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

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

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

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

2. Methods and materials

2.1. Patient selection, volume definition
and dose prescriptions

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

2.2. Cost functions and treatment technique

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

\[
\text{EUD} = \left( \frac{1}{N} \sum_{i=1}^{N} d_i^{1/a} \right)^n
\]

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 defi-
nition 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–response relationship. 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
formalism 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

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

where \( H(\text{EUD}, \text{EUD}_0) \) is a

function that

accounts for the

dose difference

between the

EUD and the

baseline

EUD. For

example,

when \( \text{EUD} = \text{EUD}_0 \),

the cost

is

zero,

and

when

\( \text{EUD} \) is

significantly

higher or lower than

\( \text{EUD}_0 \),

the cost

increases

quadratically,

providing

a

penalty

for

deviations

from

the

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

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

(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 $n=0.06$ 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 conformity, 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
the other objectives. This choice of EUD\(_0\) and weight allowed to run all plans with exactly the same cost function except for the value of \(n\), the parameter under investigation.

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

We analysed the results of fluence optimisation, performed on 5 mm\(\times\)5 mm elementary beams (beamlets).

### 2.3. Evaluation of the results

For PTV2 and PTV(1−2), the mean dose and the dose received by 99% of the volume (D\(_{99\%}\)) were evaluated. For the rectal wall, we first assessed the relative volume receiving 30, 45, 60 and 70 Gy or more (\(V_{30}, V_{45}, V_{60}\) and \(V_{70}\)) respectively. Then, to compare the overall dose distributions in the rectal wall, an additional set of EUD values was calculated (EUD\(_{\text{ev}}\)) by using a single value of the volume dependence parameter (\(n_{\text{ev}}\)) for the results of different optimisation runs.

Finally, the results were evaluated with respect to recent data about rectal wall toxicity:

#### 2.3.1. Dose–volume thresholds

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

#### 2.3.2. Maximum dose in the rectal wall (\(D_{\text{max}}\))

This parameter was found to be a very good predictor of complications, although no cut-off value was proposed [28].

To analyse the dose outside the target volumes and the rectal wall, the conformity index (CI) was calculated [12], taking 95% of the prescribed dose to PTV1 as the reference value. Furthermore, the volume of the non-specified normal tissues receiving 50 Gy or more (EXT\(_{50}\)) was compared and the distance between the 70 and 30 Gy isodose lines was measured in the slice of the isocentre in the posterior direction for the plans with \(n=1, 0.25\) and 0.08.

### 3. Results

#### 3.1. Reference technique

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

For both PTV2 and PTV(1−2), the variations of D\(_{99\%}\) associated with different values of \(n\) were within 1% for all patients. The DVHs of PTV2 were essentially identical over the whole dose range, and the differences in mean dose lower than 0.5 Gy. For PTV(1−2), small differences were found in the dose range between 65 and 70 Gy, that translated in mean dose differences always smaller than 1 Gy.

When the volumes of rectal wall irradiated at specific dose levels were compared (see Fig. 1), the differences in \(V_{30}\) between the distributions related to \(n\leq 0.12\) and the remaining ones ranged from 15 to 45%. For increasing doses, the differences decreased, and, for \(V_{45}\), they varied from patient to patient between 5 and 10%. For all patients there was a point at about 60 Gy where the DVH-curves crossed each other; between 55 and about 65 Gy all solutions produced very similar DVHs (see Fig. 2).

![Fig. 1. Rectal wall volume receiving at least 30, 45, 60 and 70 Gy as a function of the value of \(n\) for the reference technique (data for patient 4). The closed symbols represent the values of \(n\) actually tested in our study, while the lines are the result of an interpolation.](image-url)
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 V70 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 ≤ 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 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 EUDev values were compared (see in Table 2 the data for patient 2 as an example), using the parameter proposed by Burman and colleagues (n = 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 ≤ 0.25. When n = 0.25, all solutions except one showed EUDev values within 2 Gy. Finally, when the mean dose was calculated (n = 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 Dmax 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 1

<table>
<thead>
<tr>
<th>n</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
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<tr>
<td>0.08</td>
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<td>60.8</td>
<td>57.9</td>
<td>59.8</td>
<td>58.8</td>
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<td>0.25</td>
<td>45.2</td>
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<td>33.0</td>
<td>37.6</td>
<td>34.4</td>
<td>37.3</td>
<td>33.3</td>
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<td>1</td>
<td>20.8</td>
<td>25.0</td>
<td>24.0</td>
<td>25.0</td>
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### Table 2

<table>
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<th>n</th>
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<th>n_{ev} = 0.25</th>
<th>n_{ev} = 1</th>
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<td>57.8</td>
<td>51.3</td>
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<tr>
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<td>25.0</td>
<td>58.7</td>
<td>49.6</td>
<td>25.0</td>
</tr>
</tbody>
</table>

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.
when the solutions with \( n = 1 \) and 0.08 were compared. Also, the normal tissue volume receiving 50 Gy or more (\( \text{EXT}_{50} \)) 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 VT75 for all \( n \) values, while for another patient VT40 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\( K \),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\( K \),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 to the minimum dose in PTV(1\( K \),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

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
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<td>CI(0.08)</td>
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<td>1.54</td>
<td>1.59</td>
<td>1.56</td>
<td>1.58</td>
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<td>1.55</td>
<td>1.59</td>
<td>1.60</td>
<td>1.60</td>
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<tr>
<td>CI(1)</td>
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<td>1.75</td>
<td>1.99</td>
<td>1.72</td>
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<td>562</td>
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<td>826</td>
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<tr>
<td>( \text{EXT}_{50}(0.25) )</td>
<td>590</td>
<td>449</td>
<td>564</td>
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<td>829</td>
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<tr>
<td>( \text{EXT}_{50}(1) )</td>
<td>795</td>
<td>487</td>
<td>1039</td>
<td>620</td>
<td>1134</td>
</tr>
<tr>
<td>( d_{70-30}(0.08) )</td>
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<td>5.5</td>
<td>7.3</td>
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<td>7.5</td>
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<td>2.1</td>
<td>2.4</td>
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</tbody>
</table>

Fig. 3. 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.
the purely dosimetric data (e.g., Vprescriptions to the target volumes. 

specific set of PTV definitions and minimum dose 
techniques, dose prescriptions and cost functions, the results were tested a wide range of values and different irradiation 
changes in the value 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 realiti 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., V30, V45, V60, V70 and Dmax), 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. 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 realiti is not granted. One should therefore analyse how a change in the radiobiologically correct value of n would affect the optimisation results.

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

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

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

4.2. Dose in other normal tissues and isodose distributions

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

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

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

4.3. Alternative dose prescription and cost functions

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

- Changing the value of n in the EUD optimisation for the rectal wall always results in DVH-curves that cross each other, therefore requiring a clinical judgment for selecting the best plan. With the PTV definition and requirement on target coverage used in this study, the crossing point corresponds with the minimum dose in PTV(1−2).
- The value of n determines the shape of the DVH-curve for the rectal wall, which remains the same after dose escalation and also when different requirements on the minimum dose in the PTV are set. The EUD minimisation therefore does not guarantee that specific DVH threshold will be satisfied. This is one of the reasons why the combined use of EUD and DVH-points might be beneficial in some cases [30].
- In most cases the treatment techniques ended up in dose distributions for the rectal wall below the thresholds associated to a high risk of complication. According to our results, the dose–volume threshold at 40 Gy for moderate complications is the most likely candidate to be violated in difficult cases, but only if n≤0.08 is used.
- The maximum dose, although not explicitly controlled by the EUD, remained quite stable even for n=1 and when hot spots in the target volumes up to 117% were allowed. This shows that the maximum dose in the PTV and in the rectal wall were essentially two independent variables of the optimisation.
- The optimisation process is almost insensitive to the value of n between 50 and 65 Gy. Above 65 Gy, the influence of n on the DVH-curve is small except for the solution with n=1, that leads to a significantly higher irradiated volume.
- The planning objectives usually applied to the non-involved normal tissues allowed for a large variability of the rectal wall volume irradiated at doses below 45 Gy. With more strict demands in terms of conformality (see Section 3.2.2), the solutions with a higher value of n showed significant changes. This result, combined with the increase of the CI and V90 for the reference technique with respect to the solutions with n≤0.25, showed that with a large value of n there is a conflict between reducing the EUD in the rectal wall and limiting the dose in other normal tissues.

4.4. Use of the currently proposed values of n in the optimisation

The values of n resulting from the analysis of clinical data range from 0.06 to 0.24 [8,24]. Given the different treatment techniques, scoring methods, and perhaps definition 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 conformity 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.

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### 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_{min} objective is set to guarantee that the volume \( V_i \) receives at least the dose \( D_l \) and the cost is calculated as

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

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 \( V_i \) in the cumulative dose–volume histogram. This expression holds only for \( a > D_l \) and the cost is set to 0 when \( D_a \leq D_l \).

A DVH_{max} objective is set to guarantee that the volume \( V_i \) receives at most the dose \( D_l \) and the cost is calculated as

\[
C = w \frac{1}{N} \sum_{i=1}^{N} (H(d_i - D_l) - H(d_i - D_a))(d_i - D_2)^2/D_2^2 \quad \text{(A2)}
\]

This expression holds only for \( a > D_l \) and the cost is set to 0 when \( D_a \leq D_l \).

\( D_{\text{max}} \) is a special case of DVH_{max} where \( V_i = 0 \) and therefore Eq. (A2) becomes

\[
c = \frac{1}{N} \sum_{i=1}^{N} (d_i - D_l)^2/D_l^2 \quad \text{(A3)}
\]

Table A1

<table>
<thead>
<tr>
<th>Volume</th>
<th>Type of objective</th>
<th>Parameters</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV2</td>
<td>DVH_{min}</td>
<td>Dose level (( D_l )): 95% of the prescribed dose; volume level (( V_l )): 99%</td>
<td>90</td>
</tr>
<tr>
<td>PTV(1—2)</td>
<td>DVH_{min}</td>
<td>( D_l ): 95% of the prescribed dose; ( V_l ): 99%</td>
<td>90</td>
</tr>
<tr>
<td>PTV2</td>
<td>( D_{\text{max}} )</td>
<td>( D_l ): 107% of the prescribed dose</td>
<td>90</td>
</tr>
<tr>
<td>PTV(1—2)</td>
<td>( D_{\text{max}} )</td>
<td>( D_l ): 105% of the prescribed dose</td>
<td>90</td>
</tr>
<tr>
<td>Rectal wall</td>
<td>EUD_{max}</td>
<td>EUD = 10 Gy and different values of ( n )</td>
<td>0.001</td>
</tr>
<tr>
<td>Femoral heads</td>
<td>DVH_{max}</td>
<td>( D_l ): 52 Gy; ( V_l ): 10%</td>
<td>50</td>
</tr>
<tr>
<td>Ext. contour</td>
<td>( D_{\text{max}} )</td>
<td>( D_l ): 107% of the prescribed dose (83.5 Gy)</td>
<td>90</td>
</tr>
</tbody>
</table>
References


