



ELSEVIER

Radiotherapy and Oncology xx (xxxx) 1–10

**RADIOTHERAPY  
& ONCOLOGY**  
JOURNAL OF THE EUROPEAN SOCIETY FOR  
THERAPEUTIC RADIOLOGY AND ONCOLOGY
[www.elsevier.com/locate/radonline](http://www.elsevier.com/locate/radonline)

# Sensitivity of treatment plan optimisation for prostate cancer using the equivalent uniform dose (EUD) with respect to the rectal wall volume parameter

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Received 16 February 2004; received in revised form 27 July 2004; accepted 18 August 2004

## Abstract

**Background and purpose:** To analyse the sensitivity of plan optimisation of prostate cancer treatments with respect to changes in the volume parameter ( $n$ ), when the EUD is used to control the dose in the rectal wall.

**Patients and methods:** A series of plans was defined, by varying  $n$  over a range between 0.08 and 1, and testing different cost functions and beam arrangements. In all cases, the aim was to minimise the EUD in the rectal wall, while ensuring specific dose coverage of the PTV, and limiting the dose in the other OARs. The results were evaluated in terms of 3-D dose distribution and with respect to the current clinical knowledge about late rectal toxicity after irradiation.

**Results:** Different values of  $n$  lead to very similar dose distributions over the PTV (differences in mean dose  $< 1$  Gy, differences in dose given to 99% of the volume  $< 1\%$ ). For the rectal wall, the following observations were made: (a) all cumulative DVH curves crossed each other around 60 Gy; (b) the rectal wall volume receiving doses between 30 and 45 Gy could change by 45 and 30%, respectively, depending on the value of  $n$ ; (c) for doses higher than 70 Gy the differences were typically within 5%. Different values of  $n$  also affected the position of isodose surfaces. The distance between the 70 and the 30 Gy isodose curves changed in the AP direction by a factor of 3 when  $n$  decreased from 1 to 0.08. High values of  $n$  were associated with less dose conformity and a larger volume (at least 20%) of normal tissues receiving 50 Gy or more. All DVHs for the rectal wall were below published dose toxicity thresholds except when the prescribed dose was escalated up to 86 Gy.

**Conclusions:** In most cases, the solutions associated with  $n$  values up to 0.25 produced similar dose distribution in the rectal wall for doses above 45 Gy, complying with the dose–toxicity thresholds we analysed. The choice of a specific value of  $n$  in the optimisation requires an analysis of its effects on the dose distribution for the rectal wall, but also on other aspects, such as the value of the dose to the non-involved normal tissues.

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**Keywords:** Equivalent uniform dose; IMRT; Optimisation; Prostate cancer; Rectal wall toxicity

## 1. Introduction

Computer optimisation of radiotherapy treatment plans requires a well-defined objective cost function, whose quality is determined by three factors: first, the accuracy of the clinical data on which it relies, second, the validity of the functions translating the clinical knowledge into a mathematical expression, third, the suitability of these functions for a computer-based

optimisation process. Most commercial treatment planning systems allow cost functions defined only by points in the dose–volume histogram (DVH) space, but this approach has clear limitations. A DVH point is a reliable descriptor of the dose–response relation only for organs at risk (OARs) that are purely serial. For these organs, for example, the spinal cord, the maximum dose is sufficient to calculate the probability of complication. If a volume effect exists for the OAR, we should be able to control the whole dose range, a task not easily achievable with a few DVH points.

The equivalent uniform dose (EUD) is a concept proposed with different formulations in the past years,

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113 either as a method to describe the dose–response relation for  
 114 tumour and normal tissues [6,20,22,23,27] and as a tool to  
 115 drive the optimisation process [26,30,32]. Recent studies by  
 116 Wu et al. [30] showed that the EUD in combination with a  
 117 sigmoidal cost function is an effective tool to minimise the  
 118 dose in an OAR without requiring extensive trial and error,  
 119 as often needed in DVH-based optimisation. Wu et al. used  
 120 a simple formulation of the EUD [23] (see Section 2.1 for  
 121 details) that requires just one volume parameter consistent  
 122 with the Lyman–Kutcher–Burman (LKB) model for normal  
 123 tissue complications (NTCP) [30]. Thanks to this consist-  
 124 ency, the EUD can be used not only as a tool to easily shape  
 125 a dose distribution, but also as a phenomenological  
 126 description of the dose–effect relation for an OAR.

127 If the EUD is to be used as a radiobiological model in a  
 128 cost function, one must take into account that for some  
 129 organs the value of the volume parameter is not accurately  
 130 known. For the rectal wall, an estimate of this parameter  
 131 was proposed more than 10 years ago [4]. Several studies  
 132 appeared since then about rectal wall toxicity, providing  
 133 physical and clinical parameters correlated with sequelae to  
 134 the rectal wall [2,9,13,28]. In the study by Boersma et al.  
 135 [2], the results did not correlate with the estimated NTCP  
 136 calculated according to Burman et al. [4], and an inaccurate  
 137 value of the volume parameter was considered one possible  
 138 cause of this discrepancy. Recently, the results of a large  
 139 multicenter study suggested that the value of the volume  
 140 parameter is significantly different from the one originally  
 141 proposed, and that different degrees of toxicity are better  
 142 described with two different values of this parameter [24].

143 While using the EUD in the optimisation of IMRT, one  
 144 must also take into account that the dose distributions used  
 145 to derive the parameter value in all the studies mentioned  
 146 above were obtained with conventional irradiation tech-  
 147 niques that are in general not representative of what can  
 148 nowadays be achieved with IMRT.

149 Because of these uncertainties, it is important to under-  
 150 stand how robust the results of planning optimisation are  
 151 with respect to changes in the volume parameter. The aim of  
 152 our study is to perform a sensitivity analysis that  
 153 quantitatively addresses the implications of using EUD for  
 154 controlling the dose in the rectal wall in the plan  
 155 optimisation of prostate cancer treatment.

## 157 2. Methods and materials

### 158 2.1. Patient selection, volume definition 159 and dose prescriptions

160 CT datasets and delineated contours of 5 prostate cancer  
 161 patients treated in our centre with IMRT were selected for  
 162 this study. For all patients, the simultaneous boost technique  
 163 was applied [3], in which two PTVs are irradiated. The PTV  
 164 of the primary treatment, PTV1, resulted from of a 10 mm  
 165 isotropic expansion of the CTV, defined as the prostate plus  
 166 seminal vesicles. The boost PTV, PTV2, consisted of an  
 167 expanded CTV, with 0 mm margin towards the rectum and  
 168 5 mm margin elsewhere. PTV(1–2) was defined as the  
 169 annular region formed by PTV1 from which PTV2 was  
 170 subtracted. PTV(1–2) partly overlapped with the rectum at  
 171 the posterior aspect of the prostate, and 15% to 20% of the  
 172 rectal wall volume was within PTV(1–2) for the patients  
 173 analysed in this study. The organs at risk were identified as  
 174 the rectal wall, the femur heads and the non-specified  
 175 normal tissues, i.e., all the remaining volume included in the  
 176 body contour. Details about the treatment technique and the  
 177 volume definition can be found elsewhere [3].

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### 2.2. Cost functions and treatment technique

In this study, the EUD was defined by the relation:

$$\text{EUD} = \left( \frac{1}{N} \sum_{i=1}^N d_i^{1/n} \right)^n \quad (1)$$

where  $N$  is the number of voxels of the anatomical structure of interest,  $d_i$  the dose associated with the  $i$ th voxel and  $n$  a parameter that, for each organ, describes the volumetric dependence of the dose–response relationship. This definition of EUD is identical to the effective uniform dose proposed by Mohan et al. [21] and can be derived from the DVH reduction scheme of the LKB NTCP model [4,19]. It should be noted that Eq. (1) can also be obtained from a formalism (the so-called general parallel model) that defines a dose–effect relation as a weighted mean of the dose distribution [27]. According to this approach, the definition of EUD is the result of choosing a power law weighting function. Eq. (1), finally, is equivalent to the definition of the generalised EUD proposed by Niemierko [23] by changing the parameter  $n$  into  $1/a$ . This last definition of EUD was also adopted by Wu and colleagues in their recent papers [30,32]. It is a matter of discussion whether  $n$  or  $1/a$  is used to indicate the volume parameter:  $n$  should be used if the purpose is to be consistent with fits of NTCP models, while  $a$  should be used to be consistent with recent publications on EUD-based optimisation [32]. For this study, we decided to use the parameter  $n$ , to underline the consistency between the EUD formalism and the LKB model.

The choice of  $n$  determines the relative importance of different dose ranges on the value of EUD. For example, with  $n=1$  the EUD is equal to the mean dose, while, when  $n$  is positive and approaches 0, the EUD approaches the maximum dose.

The cost  $C_{\text{EUD}}$  associated with the EUD was calculated with a quadratic penalty function that for an organ at risk is expressed by the relation

$$C_{\text{EUD}} = H(\text{EUD}, \text{EUD}_0) \left( \frac{\text{EUD} - \text{EUD}_0}{\text{EUD}_0} \right)^2 \quad (2)$$

where  $EUD_0$  is a user-defined parameter and  $H$  is the Heaviside step function defined as follows:

$$H(EUD, EUD_0) = \begin{cases} 1, & EUD > EUD_0 \\ 0, & EUD \leq EUD_0 \end{cases} \quad (3)$$

In the definition of cost functions (see details in Appendix A), the planning aims for the PTV were expressed in terms of DVH points only. Large weighting factors were associated with these objectives, to ensure that the dose reduction in the rectal wall did not cause underdosage in the target volumes. For both PTVs, at least 99% of the volume should receive 95% of the prescribed dose and two objectives were also set to limit the maximum dose. The EUD-based cost function of Eq. (2) was applied to reduce the dose in the rectal wall. Finally, a planning aim was associated also with the femoral heads, in order to facilitate the creation of a conformal plan, and to the non-specified normal tissues, to avoid ‘hot spots’ outside the target volumes. In agreement with our clinical practice, no constraints were set for the bladder. Previous studies carried out at our institution showed large variations in bladder volumes in successive CT scans [17] and did not show statistically significant correlations between DVH points and genitourinary complications [2]. Finally, DVH thresholds currently proposed (e.g. in RTOG protocol p-0126) are easily satisfied with IMRT when a conformal dose distribution is achieved.

In order to study the influence of the value of  $n$  on different aspects of the dose distribution, we started by testing one technique and one cost function as a reference. This reference technique is a simultaneous boost approach [3], where five beams with predefined directions (36, 100, 180, 260 and 324 degrees) are applied to irradiate the two PTVs. The prescribed dose is 68 Gy for PTV(1–2) and 78 Gy for PTV2, the maximum dose allowed in the PTVs is 105% and 107% of 78 Gy for PTV(1–2) and PTV2, respectively. As the treatment course lasts for 39 sessions, the dose per fraction is 1.74 Gy for PTV1 and 2 Gy for PTV2. No more than 10% of the femoral head was allowed to receive 52 Gy or more [15]. Details of the cost function are provided in Appendix A.

This technique was applied to all 5 patients, and 5 values of  $n$  were tested (0.08, 0.12, 0.25, 0.5 and 1).  $n=0.08$  was chosen as the lowest value after preliminary tests showing that a further decrease caused no changes in the dose distribution. The value proposed by Burman et al. [4] ( $n=0.12$ ) is still commonly used in the literature, although recently a multicenter study found that  $n=0.26$  and  $=0.06$  are the best values to describe mild and severe rectal wall complications and only severe complications, respectively [24]. The applicability of these results to the IMRT domain will be addressed in the discussion.

As in every optimisation problem, it is important to understand which properties of the final dose distribution are directly controlled by specific parameters of the cost

function, which are not directly controlled but result from other planning objectives and which, finally, are the inevitable result of ‘hard constraints’ such as the PTV definition or the patient anatomy. We therefore tested also the following alternative dose prescriptions and cost functions:

### 2.2.1. Change in dose prescription

The prescription dose was increased by about 10% and set to 86 Gy for PTV2 and 75 Gy for PTV(1–2). The planning objectives relative to both PTV and to the maximum dose in non-involved normal tissues were rescaled accordingly.

### 2.2.2. Changes in cost function

Three different changes were tested:

- (1) The maximum dose allowed in the PTV was increased to 115 and 117% for PTV(1–2) and PTV2, respectively. The maximum dose allowed to the non-involved normal tissues remained fixed at 107% of the prescribed dose for PTV2. The aim of this test was to assess the relation between the maximum dose in the PTV and the maximum dose in the rectal wall.
- (2) The minimum dose in PTV(1–2) was increased from 64.6 to 70 Gy, to test a situation where it is more difficult to satisfy currently used dose–volume thresholds for rectal wall toxicity (see next paragraph for details).
- (3) The maximum dose in all tissues, except a 2 cm expansion of PTV1, was limited to 50 Gy to set more stringent demands on dose conformality, to see how this restriction affects the rectal wall volume receiving medium to low doses.

Each of these tests was performed on three patients and for three values of  $n$  (0.08, 0.25 and 1).

Finally, further tests showed that alternative beam arrangements, with three or seven beams, did not provide more insight on the properties of EUD-based optimisation for prostate cases, so the results of these tests will not be presented.

In each optimisation run, the aim was to find the minimum EUD value for the rectal wall that still satisfies the requirements for dose coverage of the targets and dose sparing of the other normal tissues.

The cost function was therefore defined in such a way that, at the end of the optimisation, only the costlet related to the rectal wall had a value different from 0, while all the other costlets were zero or at least 2 orders of magnitude smaller than the costlet of the rectal wall. To reach such a situation, in all plans a value of  $EUD_0$  was selected that could never be achieved (10 Gy), combined with a very low weight (0.001): the value of  $EUD_0$  guaranteed that the relevant costlet did never reach zero, while the low weight ensured that this planning objective did not override

337 the other objectives. This choice of EUD<sub>0</sub> and weight  
 338 allowed to run all plans with exactly the same cost function  
 339 except for the value of *n*, the parameter under investigation.

340 The treatment planning system (TPS) used in this study  
 341 was Pinnacle, version 7.1a (Philips Medical Systems, Best,  
 342 The Netherlands), with the Orbit IMRT module (RaySearch  
 343 Laboratories, Stockholm, Sweden). The difference between  
 344 the current clinical version of the TPS and the one we used  
 345 for this study is only in the use of EUD in the optimisation  
 346 module: all other issues, e.g., the use of dose calculation  
 347 algorithms during the optimisation, optimisation libraries  
 348 and even the equations to calculate the cost are the same as  
 349 in the version available for clinical use. As applied in most  
 350 commercial treatment planning systems, Pinnacle uses a  
 351 gradient algorithm to find the minimum of the cost function.  
 352 This approach is unable to avoid local minima, raising  
 353 the question how much this issue represents a problem in the  
 354 optimisation of clinical plans. This subject has been studied  
 355 by several authors [14,18,25,29,31], suggesting that the  
 356 presence of local minima is unlikely to cause clinically  
 357 relevant differences when realistic situations are considered.  
 358 A recent paper by Zhang et al. [34] concluded that  
 359 EUD-based optimisation of clinical cases is not affected  
 360 by local minima provided that uniform initial beamlet  
 361 intensities are chosen, which is the case in our study.

362 We analysed the results of fluence optimisation,  
 363 performed on 5 mm × 5 mm elementary beams (beamlets).

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 365 **2.3. Evaluation of the results**  
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367 For PTV2 and PTV(1–2), the mean dose and the dose  
 368 received by 99% of the volume (*D*<sub>99%</sub>) were evaluated. For  
 369 the rectal wall, we first assessed the relative volume  
 370 receiving 30, 45, 60 and 70 Gy or more (*V*<sub>30</sub>, *V*<sub>45</sub>, *V*<sub>60</sub> and  
 371 *V*<sub>70</sub>, respectively). Then, to compare the overall dose  
 372 distributions in the rectal wall, an additional set of EUD  
 373 values was calculated (EUD<sub>ev</sub>), by using a single value of  
 374 the volume dependence parameter (*n*<sub>ev</sub>) for the results of  
 375 different optimisation runs.

376 Finally, the results were evaluated with respect to recent  
 377 data about rectal wall toxicity:  
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 380 **2.3.1. Dose–volume thresholds**

381 Based on the data available in the literature, two sets of  
 382 dose–volume thresholds were identified to assess the risk for  
 383 rectal wall damage; the first for moderate (Grade ≥ 2) and  
 384 the second for severe (Grade ≥ 3) complications. For  
 385 moderate complications, cut-offs were set at 40, 60 and  
 386 70 Gy, with corresponding volume thresholds of 60% [11],  
 387 40% [13] and 25% [10,11] of the volume. For serious  
 388 complications, a set of thresholds was defined based on  
 389 the study carried out at our institution by Boersma et al. [2].  
 390 These authors recommended three dose thresholds at 65, 70  
 391 and 75 Gy with corresponding values of 40, 30 and 5% of  
 392 the volume.

2.3.2. Maximum dose in the rectal wall (*D*<sub>max</sub>)

393 This parameter was found to be a very good predictor of  
 394 complications, although no cut-off value was proposed [28].  
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396 To analyse the dose outside the target volumes and the  
 397 rectal wall, the conformity index (CI) was calculated [12],  
 398 taking 95% of the prescribed dose to PTV1 as the reference  
 399 value. Furthermore, the volume of the non-specified normal  
 400 tissues receiving 50 Gy or more (EXT<sub>50</sub>) was compared and  
 401 the distance between the 70 and 30 Gy isodose lines was  
 402 measured in the slice of the isocentre in the posterior  
 403 direction for the plans with *n* = 1, 0.25 and 0.08.  
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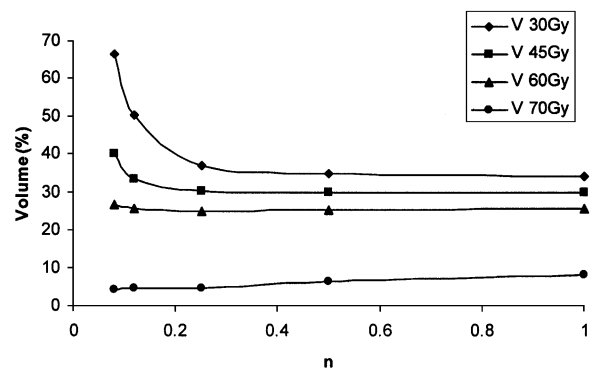
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 408 **3. Results**  
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410  
 411 **3.1. Reference technique**

412 For all patients and all values of *n*, the final dose  
 413 distributions satisfied the requirements set by the cost  
 414 function. At the end of the optimisation, only the costlet  
 415 associated with the EUD of the rectal wall was  
 416 significantly different from zero, representing 98 to 99%  
 417 of the residual cost.

418 For both PTV2 and PTV(1–2), the variations of *D*<sub>99%</sub>  
 419 associated with different values of *n* were within 1% for all  
 420 patients. The DVHs of PTV2 were essentially identical over  
 421 the whole dose range, and the differences in mean dose lower  
 422 than 0.5 Gy. For PTV(1–2), small differences were found in  
 423 the dose range between 65 and 70 Gy, that translated in mean  
 424 dose differences always smaller than 1 Gy.

425 When the volumes of rectal wall irradiated at specific  
 426 dose levels were compared (see Fig. 1), the differences in  
 427 *V*<sub>30</sub> between the distributions related to *n* ≤ 0.12 and the  
 428 remaining ones ranged from 15 to 45%. For increasing  
 429 doses, the differences decreased, and, for *V*<sub>45</sub>, they varied  
 430 from patient to patient between 5 and 10%. For all  
 431 patients there was a point at about 60 Gy where the  
 432 DVH-curves crossed each other; between 55 and about  
 433 65 Gy all solutions produced very similar DVHs (see Fig. 2)



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 445 Fig. 1. Rectal wall volume receiving at least 30, 45, 60 and 70 Gy as a  
 446 function of the value of *n* for the reference technique (data for patient 4).  
 447 The closed symbols represent the values of *n* actually tested in our study,  
 448 while the lines are the result of an interpolation.

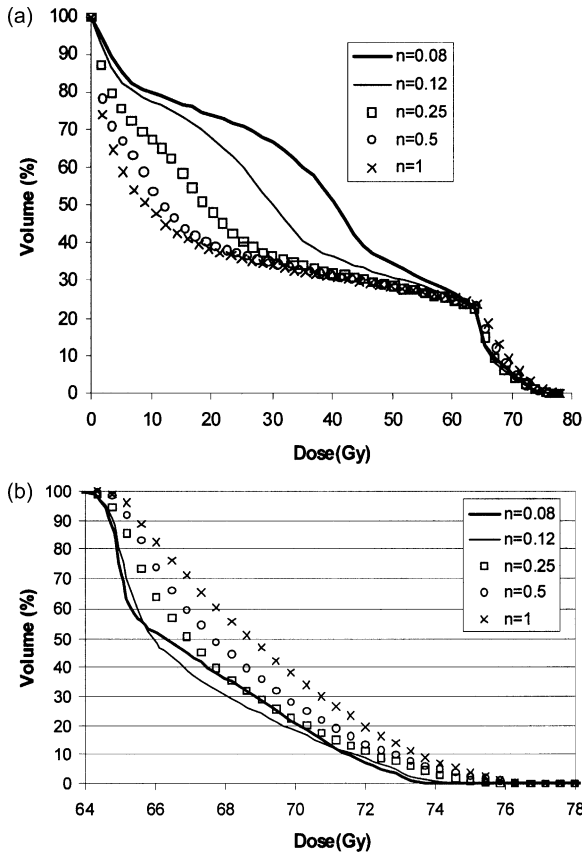


Fig. 2. (a) DVH-curves of the rectal wall for patient 4 associated with the reference technique and five values of  $n$ . (b) DVH-curve of the overlap region between the rectal wall and PTV(1–2) for the reference technique and different values of  $n$ .

as an example). The upper value of this interval (65 Gy) corresponds to the planning prescription concerning the coverage of PTV(1–2) (see Appendix A), which always had a geometrical intersection with the rectal wall. The values of  $V_{70}$  were always between 1.5 and 5% for  $n=0.25, 0.12$  and  $0.08$  and between 2 and 9% for  $n=1$  and  $0.5$ .

Looking at the overlap region between PTV(1–2) and the rectal wall (Fig. 2b), one can see that the minimum dose (around 64.5 Gy) did not depend on  $n$ , as it was determined by the cost function. A value of  $n \leq 0.12$  resulted in smaller volumes irradiated with a dose of 65 Gy or more when compared with the solutions for  $n > 0.12$ .

In the comparison of the EUD values of the rectal wall, two kinds of variation were found:

- *Inter-patient variations.* When data obtained from different patients but with the same value of  $n$  were compared (see values by rows in Table 1), the differences between the values of the EUD at the end of the optimisation were always within 5 Gy. No correlation was found between the values of EUD and the volume of rectal wall encompassed by PTV(1–2).
- *Intra-patient variations.* When the dose distributions associated with the same patient but obtained by optimising the dose distribution with different values of

Table 1  
EUD values in Gy of the rectal wall at the end of the optimisation for the reference technique for the five patients included in the study and for different values of  $n$

$n$	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
0.08	58.5	60.8	57.9	59.8	58.8
0.12	54.7	57.3	54.1	57.0	54.8
0.25	45.2	48.8	45.5	48.7	45.4
0.5	33.0	37.6	34.4	37.3	33.3
1	20.8	25.0	24.0	25.0	20.3

$n$  were compared the changes were much more dramatic, being more than 30 Gy for the two extremes values of  $n$  (1 and 0.08) (see Table 1). These large differences were due to two different reasons: first, the dose distributions in the rectal wall were indeed different, and, second, the EUDs were calculated with different values of  $n$ , i.e., the value used in each optimisation run. When  $EUD_{ev}$  values were compared (see in Table 2 the data for patient 2 as an example), using the parameter proposed by Burman and colleagues ( $n_{ev}=0.12$ ) the differences were always smaller than 4 Gy, and they were reduced to less than 2 Gy for the three solutions associated with  $n \leq 0.25$ . When  $n_{ev}$  was set to 0.25, all solutions except one showed  $EUD_{ev}$  values within 2 Gy. Finally, when the mean dose was calculated ( $n_{ev}=1$ ), the differences between the results obtained with the two extreme values of  $n$  increased to 13 Gy.

When the dose distributions of the rectal wall were evaluated with respect to published data related to side effects, no violations were found for all thresholds for both moderate and severe complications, although the solutions with  $n=0.08$  were in two cases close to the threshold of 60% of the volume receiving 40 Gy or more. For all patients, the maximum dose in the rectal wall increased for increasing values of  $n$ , being in the range of 73–74 Gy for  $n=0.08$  and 76–77 Gy for  $n=1$ . For each individual patient, the difference in  $D_{max}$  between the solutions associated with the two extremes values of  $n$  (1 and 0.08) ranged from 1.5 to 4.0 Gy.

With regard to the dose in other normal tissues and the isodose distributions (see Table 3), the solutions associated with higher values of  $n$  had a higher CI, that translated into a 10–20% increase of the volume receiving 64.6 Gy or more,

Table 2  
Distribution of  $EUD_{ev}$  values (Gy) for patient 2, for the reference technique, when three values of  $n_{ev}$  are used to evaluate the results of the optimisation obtained with different values of  $n$ . Note that the second column shows the same values as presented in Table 1 for this patient

$n$	$n_{ev}=n$	$n_{ev}=0.12$	$n_{ev}=0.25$	$n_{ev}=1$
0.08	60.8	57.8	51.3	38.3
0.12	57.3	57.3	49.6	33.7
0.25	48.8	57.4	48.8	28.5
0.5	37.6	57.8	49.0	25.8
1	25.0	58.7	49.6	25.0

Table 3

Values of the CI, the volume receiving 50 Gy or more (EXT<sub>50</sub>) and the distance between the 70 and the 30 Gy isodose lines in the posterior direction ( $d_{70-30}$ ) for the reference technique (see also Fig. 3). The value of EXT<sub>50</sub> is in cm<sup>3</sup>, the distance in cm. The number in parentheses is the value of  $n$  used in the optimisation

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
CI(0.08)	1.56	1.54	1.59	1.56	1.58
CI(0.25)	1.61	1.55	1.59	1.60	1.60
CI(1)	1.86	1.75	1.99	1.72	1.72
EXT <sub>50</sub> (0.08)	565	433	562	443	826
EXT <sub>50</sub> (0.25)	590	449	564	457	829
EXT <sub>50</sub> (1)	795	487	1039	620	1134
$d_{70-30}$ (0.08)	6.8	5.5	7.3	3.2	7.5
$d_{70-30}$ (0.25)	3.2	2.1	2.4	1.7	2.5
$d_{70-30}$ (1)	2.4	0.9	2	1.2	1.9

when the solutions with  $n=1$  and 0.08 were compared. Also, the normal tissue volume receiving 50 Gy or more (EXT<sub>50</sub>) increased for increasing values of  $n$ , in one case (patient 3) by a factor of almost 2.

Looking at the transversal dose distributions (see Fig. 3), the anterior part is very similar for all solutions, while significant differences appear in the posterior part, where an increasingly steep dose gradient was found in the AP direction for increasing values of  $n$  (Table 3). On the other hand, the dose gradient in the LR direction was shallower for increasing values of  $n$ .

3.2. Alternative dose prescription and cost functions

We present the results only for the rectal wall because, similar to the situation for the reference technique,

the choice of  $n$  had very little effect on the dose distribution for the PTVs.

3.2.1. Change in dose prescription

Increasing the prescription dose from 78 to 86 Gy caused a displacement of the DVH-curves for the rectal wall along the dose axis, without noticeable changes in its shape. For one patient, the resulting dose distributions violated VT<sub>75</sub> for all  $n$  values, while for another patient VT<sub>40</sub> was violated when  $n$  was set to 0.08.

3.2.2. Change in cost functions

By allowing the maximum dose in the targets to be as high as 115 and 117% of the prescribed dose in PTV(1–2) and PTV2, respectively, the typical increase of the maximum dose in these volumes was between 4 and 5 Gy. The maximum dose in the rectal wall increased in six out of nine cases with respect to the reference technique, but always by less than 1 Gy. In the remaining three cases, it slightly decreased, up to 1 Gy.

Increasing the minimum dose in PTV(1–2) up to 70 Gy resulted in an increased dose in the rectal wall in the dose range from 30 Gy to the maximum dose. The DVH for different values of  $n$  still cross each other at a point close the minimum dose in PTV(1–2), i.e., 70 Gy. When the volume receiving a given dose was correlated with the value of  $n$ , the resulting curves are similar to those for the reference technique (Fig. 4). In two out of three cases, the solution for  $n=0.08$  violated the dose–volume threshold at 40 Gy.

Restricting the allowed dose in the non-involved normal tissues always caused an increase of the EUD of the rectal wall. The plans associated with  $n=0.08$  and 0.25

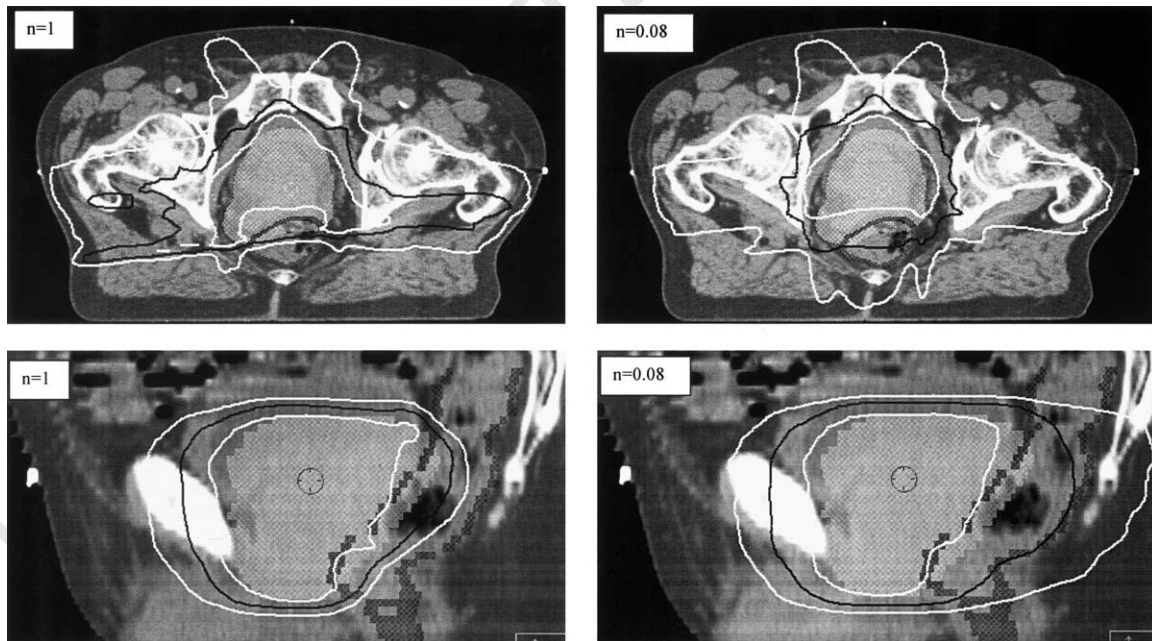


Fig. 3. D dose distribution of the reference technique in a transversal and in a sagittal plane for patient 1 for  $n=1$  and 0.08. The three solid lines represent the 70, 50 and 30 Gy isodose curves. The areas in light and dark grey show PTV1 and the rectal wall, respectively.

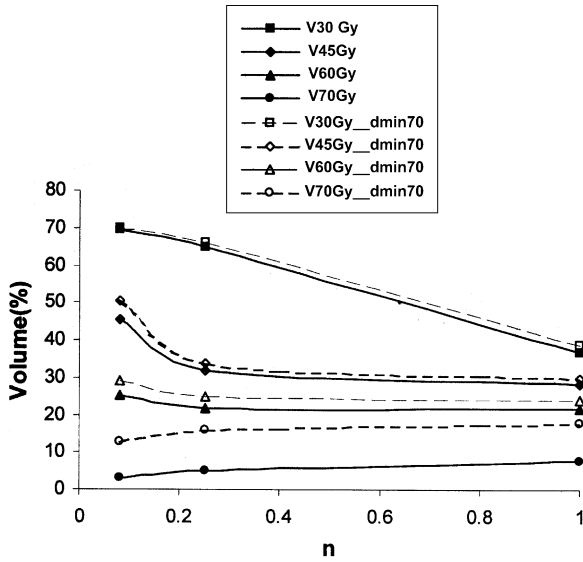


Fig. 4. Rectal wall volume receiving at least 30, 45, 60 and 70 Gy as a function of the value of  $n$  for the reference technique and for the plans with 70 Gy minimum dose in PTV(1–2) (data for patient 5).

showed an increase of the EUD of less than 2%, while for  $n = 1$  the increase was at least 10%.

#### 4. Discussion

We analysed the sensitivity of the optimisation process for IMRT plans of prostate cancer with respect to the values of the volume parameter  $n$  in the EUD for the rectal wall. This analysis is needed before introducing EUD-based cost functions in clinical practice, even when the EUD is considered a reliable radiobiological index and not just a tool to drive the optimisation. The values of  $n$  proposed so far, based on clinical studies, not only vary over a range but also were obtained from patients treated with CRT, and thus the applicability of these results to the IMRT realm is not granted. One should therefore analyse how a change in the radiobiologically correct value of  $n$  would affect the optimisation results.

In our study, the EUD proved to be an effective tool to easily obtain a large variety of dose distributions by changing just one parameter of the cost function. Having tested a wide range of  $n$  values and different irradiation techniques, dose prescriptions and cost functions, the results are an overview of the achievable dose distributions, for a specific set of PTV definitions and minimum dose prescriptions to the target volumes.

A general property of the results was that, by looking at the purely dosimetric data (e.g.,  $V_{30}$ ,  $V_{45}$ ,  $V_{60}$ ,  $V_{70}$  and  $D_{max}$ ), there was not one solution better than the others for all parameters. In the comparisons of 3D-CRT vs. IMRT [1,5,7,16,33], the latter technique was often superior to the former in the whole dose range and for both the target and OARs. The primary cause of this superiority was

the enormous differences in the degrees of freedom available for the two approaches. Our comparison involves a series of solutions all obtained with IMRT, having the same number of degrees of freedom. The results are a series of trade-offs about the irradiation of different organs at risk and/or different dose distributions within an organ at risk. As a consequence, the results are more difficult to interpret and a complete knowledge of the dose–response relation, or a clinical judgment, is needed to decide which solution is preferable.

#### 4.1. 3-D dose distribution in the PTVs and in the rectal wall

The minimum dose in the PTVs was not affected by changes in the value of  $n$ , because achieving an adequate dose coverage while limiting the overdosage was given a higher priority in the cost function than the reduction of the dose in the rectal wall (see Appendix A). With looser constraints on PTVs minimum dose, the resulting dose distributions would not only be determined by the value of  $n$ , but also by the weighting factors set for the PTVs and the rectal wall. By setting the weighting factors in such a way that the PTVs coverage was always the same, we could focus on the influence of  $n$  on the end results.

The small impact of  $n$  on PTV(1–2) mean and maximum dose was not determined by the cost function definition. The cost function allowed a difference between minimum and maximum dose in PTV(1–2) as large as 17.3 Gy (see Table A1) for the reference technique. As no objectives were set to raise the dose in PTV(1–2) above the minimum, the dose in this volume would increase only if this resulted in a lower cost value, i.e., in a lower EUD of the rectal wall. The fact that no dose increase was observed in PTV(1–2) suggests that, regardless of the  $n$  value, raising the dose in this target volume could not improve the rectal wall sparing.

The dose distributions in the target volumes were not very sensitive to the PTV definition, given the high priority on PTV coverage. PTV1 was defined by expanding the GTV by 10 mm, which is a margin quite commonly applied. We did a further test on one patient, expanding the GTV by 15 mm in the posterior direction to increase the overlap volume, while the margins in all other directions were kept at 10 mm. Even then, the choice of  $n$  did not cause significant differences in PTV(1–2) dose distributions.

With respect to the rectal wall, the results showed how the choice of values of  $n$  translated always in a balance between the rectal wall volume receiving a dose lower than 50 Gy and a dose higher than 65 Gy (all DVH-curves being very similar between 55 and 65 Gy). The higher dose value (65 Gy) was due to the dose prescription and the overlap between rectal wall and PTV(1–2) and. In fact, 15–20% of the rectal wall was within PTV(1–2), which should receive at least 64.6 Gy. As a consequence, for a good

785 coverage of PTV(1–2), at least this volume percentage of  
 786 rectal wall should receive 64.6 Gy or more.

787 For any pair of DVH-curves, the curves cross, at  
 788 approximately 60 Gy. This means that we could not  
 789 tell which solution was best from a dosimetric analysis  
 790 alone.

791 In the region where the rectal wall overlaps with  
 792 PTV(1–2), the choice of  $n$  had a strong influence on the  
 793 relative volume receiving doses higher than 65 Gy  
 794 (Fig. 2b). The reason why these differences were not  
 795 evident in the DVH of the rectal wall (Fig. 2a) was that  
 796 the overlap represents only 15–20% of the total volume of  
 797 the organ.

800 *4.2. Dose in other normal tissues and isodose distributions*

801 The choice of  $n$  had a marked influence on the shape of  
 802 isodose curves and, in particular, on the dose gradient in  
 803 the posterior direction. The large differences shown in  
 804 Fig. 3 were obtained because different values of  $n$  had  
 805 opposing effects on the position of both high and low dose  
 806 levels. When  $n=0.08$ , the optimisation process tends to  
 807 move the high dose region (e.g. the 70 Gy isodose curve)  
 808 as far as possible from the rectal wall, thus moving the  
 809 70 Gy isodose curve in the anterior direction. At the same  
 810 time, there was no incentive in reducing the volume of  
 811 rectal wall receiving lower doses, which was the reason  
 812 why the dose gradient in the posterior direction was  
 813 shallow. On the contrary, for  $n=1$ , high and low doses  
 814 are equally penalised in the optimisation process, and  
 815 therefore the 70 Gy isodose level is more posterior,  
 816 because this allows a reduction of the mean dose. This  
 817 is also the reason why the 30 Gy isodose curve moves in  
 818 the anterior direction.

819 An important consequence of different widths of the dose  
 820 gradient in the anterior–posterior direction can be the  
 821 sensitivity of these solutions to set-up errors and organ  
 822 motion, particularly in the AP direction. It is therefore  
 823 possible that, after taking into account the effect of these  
 824 uncertainties, the differences between the solutions are  
 825 different from those depicted in the DVH comparison of the  
 826 static solution.

827 It is also evident (Table 3) that the solutions associated  
 828 with a steep dose fall in the AP direction showed a  
 829 significant increase of the volume irradiated at both 64.6 Gy  
 830 or more (shown by the increase of the CI) and 50 Gy or  
 831 more. This happened because, for high values of  $n$ , the dose  
 832 gradient was considerably shallower in the LR direction (see  
 833 Fig. 3), thus producing a dose distribution with a higher CI.  
 834 As a consequence, for high values of  $n$ , the limiting factor  
 835 for a further decrease of the EUD of the rectal wall is likely  
 836 to be not the minimum dose to the PTV, but rather the  
 837 dose to the femoral heads and to the other non-involved  
 838 normal tissues.

841 *4.3. Alternative dose prescription and cost functions*

842 By combining the results of all dose prescription values  
 843 and cost functions, we could observe that:

- 844 – Changing the value of  $n$  in the EUD optimisation for the  
 845 rectal wall always results in DVH-curves that cross each  
 846 other, therefore requiring a clinical judgment for  
 847 selecting the best plan. With the PTV definition and  
 848 requirement on target coverage used in this study,  
 849 the crossing point corresponds with the minimum dose  
 850 in PTV(1–2).  
 851 – The value of  $n$  determines the shape of the DVH-curve  
 852 for the rectal wall, which remains the same after dose  
 853 escalation and also when different requirements on the  
 854 minimum dose in the PTV are set. The EUD minimisation  
 855 therefore does not guarantee that specific DVH  
 856 threshold will be satisfied. This is one of the reasons why  
 857 the combined use of EUD and DVH-points might be  
 858 beneficial in some cases [30].  
 859 – In most cases the treatment techniques ended up in dose  
 860 distributions for the rectal wall below the thresholds  
 861 associated to a high risk of complication. According to  
 862 our results, the dose–volume threshold at 40 Gy for  
 863 moderate complications is the most likely candidate to be  
 864 violated in difficult cases, but only if  $n \leq 0.08$  is used.  
 865 – The maximum dose, although not explicitly controlled  
 866 by the EUD, remained quite stable even for  $n=1$  and  
 867 when hot spots in the target volumes up to 117% were  
 868 allowed. This shows that the maximum dose in the PTV  
 869 and in the rectal wall were essentially two independent  
 870 variables of the optimisation.  
 871 – The optimisation process is almost insensitive to the  
 872 value of  $n$  between 50 and 65 Gy. Above 65 Gy,  
 873 the influence of  $n$  on the DVH-curve is small except  
 874 for the solution with  $n=1$ , that leads to a significantly  
 875 higher irradiated volume.  
 876 – The planning objectives usually applied to the non-  
 877 involved normal tissues allowed for a large variability of  
 878 the rectal wall volume irradiated at doses below 45 Gy.  
 879 With more strict demands in terms of conformality  
 880 (see Section 3.2.2), the solutions with a higher value of  $n$   
 881 showed significant changes. This result, combined with  
 882 the increase of the CI and  $V_{50}$  for the reference technique  
 883 with respect to the solutions with  $n \leq 0.25$ , showed that  
 884 with a large value of  $n$  there is a conflict between  
 885 reducing the EUD in the rectal wall and limiting the dose  
 886 in other normal tissues.

887 *4.4. Use of the currently proposed values*  
 888 *of  $n$  in the optimisation*

889 The values of  $n$  resulting from the analysis of clinical  
 890 data range from 0.06 to 0.24 [8,24]. Given the different  
 891 treatment techniques, scoring methods, and perhaps defini-  
 892 tion of the rectum used to obtain these values, we have to

look at them as useful suggestions about a reasonable value of  $n$  rather than precise estimates.

In this perspective,  $n=0.12$  and  $0.06$  yield almost the same results of the optimisation process. The use of  $n=0.06$  would obtain a slightly lower maximum dose, of about 1 Gy, while  $n=0.12$  would lead to a small reduction of the rectal wall volume irradiated with a dose of 40 Gy or less. In some cases, with  $n \leq 0.12$  it might be difficult to comply with the currently used dose–volume thresholds at 40 Gy.

By taking  $n=0.26$ , the volume irradiated in the 40 Gy range could in some cases be reduced by up to 10%. The price to pay for this reduction is an increased dose to the non-involved normal tissues.

It is therefore important to check whether the planning objectives for the normal tissues are strict enough. A maximum dose objective to the normal tissue is often enough to guarantee a good dose conformality as long as the optimisation is aimed at reducing the rectal wall volume irradiated at high doses only. With  $n=0.26$ , the maximum dose constraint is likely not to be sufficient, because the optimisation will try to decrease the rectal wall volume irradiated in the 40–50 Gy dose range at the expense of other normal tissues.

### 5. Conclusions

EUD-based optimisation is an effective method to control the dose distribution in the rectal wall over the whole dose range and to explore the possible results of treatment planning optimisation for prostate cancer by simply changing the volume parameter.

For cost functions and dose prescriptions commonly applied in clinical practice, different values of the volume parameter are associated with different tradeoffs between doses higher and lower than 65–70 Gy.

For most techniques used in this study, the solutions associated with  $n$  values up to 0.25 produced similar dose distributions in the rectal wall for doses above 45 Gy, that complied with the dose–toxicity thresholds we analysed.

The choice of a specific value of  $n$  in the optimisation requires an analysis of its effect not only on the dose distribution for the rectal wall, but also on other aspects such as the dose to the non-involved normal tissues and the value of all the planning objectives included in the cost function with their relative weights.

### Acknowledgements

The authors wish to thank Luc Bos for commenting the drafts of this paper. Johan Löf and Kjell Eriksson from Raysearch Laboratories are acknowledged for the details they provided about the implementation of the cost function in Pinnacle. In this study, a research version of Pinnacle was

used, thanks for the collaboration of our institution, Philips Medical Systems and Raysearch Laboratories. This project was financially supported by The Dutch Cancer Society (NKB Grant NKI 2000-2212).

### Appendix A. Cost function, treatment techniques and dose prescription

The reference technique consisted of 5 beam directions (36, 100, 180, 260 and 324°), of a prescribed dose of 68 and 78 Gy for PTV(1–2) and PTV2, respectively, and of the cost function reported in the table below (Table A1).

A DVH<sub>min</sub> objective is set to guarantee that the volume  $V_1$  receives at least the dose  $D_1$  and the cost is calculated as

$$C = w \frac{1}{N} \sum_{i=1}^N (H(d_i - D_a) - H(d_i - D_1))(d_i - D_1)^2 / D_1^2 \quad (A1)$$

where  $w$  is the weight factor associated with the objective,  $N$  is the number of voxels of the anatomical structure of interest,  $d_i$  the dose associated with the  $i$ th voxel,  $H$  is the Heaviside step function and  $D_a$  is the actual dose level at  $V_1$  in the cumulative dose–volume histogram. This expression holds only for  $D_a \geq D_1$  and the cost is set to 0 when  $D_a \leq D_1$ .

A DVH<sub>max</sub> objective is set to guarantee that the volume  $V_1$  receives at most the dose  $D_1$  and the cost is calculated as

$$C = w \frac{1}{N} \sum_{i=1}^N (H(d_i - D_1) - H(d_i - D_a))(d_i - D_1)^2 / D_1^2 \quad (A2)$$

This expression holds only for  $D_a > D_1$  and the cost is set to 0 when  $D_a \leq D_1$ .

$D_{max}$  is a special case of DVH<sub>max</sub> where  $V_1=0$  and therefore Eq. (A2) becomes

$$c = \frac{1}{N} \sum_{i=1}^N H(d_i, D_1)(d_i - D_1)^2 / D_1^2 \quad (A3)$$

Table A1  
Cost function

Volume	Type of objective	Parameters	Weight
PTV2	DVH <sub>min</sub>	Dose level ( $D_1$ ): 95% of the prescribed dose; volume level ( $V_1$ ): 99%	90
PTV(1–2)	DVH <sub>min</sub>	$D_1$ : 95% of the prescribed dose $V_1$ : 99%	90
PTV2	$D_{max}$	$D_1$ : 107% of the prescribed dose	90
PTV(1–2)	$D_{max}$	$D_1$ : 105% of the prescribed dose for PTV2	90
Rectal wall	EUD <sub>max</sub>	EUD <sub>0</sub> = 10 Gy and different values of $n$	0.001
Femoral heads	DVH <sub>max</sub>	$D_1$ : 52 Gy $V_1$ : 10%	50
Ext. contour	$D_{max}$	$D_1$ : 107% of the prescribed dose (83.5 Gy)	90

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