan therapy (type of operation, range of lymphadenectomy, adjuvant therapy), one should evaluate the clinical and pathological grade of the lesion, the so-called staging. Nowadays, the most commonly applied cancer classifications include the TNM classification, according to the American Joint Committee on Cancer (5) and Duke’s classification, modified by Astler and Coller. The application of similar classifications ensures the comparability of treatment results and facilitates the cooperation between centers, considering therapeutic result improvement.

Surgical treatment is the basic therapeutic method considering colorectal carcinoma therapy. In spite of progress considering operative techniques, asepsis, and oncological radicalness, rectal cancer treatment results remain unsatisfactory. In order to improve these results surgical treatment of rectal cancer is accompanied by adjuvant therapeutic methods, such as chemotherapy, radiotherapy or both. Investigations concerning gene and monoclonal antibody therapy are under way, although the above-mentioned are not considered as standard treatment (6).

Radiotherapy (RTH) consists in the irradiation of the neoplastic lesion by means of gamma rays, at a dose of 25 to 60 Gy, during a period ranging between 5 and 42 days. The aim of radiotherapy is to prevent local recurrence, cytoreduction, and decrease the size of the tumor. Radiotherapy can be applied as adjuvant pre- and postoperative therapy, depending on the preferred therapeutic scheme (7). II and III stage rectal cancer patients are qualified towards radiotherapy, with the lesion localized no more than 15 cm from the sphincters (8). Nowadays, radiotherapy is mostly applied preoperatively, due to ensuing benefits, as compared to postoperative radiotherapy:

- the intestinal obstruction ratio is significantly reduced 5% vs 11% (8). In case of postoperative radiotherapy small bowel loops localized at the site of the excised rectum are subject to irradiation. Thus, the adhesions increase the risk of ileus, as well as postradiotherapy enteritis (9),
- preoperative irradiation enables to perform sphincter-sparing operations (10),
- neorectum irradiation is absent as well as ensuing postradiation damage, such as necrosis and anastomotic fistula development (11).

The beneficial effect of preoperative radiotherapy was confirmed by a Swedish, randomized trial (12), which demonstrated a local recurrence rate of 13%, as compared to the postoperative radiotherapy rate amounting to 22%. The observation period was five years following surgery.

Preoperative radiotherapy is used in two systems—prolonged and short-term (short and long path) (13):

- in case of the prolonged system, irradiation usually lasts 6–8 weeks. The total irradiation dose amounts to 60 Gy (1.8–2 Gy daily). After a dose of 40 Gy a one week break is required. Surgery is performed 4 – 6 weeks after the final irradiation. This system is mostly applied in the United States, while in Europe, only in case of tumors suspected of non-resectability;
- in case of the short-term system the total irradiation dose amounts to 25-25.5 Gy (5 fractions, 5-5.1 Gy each). Surgery is performed up to five days since the last irradiation dose (14). Radiotherapy in case of the short-term system assures “oncological” sterilization of the operative field (15). The beneficial effect of such management consists in surgery being initiated immediately after radiotherapy. Considering Polish conditions the availability of irradiation is a significant aspect. The short-term system enables to treat a greater number of patients, as compared to the “long path”, which seems significant. Preoperative radiotherapy reduces the local recurrence rate
from 26% to 9-12% during a five-year observation period (16).

Another variant of adjunctive therapy is chemotherapy (11). The aim of chemotherapy consists in treating potential metastatic lesions. Chemotherapy should be initiated 4-6 weeks after the surgical procedure or after postoperative wound healing. In selected cases preoperative chemotherapy is applied, especially in case of stage IV cancer patients (17). Nowadays, the most common chemotherapy schemes are based on intravenous 5-FU (5-fluorouracyl).

Aims of the study:
1. Comparison of adjuvant therapy results in patients with rectal cancer subject to the following:
   - preoperative radiotherapy with subsequent radical oncological surgery and postoperative chemotherapy,
   - radical oncological surgery with postoperative chemotherapy.
2. Evaluation of therapeutic end-points:
   - five-year survival after different variants of combined rectal cancer treatment.

MATERIAL AND METHODS

During the period between 01.01.1998 and 31.12.2001, 233 patients with rectal cancer were subject to surgical treatment at the II Chair and Department of General, Gastrointestinal and Oncological Surgery of the Alimentary Tract, Medical University in Lublin. The study group comprised 132 patients subject to planned surgery, diagnosed with stage B (pT 3-4, pN0, pM0) or stage C rectal cancer (pT 1-4, pN 1-3, pM0), according to Duke’s classification determined on the basis of computer tomography, or transrectal endoscopic ultrasonography. Patients subject to emergency surgery or diagnosed with stage A and D rectal cancer were excluded from the study.

Inclusion criteria were as follows: age ranging between 18 and 65 years, histological confirmation of rectal cancer, diagnosed stage B or C cancer, the upper edge of the neoplastic lesion localized no more than 15 cm from the rectal sphincter, planned surgery by means of laparotomy, Karnofski’s Index > 70, and patients' conscious consent.

Exclusion criteria were as follows: non-resectable lesion (confirmed pre- or intraoperatively), carcinoma stage D according to Duke’s classification, history of chemotherapy, immunotherapy or radiotherapy, other coexisting neoplastic disease (history or present), significant heart disease, metabolic diseases, and lack of patient consent.

Patients were divided into two groups and treated according to the following therapeutic schemes:
I – surgery followed by chemotherapy,
II – preoperative radiotherapy, surgery and postoperative chemotherapy.

Based on random selection patients were qualified to the appropriate therapeutic variant (with or without preoperative radiotherapy). Patients with rectal cancer were subject to irradiation with a dose of 25 Gy applied in 5 equal fractions (5 x 5 Gy) during a period of five days.

Surgery was performed 3 to 5 days after the last dose of RTH by means of the TME method. Based on the histopathological examination the following features were determined: depth of infiltration, resection margins free of neoplastic cells, and nodular involvement. Patients were classified according to the TNM, Duke’s and R classifications. Complications which developed during the initial 30 days after the operation were considered as perioperative.

Chemotherapy was initiated during the initial 4-6 weeks after surgery. Leucovorin was used at a dose of 20 mg/m² daily, and 5-FU at a dose of 375-420 mg/m² daily for a period of five days every 28-36 days (6 courses).

Control visits were planned during the initial 60 months after surgery, where patients were subject to physical examination, CEA blood sampling, ultrasound, CT, colonoscopy and chest x-ray examinations, according to the planned scheme.

RESULTS

The study group comprised 132 patients (53 women and 79 men) aged between 20 and 65 years (mean age – 57.5 years), divided into two groups:
I – patients who did not receive preoperative radiotherapy (62 patients, which constituted 47% of the group),
II – patients subject to preoperative radiotherapy (70 patients, which constituted 53% of the group).
Considering both study groups stage B predominated, although differences were statistically insignificant (p=0.9) (tab. 1).

Carcinoma grading was also determined. G2 patients dominated (more than 50% in both groups). Statistically significant differences were not observed.

A higher perioperative mortality rate and longer hospitalization period after surgery were observed in the RTH “−” group. The overall number of complications was higher in the RTH “+” group. Perioperative mortality was observed during the period between 1 and 11 days after surgery, being connected with acute respiratory and circulatory insufficiency. The above-mentioned was statistically insignificant (tab. 2).

The RTH “+” group was characterized by a higher ratio of R0 operations, as compared to the RTH “−” group. No statistically significant differences were observed when comparing groups R0 vs R1/R2 (tab. 3).

Local recurrence was diagnosed in case of previously performed R0 resections.

Considering all patients, the local recurrence ratio (nodular and retroperitoneal space) amounted to 16.6% (22 patients), with a higher rate in case of patients subject to surgery, and those diagnosed with stage C carcinoma, according to Duke’s classification.

Differences in the recurrence rate, depending on the therapeutic method used were statistically significant (p=0.03). Similarly, the stage of cancer (B/C) was connected with the recurrence rate, being statistically significant. In case of stage B carcinoma the therapeutic method had no significant influence on the recurrence rate. On the contrary, stage C patients subject to surgery alone presented with a higher recurrence rate (tab. 4).

Considering the 132 radical rectal cancer operations, anterior resections dominated (86 pts- 65.15%), with the advantage in the RTH “+” group (51 patients). The type of performed

<table>
<thead>
<tr>
<th>Stage of disease</th>
<th>Number of cases</th>
<th>RTH “−” n=62</th>
<th>RTH “+” n=70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dukes B (pT3-4 N0 M0)</td>
<td>73 (55.30%)</td>
<td>34 (54.80%)</td>
<td>39 (55.70%)</td>
</tr>
<tr>
<td>Dukes C (pT1-4 N1-2 M0)</td>
<td>59 (44.70%)</td>
<td>28 (45.20%)</td>
<td>31 (44.30%)</td>
</tr>
<tr>
<td>Total</td>
<td>132</td>
<td>62</td>
<td>70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perioperative death</th>
<th>RTH “−”</th>
<th>RTH “+”</th>
<th>Ogółem / Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization in days after surgery</td>
<td>1-45 śr.13,88</td>
<td>7-24 śr. 12,5</td>
<td>13,15</td>
</tr>
<tr>
<td>Complications (fistulas, prolonged healing, wound infections)</td>
<td>20 (32,25%)</td>
<td>24 (34,28%)</td>
<td>44 (33,33%)</td>
</tr>
<tr>
<td>Fistulas</td>
<td>4 (6,45%)</td>
<td>4 (5,70%)</td>
<td>8 (6,06%)</td>
</tr>
<tr>
<td>Prolonged wound healing, infection</td>
<td>4 (6,45%)</td>
<td>6 (8,57%)</td>
<td>10 (7,57%)</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>8 (12,90%)</td>
<td>10 (14,28%)</td>
<td>18 (13,63%)</td>
</tr>
<tr>
<td>Occlusion 1 year after surgery</td>
<td>4 (6,45%)</td>
<td>4 (5,70%)</td>
<td>8 (6,06%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ogólna liczba / Total</th>
<th>R0</th>
<th>R1</th>
<th>R2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy and surgery</td>
<td>70</td>
<td>65 (92,85%)</td>
<td>4 (5,71%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>62</td>
<td>53 (85,48%)</td>
<td>5 (8,06%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiotherapy and surgery R0</th>
<th>Surgery R0</th>
</tr>
</thead>
<tbody>
<tr>
<td>local recurrence</td>
<td>total</td>
</tr>
<tr>
<td>Dukes B</td>
<td>2</td>
</tr>
<tr>
<td>Dukes C</td>
<td>6</td>
</tr>
</tbody>
</table>
Multimodal treatment of rectal cancer – evaluation of preoperative radiotherapy

Operations showed no statistically significant group difference (tab. 5).

Patients with pT2 rectal cancer presented with the longest five-year survival rate – 66.66%. The above-mentioned decreased in case of a higher stage of the disease: pT3 – 64.7% and pT4 – 40%. The comparison of pT2 and pT3 tumors, and pT2 and pT4 tumors demonstrated that survival differences were statistically insignificant. This was probably connected with the small number of pT2 patients. Statistical significance was observed when comparing pT3 and pT4 patients (p=0.01) (fig. 1).

There were no statistically significant differences considering the five-year survival rate, depending on the pN feature (pN0 and pN1). The five-year survival rates amounted to 69.86% and 73.33%, respectively. In case of pN2 patients the five-year survival rate was significantly lower – 13.79% (fig. 2).

Independently of the therapeutic method the five-year survival rate in case of patients with stage B cancer was prolonged, as compared to stage C patients. This feature was statistically significant (p=0.014) (fig. 3).

Figures 4, 5, 6 and tab. 6, 7, 8 presented the positive influence of preoperative radiotherapy on distant rectal cancer treatment results. Table 6 and fig. 4 demonstrate the five-year survival rate in case of patients subject to combined treatment. The percentage was significantly higher, as compared to patients treated by means of surgery followed by postoperative chemotherapy.

The five-year survival rate in case of stage B patients subject to preoperative radiotherapy

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>RTH &quot;-&quot;</th>
<th>RTH &quot;+&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hartmann’s resection</td>
<td>5 (3.78%)</td>
<td>4 (6.45%)</td>
</tr>
<tr>
<td>Anterior resection of the rectum</td>
<td>86 (65.15%)</td>
<td>35 (56.45%)</td>
</tr>
<tr>
<td>Mile’s operation</td>
<td>41 (31.06%)</td>
<td>23 (37.09%)</td>
</tr>
<tr>
<td>Total</td>
<td>132</td>
<td>62</td>
</tr>
</tbody>
</table>
Radiotherapy and survival-all patients

Log-Rank Test $p = 0.031$

Stage B cancer in relationship to radiotherapy

Log-Rank Test $p = 0.027$

Stage C cancer in relationship to radiotherapy

Log-Rank Test $p = 0.047$

Table 6. Five-year survival rate depending on whether radiotherapy was used

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>Number of pts</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTH &quot;-&quot;</td>
<td>62</td>
<td>33 (53.22%)</td>
</tr>
<tr>
<td>RTH &quot;+&quot;</td>
<td>70</td>
<td>44 (62.58%)</td>
</tr>
</tbody>
</table>

Table 7. Five-year survival rate depending on radiotherapy use, stage B patients

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>Number of pts</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTH &quot;-&quot;</td>
<td>34</td>
<td>22 (64.70%)</td>
</tr>
<tr>
<td>RTH &quot;+&quot;</td>
<td>39</td>
<td>29 (74.35%)</td>
</tr>
</tbody>
</table>

Table 8. Five-year survival depending on radiotherapy use, stage C patients

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>Number of pts</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTH &quot;-&quot;</td>
<td>28</td>
<td>11 (39.28%)</td>
</tr>
<tr>
<td>RTH &quot;+&quot;</td>
<td>31</td>
<td>15 (48.38%)</td>
</tr>
</tbody>
</table>

Py-surgery-postoperative chemotherapy was 10% higher, as compared to patients without preoperative radiotherapy. Statistical significance was observed ($p=0.027$) (tab. 7, fig. 5).

In case of patients with stage C cancer the five-year survival rate in each investigated group (RTH "-" and RTH "+"") was 25% lower than that observed in case of stage B. Differences in the five-year survival rate of stage C patients was 10% (similar to the difference observed in case of stage B tumors) (tab. 8, fig. 6).

Considering the 132 study group patients, 70 were subject to preoperative radiotherapy and 44 (62.58%) survived five years, which was a significantly better result as compared to patients subject only to surgery – 53.2% ($p=0.031$). Detailed analysis of such parameters as B/C staging confirmed the beneficial effect of preoperative radiotherapy on the five-year survival rate, independently of the carcinoma stage, according to Duke's classification (fig. 4, 5, 6 and tab. 6) ($p=0.027$ in case of stage B and $p=0.047$ in case of stage C). One should also note the significantly higher survival rate in case of stage B patients, as compared to stage C, independently of the therapy used (RTH "+" and RTH ":" before surgery) – 64.7% and 74.35% vs 39.3% and 48.4%.

**DISCUSSION**

After a five-year observation period and comparison of both groups one can come to the conclusion that treatment of stage B and C
rectal cancer (Dukes classification): preoperative radiotherapy + surgery + chemotherapy is a safe and effective method, reducing the number of local recurrences (18), and increasing the number of sphincter-sparing operations (19). The intention of the authors of the study was to verify the value of preoperative radiotherapy in the treatment of rectal cancer. Based on literature data and previous Authors’ studies, surgical treatment results, in spite of increased oncological radicality (especially since the introduction of the TME technique) remain unsatisfactory. Thus, the introduction of adjuvant therapeutic methods, such as preoperative radiotherapy and postoperative chemotherapy (20). Only combined therapy increased the effectiveness of treatment in case of rectal cancer. Literature data described survival in case of stage II and III cancer patients amounting to 72-80% during five-year observation periods (11, 21). Considering our material survival in case of stage II was 74.35%, while in stage III – 48.38%.

In our study the preoperative radiotherapy variant was selected, due to the significantly smaller number of distant complications, such as occlusion ileus as an effect of irradiation, and enteritis during postoperative therapy (21, 22). Data obtained from review studies showed that in case of preoperative radiotherapy intestinal obstruction was observed in 11% of patients, as compared to 5% subject to preoperative radiotherapy (9). In case of our patients the percentage of occlusion ileus during a period of one year amounted to 5.7%. The frequency of obstruction is similar to that observed in case of patients’ subject only to surgery (23). Benefits of preoperative radiotherapy include higher therapeutic efficacy, such as reduced number of local recurrences (9-15%), as compared to postoperative irradiation (20-22%) (24, 25).

Local recurrence was considered when patients underwent R0 operations, and after some time developed cancer disease (22 pts). Patients subject to R1 and R2 operations, which were considered as oncologically non-radical were excluded from recurrence analysis (7 pts). In case of patients subject to radiotherapy, local recurrence during the five-year observation period was noted in 8 (11.42%), while in the RTH “−” group in 14 (22.58%) patients. The obtained results are statistically significant (p=0.03) and comparable to those from literature data: 9-12% recurrence rate in the RTH “+” group, and 22-26% in the RTH “−” group (26).

Considering patients with stage B rectal cancer (tab. 5) the local recurrence rate in the group subject to radiotherapy and surgery amounted to 5.1%, as compared to patients subject to surgery alone – 11.76% (p=0.1). Lack of statistically significant difference might be connected with the small number of patients. In case of stage C carcinoma the local recurrence rate amounted to 19.35% and 35.71%, respectively (p=0.049). The above-mentioned data confirmed the efficacy of radiotherapy in the reduction of the local recurrence rate after rectal cancer surgery by nearly 50%, independently of the stage of the disease. Review articles confirmed the above-mentioned (21, 24).

The high therapeutic efficacy of combined treatment (preoperative radiotherapy-surgery, postoperative chemotherapy) is explained by the fact that a high radiation dose is applied in a short time, assuring oncological “sterilization” of the operative field (13). Additionally, one can observe the phenomena of downstaging and downsizing, which technically improves the conditions of the operation (24, 27). Another important aspect of preoperative radiotherapy is the increased number of sphincter-sparing operations, as compared to those not subject to preoperative radiotherapy: 74.3% (39 pts) vs 62% (52 pts). The study results are consistent with literature data, group differences amounting to 17% (28).

Comparing the distant results in case of patients with rectal cancer, the five-year survival rate was as follows: 62.8% in the “RTH +” group, including stage B – 74.35% and stage C – 48.38, while in case of the RTH “−” group - 53.2% (stage B – 64.7 and stage C – 39.28%). Preoperative radiotherapy significantly increased the five-year survival rate by nearly 10% (p= 0.031 for all cases, including stage B–p=0.027, and stage C–p=0.047). Similar results were observed in case of review articles (28).

Additionally, the use of radiotherapy had no influence on perioperative mortality (nearly 2.5%). Considering the investigated group the mortality index in case of the RTH “+” group amounted to 2.85%, while in case of the RTH “−” group – 4.8%. The number of early complications (fistulas, prolonged wound healing) was similar in both groups. Preoperative
radiotherapy had no significant influence on the development of postoperative complications.

CONCLUSIONS

1. Preoperative radiotherapy is beneficial considering the percentage of radical operations. This is especially visible in case of stage B rectal cancer patients, according to Duke’s classification.
2. Short-term radiotherapy in case of patients with rectal cancer before surgery is characterized by a statistically significant increase in the five-year survival rate.
3. The beneficial effect of preoperative radiotherapy is independent of the stage of the tumor. Statistically significant prolonged five-year survival was observed in stage B and C patients (according to Duke’s classification).
4. The use of preoperative radiotherapy increases the number of rectal sphincter-sparing operations.
5. Preoperative radiotherapy reduces the rate of local neoplastic recurrence, as compared to patients not subject to the above-mentioned.

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Received: 29.09.2010 r.
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