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Original article

POSTOPERATIVE ADJUVANT INTENSITY-MODULATED RADIOTHERAPY FOR RADICALLY RESECTED RECTAL ADENOCARCINOMA: DATA FROM EVERYDAY PRACTICE

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Abstract

Introduction: Adjuvant radiochemotherapy is a standard treatment in patients with surgically treated stage II or III rectal adenocarcinoma who did not undergo neoadjuvant radiotherapy. Intensity-modulated radiation therapy (IMRT) was only marginally investigated in postoperative setting.

Material and methods: A longitudinal observational analysis was conducted in patients with radically resected stage II or III rectal adenocarcinoma treated with IMRT at the University Clinic for Radiotherapy and Oncology as part of the adjuvant postoperative treatment. The dose-volume parameters of the radiotherapy plans, as well as acute side effects of 40 patients were analyzed.

Results: The average dose received by the target volume was 49.95 Gy (range 27-54 Gy). The mean volume of peritoneal cavity receiving 45 Gy (V45) was 102.73 cm3 (±52.10), V30 for pelvic bones was 38.3% (±5.48), V40 for bladder 52.48% (±10.9). The most frequent acute side effects were diarrhea in 17 (42.5%), lymphopenia in 34 (85%) and thrombocytopenia in 26 patients (65%). Most of the side effects were self-limiting and caused disruption of the radiation treatment only in 3 patients (7.5%).

Conclusion: Integrating IMRT in the adjuvant treatment of locally advanced rectal cancer provides a good dose distribution and organs at risk sparing. The treatment is well tolerated, the side effects are mainly of lesser degrees and easily managed. A prospective trial comparing IMRT with 3-dimensional conformal radiotherapy is needed to assess whether IMRT offers a better perspective for adjuvant treatment.

Keywords: rectal adenocarcinoma, adjuvant treatment, remove adjuvant treatment, intensity-modulated radiotherapy, acute side effects

Introduction

Radiotherapy is an integral part of rectal cancer treatment. Several randomized trials have demonstrated that incorporating radiotherapy (with or without concomitant chemotherapy) in the treatment of locally advanced rectal carcinoma resulted in improved locoregional control and survival rates. Also, several randomized trials have demonstrated improved locoregional control and survival rates with preoperative or postoperative chemoradiotherapy in patients with stage II and III rectal cancer[1,2]. Preoperative radiotherapy or radiochemotherapy became

preferred treatment options due to improved local recurrence and disease-free survival rates, enhanced sphincter preservation, and mostly due to a lower treatment-related toxicity compared to postoperative radiochemotherapy[3,4]. Successful implementation of the neoadjuvant approach requires precise preoperative staging using pelvic MRI, which has its limitations, especially for predicting lymph node involvement[5,6], resulting in a significant percentage of patients being clinically understaged and surgically treated without neoadjuvant radiotherapy, hence in need of adjuvant chemoradiotherapy. Intensity-modulated radiotherapy (IMRT) improves conformity of the radiation dose to the three-dimensional shape of the target volume compared to 3D conformal radiotherapy (3-D CRT), and therefore reduces the dose to small bowel and other organs at risk (OARs) and consequently reduces the risk of acute and late radiotherapy-related toxicity. To date, most of the published research on IMRT for rectal cancer focused on the preoperative treatment[7-11]. Following total mesorectal excision for rectal cancer a larger volume of small bowel descends in the pelvis, whereas the postoperative adhesions can immobilize the intestinal loops in vicinity to the treatment volume[12]. These factors additionally stress the need for highly conformal radiotherapy in postoperative setting. Despite the potential advantages, IMRT was only marginally studied in adjuvant setting[13,14]. This study aimed to examine the acute toxicities, oncologic outcomes and interaction of radiotherapy with fluorouracil (5-FU)-based regimen in the adjuvant treatment of locally advanced rectal cancer with IMRT. In addition, we present the experiences of the University Clinic for Radiotherapy and Oncology in Skopje with IMRT in the adjuvant treatment of curatively resected rectal carcinomas with special reference to the dosimetric characteristics and acute treatment toxicity.

Materials and methods

Patient selection

Adjuvant radiotherapy was indicated for patients with histopathologic T3-4 N0 and any T + N1-2 rectal adenocarcinoma in concordance with the guideline proposed by the National Comprehensive Cancer Network (NCCN). Patients with T3 N0 R0 resected carcinoma of the proximal third of the rectum were not irradiated. Patients with metastatic lesions at time of diagnosis or postoperative macroscopic residual disease were excluded. All medical records and dose-volume histograms (DVH) were meticulously reviewed.

Radiotherapy

Computed tomography (CT) simulation in the supine position with 2.5 mm thickness, full bladder and arms on chest was performed for all patients. Radiopaque markers were placed on the anus of patients with low anterior rectal resection (LAR) and on the cephalad and caudate end of the perineal scar in patients with abdominoperineal resection (APR). Varian's SomaVisionTM software was used for target volume and organs at risk delineation. Radiation Therapy Oncology Group (RTOG) consensus atlas was used for target volume delineation[15]. The intermediate risk clinical target volume (CTV1) encompassed the tumor bed as well as the remaining rectum and mesorectum (at least 2 cm margin superior and inferior to the anastomosis), pre-sacral, obturator and internal iliac nodal regions extending cephalad to the bifurcation of the common iliac vessels (approximate bony landmark: sacral promontory) and caudad to the pelvic floor. Entire perineal scar was included in CTV1 in patients with APR. Anteriorly, a margin of 1-1.5 cm was added into bladder to account for changes in bladder and rectal filling[16,17]. The external iliac lymph nodes were included in CTV1 only if tumor invasion of anterior pelvic organs (e.g., prostate, vagina) was identified on pathologic record. The high-risk clinical target volumes (CTV2) included the parts of the remaining rectum that was within 2 cm longitude to the surgical anastomosis, the tumor bed (including the perineal scar for APR), and presacral space. A 10 mm expansion of CTV1 and CTV2 was used to

create planning target volume PTV1 and PTV2 accordingly. For the inverse planning, the organs at risk included the urinary bladder, bowel bag, femoral heads, pelvic bones, and external genitals. All organs at risk were delineated in concordance with the RTOG atlas[18].

IMRT was given as 45 Gy/25 fractions to the PTV1, whereas the PTV2 additionally received 5.4 Gy in 3 fractions using 3D conformal radiotherapy. In terms of general planning strategy, the highest priority was given to PTV coverage, then to minimizing dose to the bowel bag. Of intermediate priority were reducing dose to the bladder, femoral head/neck, pelvic bones, external genitals, and normal tissues outside the contoured regions. Dose limitations recommended by Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) were followed[19]. In addition to the commonly reported bowel bag volume receiving 45 Gy (V45), we analyzed the volumes receiving lower doses (V30, V15) due to the established correlation of the small bowel volume receiving 15 Gy with the severity of GI toxicity[20,21]. Up to 50% of the hematopoietically active bone marrow in adults is in proximity to the conventional treatment fields for pelvic radiotherapy, and given its inherited radiosensitivity, increasing the volume of pelvic bones that receives relatively low radiation doses (10 or 20 Gy) results in a significant myelosuppression[22,23]. On the other hand, the bladder and the femurs are considered less radiosensitive organs and thus, we opted to evaluate volumes receiving higher doses (V30, V40).

Chemotherapy

Concomitant chemotherapy consisted of oral capecitabine 825 mg/m^2, administered twice daily every weekday during the radiotherapy. The first dose of capecitabine was given approximately 30-120 minutes before radiotherapy, whereas the second dose was given 10-12 h after radiotherapy. Adjuvant chemotherapy consisted of 6 cycles of CAPOX protocol in patients with stage III disease aged 70 or younger or capecitabine monotherapy in the remaining patients. CAPOX regimen was composed of intravenous oxaliplatin 130 mg/m^2 on the first day and oral capecitabine at a dose of 1000 mg/m^2 every 12 hours on days 1 and 14. This protocol was applied every 21 days, two cycles prior and 4 cycles after radiochemotherapy. Capecitabine monotherapy included oral capecitabine at a dose of 1250 mg/m^2 every 12 hours on days 1 and 14 out of 21-day-regimen, two cycles prior and 4 cycles after radiochemotherapy.

Investigations and follow-up

Patients were evaluated before every cycle of adjuvant chemotherapy and weekly during radiochemotherapy. Laboratory analysis included weekly CBC during radiochemotherapy, detailed biochemistry analysis on day 1 of every chemotherapy cycle, as well as days 1 and 25 of radiochemotherapy. Acute toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE, v. 4.0)[24].

Statistical analysis

All statistical analyses were performed by using MS Excel and free software available online. To test the normality of distribution, the data were subjected to the Kolmogorov-Smirnov normality test. Parametric and non-parametric tests for independent samples (Student t-test for independent samples, Mann-Whitney test, Chi-square test) were used to test correlation between the analyzed variables. A p-value less than 0.05 was considered statistically significant.

Results

Forty patients treated with adjuvant radiochemotherapy using IMRT for rectal cancer during the period from 2016 to 2019 were identified at our department. The relevant clinical factors are summarized in Table 1. Median age of the treated patients was 63.4 ± 8.2 years (range 35-73, normally distributed KS test D=0.14). Most of the study population had stage

III rectal cancers (28 out of 40 pts, 70%), although 18 patients (45%) had fewer than 12 lymph nodes examined and therefore questionable N stage. Mid-third rectum was the predominant tumor localization (21 out of 40 pts, 52.5 %), and low or ultra-low anterior resection was most frequent surgical intervention (28 out of 40 pts, 70%). Only one patient had a positive resection margin, thus receiving a higher dose adjuvant radiotherapy (54 Gy).

Table 1. Clinical and histopathological parameters

	Number	**%**
Sex		
Male	23	57.5
Female	17	42.5
Localization		
>10 cm	4	10
5-10 cm	21	52.5
<=5 cm	15	37.5
Anus preserving surgery		
Yes	28	70
No	12	30
pT		
2	6	15
3	32	80
4a	1	2.5
4b	1	2.5
pN		
0	12	30
1a	12	30
1b	2	5
1c	6	15
2a	6	15
2b	2	5
No. of lymph nodes evaluated		
≥12	22	55
<12	18	45
Grade		
Moderately differentiated	36	90
Poorly differentiated	3	7.5
Undetermined	1	2.5
Lymphovascular invasion		
Yes	20	50
No	15	37.5
Undetermined	5	12.5
Age		
30-39	1	2.5
40-49	3	7.5
50-59	13	32.5
60-69	20	50
>70	3	7.5
Status of resection margins		
R0	39	97.5
R1	1	2.5

Table 2. Acute toxicities, hematologic

Toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Anemia	14	4	1	0
Neutropenia	5	2	0	0
Lymphopenia	6	24	4	0
Thrombocytopenia	26	0	0	0

Table 3. Acute toxicities, non-hematologic

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
TBil elevation	5	5	0	0
AST elevation	13	1	0	0
ALT elevation	9	0	0	0
LDH elevation	12	0	0	0
Hypoproteinemia/hypoalbuminemia	3	1	0	0
Fatigue	10	4	1	0
Diarrhea	16	4	1	0
Nausea	6	1	1	0
Vomiting	2	1	1	0
Tenesmus	5	5	0	0
Abdominal pain	6	3	0	0
Radiodermatitis	17	15	0	0
Sensory neuropathy	13	4	0	0
Hand foot Sy	1	3	0	0
Cystitis	6	2	0	0

Table 4. Other relevant treatment parameters

	Number	**%**
Type of adjuvant chemotherapy		
Capecitabine	16	40
CAPOX	24	60
Concordance with prescribed dose		
Received whole prescribed dose	37	92.5
Interrupted due to toxicity	3	7.5
Concordance with chemotherapy		
Received without interruption	32	80
Interrupted/terminated due to toxicity	6	15
Terminated due to personal reasons	2	5

The frequency of different acute toxicities is demonstrated in Table 2 (hematologic) and Table 3 (non-hematologic). No grade 4 or 5 toxicities were encountered. The most encountered dose limiting toxicities were diarrhea (≥ Grade 2 in 10% of patients and Grade 3 in 2.5%), hyperbilirubinemia (≥ Grade 2 in 12.5%), and neutropenia (≥ Grade 2 in 5%). All the ≥ Grade 2 side effects were manageable with either dose adjustment or discontinuation of chemotherapy. Acute toxicity was the reason for interruption or discontinuation of concomitant chemotherapy in 6 patients (15%), whereas 2 patients (5%) refused concomitant chemotherapy for personal reasons. The preplanned radiotherapy was prematurely terminated due to gastrointestinal toxicities in only 3 patients (7.5%), 2 of which received generally acceptable dose of 45 Gy (Table 4). Therefore, the median dose received was 49.95 Gy.

Descriptive statistics of dose-volume parameters is listed in Table 5. The mean volume of peritoneal cavity receiving 45 Gy (V45) was 102.73 cm3 (±52.10), V30 for pelvic bones was 38.3% (±5.48), V40 for bladder 52.48% (±10.9). The mean dose received by the femur head/ neck was 19.1 Gy for the right one, and 19.33 for the left one.

The data were analyzed for potential predictive factors of increased treatment-related toxicity. Using the two-sided Mann-Whitney U test, a statistically significant correlation between the type of chemotherapy used and hematologic toxicity was not detected (p=0.22). Association between hematological toxicity and pelvic bones volume receiving doses of 10 and 30 Gy was also examined, but only weak, statistically not significant correlation was found (R^2 = 0.0000007, R^2 = 0.08) (Figure 1). No significant correlation between cystitis and the volume of bladder receiving 30 or 40 Gy was detected (p=0.77 for V30 and p=0.98 for V40). Examination of the dependence of gastrointestinal toxicity (diarrhea and others listed in Table 3) with the

dose-volumetric parameters showed a weak correlation between the volume of peritoneal cavity receiving 15 Gy (V15) and diarrhea (R^2 = 0.11).

Table 5. Dose-volume parameters

Parameter	Mean	SD
Bowel bag (cm3)		
V15	679.74	225.22
V30	353.29	98.7
V45	102.73	52.10
Mean (Gy)	25.61	2.79
Bladder (%)		
V30	73.55	10.83
V40	52.48	10.9
Mean (Gy)	38.46	3.17
Right femur head/neck (%)		
V30	9.69	6.13
V40	0.69	1.04
Mean (Gy)	19.10	3.19
Left femur head/neck (%)		
V30	10.75	7.63
V40	1.03	1.18
Mean (Gy)	19.33	2.93
Pelvic bones (%)		
V10	78.17	6.31
V20	62.53	5.72
V30	38.24	5.48
Mean (Gy)	24.89	2.27
PTV (Gy)		
Dmax	51.86	1.86
Dmin (за PTV 45)	40.38	1.16

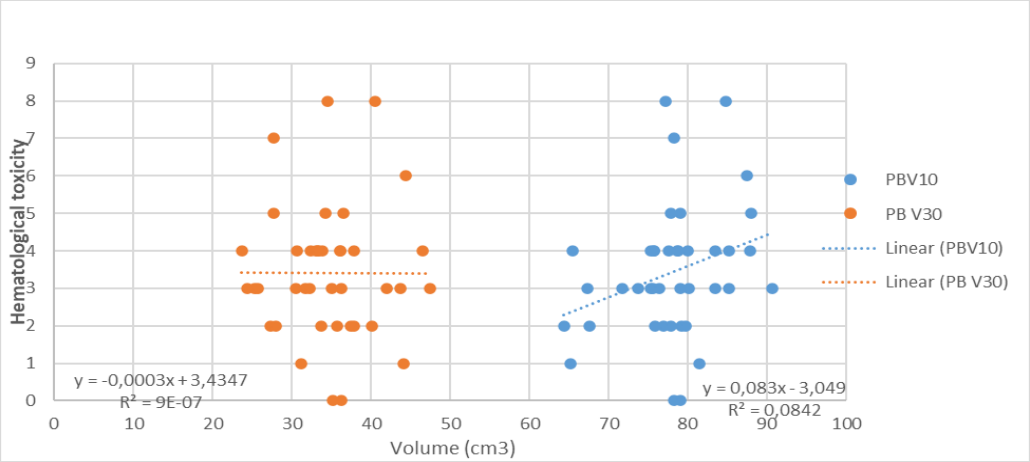

Fig. 1. Association between hematological toxicity and PB V30Gy and V10Gy

Discussion

The aim of this study was to determine whether adjuvant radiotherapy with favorable toxicity could be delivered using IMRT to patients with radically resected stage II and III rectal carcinoma, since the data in the available literature are scarce. The hypothesis is that by implementing inverse planning and improving conformality of the target volumes, IMRT will reduce the dose to nearby organs at risk and consequently provide a favorable toxicity profile of the entire adjuvant treatment.

Generally, the treatment was well tolerated, which was demonstrated by the good patient compliance. This is of outmost importance considering that treatment breaks or treatment prolongations are associated with a higher risk of locoregional relapses[3].

One of the most problematic acute side effects of chemoradiation to the pelvis is the development of gastrointestinal side effect, in particular diarrhea. Although more than half of our patients developed diarrhea during treatment (52.5%), only 4 of them (10%) manifested with Grade 2 and 1 (2.5%) with Grade 3 diarrhea. These results are favorable to the results of the historic studies of adjuvant chemoradiotherapy using 3-D conformal planning. The German CAO/ARO/AIO-94 trial reported rates of 19% Grade 2 and 13% Grade 3-4 diarrhea in their postoperative group[25]. Current studies are predominantly concentrated on preoperative chemoirradiation and as expected, report few GI side effects especially in IMRT groups; such is the study by Jabbour *et al.*[10] (g 3-4 and 29% g 0-2 diarrhea). Our rates of acute gastrointestinal toxicities are comparable to many of the studies for preoperative radiochemotherapy using IMRT. Ng *et al.*[26] and Parakesh *et al.*[9] report grade ≥ 2 diarrhea in 10% of patients, whereas Samuelson *et al.* [11] in their retrospective study, which incorporated both preoperative and postoperative patients, report Grade ≥ 2 diarrhea in 23% of patients in the IMRT arm. A potential explanation for the favorable GI toxicity profile in our study is the fact that the V45 for peritoneal cavity is 102.7 cm^3, well below the widely accepted volume of 195 cm3 in the neoadjuvant chemoradiotherapy recommended by QUANTEC[19]. Although we have not established a correlation between the dose received by the peritoneal cavity and the acute GI toxicity, it is well described in the literature[20,21].

We observed a high incidence of mild Grade 1-2 hematologic toxicity (65% thrombocytopenia, 45% anemia, 17.5% neutropenia), but excluding the clinically insignificant lymphopenia, higher-grade events occurred in only 2.5% of study patients. IMRT has been shown to reduce bone marrow exposure and associated hematologic suppression in patients undergoing chemoradiotherapy for anal or gynecologic carcinomas[22,23]. However, the concomitant chemotherapy used in these studies (mitomycin or cisplatin) was associated with more pronounced hematologic suppression compared to capecitabine used in radiochemotherapy for rectal cancer. Thus, we decided not to prioritize marrow sparing, assuming that such efforts could compete with bowel sparing.

In terms of dosimetric parameters in our study, they are comparable and even superior to other adjuvant radiochemotherapy studies[14], with the apart from the doses received by the bladder. Since our institution did not provide daily KV positioning checks or cone-beam CT, we opted to include 10-15 mm of the posterior wall of or the bladder into the CTV2 to compensate for the expected variation in bladder filling, resulting in higher doses received by the bladder. The dose received by the bladder did not result in a significant increase of genitourinary tract toxicity compared to other studies[10,13].

Our study has several limitations, starting with the small sample size. Since daily set up positioning checks are not available in our institution, to enhance patient set-up reproducibility our patients were treated in the supine position. However, prone positioning (with or without abdominal compression on a belly board) has been associated with reduction in pelvic small bowel volume[27,28], although it is unclear whether the dosimetric advantages result into clinically reduced GI toxicity[29]. The short follow-up time is insufficient for accurate assessment of the late toxicity and locoregional disease control. And finally, without comparison with a relevant control group of patients treated with 3D-CRT, the conclusions of the study remain vague and underestimated.

Conclusion

Integrating IMRT in the adjuvant treatment of locally advanced rectal cancer provides good dose distribution and organs at risk sparing. The treatment is well tolerated, the side

effects are mainly of lesser degrees and easily managed. A comparison with 3-dimensional conformal radiotherapy is needed to assess whether IMRT offers a better opportunity for radiotherapy.

Conflict of interest statement. None declared.

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