Preoperative radiotherapy ± chemotherapy became the standard treatment for locally advanced rectal cancer. Despite better local control with this approach, there was not seen a significant improvement in overall survival and disease free survival, yet. The main disadvantage is toxicity that can be developed, especially concomitantly with chemotherapy. Toxicity can be acute and late. Acute complications are transitory, but late might lead to permanent damage and consequently are more significant for patients. Today, there are technical opportunities in reduction of acute and late radiation toxicity in the treatment of rectal cancer. With the implementation of 3D conformal radiotherapy (3D CRT) and intensity modulated radiation therapy (IMRT) techniques in clinical practice significant accuracy, better dose distribution and safety that in the treatment of rectal cancer patients is achieved, with maximal sparing of surrounding normal tissue. Utilization of advanced techniques and new software solutions can keep adverse effects on satisfactory levels with excellent local control.

Keywords: rectal cancer, preoperative radiotherapy, toxicity, radiotherapy techniques.

**INTRODUCTION**

Treatment of colorectal cancer requires a multi-disciplinary approach with significant role of radiotherapy. Proportion of rectal cancer among cancers of colorectum varies from 27 to 58%. The main treatment for rectal cancer is surgery. For locally advanced disease (T3-T4 and/or N+), even with the total mesorectal excision, surgery alone have an inferior outcome compared to surgery combined with preoperative radiotherapy. Based on several large trials it is well known today that the application of radiotherapy in preoperative setting with or without chemotherapy is associated with good pathological tumor response, improved tolerance, tumor downstaging, facilitating complete resection, increased likelihood of sphincter preservation and 5-year local control. Before the decision of neoadjuvant treatment, initial staging with pelvic magnetic resonance imaging (MRI) is obligatory, in order to avoid over-treating of patients with early stages rectal cancers.

Although radiotherapy has significant role in treatment of rectal cancer, the main disadvantage is toxicity which might be developed, especially if it is combined with chemotherapy.

Toxicity as consequence of radiotherapy treatment can be classified as acute and late.

Acute radiation toxicity is occurred during radiotherapy till 3 - 6 months after. Late toxicity can be developed later, after six months to several years after radiotherapy.

The most commonly symptoms as result of acute bladder radiation toxicity are frequent urination and dysuria. In late bladder toxicity there are microscopic hematuria, dysuria or incontinence, reduction of bladder capacity, severe hemorrhagic cystitis, necrosis.

Symptoms related to bowel acute toxicity can be various degrees of diarrhea, weight loss, GI bleeding requiring transfusion, tenesmus, abdominal pain, fistula, acute or subacute obstruction, perforation. As a result of late toxicity patients may have various degrees of diarrhea, obstruction, necrosis, perforation, fistula and bleeding requiring surgery. Acute complications are transitory and they pass to adequate symptomatic treatment. On contrary late complications might lead to permanent damage and consequently are more significant for patients.

The most commonly used scales for grading of acute and late toxicity are The Common Toxicity criteria, version 2.0 and RTOG/European Organization for Research and treatment of Cancer late morbidity scoring systems as well as the SOMA/LENT scoring system and European Organization Treatment of Cancer (EORTC).
Another complication that can occur, which is less evaluated, is sexual dysfunction. In males, disorders with ejaculatory and erectile function can be result of late radiation damage of seminal vesicles and small vessels. In females, radiotherapy can lead to vaginal dryness, decreasing sexual satisfaction and premature menopause.

**PREOPERATIVE VS. POSTOPERATIVE RADIOCHEMOTHERAPY**

In the late 80's and early 90's postoperative radiochemotherapy in patients with stage Dukes B2 and C was introduced in treatment for locally advanced rectal cancer, with increased local control compared to surgery alone. Further, based on this conclusion the preoperative radiochemotherapy (RT-HT) approach was incorporated in treatment strategy, due to the better perfusion of the pelvis before surgery with expected significant tumor response, better result in local control, OS and DFS and decrease in acute and late toxicity. This was tested by several large trials and meta analysis. In the systematic overview from 22 randomized trials in 2001, done by the Colorectal Cancer Collaborative Group, the application of radiotherapy either before or after surgery showed the improvement in local control compared to surgery alone. The significant reduction of local recurrences was shown in the preoperative radiotherapy group compared to the postoperative radiotherapy group if larger therapeutic dose was applied (>30Gy).

In the German CAO/ARO/AIO-94 trial 5-years local recurrences rate was 6% in the group assigned to preoperative radiochemotherapy and 13% in the group assigned to postoperative radiochemotherapy (p=0.006). At 10 year follow-up the rates were 6.8% and 10.5%, respectively (HR, 0.54; 95% CI, 0.3 to 0.9; p=0.02). This trial consolidated the role of preoperative radiochemotherapy and made it the standard of care in the most of countries. In addition to better local control the German trial found statistically significant difference in acute and late toxicity in preoperative and postoperative setting. Overall acute toxicity grade 3 or 4 was 27% vs. 40% in preoperative and postoperative radiochemotherapy respectively (p=0.001). Acute diarrhea was the most common side effect in preoperative and postoperative radiochemotherapy with 12% vs. 18% (p=0.04). Similar results were found in late toxicity. At 5 years follow up the rates of overall grade 3 or 4 side effects were 14% and 24%, respectively (p=0.01). The most common late side effects were strictures at anastomotic site with 4% and 12% (p=0.003). Minski and al. found significantly less acute grade 3 to 4 toxicity with preoperative versus postoperative therapy (13% vs. 48%; p=0.045).

Despite the proven role of preoperative treatment with less toxicity, postoperative radiotherapy ± chemotherapy still has its place in guidelines at strict indications like positive surgical margins, stage Dukes C or boost dose to the tumor bed.

### Table 1. late radiation morbidity scoring criteria

<table>
<thead>
<tr>
<th>Organ</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Slight atrophy</td>
<td>Patch atrophy</td>
<td>Marked atrophy</td>
<td>Ulceration</td>
</tr>
<tr>
<td></td>
<td>Pigmentation change</td>
<td>Moderate telangiectasia</td>
<td>Gross telangiectasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Some hair loss</td>
<td>Total hair loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>Slight epithelial atrophy</td>
<td>Moderate frequency</td>
<td>Severe frequency and disuria</td>
<td>Necrosis/contracted bladder</td>
</tr>
<tr>
<td></td>
<td>Minor telangiectasia</td>
<td>Generalized telangiectasia</td>
<td>Severe generalized telangiectasia</td>
<td>(&lt;100 cc)</td>
</tr>
<tr>
<td></td>
<td>(microscopic hematuria)</td>
<td>Intermittent macroscopic hematuria</td>
<td>(often with petechiae)</td>
<td>Severe hemorrhagic cystitis</td>
</tr>
<tr>
<td>Small/large bowel</td>
<td>Mild diarrhea</td>
<td>Moderate diarrhea and colic</td>
<td>Obstruction or bleeding requiring surgery</td>
<td>Necrosis/perforation Fistula</td>
</tr>
<tr>
<td></td>
<td>Mild cramping</td>
<td>Bowel movement &gt; 6 times daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bowel movement 5 times daily</td>
<td>Excessive rectal mucus or intermittent bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Slight rectal discharge or bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In this report, we will only assess the treatments complications like acute and late toxicity in these two approaches. Buiko et al. compared two groups of patients treated with 5FU-LV in first and fifth weeks of radiotherapy followed by surgery after 4-6 weeks and short course radiotherapy with 25Gy in 5 fractions and surgery alone. They observed significantly higher rates of acute toxicity (grade 3–4: 18.2% LC vs. 3.2% SC), but abdominal pain between radiotherapy and surgery alone groups (p<0.01). Irradiated patients were also more inclined to nonspecific infections then patients with surgery alone (p<0.01). No difference was found in the specific skin, gynecologic, urologic, neurologic and orthopedic disorders between these two groups. For late hospital admissions (more than 6 months after therapy) no difference in rates of admissions was seen between the groups (RR=0.95; 95% CI, 0.8 to 1.12). The Dutch rectal cancer trial randomly assigned 1861 patients to either preoperative radiotherapy treated with 25Gy in 5 fractions and total mesorectal excision (TME) or TME alone. At 2 years, the local recurrence rates were 2.4% and 8.2% in the irradiated group and non irradiated group, respectively (p<0.001). Moreover, after a median follow-up of approximately 5 years,16 irradiated patients, compared with nonirradiated patients, reported increased rates of fecal incontinence (62% v 38%, respectively; p<0.001) and pad wearing (56% vs. 33%, respectively; p<0.001), anal blood loss (11% vs. 3%, respectively; p=0.004), and mucus loss (27% vs. 15%, respectively; p=0.005). These two trials established the use of short course radiotherapy as a safe and effective treatment modality.

There are still some controversies about the superiority of short course radiotherapy vs. long course radiotherapy as treatment modality. Currently only two trials directly compared these two treatments7,18. We will only assess the treatments complications like acute and late toxicity in these two approaches. Buiko et al. compared two groups of patients treated with long course radiotherapy with 50.4 Gy in 28 fractions with 2 courses of chemotherapy 5-FU/LV in first and fifth weeks of radiotherapy followed by surgery after 4-6 weeks and short course with 25 Gy in 5 fractions and surgery one week after radiotherapy. They observed significantly higher rates of acute toxicity (grade 3–4: 18.2% LC vs. 3.2% SC), but

**TABLE 2**

**QUANTITATIVE ANALYSIS OF NORMAL TISSUE EFFECTS IN THE CLINIC SUMMARY (QUANTEC)**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Radiotherapy treatment</th>
<th>Toxicity endpoint</th>
<th>Volume of organ receiving current dose (Gy)</th>
<th>Rate of developing toxicity endpoint (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>3D-CRT</td>
<td>Grade ≥ 3, Late toxicity</td>
<td>V65≤50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>V70≤35%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>V75≤25%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>V80≤15%</td>
<td></td>
</tr>
<tr>
<td>Small bowel (individual loops)</td>
<td>Grade 3+ toxicity</td>
<td>V15&lt;120cc</td>
<td>&lt;10%</td>
<td></td>
</tr>
<tr>
<td>Small bowel (peritoneal cavity)</td>
<td>Grade 3+ toxicity</td>
<td>V45&lt;195cc</td>
<td>&lt;10%</td>
<td></td>
</tr>
<tr>
<td>Femoris heads</td>
<td></td>
<td></td>
<td>5Gy&lt;5%</td>
<td>(main dose ≤50Gy)</td>
</tr>
</tbody>
</table>
after follow-up of approximately 48 months, late toxicity rates was not significant (28.3% SC vs. 27% LC, p=0.810). The same outcome was found in the TROG trial\(^\text{18}\) in which the long course were associated with higher acute toxicity (grade 3-4, 28% vs 1.9%). The observed late toxicity rates did not show statistical significance (grade 3-4, 5.8% vs. 8.2%, p=0.53, follow up ~6 years). Surgery typically occurs a week after preoperative short-course RT, and there is no chemotherapy, so the rates of grade 3/4 acute toxicity are lower with short-courses\(^\text{17,18}\). This was also confirmed in the Stockholm III trial.\(^\text{19}\) In this trial three different radiotherapy regiments were assessed: in first arm 25 Gy in 5 fractions was followed with immediate surgery, in second arm 25 Gy in 5 fractions follo- wed with surgery after 4-6 week and in third arm the long course radiotherapy of 50Gy in 25 fractions without chemotherapy followed with delayed surgery after 4-6 weeks. Acute toxicity was 0% in the 25 Gy + immediate surgery arm, 4.2% in 25Gy + delayed surgery and 5% in long course radiotherapy. This study confirmed that short course radiotherapy with delayed surgery gives similar acute toxicity rates as long course radiotherapy. Similar results were found in the Meta analysis of Zhou et al.\(^\text{20}\). Acute toxicity grade 3 and 4 was reported in 1435 out of 2187 rectal cancer patients Long course radiotherapy significantly increased the grade of acute toxicity compared with short course (RR=0.13, 95% CI (0.06, 0.28), p=0.00001). Late toxicity gr. 3 and 4 was reported in 901 rectal cancer patients with no significant difference between these two groups [RR = 1.30, 95%CI (0.55, 3.11), p=0.55].

Related to data from these trials, there is an advantage related to acute toxicity in applying short course radiotherapy. In late toxicity there is no di- ference between short vs. long course radiotherapy. But, there are benefits from long course radiotherapy in percent of pathological complete response (pCR), resectability and sphincter preservation surgery. The optimal approach should be an individual and considered from patient to patient.

**CONCOMITANT CHEMOTHERAPY**

Adding chemotherapy to the preoperative radiotherapy setting is used with the aim of radiopotentiation (better effect of radiation on the tumor) and to improve DFS and OS. With this approach is usually expected increased toxicity of combined treatment in relation to the application of radiotherapy only. Despite better local control there was not seen a significant improvement in OS and DFS as the relative high rates of distant metastases is present. This is the reason why new combinations of cytostatic agents with 5-FU (oxalipatin, capecitabine etc.) and biological therapy (EGFR, VGFR) are investigated nowadays.

Gerard et al.\(^\text{21}\) tested preoperative radiotherapy (with 45 Gy in 25 fractions during 5 weeks) and preoperative radiochemotherapy (concurrent chemotherapy with fluorouracil 350 mg/m\(^2\)/d during 5 days, with leucovorin, was administered during the first and fifth week) on 733 patients with rese- table T3-4 tumors of rectum. There was no difference in OS and DFS between two groups. Significant difference was found in local recurrence. At the end of 5 year follow-up period cumulative local recurrence rate was 16.5% in the radiotherapy group and 8.1% in the radiochemotherapy group (p=0.004). This was asso- ciated with more frequented overall acute toxicity grade 3-4 2.9% vs. 14.9% in radiotherapy and radiochemotherapy groups, respectively. Nonhematological toxicity grade 3-4 was 2.2% and 13.5% in radiotherapy and radiochemotherapy groups, respectively. Similar result in same two groups of patients was found by Bosset et al.\(^\text{3}\). Grade 3 or higher acute toxic effects occurred in 7.4% and 13.9% of patients, in radiotherapy and radiochemotherapy groups, respectively. This study reported no differ- ence in late side effects between groups. Also there was no significant difference between 5-year overall sur- vival rates. In the preoperative radio- therapy group and radiochemotherapy group the OS and DFS was 64.8%
and 65.8% (p=0.84) and 54.4% vs. 56.1% (p=0.52). The cumulative incidences of local recurrences at 5 years were 17.1% vs. 8.7%, confirmed significant difference between radiotherapy group and radiochemotherapy group (p=0.002). In the meta analysis of DeCaluwé et al., in about 2000 patients, grade 3 or 4 acute toxicity was developed in 14.9% treated with radiochemotherapy while in patients treated with radiotherapy alone, this occurred in 5.1% cases, which was statistically significant (OR 1.68-10, p=0.002).

Several trials considered the role of new chemotherapeutic drugs or their combinations. The German CAO/ARO/AO-04 trial added oxaliplatin to fluorouracil-based neoadjuvant radiochemo-therapy and adjuvant chemotherapy. A significantly improved disease-free survival of patients with clinically staged cT3–4 or cN1–2 rectal cancer compared with former fluorouracil-based combined modality regimen was found with a median follow-up of 50 months, the DFS at 3 years was ~76% in the investigational group and 71.2% in the control group (p=0.03). Preoperative grade 3–4 toxic effects occurred in 24% of patients who received fluorouracil and oxaliplatin chemotherapy and in 20% of patients who actually received fluorouracil chemotherapy. Late grade 3–4 adverse events occurred in 25% of patients in the investigational group, and in 21% in the control group.

In the RTOG 0247 trial 146 patients were enrolled to receive preoperative RT (50.4 Gy in 1.8 Gy fractions) with concomitant capcitabine and irinotecan, or concomitant capcitabine and oxaliplatin. Due to excessive gastrointestinal toxicity the initial protocol was modified. Seven of 18 patients developed grade 3/4 diarrhea in the irinotecan group and 5/17 patients developed grade 3 diarrhea and 1 patient died following hospitalization for diarrhea in the oxaliplatin group. The doses of neoadjuvant HT were decreased. The 35 patients accrued prior to the chemotherapy dose correction were not included in the primary analysis. The pCR rate was 11.8%; in irinotecan group and 23.1%; in oxaliplatin group. After the chemotherapy doses reduction grade =3 acute toxicity were reported in 27% in irinotecan group, and 27% in the oxaliplatin group. Preoperative treatment-related grade =3 GI acute toxicity were reported in 12% and 19% respectively.

The use of EGFR tyrosine kinase inhibitor (gefitinib) was tested in the study conducted by Valenti et al. In this study 41 patients were enrolled, 33 patients were evaluated, and pCR was recorded in 10 patients (30.3%). Overall, grade 3+ toxicity was noted 41%. These included grade 3+ gastrointestinal toxicity in 20.5%, grade 3+ skin toxicity in 15.3%, and grade 3+ genitourinary toxicity in 10.2%. A dose reduction of gefitinib was necessary in 24 patients (61.5%).

Monoclonal antibody EGFR (cetuximab) applied with oxaliplatin/capcitabine or 5-FU CRT shown low pCR rates of only 9% and 7.7% respectively. The incidence of grade 3–4 diarrhea was restricted to 19%. Postoperative complications of any grade occurred in 33% of patients.

The use of antiangiogenic agents like bevacizumab added to 5-FU based CRT24,25 shown pCR in 16% (5 of 32 enrolled patients) of patients. Most common grade 3 acute toxicity was diarrhea in 7 of 32 patients. Most adverse effects were grade 2 and less.

**RADIOTHERAPY TECHNIQUES: 3D CONFORMAL THERAPY (3D CRT) AND INTENSITY MODULATED RADIATION THERAPY (IMRT)**

Radiotherapy may be conducted with conventional techniques or nowadays with modern techn-i-ques such as 3D-conformal radiotherapy (3D CRT) or Intensity Modulated Radiotherapy (IMRT).

As opposed to the application of conventional radiotherapy techniques (2D), implementation of modern technique as 3DCRT and IMRT, contributed to a reduction in adverse effects whilst preserving therapeutic effect.

The main advantage of 3DCRT in comparison to the conventional RT is in its more precise irradiation of a tumor with less involvement of the surrounding normal tissues in treated volume. Also there is possibility to analyze the prescribed dose to the tumor and the healthy tissues by dose volume histogram (DVH). 3DCRT radiation beams are shaped to fit (conform) the tumor area, using a multileaf collimator (MLC) with a variable number of beams. This conforming beams allow further exclusion of surrounding healthy structures and reduce the dose applied to them. It provides the reduction of relative radiation toxicity of surrounding normal tissues and allows a higher irradiation dose to the tumor compared to conventional techniques.

There are several steps during the planning of 3D conformal radiotherapy according to recommendations. The first step is simulation, based on imaging technologies (CT, MR). Volume of irradiated small bowel during radiotherapy plays a significant role in the development of acute radiation toxicity. There are some physical maneuvers and immobilization devices that reduce the volume of small bowel in the radiation field. For example during the simulation and radiotherapy treatment, patient lies on the flat table in prone position in the special design mold called “belly board” and with full urinary bladder. This allowed reduction of small bowel volume compared to supine position, as high as 70-74%.

A at 3D CT images, radiation oncologist determines the radiation dose and performs delineation of target volumes such as GTV-gross tumor volume, CTV-clinical target volume, PTV-Planning target volume and organs at risk volumes. The limiting factors for delivering tumoricidal doses of radiotherapy according to recommendations are prescribed (Figure 1.4). In order to avoid occurrence of severe complications at surrounding normal tissue, it is necessary to follow dose constraints of organs at risk (bladder, small bowel and femoral heads).

Medical physicist calculates dose distributions and fields arrangement, based on prescriptions done by radiation oncologist.
Further, radiation oncologist reviews radiotherapy plan, and performs the analysis of Dose Volume Histogram (DVH) (Figure 2.).

DVH includes all structures and targets of interest in the radiotherapy plan. In coordinate system the relationship between a percent volume and radiation dose are presented. That enables the selection of the most appropriate plan with maximal radiotherapy dose to the tumor and minimal dose to surrounding organs of risk. The approval is necessary for the beginning of the radiation treatment.

Nowadays, there are strict criteria for inclusion organ of risk in irradiated volume. Assessment of the probability for development of toxicity can be determined towards to volume of organ at risk receiving certain doses of radiotherapy. It is showed by The Quantitative Analysis of Normal Tissue Effects in the Clinic summary (Quanotec) (Table 2)\textsuperscript{35}

The introduction of 3D conformal radiotherapy (3D CRT) provided significant precision and safety in the treatment of rectal cancer patients. At the beginning of 2000, there was further progress and development of technology of linear accelerator with intensity modulated radiation therapy (IMRT). 3D CRT and IMRT are advanced techniques which requires a very high precision in all segments of treatment planning and they are time consuming (requiring few hours per patient). IMRT as next step in radiotherapy, enables a greater conformity of the radiation beams towards the target, allowing further dose escalation with the same or lower level of the adverse effects. This is achieved by applying a large number of fields from different angles and different intensity of the radiation in multiple small volumes in each field with reducing dose on the surrounding organs. However, when applying the IMRT, a much greater volume of a normal tissue is irradiated by small dosages in comparison to the conventional and 3DCRT. There have been numerous dosimetric and clinical researches in order to established the dose volume limits which would reduce the incidence of acute diarrhea in RT of the pelvis (12-40\%\textsuperscript{4,36,37}).

Urbano et al.\textsuperscript{37} performed a dosimetric research comparing the 3D conformal and different IMRT plans. The conclusion was that the IMRT application significantly reduced the intestinal volume irradiated by 45-50Gy. When applying IMRT, the volume reduction is 26% to 42%.

Reis et al.\textsuperscript{38} observed on 45 patients treated with neoadjuvant radiochemotherapy that the best predictor of acute complications grade 2-3 is V5 (the volume of the intestines which receives 5Gy). Patients with this volume under 300cm\textsuperscript{3} had considerably less complications (29% vs. 82%).

Parekh et al.\textsuperscript{39} performed a retrospective analysis on 48 patients treated with 3DCRT or IMRT in the period from 2002 to 2010 in Boston Medical Center. 28 were treated with 3D-CRT and 20 patients with IMRT. Overall acute grade 2 and higher toxicity rate was reduced in the IMRT group compared to 3DCRT group (40% vs. 75%, p=0.015). Most significant difference between IMRT and 3DCRT acute gastrointestinal toxicity was in the grade 2 and higher diarrhea. In the IMRT group 10% of the patients had grade 2 and higher diarrhea vs. 43% of those treated with 3DCRT (p=0.014).

Related to these data, there is a confirmed benefit from IMRT related to acute toxicity, but data about late adverse effects is scarce, so long-term follow-up is necessary to assess the influence of IMRT on late toxicity and pelvic control.

**SPECIAL RADIOThERAPY TECHNIQUES AND RE-IRRADIATION**

Volumetric Arc Therapy (VMAT) or Rapid Arc\textsuperscript{\textregistered} Radiotherapy Technology is an advanced form of IMRT that delivers a precisely-sculpted 3D dose distribution with a 360-degree rotation of the gantry in a single or multi-arc treatment. VMAT / Rapid Arc can deliver the dose to the entire tumor in a 360-degree rotation, typically in less than two minutes.\textsuperscript{40} With this advanced technique we can further reduce the volume of the small bowel that is irradiated due to its enhanced conformity and dose distribution. Several studies compared IMRT, 3DCRT and VMAT in means of local control, acute and late toxicity.\textsuperscript{31,42} These studies confirmed the assumption from dosimetric studies that reduced small bowel volume would decrease the rate of acute and late adverse effects. Droge et al.\textsuperscript{41} found overall acute toxicity was less in the VMAT group 5% vs. 20% in the 3DCRT group (p=0.008). Most significance were found in skin reaction (0% vs. 7%, p=0.01), and proctitis (2% vs. 12%, p=0.01). Also the late toxicity rates were less in the VMAT group 6% vs. 22% in the 3DCRT group(p=0.0039) after median follow up of 61.5 months (range, 4.0-105.7 months) in the 3DCRT group and 18.3 months (range, 4.0-59.2 months) in the VMAT group. Richetti et al.\textsuperscript{42} found that about 50% of patients showed diarrhea up to grade 3 (G3 in the 8% of VMAT patients and 5% in the 3DCRT patients). 28% of VMAT patients manifested local erythema of grade 1 or 2, and 15% in the 3DCRT group of patients. No grade 3 erythema or higher were observed. Two patients in the 3DCRT group developed dysuria/incontinency, none for VMAT. From the available studies late effects data is scarce, so a longer follow up period is required to determine the true value of VMAT.

The development of image guided radiotherapy and small LINAC, that can be mounted on a robotic arm, enabled radiation oncologist worldwide to treat tumors and local recurrences on previously irradiated grounds, as before it was not an option due to the higher risk of acute and late complications. This is called Stereotactic Body Radiation Therapy (SBRT). A specially designed coordinate-system is used for the exact localization of the tumors in the body in order to treat it with limited but highly precise treatment fields. The best representative of SBRT is the LINAC based Robotic Radiosurgery System. This is a non-invasive treatment of cancerous and benign tumors in the body, including the prostate, lung, brain, spine, liver, pancreas and kidney. The treatment
delivers beams of high dose radiation, to tumors with extreme accuracy. SBRT offers excellent tumor coverage and minimal dose to the neighboring organs at risk. In the single institution retrospective study conducted at the Centre Oscar Lambret, 16 patients with lateral pelvic wall recurrence were treated with SBRT, 4 of them were rectal cancer patients. Taking into account just toxicity in this study, only grade 1 and 2 acute toxicity were reported, and 25% of the patients had acute toxicity during or immediately after the treatment. Treatment provided a total dose of 36 Gy in six fractions over three weeks with a 6 MeV beam and one patient received 45 Gy in 3 fractions. Kim et al. performed SBRT treatment to 23 rectal cancer patients with local recurrences. Dose applied ranged from 36 to 51 Gy (median 39 Gy). They reported that 9 (39%) of the 23 patients exhibited grade 1 or 2 acute toxicities (nausea, vomiting and/or pain). Grade 4 toxicity was reported in one patient. Aburasri et al. treated 33 patients with pelvic region re-irradiation, 13 of them were primarily rectal cancer patients. They applied a median dose of 34 Gy (range: 8-60 Gy). Only grade 1 and 2 acute toxicity were observed, also late toxicity did not exceed grade 2 toxicity (median follow up 15 months range: 2-52 months).

As the treatment of local recurrences is fundamentally palliative and the prime goal is pain relief, the application of SBRT offers new possibilities in the treatment of local recurrence with excellent palliative results and tolerable acute toxicity.

CONCLUSION:

The application of radiotherapy retains an important place in the treatment of rectal cancer, especially with combination with surgery and chemotherapy. Despite better local control there was not seen a significant improvement in OS and DFS. This is the reason why new combinations of cytostatic agents are investigated today. In addition to the many benefits of implementing this type of therapy, the main disadvantage is development of toxicity, particularly if radiotherapy is delivered concomitant with chemotherapy.

Advanced technology with the development of modern radiotherapy machines and new software solutions today enable more adequate distribution of radiation dose to target volume in order to provide better local control of disease. In the same time, these technologies provide better protection of surrounding healthy tissues and reduction of acute and late radiation toxicity which is necessary for ensuring a better quality of life.

SUMMARY

Preoperativna radioterapija ± hemoterapija je standardna terapija u lečenju lokalno uznapredovalog karcinoma rektuma. Uprkos boljoj lokalnoj kontroli bolesti, do sada nije postignuto značajno poboljšanje u sveukupnom preživljanju, kao ni preživljanju bez znakova bolesti.

Najveći nedostatak ovakvog pristupa lečenja je pojava toksičnosti, posebno kada se uz radio-terapiju primenjuje i hemoterapija. Tokušnost može biti rana i kasna. Akutne komplikacije su prolaznog karaktera, dok kasne mogu uzrokovati trajna oštećenja, te su mnogo značajnije za samog pacijenta.

Danas, napredne tehnologije u radioterapiji omogućavaju smanjenje učestalosti pojave ranih i kasnih komplikacija u lečenju karcinoma rektuma. Sa uvođenjem konformalne radiotherapije (3D CRT) i inzitetom modulisane radiotherapije (IMRT) u kliničku praksu postignuta je značajna preciznost, bolja distribucija doze, sigurnost i maksimalna zaštita okolnih zdravih tkiva u toku zračenja. Primenom naprednih radioterapijskih tehnika i novih sofтверnih rešenja omogućava odličnu lokalnu kontrolu bolesti uz zadovoljavajući nivo pojave kasnih komplikacija.

Ključne reči: karcinom rektuma, preoperativna radioterapija, toksičnost

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