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Late RTOG/EORTC, LENT SOMA and CTCAE graded rectal toxicity in relation to dose distributions in the rectum during radiotherapy for prostate cancer

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Background and Purpose

Patients treated with radiotherapy for prostate cancer are likely to sustain mild to moderate side effects as a result of their treatment. Some of these side-effects may persist or occur months to years after completion of therapy. A number of toxicity grading systems has been developed to classify the severity of these side-effects. However, the available grading systems use different criteria to translate symptoms into grades of toxicity (Table 1). In the studies that identified relationships between rectal dose distributions and side-effects, different grading systems were used. This complicates the ability to make general statements regarding these relationships.

The main purpose of this prospective study was to grade rectal toxicity of patients receiving radiation therapy for prostate cancer using the RTOG/EORTC, the LENT SOMA as well as the CTCAE version 3.0 grading systems simultaneously, and to investigate the association between these toxicity grading systems and the dose distributions in the rectum. Eventually, our aim was to apply the different grading systems to identify the most optimal thresholds for dose volume constraints for the rectum to be used in treatment planning for prostate cancer (Fig. 2).

	Threshold for a score ≥ grade 2 according to each of the systems *		
Patient self-reported complaints	RTOG/EORTC	LENT SOMA	CTCAE
Painful stools	(no reference)	Intermittent	Moderate
Painful cramping	Moderate	Intermittent	Moderate
Urgency	(no reference)	intermittent	Moderate
Mucus loss	Excessive	Intermittent	Moderate
Unintended mucus / faecal loss	(associated with acute symptoms)	Intermittent	(accounted for with diaper use)
Use of diapers for mucus / faecal loss	(associated with acute symptoms)	Intermittent	daily
Macroscopic rectal bleeding	intermittent	> 2 times / week	Intervention indicated
Daily stool frequency	> 5	≥ 5	Increase > 4 over baseline
Diarrhoea	Moderate	Antidiarrheal indicated	(accounted for with stool frequency)

* symptoms or treatment classified as grade 3 or 4 are taken into account as well for all subsequent grading systems to result in a combined score of ≥ grade 2 complications for each scale.

Table. 1. Symptoms resulting in ≥ grade 2 rectal toxicity according to RTOG/EORTC, LENT SOMA, and CTCAEv3.0 criteria

	Rectal toxicity					
	RTOG/EORTC		LENT SOMA		CTCAE v3.0	
Patients reporting pre-RT ≥ grade 2	0.8%	(1/124)	2.4%	(3/124)	2.4%	(3/124)
Patients reporting late ≥ grade 2 toxicity	31.7%	(39/123)	48.0%	(58/121)	43.0%	(52/121)

Table 2. Frequency of pre-radiotherapy and late ≥ grade 2 rectal toxicity according to RTOG/EORTC, LENT SOMA, and CTCAEv3.0 criteria

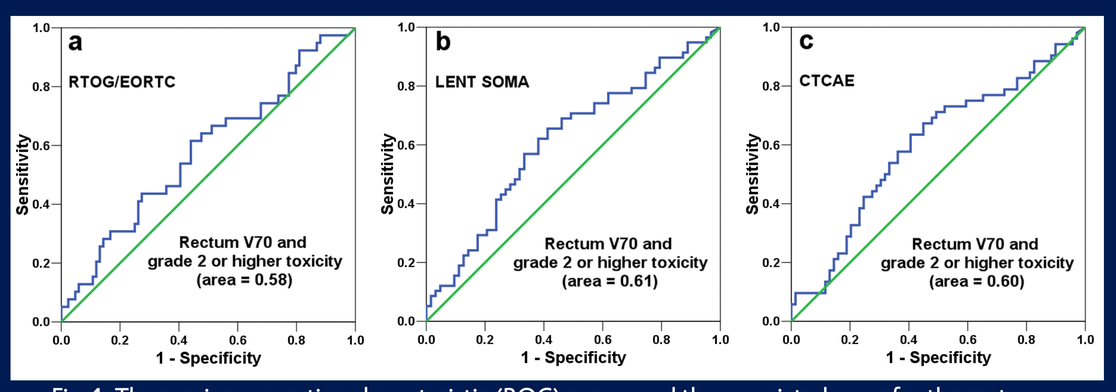

Fig. 1. The receiver operating characteristic (ROC) curves and the associated areas for the rectum relative V70 as predictor of ≥ grade 2 rectal toxicity, using the RTOG/EORTC (a), LENT SOMA (b), and CTCAE (c) grading systems. The ROC analysis was used to determine the predictive value of the dose-volume parameters. The green line at a 45° angle demonstrates what would be expected of a test with no predictive value. The closer the blue curve is to the upper-left corner of the graph, the more accurate it is.

	RTOG/EORTC		LENT SOMA		CTCAE v3.0	
	Univariate analysis p-values	Multivariate* analysis p-values	Univariate analysis p-values	Multivariate* analysis p-values	Univariate analysis p-values	Multivariate* analysis p-values
Relative volumes						
V70 continuous [%]	ns	ns	0.029	ns	ns	ns
V70 [20%]	ns	ns	0.010	0.043	0.020	0.037
Absolute volumes						
V70 continuous [cm³]	ns	ns	ns	ns	ns	ns
V70 [12 cm³]	ns	ns	0.032	0.005	ns	ns
V70 [28 cm³]	ns	ns	ns	ns	ns	0.008

* covariates: age, T-classification, N-classification, protocol, WHO performance score, hormonal therapy, rectum volume

Table 3. Relative and absolute dose-volume parameters in a logistic regression model designed to predict ≥ grade 2 toxicity according to RTOG/EORTC, LENT SOMA, and CTCAEv3.0 criteria

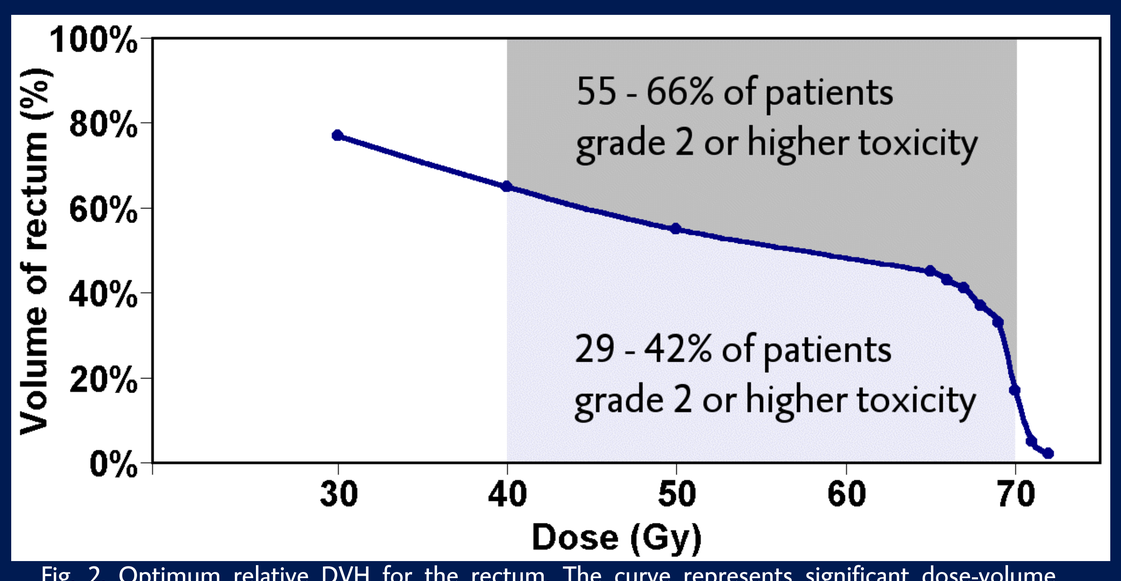

Fig. 2. Optimum relative DVH for the rectum. The curve represents significant dose-volume thresholds discriminating patients with ≥ grade 2 toxicity according to the LENT SOMA scale.

Materials and Methods:

124 patients received three-dimensional conformal radiotherapy (3D-CRT) for prostate cancer. A total dose of 70 Gy in 2-Gy fractions was applied with conventional fractionation. All patients filled in questionnaires regarding rectum complaints before, during, and after radiotherapy (median follow-up 36 months). DVH-parameters of the rectum [outer contour, from the anal verge to the sigmoid flexure], were analysed in relation to late (> 3 months post-RT) rectum grade ≥ 2 toxicity, according to RTOG/EORTC, LENT SOMA, and CTCAE criteria. ROC analyses were performed to assess the most predictive DVH parameters (Fig. 1), and logistic regression analyses were used to analyse the association with DVH-parameters and toxicity. Patients with pre-treatment toxicity were excluded from statistical analyses (Table 2).

Results:

The relative and absolute rectal volumes receiving ≥ 70 Gy (V70) were the most predictive parameters for late grade ≥ 2 toxicity with each of the grading systems. However, significant associations were only found for the relative V70 with use of the LENT SOMA system (Table 3). On the basis of the ROC co-ordinates, V70 was dichotomised by a volume of 20%. Significant associations between this factor and toxicity were found with use of the LENT SOMA and CTCAE systems. In a multivariate model including other prognostic and volumetric factors, the dichotomised V70 remained significant with use of the LENT SOMA and CTCAE systems. V70, dichotomised by an absolute volume of 12 cm^3, was significantly associated with the LENT SOMA system in univariate and multivariate analyses. Significant associations were found with the CTCAE system when V70 was dichotomised by an absolute volume of 28 cm^3. No such associations were found with use of the RTOG/EORTC system.

On the basis of the ROC co-ordinates, patients were divided into two groups according to relative rectal volumes that received a particular dose. It appeared that with use of the LENT SOMA system, there was a range of threshold values significantly discriminating patients with and without grade ≥ 2 toxicity (Fig. 2).

Conclusions:

The rectal V70 was the most important prognostic factor with regard to radiation-induced rectal toxicity.

The rectal V70 had the strongest association with rectal toxicity when the LENT SOMA grading system was used.

Dose-volume thresholds, best discriminating patients with and without grade ≥ 2 toxicity, were of higher significance when the LENT SOMA system was used.

Dose-volume effects for the rectum are present but their clinical significance depends on the grading system used.

Abbreviations:
RTOG/EORTC = Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer
LENT SOMA = Late Effects of Normal Tissue working group scales, representing Subjective (S), Objective (O), Medical Management (M), and Analytic evaluation of injury (A)
CTCAE = National Cancer Institute Common Toxicity Criteria for Adverse Effects

General classification of treatment related morbidity
Grade 1 = Minor symptoms, no treatment required
Grade 2 = Symptoms responding to outpatient treatment, no change in performance status
Grade 3 = Distressing symptoms altering a patient's lifestyle and/or requiring hospitalisation for minor surgical intervention
Grade 4 = Major Surgical intervention or prolonged hospitalisation
Grade 5 = Fatal complications