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Evaluating the predictive value of quantec rectum tolerance dose suggestions on acute rectal toxicity in prostate carcinoma patients treated with IMRT

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ABSTRACT

Aim: To investigate the predictive value of convenience of rectum dosimetry with Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) dose limits, maximum rectum dose (Dmax), total rectal volume (TVrectum), rectal volume included in PTV (VrectumPTV) on Grade 2–3 acute rectal toxicity for utilization in clinical practice.
Background: Numerous previous data have reported frequent acute proctitis after external-beam RT of prostate cancer. Predicting toxicity limited with dose information is inadequate in clinical practice due to comorbidities and medications used.
Materials and Method: Sixty-four non-metastatic prostate cancer patients treated with IMRT were enrolled. Patients were treated to a total dose of 70–76 Gy. Rectal dose volume histograms (DVH) of all patients were evaluated retrospectively, and a QUANTEC Score between 0 and 5 was calculated for each patient. The correlation between the rectal DVH data, QUANTEC score, TVrectum, VrectumPTV, rectum Dmax and Grade 2–3 rectal toxicity was investigated.
Results: In the whole group grade 1, 2 and 3 acute rectal toxicities were 25%, 18.8% and 3.1%, respectively. In the DVH data, rectum doses of all patients were under RTOG dose limits. Statistically significant correlation was found between grade 2–3 rectal toxicity and TVrectum ($p = 0{,}043$); however. It was not correlated with QUANTEC score, VrectumPTV and Dmax.
Conclusion: Our results were not able to show any significant correlation between increasing convenience with QUANTEC limits and lower rectal toxicity. Conclusively, new dosimetric definitions are warranted to predict acute rectal toxicity more accurately in prostate cancer patients during IMRT treatment.

1. Background

Numerous previous data have reported acute proctitis frequency after external-beam RT of prostate cancer with conventional fractionation, hypofractionation or SBRT between 5–20%.[1–3] The most common method of predicting the normal tissue complication probability after RT is the Lyman-Kutcher-Burman (LKB) model,[4] a method based on dose-volume histograms. Burman et al. were the first to compute the model parameters for late rectal bleeding.[5] QUANTEC recently recommended new values to apply LKB model for the same endpoint.[6–8] In the last decade many studies have been published about NTCP models for various end points, such as late rectal bleeding, moderate/mild toxicity as high stool frequency, loose stools and rectal urgency.[9–12] Predicting toxicity limited with dose information is a restrictive aspect of traditional NTCP which is confirmed by plenty of consequent studies identifying many individual factors, such as drugs used (antihypertensives and/or anti-coagulants), smoking history, previous abdominal surgery, comorbidities (hypertension, cardiovascular history, diabetes mellitus), presence of acute gastro-intestinal toxicity with rectal injury.[10,13–17]

The definition of toxicity after radiotherapy is also a complicated issue. Several different scales have been introduced and validated in an attempt to ensure an accurately reported toxicity with a common language.[18–20]

Radiation-induced proctopathy can arise with rectal pain, cramps, incontinence, diarrhea, mucus, rectal bleeding, and increased frequency of bowel movements. These symptoms are classified according to the EORTC/RTOG grading system for gastrointestinal side effects.[20] However, rectal mucosal damage is not

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Table 1
RTOG Dose suggestions in protocol 415.

	Dose/fx	Volume	Dose
[a]D50	1.8 Gy	50%	<60 Gy
[b]D35	1.8 Gy	35%	<65 Gy
[c]D25	1.8 Gy	25%	<70 Gy
[d]D15	1.8 Gy	15%	<75 Gy

[a] Dose with 50% of rectum volume exposed.
[b] Dose that 35% of rectum volume exposed.
[c] Dose that 25% of rectum volume exposed.
[d] Dose that 15% of rectum volume exposed.

directly correlated with clinical symptoms; therefore. endoscopy is recommended for accurate estimation of the rectal mucosal status and radiation-induced changes. Type and severity of mucosal damage is found to be dependent on the total dose and irradiated volume.[21,22]

2. Aim

In this study, we retrospectively evaluated the dosimetric data and cute rectal toxicity profile of prostate carcinoma patients for whom we performed IMRT planning by taking into consideration RTOG tolerance dose suggestions for critical organs. QUANTEC Score between 0 and 5 was calculated for each patient according to the number of parameters that matched the tolerance doses defined in QUANTEC. The predictive value of QUANTEC Score, Dmax, TVrectum, VrectumPTV on Grade 2–3 acute rectal toxicity was investigated.

3. Methods and materials

We retrospectively evaluated the dose – volume data of 64 patients who received definitive IMRT for prostate cancer between January 2015 and February 2018. Patients with biopsy proven prostate cancer who received neoadjuvant and concurrent hormonal therapy were included. The DVH data for 64 patients were reevaluated in terms of rectal toxicity suggestions from QUANTEC. The acute toxicity reports were recorded weekly during the treatment, and monthly for the first 3 months after the treatment. All rectal complications were graded using the criteria from RTOG.

3.1. RT techniques

All patients underwent simulation and treatment in a supine position with a full bladder. Vacuum-lock bags were used for immobilization. CT images using a 2.5-mm slice thickness for planning were acquired for IMRT on a CT scanner (Excel Select, General Electric Medical Systems). The clinical target volume 1 (CTV 1) for the initial 46 Gy included the prostate and seminal vesicles and the pelvic lymph nodes (internal iliac, external iliac, obturatory). Consequently, the seminal vesicles and prostate were contoured as CTV 2 treated to 70 Gy. Afterwards, the prostate in intermediate risk or the prostate + proximal seminal vesicles in high risk patients were treated to 76 Gy as CTV 3. PTV was 0.5 cm around the CTV in the anterior, superior and inferior directions and 0.3 cm in the posterior direction. The details of RT have been previously described (16). In brief, patients were initially treated to 46 Gy at 2 Gy/ fraction to the isocenter using 6-MV photons with seven-field intensity modulated radiotherapy. After the initial 46 Gy, a five-field IMRT approach was used to boost the total isocenter dose to 76 Gy. All patients were treated at 2 Gy/fraction using 6-MV photons prescribed to the isocenter. Daily position reproducibility was provided via skin marks and daily electronic portal films. RTOG suggestions were considered in terms of rectum and bladder dose limitations were (Table 1).

Table 2
QUANTEC Dose suggestions (predicted <10% Gr 3 rectal toxicity).

The volume exposed to specific dose	Percentage of volume
[a]V50	<50%
[b]V60	<35%
[c]V65	<25%
[d]V70	<20%
[e]V75	<15%

[a] Volume of rectum that was exposed to 50 Gy.
[b] Volume of rectum that was exposed to 60 Gy.
[c] Volume of rectum that was exposed to 65 Gy.
[d] Volume of rectum that was exposed to 70 Gy.
[e] Volume of rectum that was exposed to 75 Gy.

3.2. Dosimetric evaluation

DVH data of all patients were investigated in terms of accordance with QUANTEC suggestions (Table 2). The convenience of rectum dose parameters with QUANTEC criteria was scored as 0–5 (0: none of the parameters were within the QUANTEC limits -5: all parameters were within the QUANTEC limits) for each patient. Acute rectal toxicity is reported weekly during the treatment and monthly utill 3 months after the treatment using RTOG toxicity grading system (Table 3).[23]

3.3. Statistical analysis

The V50, V60, V65, V70, V75 (volume exposed to dose higher than indicated), TVrectum, $V_{RectumPTV}$, Dmax values for the 2 defined groups (Gr 0–1 and 2–3 acute rectal toxicity) were compared via independent samples t test and Mann–Whitney U test in parametric and nonparametric data, respectively. The correlation between V50, V60, V65, V70, V75 and Grade 2–3 acute rectal toxicity and the correlation of Grade 2–3 acute rectal toxicity with QUANTEC score, TVrectum, $V_{RectumPTV}$ and rectum Dmax were also analyzed via Spearman's correlation.

4. Results

Acute rectal toxicity distribution among patients according to grade is shown in Table 4. Of the 64 patients studied, 14 had Grade 2 or higher acute rectal complications. No patient developed Grade 4 complications (Table 4). The median time to developing Grade 2 or higher complications was 3 weeks.

In the whole group, grade 1, 2 and 3 acute rectal toxicities were 25%, 18.8% and 3.1% respectively. DVH data in terms of rectum doses of all patients were convenient with RTOG rectum tolerance dose suggestions determined by D50, D35, D25, and D15. QUANTEC score was 0, 1, 2, 3, 4 and 5 in 3, 5, 6, 3, 13, 34 patients, respectively. Median Dmax, TVrectum and $V_{rectumPTV}$ values for the whole group were 78 Gy (72,25–80,62 Gy); 63,83cc(23,18–139,57cc) and 18,29% (5,39–59,01%), respectively. Mean V50, V60, V65, V70 and V75 values were calculated as 45,45% (±9,56), 29,33% (±7,92), 22,01% (±7,22), 14,5% (±6,64) and 6,5% (±4,73), respectively. No statistically significant difference was found between mean V50, V60, V65, V70 and V75 values of the 2 groups (p = 0,354–0,0,712). Dmax and VrectumPTV were also not significantly different between the 2 groups (p = 0,175 ve p = 0,0845). However, the TVrectum difference was statistically significant (p = 0,044). Gr 2–3 acute rectal toxicity was not correlated with V50, V60, V65, V70 and V75 volumes (p = 0,18–0,75). Spearman's correlation analysis for QUANTEC score, Dmax, TVrectum, $V_{rectumPTV}$ and Gr 2–3 acute rectal toxicity was found statistically significant only for TVrectum ($p < 0,05$) Correlation coefficients are shown in Table 5.

Table 3
RTOG acute rectal toxicity grading system.

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
No changes	Increased frequency, change in bowel habits, or rectal discomfort not requiring medications or analgesics	Diarrhea requiring parasympatholytic drugs, mucous discharge not necessitating sanitary pads, abdominal or rectal pain requiring analgesics	Diarrhea requiring parenteral support, severe bloody or mucous discharge necessitating sanitary pads, abdominal distention	Acute or subacute obstruction, fistula or perforation, GI bleeding requiring transfusion, abdominal pain or tenesmus requiring tube decompression or diversion

Table 4
Frequency of acute rectal toxicity.

Toxicity	Frequency	Percent
GR 0	34	53,1
GR 1	16	25
GR 2	12	18,8
GR 3	2	3,1

Table 5
Results of Spearman's rank correlation coefficients of duration of Grade 2–3 rectal toxicity.

	Correlation coefficient	p
QUANTEC score (0–5)	0.061	0.611
Volume of Rectum	−0.254	**0.043**[a]
$V_{Rectum-PTV}$	0,025	0.847
Dmax	0.171	0.177

$V_{Rectum-PTV}$: Percent of rectum volume inside PTV, *Dmax:* Maximum rectum dose.
[a] Statistically significant p value.

5. Discussion

Radiotherapeutic treatment modalities for localized prostate cancer (PCa) include different types of external-beam radiation therapy (EBRT) or brachytherapy administrations, with or without androgen deprivation.[24] Treatment modality preference depends on numerous factors such as patient age, comorbidities, tumor stage, grade, intent and institutional standards and availabilities.[25–27] Recent improvement of RT planning and delivery and application ensured a reduction in both acute and late side-effects.[12–14,28–31] These technical developments provided target dose escalation resulting in better cancer control rates and fewer or similar side-effects.[32–35] Intensity-modulated radiation therapy (IMRT) ensures more conformal treatment while mitigating the harmful exposure to the rectum in terms of both acute and late toxicity.[36–39] In addition, real-time tracking of the target as in image-guided tomotherapy or volumetric-modulated arc therapy allows more accurate dose delivery.[40,41] Despite these improvements, acute and late rectal toxicity still remains as to be the main dose-limiting issue.[42,43]

5.1. Post RT rectal injury: clinic and mucosal detection

Improved local tumor control with higher doses is demonstrated by many randomized trials; however, dose escalation causes acute and late side effects.[30,35,44] Rectal complications are most frequently considered dose limiting in prostate radiotherapy. In order to report acute and late toxicity, usually Radiation Therapy Oncology Group (RTOG) toxicity scale is used.[45] We also scored acute rectal toxicity according to RTOG scale. However, some modifications have been proposed to the criteria based on patient characteristics such as advanced age; rectal volume; a history of prior abdominal surgery; the concomitant use of androgen deprivation; and preexisting diabetes mellitus, hemorrhoids, or inflammatory bowel disease (IBD).[23,30,46–49] In addition, a diagnosis of acute rectal toxicity is reported to be associated with an increased risk of late rectal sequela.[36,50,51]

The definition of rectal toxicity after radiotherapy is also a complex issue. Various scales have been introduced and validated to provide accurate report of the toxicity.[18–20] However, ongoing controversy on the best scale encouraged clinical trials which proposed modifications.[13,33] Accurate reporting of the toxicity is so important because it is critical for the feedback of treatment development which supports establishing the cause and effect. Dose-distribution to the rectum is correlated with late rectal toxicity[52–55] and development of new techniques entailed new normal tissue constraints to be developed. The constraints are not consistent in the literature due to variations in collecting and reporting of toxicity. Last but not least; rectal mucosal damage is not always directly correlated with symptoms. Endoscopy is recommended for straight detection of radiation injury in rectal mucosa. Even an endoscopic scaling system; Vienna rectoscopy score (VRS), was presented for this purpose in 2000[56] (Table 6). However, a scoring system must be applicable in different centers and must have been used for a long time such as the EORTC and RTOG score.

Type and severity of mucosal damage is reported to be related to total dose and irradiated volume.[21,22]

5.2. Previous publications reporting on rectal radiation injury after prostate IMRT

Zelefsky et al.[57] reported late toxicity results of 561 patients who had been treated with IMRT up to 81 Gy IMRT at the Memorial Sloan–Kettering Cancer Centre. After 8 years of follow-up, the rate of rectal bleeding was 1.6% and grade 3 rectal toxicity according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) was 0.1% with a fraction size of 1.8 Gy. Vora et al. reported acute RTOG grade >2 toxicity in 49% (only 1% grade 3) in patients whose rectal volume receiving >70 Gy was limited to 30%.[58]

The Gr 2 and 3 toxicities we reported in our patients were 16.7 % and 5.6 %, respectively, which was not in accordance with the above-mentioned results.

Although hypofractionation attempts are frequently reported, in our patients we used a conventional fractionation scheme of 200 cGy daily fractions. Pelvic lymph nodes were treated to 4600 cGy followed by the first boost of 2400 cGy to a volume including the seminal vesicles and prostate and the last boost of 600 cGy to the prostate and proximal seminal vesicles.

In a recent study by Wortel et al., dose distributions in patients with and without grade ≥2 acute proctitis were significantly different for IG-IMRT and 3D-CRT. The authors demonstrated a significant relationship between acute rectal toxicity and local dose distributions. And they suggested that this finding could help to develop consequent dose-effect models with improved dose constraints for IGRT or IMRT.[59]

DVH, which is the basic tool for analyzing dose distribution and treatment plan approval, is based on a CT planning-scan showing only a snapshot of the patient anatomy.[60] Besides, the spatial components are also not represented in the DVH.[61] Therefore,

Table 6
Vienna Rectoscopy Score, Wachter et al.

VRS	Mucosal Congestion	Telangiectasia	Ulceration	Stricture	Necrosis
0	Grade 1	(−)	(−)	(−)	(−)
1	Grade 2	Grade 1	(−)	(−)	(−)
2	Grade 3	Grade 2	(−)	(−)	(−)
3	Any	Grade 3	Grade 1	(−)	(−)
4	Any	Any	Grade 2	Grade 1	(−)
5	Any	Any	Grade ≥ 3	Grade ≥ 2	(+)

alternative longitudinal definitions are proposed as done in TAME study[62] which defines a metric incorporating a number of aspects of toxicity.[63] Also, several definitions, such as integrated longitudinal toxicity (ILT) for late rectal toxicity which incorporates the severity and duration of toxicity, were suggested in previous publications.[64] And it was recommended as a powerful measure while it is sensitive to the differences in the time course of the different end-points.

ROC was another method which successfully derived constraints that indicating the incidence of toxicity. The advantage of ROC analysis is the ability to explore all possible cut-points for each endpoint tested. The effects of confounding factors, such as co-morbidities and individual patient radiation sensitivity,[65] are added to the results. The same ROC method of analysis was suggested to be applied to toxicity definitions which take into account longitudinal data. And two uncorrelated definitions of late rectal toxicity to derive dose–volume constraints using ROC analysis were demonstrated in the same study concluding that longitudinal definition of toxicity adds value to the analysis of late toxicity data.[63]

Liu et al. validated a predictive model for late rectal bleeding for patients treated with 74 Gy in 2 Gy/fraction. Rectal dose volume histograms were extracted and fitted to a Lyman-Kutcher–Burman NTCP model. Multivariate logistic regression with dose-volume parameters (V50, V60, V70, etc.) was found non-significant.[66] When we evaluated the convenience of our patients' rectal dose data with QUANTEC dose suggestions, where RTOG dose limits were routinely taken into consideration in IMRT plans, we were unable to show any decrease in Gr 2–3 acute rectal toxicity with increasing convenience to QUANTEC dose suggestions. Besides, none of the dose-volume parameters suggested by QUANTEC was found significant in the Spearman's correlation analysis in terms of Gr 2–3 acute rectal toxicity.

Rectum Dmax was included in neither QUANTEC nor RTOG dose suggestions. In concordance with this approach, no correlation was found between rectum Dmax and Gr 2–3 acute rectal toxicity. Some previous studies reported a relation between absolute rectal volume exposed to a specific dose and acute rectal toxicity or rectal bleeding. Mirjolet et al. have shown that absolute rectal volume exposed to 25 Gy–50 Gy may predict any acute rectal toxicity.[67] Similarly, Kotabe et al. also found that absolute rectal volume, rather than relative rectal volume, exposed to 60 Gy is correlated with rectal bleeding in prostate IMRT treatment. And the authors suggested the absolute rectal volume exposed to 60 Gy to be <5cc.[68] In our study, TVrectum was found to be the only parameter significantly correlated with Gr 2–3 acute rectal toxicity.

There are several limitations of our study to be indicated. First is a small patient group which obliged us to use nonparametric statistical evaluation. Second is focusing the results on acute rectal injury in a short follow up period. And the last one is the absence of any objective assessment, such as proctoscopy or pathologic examination.

6. Conclusions

Rectum dose parameters after IMRT treatment plans in prostate cancer may provide the tolerance doses suggested in RTOG guidelines where the same plan may exceed QUANTEC dose limits. Our results were not able to show any significant correlation between increasing convenience with QUANTEC limits and lower rectal toxicity. Rectal volume was the only effective variable for prediction of Gr 2–3 toxicity. Conclusively, new dosimetric definitions are warranted to predict acute rectal toxicity more accurately in prostate cancer patients during IMRT treatment.

Conflict of interest

None.

Financial disclosure

All authors disclose that there are no possible conflict of interest issues to declare.

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