New dosimetric parameters to predict ano-rectal toxicity during radiotherapy treatment

Antonella Sanfratello a, Davide Cusumano b,c, Antonio Piras d,x, Luca Boldrini c,e, Andrea D’Aviero f, Piero Fricano d, Marco Messina g, Marina Vaglica h, Daniele Galanti i, Massimiliano Spada h, Guido Martorana j, Goffredo Arena k,l,m, Tommaso Angileri n, Antonino Daidone d

a Università degli Studi di Palermo, Radioterapia Oncologica, Palermo, Italy
b Medical Physics, Mater Olbia Hospital, Olbia, Italy
c UOC Radioterapia Oncologica, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Dipartimento di Diagnostica per immagini, Radioterapia Oncologica ed Ematologia, Rome, Italy
d UO Radioterapia Oncologica, Villa Santa Teresa, Bagheria, Italy
e Università Cattolica del Sacro Cuore, Rome, Italy
f Radiation Oncology, Mater Olbia Hospital, Olbia, Sassari, Italy
g UOC Oncologia Medica, ARNAS Ospedali Civico Di Cristina Benefratelli, Palermo, Italy
h UOC Oncologia Medica, Fondazione Istituto G. Giglio, Cefalù, Palermo, Italy
i UOC Oncologia Medica, Ospedale B. La Ferla Fatebenefratelli, Palermo, Italy
j UOC Chirurgia Generale, Ospedale B. La Ferla Fatebenefratelli, Palermo, Italy
k Department of Surgery, McGill University, Montreal, Quebec, Canada
l Fondazione Istituto G. Giglio, Cefalù, Italy
m Mediterranean Institute of Oncology, Viagrande, Italy
n UO Radiologia, Villa Santa Teresa, Bagheria, Palermo, Italy

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ABSTRACT

Purpose: Radiotherapy is essential in the treatment of locally advanced rectal cancer. Side effects of radiotherapy in the treatment of rectal cancer have a great effect on quality of life. The aim of this retrospective study is to evaluate the correlation between dosimetric parameters and acute toxicity in rectal cancer patients.

Methods: We analyzed the Dose Volume Histogram parameters for both the target structures and the Organs at risk of 89 patients. A dedicated statistical analysis was performed for all the acute toxicities showing a frequency rate higher than 20%.

A linear logistic regression model was elaborated using the variable showing the highest level of significance at the univariate analysis.

Results: The occurrence of proctitis was significantly correlated with three dosimetric parameters: D98% of low ano-rectum, D98% and Dmean of low ano-rectum wall.

A predictive linear logistic regression model reports that the D98% of the wall of the low ano-rectum must be < 38.5 Gy to decrease the rate of proctitis.

A general analysis on grade 2 acute toxicity occurrence reported that it was correlated with D98% of low ano rectum.

Conclusions: Two dose constraints were elaborated: D98%< 33.5 Gy for low ano rectum to prevent grade 2 acute toxicity and D98%< 25 Gy for low ano-rectum wall to prevent proctitis (grade 1 or superior).
Introduction

Colorectal carcinoma is the third most common malignancy, with rectal carcinoma accounting for almost one-third of colorectal carcinomas [1].

In Italy colorectal cancers are absolutely the most frequent (13% of new cancers diagnosed per year in both sexes) and in particular they represent the third most frequent neoplasia in men (after prostate and lung cancer) and the second in women (after breast cancer), in the last 10 years in Italy there has been a reduction in both the incidence and the mortality from rectal cancers in both sexes [2].

The improvements in the treatment of rectal cancer derived from a multimodal approach [3]. Surgery, radiotherapy (RT) and systemic therapy combine to achieve the goal of cure.

During the latest decades, neoadjuvant RT with or without concomitant chemotherapy (CHT) followed by Total Mesorectal Excision (TME) has become the gold standard for locally advanced rectal cancer (cT3-4 and/or N1-2) treatment resulting in a significant improvement of local control [4].

Considering the improvement in local control reached with neoadjuvant treatments and surgical TME technique, the new priority now is the reduction of treatment-related side-effects and postoperative complications.

In order to optimize the treatment, CHT can be administered either before or after neoadjuvant RT, referred to as Total Neoadjuvant Therapy (TNT) that is a new promising strategy in locally advanced rectal cancer [5,6].

Within the analysed cohort, patients underwent the following treatments according to internal institutional guidelines:

- simultaneous RT and chemotherapy (CRT) long course, which is indicated in both cT2-3 N0 of the low rectum to avoid abdominal perineal amputation with permanent ostomy and allow sphincter preservation and in cT3-4 N0-2 M0 rectal cancers.
- exclusive RT short course in cT3 N0 M0 medium-high rectal cancers and in T3-T4 N0-N2 when there are absolute contraindications to CHT.

Postoperative CRT may be offered to avoid local recurrence in patients with high risk histology features who have not received preoperative CRT [7]. Therefore, in patients with rectal cancer, RT can be used for both neoadjuvant and adjuvant purposes. Neoadjuvant treatment is superior in terms of treatment compliance, toxicity and down-staging while adjuvant treatment allows for better selection of patients based on pathologic stage, although it might have greater toxicity. However, both approaches have similar rates of distant recovery and overall survival [7,8].

Experiences reported in literature show a relationship between radiation treatment and adverse effects that might affect the organs at risk (OARs), which are diarrhea, cystitis, perineal dermatitis, genitourinary dysfunction [9,10].

Side effects of radiotherapy in the treatment of rectal cancer have a great effect on quality of life and play an important role in the well-being of the patients [3].

The aim of this retrospective study is to evaluate the correlation between dosimetric parameters and acute toxicity in rectal cancer patients.

Materials and methods

Patients characteristics

We performed a retrospective analysis of 89 patients with rectal cancer, treated in our center from 01/01/2015 to 31/05/2021 (Table 1).

The mean age at the time of treatment was 68.3 years (range 43 to 88 years), 42 were females and 47 males. Every patient was studied with endoscopy procedures, biopsy and magnetic resonance imaging (MRI) and underwent thoracic and abdominal computed tomography (CT) and/or positron emission tomography (PET) for routine disease staging. Histology for all patients was compatible with adenocarcinoma. Rectal cancer stage ranged from stage II to stage IVa according to the 7th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging system [11]. Specific informed consent was administered to all patients according to internal protocols.

Hygienic advices were given to the patient prior to RT course start and appropriate support therapy such as probiotics and simethicone to reduce abdominal distention as well as daily applications of skin protecting cream to prevent skin erythema were routinely prescribed.

During the treatment, the patients were examined weekly and blood tests were done every 7 days. To evaluate the toxicity we used the Common Terminology Criteria for Adverse Events (CTCAE) scale version 4.0 from 2015 to 2017 while we used CTCAE scale version 5.0 to evaluate the side effects presented by our patients from 2018 [12,13].

Treatment

67 patients underwent neoadjuvant RT and 22 patients underwent adjuvant RT (three patients had undergone an abdomino-perineal resection, 16 patients received a low anterior resection, 1 had a TME and 2 had a Hartman surgery). All patients were simulated in the supine position and immobilized to the bed treatment with the Combifix™, a baseplate system providing enhanced positioning for the pelvic region. The simulation CT was acquired with 2.5 mm thick slice, 20–30 min after drinking 500 ml of water to fill the bladder. Setup marks were drawn on the skin of the patients after laser alignment. About contouring in 2015 the clinical target volume (CTV) of the pelvis was contoured according to “La Radioterapia dei Tumori Gastrointestinali-Indicazioni e Criteri Guida 2014” [7] while from 2016 CTVpeltis was contoured according to “Rectal cancer guidelines” published on Radiotherapy and Oncology [14]. The CTVboost was defined as the tumor bed identified through the fusion of MRI images with the images of our simulation CT or through the visualization of the surgical alteration. The planning target volume (PTV) of pelvis and of boost were created by adding an isotropic 8 mm margin expansion to CTVpeltis and CTVboost respectively. The OARs (bladder, bowel bag, bowel loops, femoral heads) were delineated according to RTOG guidelines [15]; anorectum was outlined from the anal margin (from the level of the ischial tuberosities) extending cranially up to 7 cm; the wall of the low ano-rectum, contoured with a thickness of about 3 mm, it was cropped to contoured Gross Tumor Volume (GTV) on T2-weighted sequences of co-registered MRT [16,17].

All treatments were carried out on a Linac Synergy® (Elekta, Stockholm, Sweden). This Linac is equipped with an 80-leaves multi-leaf collimator and a kilovolt Cone Beam (kV CBCT) as on-board imaging.

Twenty two patients underwent adjuvant treatment. The prescribed RT dose was between 39.6 and 45 Gy to PTVpeltis and between 46.8 and 55 Gy to PTVboost according to tumor stage as for international guidelines [18].

Following internal protocols, 16 patients carried out concomitant...
A dedicated statistical analysis was performed for all the acute toxicities showing a frequency rate higher than 20%.

A comprehensive analysis was also performed considering any grade 2 acute toxicity as adverse event, independently by the type of toxicity observed.

In particular, the ability of each clinical and dosimetric parameter in predicting the acute toxicity occurrence after RT was assessed at the univariate analysis by considering the Wilcoxon Mann Whitney (WMW) test or the t-test, depending on the normality of data distribution, which was previously evaluated using the Shapiro-Wilk test [19].

A linear logistic regression model was elaborated using the dosimetric variable showing the highest level of significance at the univariate analysis.

The predictive performance of the model elaborated was evaluated using the area under the Receiver Operating Characteristic (ROC) curve (AUC), with the 95% confidence intervals calculated using the bootstrap method with 2000 iterations [20].

The best cut-off threshold was identified maximizing the Youden Index (J), and values of sensitivity and specificity at the best threshold were calculated [21].

A dynamic nomogram was finally elaborated, and a dose constraint was calculated considering as acceptable an occurrence probability lower than those observed in the clinical cohort.

The whole statistical analysis was performed using R software (version 3.6.1, Wien Austria) and dedicated packages [22].

Results

Table 3 resumes data of acute toxicities rates.

No significant correlation with the variables collected in the database was observed with regards of diarrhea and dysuria.

Significant parameters were found for grade 2 acute toxicities and proctitis, so two predictive models were elaborated considering dosimetric parameters for such toxicities.

Predictive model for grade 2 acute toxicities

As regards the presence of grade 2 toxicities, a significant correlation was observed with two clinical parameters (age and sex with p equal to 0.030 and 0.045 respectively), one technical parameter (type of technique, p = 0.03) and one dosimetric parameter (D98% of low rectum, p = 0.043).

Grade 2 toxicities resulted to be less frequent in men, younger than 58 years and treated with IMRT technique.

A linear logistic regression model was elaborated to correlate the D98% of low rectum and the probability of observing a grade 2 acute toxicity.

The mathematical formulation of the predictive model was the follows:

\[ b \left[ \frac{p(x)}{1 - p(x)} \right] = ax + b \]

Table 3

<table>
<thead>
<tr>
<th>Acute Toxicity</th>
<th>n. pt</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>29</td>
<td>32.6</td>
</tr>
<tr>
<td>Proctitis</td>
<td>23</td>
<td>25.8</td>
</tr>
<tr>
<td>Dysuria</td>
<td>18</td>
<td>20.2</td>
</tr>
<tr>
<td>Urinary tract pain</td>
<td>9</td>
<td>10.1</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td>8.9</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>2</td>
<td>2.2</td>
</tr>
</tbody>
</table>
where p(x) is the probability of grade 2 toxicity, x was the D98% of low rectum, a was equal to 0.02 ± 0.01 Gy⁻¹ and b to −1.92 ± 0.54.

At the best cut-off value (30%) corresponding to a value of Youden Index of 0.30, the predictive model exhibits a specificity of 73% and a sensitivity of 57%. The ROC curve of the model has an AUC of 0.65 (0.50–0.79 as 95% confidence interval) and it is reported in Fig. 1. To reduce the probability of grade 2 acute toxicities lower than 25% a D98% of low rectum lower than 35 Gy has to be maintained.

Fig. 1 reports the probability to suffer from grade 2 toxicity 1 in function of the D98% of the low ano-rectum.

**Predictive model for proctitis**

Given the statistically significant results obtained, we focused our attention on the statistical analysis of the “proctitis” parameter to find a predictive model for this event in patients being treated for rectal cancer.

The occurrence of proctitis was significantly correlated with three dosimetric parameters: D98% of low ano-rectum (p = 0.003), D98% and Dmean of low ano-rectum wall (p = 0.005 and p = 0.01 respectively).

At the correlation analysis performed using Pearson Correlation Coefficient, the most significant three dosimetric significant parameters resulted to be correlated among each other with correlation coefficients always higher than 0.5 (minimum value between D98% of low ano rectum and mean dose of low rectal wall equal to 0.58).

The predictive model related to proctitis considers the D98% of low rectum wall as variable, with a parameter equal to 0.04 ± 0.01 Gy⁻¹ and b to −2.55 ± 0.65. At the best cut-off value (31%) corresponding to a value of Youden Index of 0.40, the predictive model exhibits a specificity of 69% and a sensitivity of 73%. (Table 4).

Fig. 2 reports the ROC curve of the predictive model elaborated considering the D98% of low ano-rectal wall as variable and the occurrence of proctitis as outcome: the AUC was equal to 0.72, with a 95% confidence interval ranging from 0.59 to 0.84.

Fig. 3 reports the probability to suffer from proctitis calculated using the elaborated predictive model in function of the D98% of the low ano-rectum wall: to maintain an occurrence rate below to 27% a dose value below 25 Gy should be maintained.

**Discussion**

This is a retrospective study whose aim was to find any correlation between dosimetric parameters and toxicity in patients with rectal cancer undergoing radiation treatment. Many studies in the literature have shown a significant association between rectal toxicity and different variables such us rectal volume exposed to high doses, RT techniques, contouring and DVH parameters.

Bakkal et al. pointed out that modern RT techniques (IMRT, SIB) aim to reduce the doses of OARs providing safer doses for the treatment of rectal cancer. Buettner et al. showed that the fraction of the circumference of the rectal wall irradiated at high doses is specifically important. Kroli et al. confirmed that less exposure of the rectal wall to intermediate or high doses of radiations, leads to fewer changes and complications [16,23–29].

In the era of personalized medicine, it is increasingly important to be able to predict toxicity and response to radiation treatment through radiomics and dosimetric parameters [30–35].

Rectal RT toxicity involves many early adverse effects that could interfere with the patient’s quality of life and daily activities.

In the analysed cohort the most common adverse effects were diarrhea, dysuria and proctitis. In order to prevent these side effects, we looked for variables that were associated with them in an attempt to find any useful correlation.

As Grade 1 toxicity has been shown to be uncertain and not correlated to treatment parameters, we performed an analysis considering as complications any events with Grade ≥ 2.

A correlation was observed for Grade ≥ 2 toxicity with both clinical and technical parameters.

Consistently to previously reported experiences [23], the type of technique was significantly correlated to the development of toxicity events (p-value of 0.03). Also for the D98% of the wall of the low ano-rectum, a statistical significance correlation was found (p-value of 0.043).

Long-term results of the German CAO/ARO/AIO-94 phase III trial have shown that acute organ toxicity occurrence can be predicted based on basic patient characteristics such as gender in RT treatments [36,37]. Also in our cohort, Grade 2 toxicities resulted to be less frequent in men younger than 58 years, as the variable sex and age were significantly correlated to toxicity events (p-value of 0.03 and 0.045 respectively).

Focusing on proctitis we found a correlation with the Dmean of the wall of the low ano-rectum (p-value of 0.03 and the p-adjust is 0.4) and a significant correlation with D98% of the low ano-rectum (p-value of 0.005 and the p-adjust is 0.08) and finally for D98% of the wall of the low ano-rectum we found a correlation with good statistical significance (p-value of 0.003 and a p-adjust of 0.06).

This new model predicts that proctitis can be significantly reduced if the D98% of the wall of the low ano-rectum is < 38.5 Gy, allowing us to predict the risk of developing proctitis in relation to DVH and consequently to adjust it. This parameter may help radiation oncologists to reduce this side effect, especially if the tumor is located in the middle or upper rectum, but in general in all pelvic district cancers.

In the case of tumors located in the ultra-low rectum, however, it may be more difficult to apply such a model because we may encounter target under-dosage. Therefore, to minimize the risk of this toxicity, this new parameter should simply be examined during the treatment planning validation. In our opinion it can be a valuable tool to help reducing acute toxicity from proctitis.

Our study was a single-center retrospective series with a limited number of patients and therefore no definite conclusions can be drawn. It would be desirable to increase this type of research also in other centers to try in order to validate the model and find correlations between RT parameters and other side effects in patients undergoing RT for rectal cancer.

![ROC curve of the predictive model elaborated for grade 2 toxicities with the 95% confidence intervals depicted in dash lines.](image-url)
Conclusions

Although this study has several limitations such as being retrospective and the limited number of patients, the highly statistically significant value found is appealing and demands further research. Two dose constraints were elaborated: D98% < 33.5 Gy for low ano rectum to prevent grade 2 acute toxicity and D98% < 25 Gy for low ano-rectum wall to prevent proctitis (grade 1 or superior).

Table 4
Elaborated predictive model data.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Threshold</th>
<th>J_index</th>
<th>AUC</th>
<th>Low_AUC</th>
<th>High_AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training</td>
<td>72.72727</td>
<td>69.35484</td>
<td>0.335132</td>
<td>0.420821</td>
<td>71.81085</td>
<td>0.590936</td>
<td>0.8452807</td>
</tr>
</tbody>
</table>

Fig. 2. Histogram of the probability of grade 2 toxicities in function of D98% of low ano rectum.

Fig. 3. ROC curve of the predictive model elaborated for proctitis with the 95% confidence intervals depicted in dash lines.

Fig. 4. Histogram of the probability of proctitis occurrence calculated using the elaborated predictive model.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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