Received:
26 April 2016

Revised:
13 October 2016

Accepted:
28 November 2016

<https://doi.org/10.1259/bjr.20160370>

Cite this article as:

Nitsche M, Brannath W, Brückner M, Wagner D, Kaltenborn A, Temme N, et al. Comparison of different contouring definitions of the rectum as organ at risk (OAR) and dose-volume parameters predicting rectal inflammation in radiotherapy of prostate cancer: which definition to use? *Br J Radiol* 2017; **90**: 20160370.

FULL PAPER

Comparison of different contouring definitions of the rectum as organ at risk (OAR) and dose-volume parameters predicting rectal inflammation in radiotherapy of prostate cancer: which definition to use?

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MN and RMH contributed to the conception, design, analysis and interpretation of data and helped with the final approval of the version to be published. MN, RMH and NT helped with the drafting of the article. WB and MB contributed to the statistics of the main study. DW contributed to the acquisition of data. AK contributed to the statistics of pre-study. NT helped with the planning and implementation of radiotherapy.

Objective: The objective of this retrospective planning study was to find a contouring definition for the rectum as an organ at risk (OAR) in curative three-dimensional external beam radiotherapy (EBRT) for prostate cancer (PCa) with a predictive correlation between the dose-volume histogram (DVH) and rectal toxicity.

Methods: In a pre-study, the planning CT scans of 23 patients with PCa receiving definitive EBRT were analyzed. The rectum was contoured according to 13 different definitions, and the dose distribution was correlated with the respective rectal volumes by generating DVH curves. Three definitions were identified to represent the most distinct differences in the shapes of the DVH curves: one anatomical definition recommended by the Radiation Therapy Oncology Group (RTOG) and two functional definitions based on the target volume. In the main study, the correlation between different relative DVH parameters derived from these three contouring definitions and the occurrence of rectal toxicity during and after EBRT was studied in two consecutive collectives. The first cohort consisted of 97 patients receiving primary curative EBRT and the second cohort consisted of 66 patients treated for biochemical recurrence after prostatectomy. Rectal toxicity was investigated by clinical investigation and scored according to the Common Terminology Criteria for Adverse Events. Candidate

parameters were the volume of the rectum, mean dose, maximal dose, volume receiving at least 60 Gy (V_{60}), area under the DVH curve up to 25 Gy and area under the DVH curve up to 75 Gy in dependence of each chosen rectum definition. Multivariable logistic regression considered other clinical factors such as pelvic lymphatics vs local target volume, diabetes, prior rectal surgery, anticoagulation or haemorrhoids too.

Results: In Cohort 1 (primary EBRT), the mean rectal volumes for definitions "RTOG", planning target volume "(PTV)-based" and "PTV-linked" were 100 cm³ [standard deviation (SD) 43 cm³], 60 cm³ (SD 26 cm³) and 74 cm³ (SD 31 cm³), respectively ($p < 0.01$; analysis of variance). The mean rectal doses according to these definitions were 35 Gy (SD 8 Gy), 48 Gy (SD 4 Gy) and 44 Gy (SD 5 Gy) ($p < 0.01$). In Cohort 2 (salvage EBRT), the mean rectal volumes were 114 cm³ (SD 47 cm³), 64 cm³ (SD 26 cm³) and 81 cm³ (SD 30 cm³) ($p < 0.01$) and the mean doses received by the rectum were 36 Gy (SD 8 Gy), 49 Gy (SD 5 Gy) and 44 Gy (SD 5 Gy) ($p < 0.01$). Acute or subacute rectal inflammation occurred in 69 (71.9%) patients in Cohort 1 and in 43 (70.5%) in Cohort 2. We did not find a correlation between all investigated DVH parameters and rectal toxicity, irrespective of the investigated definition. By adding additional variables in multivariate analysis, the predictive ability was

substantially improved. Still, there was essentially no difference in the probability of predicting rectal inflammation occurrence between the tested contouring definitions.

Conclusion: The RTOG anatomy-based recommendations are questionable in comparison with functional definitions, as they result in higher variances in several

relative DVH parameters. Moreover, the anatomy-based definition is no better and no worse in the predictive value concerning clinical end points.

Advances in knowledge: Functional definitions for the rectum as OAR are easier to apply, faster to contour, have smaller variances and do not offer less information than the anatomy-based RTOG definition.

INTRODUCTION

External beam radiotherapy (EBRT) is an important option for the curative treatment of locally confined prostate cancer (PCa). Owing to the close proximity between the prostate and the rectum, radiation proctitis is a major concern with regard to patient information, treatment planning and delivery.

Symptoms of acute radiation proctitis develop during or shortly after the treatment course. They include rectal discomfort, tenesmus, changes in stool consistency, mucus and bleeding and are grouped according to the Common Terminology Criteria for Adverse Events scales. Late rectal toxicity may develop even years after EBRT and is characterized by the above-mentioned symptoms, but also rarely with faecal incontinence or strictures. The leading objective symptom for late toxicity in most studies is rectal bleeding.^{1–7}

In PCa, escalation of EBRT dose improved local control in several trials.⁸ As the dose at the rectum might increase simultaneously, higher rates of radiation side effects at the rectum have been observed.⁹ Therefore, a precise planning tool to predict possible side effects at the rectum is very important. At present, the mainstay of the prediction and evaluation of possible radiation side effects is the calculation of dose–volume histograms (DVHs). They offer a simple method for correlating the volume of the rectum with the planned dose. However, several uncertainties are still unresolved with regard to DVH calculation and interpretation. From our point of view, one problem is the lack of an internationally accepted definition of contouring the rectum as an organ at risk (OAR) when planning the CT scan. This is very important, as the calculated DVH values are directly correlated with the size and location of the OAR volume. Changes in volume may have a decisive influence on the curve of the DVH, because in the histograms, the dose is directly plotted against the respective volume. Therefore, crucial differences can occur at relevant limits depending on the OAR definition used, leading to differing evaluations of results and changes in treatment planning and delivery. So far, there are limited data on the correlation between differences in the definition of the rectum as an OAR and the clinical occurrence of side effects.^{10–12}

The present study evaluated the influence of different rectal OAR definitions on the prediction of acute and subacute rectal toxicity. The aim is the identification of an intuitive and robust rectum definition leading to DVH parameters that are correlated with rectal toxicity.

The study was conducted in two steps. First, we analyzed 13 contouring definitions in 23 patients and detected those 3 with the largest differences regarding the DVHs. In the second step,

we analyzed those three definitions with regard to multiple DVH parameters and their correlation with rectal inflammation in a large cohort of patients.

METHODS AND MATERIALS

Pre-study period

The aim of the pre-study was to identify the easiest and most robust contouring definitions of the rectum as an OAR that resulted in substantial differences in respective DVH curves.

Patients and methods

23 consecutive patients scheduled for definitive curative three-dimensional (3D) conformal EBRT for biopsy-confirmed PCa between February 2011 and June 2012 were selected for the pre-study. Patient clinical data are summarized herein: the mean age was 73 years (range, 65–80 years), and all patients received EBRT to the prostate only; 16 patients were treated with a total dose of 75.6 Gy, 6 patients were treated with a total dose of 72 Gy and 1 patient was treated with a total dose of 70.2 Gy. The mean prostate-specific antigen before EBRT was 6.4 ng ml⁻¹ (range, 0.68–13.7 ng ml⁻¹). EBRT was carried out under image guidance (image-guided radiotherapy) with three fiducial markers implanted into the prostate about 1 month before treatment planning. Planning CT scans were taken with 3 mm of slice distance (Siemens, Nürnberg, Germany). Patients were advised to have an empty bowel and a full bladder with at least 500 ml. An axial T₁ contrast-enhanced MRI scan was fused with the planning CT to allow higher precision in prostate delineation. Delineation and planning were performed with routine software [Focal contouring®, Xio® treatment planning (Elekta)]. In low-risk PCa, the gross target volume encompassed only the prostate without seminal vesicles (SV); in intermediate-risk PCa, it encompassed the prostate and 1 cm of the caudal SV. In high-risk PCa, it encompassed the prostate and 2 cm of the caudal SV. A safety margin of 0.5 cm was added to accommodate the extracapsular growth in intermediate- and high-risk Pca, defined as the clinical target volume (CTV). The planning target volume (PTV) was defined according to three different dose levels as follows: CTV + 1 cm (up to 50.4 Gy), CTV + 1 cm (0.5 cm to the rectum) (up to 66.6 Gy) and CTV + 0.5 cm and complete exclusion of the rectum (up to 75.6 Gy). The bladder (as a whole organ), the femoral heads and the rectum were defined as OARs. Treatment was planned for a Siemens Artiste linear accelerator with 6-MV and 15-MV photon energy. EBRT was performed with a combination of a classical box technique and additional beams to spare the rectum. The box consisted of four beams: two lateral–dorsal beams angled at 90° and 270° and one ventral and one dorsal beam angled at 0° and 180° respectively. These four beams translated to approximately 75% of the monitor units. In addition, we used four lateral–dorsal beams to spare the

rectum and to decrease the dose received from the rectum. Those beams were angled at 120°, 240°, 170° and 190°. In this field configuration, the rectal OAR was blocked with a multileaf collimator.

12 different definitions of contouring the rectum as an OAR were taken from the current literature and applied to each treatment plan; one definition (R13) was the result of in-house development (Table 1).^{1–3,10–23} Distinctive anatomical features characterized the first nine definitions of the rectum as an OAR, whereas the last four were functional definitions, in which the rectum was exclusively considered with regard to the PTV. All the contouring throughout the entire study was performed by one experienced consultant (RMH) to exclude interobserver variability.

For each respective rectal contour, the volumes receiving at least 5 Gy ($V_{5\text{Gy}}$), 10 Gy ($V_{10\text{Gy}}$), ..., up to 75 Gy were recorded. The rectum was contoured and analyzed in each definition as a solid organ, as no statistical significant differences in comparison with

contouring the rectal wall (1 mm) were observed in these 23 patients of the pre-study (two-sided *t*-test; data not shown).

Statistics

The SPSS® statistics software v. 23.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) was used to perform statistical analyses. To avoid the repercussions of multiple testing, *e.g.* overfitting of the statistical model or falsely rejecting the null hypothesis, DVH curves [$V_{5\text{Gy}}\text{--}V_{75\text{Gy}}$ means and standard deviations (SDs)] were compared according to the particular rectal volume definition by visual inspection. We excluded definitions that resulted in similar DVH curves (overlapping SDs). In a second step, the remaining DVH curves with distinct curve shapes between 5 Gy and 35 Gy were compared with each other to identify significant differences between the AUCs. $V_{5\text{Gy}}\text{--}V_{35\text{Gy}}$ values of these curves were analyzed with least-squares regression analysis calculating the AUCs. Using variance analysis (F-test), these areas were tested against each other. All definitions resulting in distinct curve shapes in this dose range were included in further clinical evaluations.

Table 1. The rectum as an organ at risk. 13 different definitions of contouring the rectum were available from the current literature

Definition name	Caudal limit	Cranial limit	Citation
R1	Lowest slice of ischial tuberosity including the anus	One slice below the layer in which the rectum gives up its round shape and the sigmoid anteriorly connects	de Crevoisier et al ¹³
R2	Lowest slice of ischial tuberosity	For a length of 15 cm or to the point where the rectosigmoid flexure could be identified	Michalski et al ¹⁴
R3	Lowest slice of ischial tuberosity	Inferior border of the sacroiliac joints or when the rectum anteriorly leaves the sacrum	Rasch et al ¹⁵
R4	Lowest slice of ischial tuberosity	11 cm above	Kuban et al ¹⁶
R5	2 cm below the ischial tuberosity	11 cm above	Huang et al ¹⁷
R6	Anal verge	The slice in which the rectum gives up its round shape and connects to the anterior sigmoid	Cozzarini et al; ¹ Thor et al; ¹⁸ Fonteyne et al ¹⁹
R7	One slice above the anal verge	The slice in which the rectum gives up its round shape and connects to the anterior sigmoid	Valdagni et al ²
R8	One slice above the anal verge	One slice below the rectosigmoid flexure	Vavassori et al; ²⁰ Foppiano et al ²¹
R9 “RTOG”	Lowest level of ischial tuberosity	Before the rectum loses its round shape (when the rectum leaves the sacrum anteriorly)	Vargas et al; ³ Gay et al ²²
R10 “PTV-based”	Most inferior CT slice of the PTV	Most superior CT slice of the PTV	Onal et al ¹⁰
R11 “PTV-linked”	1 cm below the most inferior CT slice of the PTV	1 cm above the most superior CT slice of the PTV	Guckenberger et al ²³
R12	2 cm below the most inferior CT slice of the PTV	2 cm above the most superior CT slice of the PTV	Liu et al ¹¹
R13	3 cm below the most inferior CT slice of the PTV	3 cm above the most superior CT slice of the PTV	In-house definition

PTV, planning target volume; Radiation Therapy Oncology Group.

Main study

Patients and methods

194 consecutive patients scheduled for EBRT of PCa were investigated in the main study between February 2010 and October 2012. Two patient cohorts were analyzed. The first cohort consisted of patients treated with primary curative EBRT for PCa ($n = 97$). The second cohort consisted of patients treated for biochemical recurrence after prostatectomy ($n = 66$). Patients irradiated within 3 months after prostatectomy ($n = 25$) were excluded, as this group experienced distinct problems during EBRT (more complications without adequate bladder filling as well as pain after surgery). Furthermore, we excluded

patients treated with palliative EBRT ($n = 6$), as they received other fractionation schedules and doses. Patient clinical data are summarized in [Table 2](#).

EBRT was planned and performed as described above. In addition, some patients in the main study received regional lymphatic radiotherapy. The CTV hereby included external, internal and commune iliac as well as partially presacral lymph nodes. A safety margin of 1 cm was applied to the CTV to define the PTV. "In EBRT for biochemical recurrence, the CTV encompassed the region of the former base and apex of the prostate and SV in the craniocaudal direction. The lateral borders included the

Table 2. Patient characteristics and toxicity of the main study

Patient characteristics	Cohort 1 $n = 97$	Cohort 2 $n = 66$
Mean age (years)	72.61 (range, 53–81)	69.68 (range, 47–74)
Fiducial markers	43	0
Dose 75.6 Gy	58	4
Dose 72 Gy	33	39
Dose 70.2 Gy	2	5
Dose 66.6 Gy	3	10
Dose OTH	1	8
RT lymph nodes	27	37
AHT	51	16
T1	2	1
T2	92	42
T3	3	20
T4	0	3
N+	2	10
M1	1	0
Gleason 4	0	1
Gleason 5	2	0
Gleason 6	56	15
Gleason 7	31	40
Gleason 8	6	7
Gleason 9	2	3
Anticoagulation	23	4
Diabetes mellitus	18	6
Haemorrhoids	20	16
Bowel surgery	6	8
Acute toxicity, Grade 1	34	27
Acute toxicity, Grade 2	35	19
Subacute toxicity, Grade 1	3	2
Subacute toxicity, Grade 2	13	9
Follow-up (mean) (months)	23.64 (range, 1–45)	25.77 (range, 3–49)

AHT, antihormonal therapy; OTH, other (dose); RT, radiotherapy.

Figure 1. In the dose–volume histogram (DVH) curves of 23 patients in the pre-study, mean values and the respective standard deviations are depicted. Three definitions of the rectum as an organ at risk showing the most distinct differences with regard to the DVH curve shapes were identified in the pre-study ($p < 0.01$; F-test). Therefore, the definitions R9 (“Radiation Therapy Oncology Group”), R10 [planning target volume “(PTV)-based”) and R11 (“PTV-linked”) were chosen for further analyses of their possible predictive values concerning acute and late rectal toxicity in the main study in large cohorts of patients.

neurovascular bundles and the intern obturatorius muscles. The posterior border was defined by the anterior part of the rectum, excluding the rectal wall. The anterior border encompassed the urethrovesical anastomosis. The PTV was defined according to two different dose levels as follows: CTV + 1 cm (up to 50.4 Gy) and CTV + 0.5 cm and complete exclusion of the rectum (up to 70.2–72 Gy”).

Treatment toxicity was scored by one single physician, who visited patients before EBRT, weekly during EBRT, at the end of EBRT, 3 months after EBRT and annually for 5 years after completion of EBRT. Only additional problems occurring during or after EBRT were graded as follows according to the Common Terminology Criteria for Adverse Events: Grade 0, no symptom; Grade 1, symptoms without clinical significance; Grade 2, outpatient treatment required; Grade 3, hospitalization; Grade 4, life threatening; Grade 5, lethal.

Statistics

Statistical analyses were performed with R (open source). The Kolmogorov–Smirnov test was used to test for normal distribution. Continuous values (mean rectal volume, mean rectal dose) were compared with analysis of variance among different contouring definitions. The end point was the occurrence of acute or late rectal inflammation [common toxicity criteria (CTC) score >0 vs CTC score = 0]. When subacute rectal inflammation status was missing (four patients in Cohort 1 and one patient in Cohort 2), the end point was determined based on the acute rectal inflammation status only. In the statistical analysis, the ability to predict occurrence of rectal inflammation was investigated by logistic regression analysis and quantified by the area under the curve (AUC) of the corresponding receiver-operating characteristic (ROC) curve. The ROC curve represents the true-positive probability as a function of the false-positive probability. Analysis was performed separately for each of the definitions R9, R10 and R11. Candidate variables considered were

the volume of the rectum, mean dose of the rectum, maximal dose of the rectum, volume of the rectum receiving at least 60 Gy (V_{60}), area under the DVH curve up to 25 Gy (AUC_{25}) and area under the DVH curve up to 75 Gy (AUC_{75}). In addition, multi-variable logistic regression was used to investigate these candidate variables together with the following variables: regional and local target volumes, risk factors of diabetes, prior rectal surgery and anticoagulation and/or haemorrhoids before EBRT.

RESULTS

Identification of rectal organ at risk definitions with the highest variance in dose–volume histogram curve shapes

The first nine contouring definitions based on anatomical structures (R1–9) showed only marginal and non-significant influences on the DVH curves, especially in the low-dose regions up to 35 Gy (not shown). In contrast, the functional definitions (R10–13) showed systematic differences in the shape of the DVH curves. Finally, three definitions (R9, R10 and R11) were identified to represent the most distinct differences in the shapes of the DVH curves ($p < 0.01$; F-test) (Figure 1). These three definitions are shown in Figure 2, and they were further

Figure 2. Definitions for the rectum as an organ at risk: R9 “Radiation Therapy Oncology Group” (red)—the cranial limit is the plane before the rectum loses its round shape in the axial plane; the caudal limit is the lowest level of the ischial tuberosities. R10 planning target volume “(PTV)-based” (yellow): the cranial limit is the most superior CT slice of the PTV; the caudal limit is the most inferior CT slice of the PTV. R11 “PTV-linked” (green): the cranial limit is 1 cm above the most superior CT slice of the PTV; the caudal limit is 1 cm below the most inferior CT slice of the PTV. The PTV is encompassed in orange.

Figure 3. Box and whiskers plots of the correlation between different dose-volume histogram (DVH) parameters and the occurrence of rectal toxicity in dependence of the respective rectal definitions R9 ("Radiation Therapy Oncology Group"), R10 [planning target volume "(PTV)-based"] and R11 ("PTV-linked"): the whiskers represent all data points that are within 1.5 times the interquartile range (height of the box). AUC_{25} , area under the DVH curve up to 25 Gy; AUC_{75} , area under the DVH curve up to 75 Gy; EBRT, external beam radiotherapy.

A cohort 1 (primary EBRT)

B cohort 2 (salvage EBRT)

evaluated in the two patient collectives of the main study. In the following, definition R9 is called “RTOG” (as it is recommended by the Radiation Therapy Oncology Group), R10 is described as “PTV-based definition” (contouring the rectum from the most inferior CT slice of the PTV to the most superior CT slice of the PTV) and R11 is described as “PTV-linked definition” (contouring the rectum 1 cm below the most inferior CT slice of the PTV to 1 cm above the most superior CT slice of the PTV).

Description of different dose-volume histogram parameters in dependence of organ at risk definition
In Cohort 1 (primary EBRT), the mean rectal volumes for definitions “RTOG”, “PTV-based” and “PTV-linked” were 100 cm³ (SD 43 cm³), 60 cm³ (SD 26 cm³) and 74 cm³ (SD 31 cm³), respectively ($p < 0.01$; analysis of variance). The mean rectal doses according to these definitions were 35 Gy (SD 8 Gy), 48 Gy (SD 4 Gy) and 44 Gy (SD 5 Gy) ($p < 0.01$). The maximal doses received by the rectum were 72 Gy (SD 2 Gy), 73 Gy (SD 2 Gy) and 73 Gy (SD 2 Gy), respectively ($p = 0.902$). The mean rectal volume receiving 25 Gy (V_{25}) was 69% (SD 18%), 97% (SD 6%) and 87% (SD 9%) ($p < 0.01$).

Very similar results were obtained for Cohort 2 (salvage EBRT): the mean rectal volumes for definitions “RTOG”, “PTV-based” and “PTV-linked” were 114 cm³ (SD 47 cm³), 64 cm³ (SD 26 cm³) and 81 cm³ (SD 30 cm³) ($p < 0.01$). The mean doses received by the rectum were 36 Gy (SD 8 Gy), 49 Gy (SD 5 Gy) and 44 Gy

(SD 5 Gy) ($p < 0.01$), while the maximal rectal doses were 70 Gy (SD 3 Gy), 70 Gy (SD 3 Gy) and 70 Gy (SD 3 Gy) ($p = 0.912$). The mean V_{25} for each definition was 73% (SD 21%), 96% (SD 7%) and 88% (SD 10%), respectively ($p < 0.01$).

Prediction of rectal toxicity by means of different dose-volume histogram parameters in dependence of organ at risk definition

Acute or subacute rectal inflammations occurred in 69 (71.9%) patients in Cohort 1 (primary EBRT) and in 43 (70.5%) patients in Cohort 2 (salvage EBRT). In [Figure 3a](#), the occurrence of rectal inflammations is displayed using box plots with several variables and the contouring definitions “RTOG”, “PTV-based” and “PTV-linked” in patients in Cohort 1 (primary EBRT). No significant differences concerning the contouring definitions were found. However, the definition “RTOG” resulted in higher variances in volume, mean dose, AUC_{25} and AUC_{75} . Only V_{60} resulted in comparable variances. Exactly the same results were obtained in patients in Cohort 2 (salvage EBRT) ([Figure 3b](#)).

Univariable logistic regression analysis of Cohort 1 (primary EBRT) revealed a small AUC of the ROC curves, indicating only a small predictive ability of the variables ([Table 3](#)). In Cohort 2 (salvage EBRT), the AUCs were higher than those in Cohort 1 ([Table 4](#)). In Cohort 2, the highest AUCs were obtained with the variables volume and mean dose. However, the differences between the variables were small and even smaller between the methods.

Table 3. Results of the univariate logistic regression analysis for each method, R9 (“Radiation Therapy Oncology Group”), R10 [planning target volume “(PTV)-based”] and R11 (“PTV-linked”), and each variable for Cohort 1

Method	Variable	OR	95% LCL	95% UCL	AUC
R9	Volume	1.01	0.995	1.02	0.586
R9	Mean dose	1.02	0.97	1.08	0.576
R9	Maximal dose	0.983	0.803	1.2	0.495
R9	V_{60}	1.01	0.921	1.1	0.491
R9	AUC_{25}	1	1	1	0.593
R9	AUC_{75}	1	1	1	0.604
R10	Volume	1.01	0.992	1.03	0.554
R10	Mean dose	1.07	0.968	1.2	0.608
R10	Maximal dose	1	0.815	1.23	0.402
R10	V_{60}	1.01	0.959	1.07	0.528
R10	AUC_{25}	1	0.992	1.01	0.523
R10	AUC_{75}	1	1	1	0.592
R11	Volume	1.01	0.993	1.02	0.579
R11	Mean dose	1	0.924	1.1	0.552
R11	Maximal dose	1.03	0.834	1.28	0.524
R11	V_{60}	1.01	0.944	1.08	0.521
R11	AUC_{25}	1	0.998	1.01	0.572
R11	AUC_{75}	1	1	1	0.604

AUC, area under the curve; AUC_{25} , area under the dose-volume histogram (DVH) curve up to 25 Gy; AUC_{75} , area under the DVH curve up to 75 Gy; LCL, lower confidence limit; OR, odds ratio; UCL, upper confidence limit.

The confidence intervals for the odds ratios indicated that none of the candidate variables showed a significant influence on the probability of rectal inflammation occurrence (Tables 3 and 4).

By adding additional variables (regional *vs* PTV, diabetes, prior rectal surgery, anticoagulation and haemorrhoids) in the logistic regression analysis, AUC values were higher (Tables 5 and 6). The predictive ability of these variables was much higher than the influence of the DVH parameters—regardless of the respective rectal contouring definition.

DISCUSSION

The objective of our study was to find a simple, straightforward contouring definition for the rectum as an OAR during EBRT of PCa with a correlation between DVH parameters and rectal toxicity. However, all relative DVH parameters derived from the three tested contouring definitions failed to predict rectal toxicity.

This is in contrast to a study by Onal *et al*,¹⁰ who investigated four different contouring definitions in 94 patients treated with 3D EBRT (70 Gy). They used OAR definitions comparable with our definitions R10 (“PTV-based”), R11 (“PTV-linked”), R5 (if the anal verge is supposed to be located about 2 cm below the ischial tuberosities) and R6. In R11 and R5, the $V_{70\text{Gy}}$ was significantly higher in patients with rectal bleeding than that in those without (R11: 30.8% *vs* 22.5%; R5: 26.9% *vs* 18.1%). R5 was the definition that resulted in the highest rectal volumes.

However, only in R5 was the mean rectal dose a significant predictor of rectal bleeding. These differing results can be best explained by the different clinical end points investigated in both studies: as in our collectives, not enough patients experienced rectal bleeding during follow-up for statistical analyses. Therefore, we focused on the occurrence of any rectal toxicity.

We contoured the rectum as a solid organ in all tested definitions, as our aim was to find a simple rectum contouring definition (not all contouring software provide a user-friendly solution for creating hollow structures). Other approaches (solid organ *vs* rectal wall²⁴ *vs* rectal surface²⁵) were compared in a retrospective planning study by Guckenberger *et al*.²³ They stated that these different methods significantly influenced the planning process, especially in intensity-modulated radiotherapy (IMRT) planning. Only modest improvements were found in 128 patients with EBRT in the fitting of normal tissue complication probability (NTCP) models for rectal bleeding when using rectal dose–wall histograms in comparison with rectal DVH.⁴ We did not further analyze this contouring option. A very promising approach seems to be the analysis of dose distributions by means of dose–surface maps.²⁵ However, these functions are not integrated in routine planning software tools, and great efforts are needed to write corresponding scripts (*e.g.* in Pinnacle®). Only specialized institutions with the scientific focus on new software algorithms apply such analyses. As we try to improve widespread daily routine procedures, we did not pursue this specific approach in our study.

Table 4. Results of the univariate logistic regression analysis for each method, R9 (“Radiation Therapy Oncology Group”), R10 [planning target volume “(PTV)-based”] and R11 (“PTV-linked”), and each variable for Cohort 2

Method	Variable	OR	95% LCL	95% UCL	AUC
R9	Volume	0.991	0.979	1	0.657
R9	Mean dose	1.04	0.971	1.11	0.608
R9	Maximal dose	1.04	0.833	1.27	0.567
R9	V_{60}	1.05	0.952	1.17	0.598
R9	AUC ₂₅	1	0.999	1	0.601
R9	AUC ₇₅	1	1	1	0.596
R10	Volume	0.981	0.959	1	0.656
R10	Mean dose	1.1	0.998	1.24	0.661
R10	Maximal dose	1	0.798	1.24	0.508
R10	V_{60}	1.04	0.984	1.11	0.612
R10	AUC ₂₅	1.01	0.996	1.02	0.654
R10	AUC ₇₅	1	1	1	0.64
R11	Volume	0.983	0.963	1	0.669
R11	Mean dose	1.11	0.994	1.25	0.65
R11	Maximal dose	1.01	0.806	1.25	0.546
R11	V_{60}	1.05	0.976	1.14	0.616
R11	AUC ₂₅	1	0.998	1.01	0.641
R11	AUC ₇₅	1	1	1	0.655

AUC, area under the curve; AUC₂₅, area under the dose–volume histogram (DVH) curve up to 25 Gy; AUC₇₅, area under the DVH curve up to 75 Gy; LCL, lower confidence limit; OR, odds ratio; UCL, upper confidence limit.

Table 5. Results of the multiple logistic regression analysis for each method, R9 ("Radiation Therapy Oncology Group"), R10 [planning target volume "(PTV)-based"] and R11 ("PTV-linked"), and each variable for Cohort 1

Method	Variable	OR	95% LCL	95% UCL	AUC
R9	Volume	1.01	0.998	1.02	0.697
R9	Mean dose	0.983	0.922	1.05	0.691
R9	Maximal dose	0.956	0.767	1.19	0.694
R9	V ₆₀	0.961	0.868	1.06	0.7
R9	AUC ₂₅	1	0.998	1	0.705
R9	AUC ₇₅	1	0.999	1	0.702
R10	Volume	1.01	0.993	1.03	0.704
R10	Mean dose	1.02	0.897	1.16	0.691
R10	Maximal dose	0.967	0.771	1.21	0.696
R10	V ₆₀	0.99	0.929	1.05	0.705
R10	AUC ₂₅	1	0.988	1.01	0.703
R10	AUC ₇₅	1	0.999	1	0.695
R11	Volume	1.01	0.995	1.03	0.7
R11	Mean dose	0.968	0.862	1.07	0.695
R11	Maximal dose	1	0.794	1.26	0.695
R11	V ₆₀	0.977	0.902	1.06	0.699
R11	AUC ₂₅	1	0.994	1.01	0.695
R11	AUC ₇₅	1	0.999	1	0.694

AUC, area under the curve; AUC₂₅, area under the dose-volume histogram (DVH) curve up to 25 Gy; AUC₇₅, area under the DVH curve up to 75 Gy; LCL, lower confidence limit; OR, odds ratio; UCL, upper confidence limit.

Boehmer et al¹² published another approach by explicitly analyzing the influence of the exposure of the posterior half of the rectum on DVH parameters in 55 patients using 3D EBRT (72.9 Gy). They used the definitions R11 ("PTV-linked") and R6 and examined the whole organ and the posterior half separately for each definition. Depending on the definition used, V₇₀ and minimum and mean rectal doses were significantly different. Still, a correlation of these planning details with clinical outcome was not investigated.

A major problem concerning the comparison of many studies is the use or interpretation of different classifications of radiation toxicity.⁵ We concentrated on the CTC. Furthermore, all patients were treated and documented by only one physician, thus ensuring robust detection and classification of side effects. The end point of our study was maximum peak toxicity. This practice is supported by an analysis performed by Gulliford et al,²⁶ who compared two definitions of toxicity: the maximum peak toxicity during follow-up and the integrated longitudinal toxicity (taking into account both the severity and the duration of side effects). They investigated these two definitions testing DVH constraints using ROC analysis for 20 Gy up to 70 Gy in 388 patients.

All patients in our study received 3D EBRT, as this was the principal technical procedure at the time when the study was planned. IMRT has been implemented in the following years at our institution. To exclude IMRT as a potential confounder, we

decided to focus on the patients treated with 3D technique. Furthermore, the focus on 3D EBRT allows us to compare our results with the majority of the published studies on this issue. For example, Vargas et al³ studied 331 patients receiving 75.6 Gy. Of these patients, 34% patients had Grade 2 or 3 rectal toxicity. Peeters et al²⁷ also reported higher rates of acute gastrointestinal toxicity (46% patients with Grade 2) in a study comparing 68-Gy with 78-Gy EBRT. In our collectives, rectal toxicity was lower with Grades 1, 2 and 3 in 39%, 31% and 0% of patients, respectively. This may be due to modern EBRT with image guidance of fiducial markers and improved multileaf collimation. These low rates of toxicity led us to analyze acute and late rectal toxicity together in order to improve statistical power. From a clinical point of view, this approach is reasonable, as several studies have demonstrated a close relationship between acute and late rectal toxicity.^{3,27,28}

Although our analyses are focused on DVH parameters, the results should not be directly applied to IMRT planning and treatment for methodological reasons. IMRT allows a higher conformality in dose distribution than 3D EBRT, which is likely to influence DVH curve shapes and values.

The present literature shows homogeneous results, suggesting DVH constraints in EBRT of PCa with regard to late rectal bleeding. Restricting rectal volumes to receiving 75 Gy and 70 Gy below 5% and 25%, respectively, has been demonstrated

Table 6. Results of the multiple logistic regression analysis for each method, R9 (“Radiation Therapy Oncology Group”), R10 [planning target volume “(PTV)-based”] and R11 (“PTV-linked”), and each variable for Cohort 2

Method	Variable	OR	95% LCL	95% UCL	AUC
R9	Volume	0.995	0.979	1.01	0.804
R9	Mean dose	1.01	0.898	1.14	0.789
R9	Maximal dose	1.08	0.809	1.4	0.793
R9	V ₆₀	1	0.882	1.14	0.772
R9	AUC ₂₅	1	0.997	1	0.763
R9	AUC ₇₅	1	0.999	1	0.787
R10	Volume	0.979	0.95	1.01	0.817
R10	Mean dose	1.12	0.97	1.31	0.813
R10	Maximal dose	1.04	0.763	1.37	0.787
R10	V ₆₀	1.04	0.968	1.12	0.796
R10	AUC ₂₅	1.01	0.993	1.02	0.831
R10	AUC ₇₅	1	1	1	0.807
R11	Volume	0.983	0.958	1.01	0.813
R11	Mean dose	1.12	0.952	1.32	0.809
R11	Maximal dose	1.06	0.782	1.39	0.791
R11	V ₆₀	1.04	0.947	1.15	0.793
R11	AUC ₂₅	1	0.994	1.01	0.811
R11	AUC ₇₅	1	0.999	1	0.808

AUC, area under the curve; AUC₂₅, area under the dose-volume histogram (DVH) curve up to 25 Gy; AUC₇₅, area under the DVH curve up to 75 Gy; LCL, lower confidence limit; OR, odds ratio; UCL, upper confidence limit.

to be predictive of a very low incidence of late rectal bleeding.^{3,6,7,17,29–33} These results were consistent, although different methods of defining the rectum have been used in these studies. This leads to the assumption that the rectum behaves as a serial-like organ when doses >70 Gy are applied and that the definition of the rectum as an OAR therefore plays a subordinate role.^{3,6,7,27,29,30,34} In our collectives, we observed very high variances using the “anatomical” R9 definition in rectal volume, mean dose, AUC₂₅ and AUC₇₅. Interestingly, the definition R9 represents the RTOG recommendations on contouring pelvic OAR.²² In contrast, variances were lower when using the “functional” definitions R10 (only the PTV-containing slices) and R11 (PTV-containing slices plus 1 cm above and below), both in direct relation to the PTV contouring. The main obstacle of “RTOG” is the variability of the cranial OAR border: as far as our experience goes, this is highly dependent on

the actual bladder volume (large volumes determine a more cranial rectosigmoid flexure in the planning CT scans). This seems to cause systematically larger variances in DVH parameters of “RTOG”, resulting in a higher risk of missing significant correlations between DVH parameters and clinical end points.

CONCLUSION

Taken together, the RTOG anatomy-based recommendations for contouring the rectum as an OAR in 3D EBRT of PCa are questionable in comparison with functional definitions, as they result in higher variances in several relative DVH parameters without ever having shown to be of better or worse predictive value concerning clinical end points than other definitions. Functional definitions (e.g. only the PTV-containing slices or PTV-containing slices plus 1 cm above and below) are easier to apply and may be more precise.

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