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Original paper

Biological optimization of simultaneous boost on intra-prostatic lesions (DILs): Sensitivity to TCP parameters

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ABSTRACT

The aim of this investigation was to explore the potential of biological optimization in the case of simultaneous integrated boost on intra-prostatic dominant lesions (DIL) and evaluating the impact of TCP parameters uncertainty.

Different combination of TCP parameters (TD50 and $\gamma 50$ in the Poisson-like model), were considered for DILs and the prostate outside DILs (CTV) for 7 intermediate/high-risk prostate patients. The aim was to maximize TCP while constraining NTCPs below 5% for all organs at risk. TCP values were highly depending on the parameters used and ranged between 38.4% and 99.9%; the optimized median physical doses were in the range 94–116 Gy and 69–77 Gy for DIL and CTV respectively. TCP values were correlated with the overlap PTV-rectum and the minimum distance between rectum and DIL. In conclusion, biological optimization for selective dose escalation is feasible and suggests prescribed dose around 90–120 Gy to the DILs. The obtained result is critically depending on the assumptions concerning the higher radioresistence in the DILs. In case of very resistant clonogens into the DIL, it may be difficult to maximize TCP to acceptable levels without violating NTCP constraints.

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Introduction

Local recurrence of tumors often happens in highly radio-resistant sub-volumes, such as hypoxic areas or regions that contain a large number of highly resistant clonogens, and this effect was also reported for prostate cancer [1]. In an effort to overcome local recurrence, the delivery of significantly higher doses on these highly resistant intra-prostatic sub-volume (named dominant intra-prostatic lesions, DIL) have been suggested and few clinical application has also been reported [2–5].

In order to explore the limits of this approach, a number of biological evaluations of planning studies have been reported using inverse optimization of static Intensity-modulated Radiotherapy (IMRT) [6] or arc IMRT, including Tomotherapy [7–9].

Recent progress in functional and molecular imaging allows a better definition of DIL [10–12]: several studies have demonstrated that diffusion weighted (DWI) Magnetic Resonance Imaging (MRI) can help differentiate malignant and benign prostatic tissue on the basis of lower Apparent Diffusion Coefficient (ADC) values of carcinoma compared with normal tissue [13–15]. The reduction of diffusion in prostate cancer is believed to be related to the more cellular environment of neoplastic tissue which restricts water molecule movement in extracellular space. The ^{11}Carbon (C)-choline Positron Emission Tomography (PET) may offer some advantages in terms of staging, tumor delineation and the description of biological processes. However, it does not result to be sufficiently validated for this type of application due to lack of studies and to the low resolution [16,17]. The additional value of choline PET-CT for tumor localization and intra-prostatic boosting is still limited compared with DWI MRI, especially when taking cost-effectiveness into account [18]. The combined use of ^{11}C-choline PET-CT and DWI MRI could be beneficial in selected patients but it should be explored [18]. On the other hand, Image-Guided Intensity Modulated Radiotherapy (IG-IMRT) permits to properly manage geometric uncertainties and to improve physical conformation of the dose distribution, even at the tumor sub-volume level [19].

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It is important to note that the selective boosting regions are patient specific but the boosting level is still based on clinical data obtained from the patient population cohort. The question is: how can the boost dose be based on patient specific information for high-risk tumor sub-volumes while avoiding injury to normal tissues? One approach is to use radiobiological models – e.g., tumor control probability (TCP), normal tissue complication probability (NTCP) or an objective function that is a combination of TCP and NTCP directly in the optimization phase through the definition of biological score functions to be minimized during optimization.

Differently from dose-volume-based optimization, biological optimization can efficiently generate dose patterns due to the main following reasons: first, biological objective functions can include individual information concerning tumor control and normal tissue toxicity, while a dose-volume-based optimization pursues a homogeneous dose to the highly inhomogeneous tumor cells organization, possibly including the physiological characteristics of different tumor sub-volumes. Secondly, using radiobiological objective functions, one can directly estimate the optimal biological trade-off between tumor cure and normal tissue complications by using radiobiological integration methods rather than the mere respect of the constraints which are employed in dose-volume-based IMRT optimization.

Biological-based optimization using a dose–response index (for instance: TCP, NTCP or the probability of uncomplicated tumor control, $P+$) started to be finally available in commercial treatment planning systems.

The Raysearch module implemented into the Varian Eclipse-Aria system (v. 8), was recently available on a research workstation at our Institute.

The goal of this work was to assess the potential of radiobiological-based optimization in selective dose escalation of DIL and to evaluate the impact of varying the TCP model parameters on plan quality when performing a simultaneous integrated boost (SIB) on one or more DILs. The availability of the results of our previous investigation using physical dose-volume histogram (DVH) constraints optimization with Tomotherapy [9] was considered as a valid starting point to guide us in properly managing this situation.

Materials and methods

Imaging and contouring procedures

Seven intermediate/high-risk prostate cancer patients were submitted to T2 weighted (T2WI) MRI, T1 weighted (T1WI) MRI and DWI MRI: imaging showed evidence of one DIL in four pts and two DILs in three patients in the peripheral zone. Details of the imaging procedures can be found in our previous work [9]. PTVDIL was obtained by 5 mm isotropic expansion of DIL. The prostate and seminal vesicles were defined as the clinical target volumes (CTV) and the corresponding planning target volume (PTV) was generated by adding 8-8-10 mm anisotropic margins to the CTV in lateral, anterior-posterior and cranial-caudal direction, respectively. Rectum, bladder, urethra and femoral heads were outlined as organs at risk (OAR). The rectum was contoured from the anus to the recto-sigmoid junction and femoral heads + femurs were contoured up to the ischial tuberosities level. A summary of geometric and volumetric data is shown in Table 1.

Table 1
Target and rectum volumes for all patients.

Pt	PTV (cc)	CTV (cc)	PTVDIL (cc)	DIL (cc)	Rectum (cc)	Min distance DIL – rectum (mm)	Overlap PTV – rectum (cc)
1	275.78	114.68	7.55	1.42	55.44	22.00	3.80
2	206.74	78.71	14.36	4.32	93.98	0.70	9.70
3	236.13	99.48	21.37	5.73	65.67	14.00	4.40
4	153.13	47.95	14.45	3.04	60.54	6.50	7.00
5	181.47	64.04	18.08	4.64	62.86	1.00	4.40
6	202.17	65.87	5.52	0.83	64.25	6.20	5.50
7	161.46	48.00	13.40	4.00	67.60	1.20	10.40

Biological models

In the biological optimization and evaluation modules of the Eclipse-Aria software (Varian Inc, v. 8.8), TCP and NTCP models estimate the radiobiological response, given a dose distribution and a fractionation schedule. Currently two of the most common models, the Poisson linear quadratic (Poisson-LQ) and the Lyman-Kutcher-Burman (LKB) models, are included together with an editable parameter database. The TCP calculations are based on the Poisson model combined with the linear quadratic cell survival while the LKB or the relative seriality model may be used for NTCP calculation [20].

The Poisson-LQ model has three radiobiological parameters: TD_{50} is the dose level at which the response probability is 50%; the α/β ratio describes the fractionation sensitivity of the tissue and γ is the slope of the dose–response curve. The γ factor describes the relative increase in TCP for a relative increase in dose. For each tumor voxel, the response probability is:

$$P = \exp\Big(-\exp\Big(e\gamma - \alpha nd - \beta nd^2\Big)\Big) \tag{1}$$

where:

$$\alpha = \frac{e\gamma - \ln\ln 2}{TD_{50}\left(1 + \dfrac{d}{\alpha/\beta}\right)} \tag{2}$$

and

$$\beta = \frac{\alpha}{\alpha/\beta} \tag{3}$$

To take into account the non-homogeneous dose distribution within the tumor (as specifically in our case) the TCP value is then calculated by the weighted product of all the control probabilities P_i corresponding to the volume v_i, receiving a certain dose nd_i:

$$TCP = \prod_{i \in V} P_i^{v_i/V_{\text{ref}}} \tag{4}$$

Here n is the number of fractions, d is the dose per fraction, V_{ref} is the reference volume and v_i the volume of voxel i.

Also NTCP can be calculated with the Poisson-LQ model with the same kind of parameters. The NTCP model further incorporates the modeling of organ seriality, expressed by the parameter S:

$$NTCP = \left(1 - \prod_{i \in V} \left(1 - P_i^s\right)^{v_i/V_{\text{ref}}}\right)^{1/s} \tag{5}$$

The radiobiological response of a serial critical organ is mainly determined by the maximum dose given to the organ since a high dose given to even only a small part of the volume will bring functional deterioration. The radiobiological response of parallel critical structures is not as sensitive to hot spots.

Another option for the NTCP calculation is the LKB model:

$$NTCP = \frac{1}{2}\left(1 - erf\left(\frac{t}{\sqrt{2}}\right)\right) \quad (6)$$

where

$$t = \frac{D_{\text{eff}} - TD_{50}}{m \cdot TD_{50}} \quad (7)$$

and

$$D_{\text{eff}} = \sum_{i=1}^{N}\left(\frac{v_i}{V_{\text{ref}}} D_i^{1/n}\right)^n \quad (8)$$

Here m determines the slope of the response curve and n specifies the volume dependence.

The individual NTCPs for the different organs can be combined into an overall NTCP, and the individual TCPs into a composite TCP for the case when the tumor volume is composed of sub-volumes, as in our case.

The probability of complication free tumor control, ($P+$), is an attempt to combine the individual TCPs and NTCPs into a single measure of the treatment plan quality; the $P+$ objective function combines the probability for tumor control and complication free treatment. The correlation between TCP and NTCP can be selected by the user.

$$NTCP = 1 - \prod_{j \in I_N}(1 - NTCP_j) \quad (9)$$

$$TCP = \prod_{j \in I_T} TCP_j \quad (10)$$

$$P+ = TCP(1 - NTCP) \text{ uncorrelated} \quad (11)$$

$$P+ = TCP - NTCP \text{ fully correlated} \quad (12)$$

Another model is the equivalent uniform dose (EUD), not included in our version optimization tool The EUD was proposed by Niemierko [21] and is defined as the uniform dose distribution giving an equivalent survival fraction to that of a given heterogeneous dose distribution. The EUD concept is advantageous over recording dose to a prescription point because it considers the biological effects of the entire dose distribution. This model is used in Monaco (Elekta) and Pinnacle (Philips) optimization tools.

Radiobiological optimization and evaluation tools

In Eclipse software there are two functionalities: Biological Optimization and Biological Evaluation. Biological Optimization may be used instead of the built-in optimization in Eclipse and includes functionality for optimizing IMRT treatment plans using radiobiological models and employing a combination of biological and physical criteria to produce an ideal fluence map. It requires the same input, i.e. an active plan with a given beam configuration, prescription dose, number of fractions, and produces the same output, i.e. optimized fluence.

The user defines the goals of optimization in the form of physical and/or biological objective functions in order to obtain optimum fluence profiles for each treatment beam and to produce a dose distribution that most closely matches the prescription.

The optimization algorithm can usually find an optimal solution typically in 25–100 iterations; a much larger maximum number of iteration can be set if the system doesn't meet the optimal solution. The software stops the optimization when the change of the composite objective values indicates that an optimal solution has been found. Basically, this is when the change in objective values is less than the tolerance level (corresponding to a change in the objective function).

The progress of optimization shows the rate at which the optimization is converging; the number of iterations, the composite objective function, the hypothetical DVH, the dose distributions and the fluence profiles are continuously updated and shown.

The fluence profiles are used as input data in the subsequent conversion step whereby the treatment plans are made deliverable. During conversion, each treatment beam is divided into a number of small segments using a multileaf collimator (MLC).

Strategies for biological optimization for DIL dose escalation

Based on the assumption that local failures are mainly due to highly radioresistant clonogens within the DILs, we considered different parameters for DILs and for the prostate/seminal vesicles outside DILs (CTV) and studied the impact of varying these parameters on IMRT biological optimization.

To gain an understanding of the effect of misclassifying high-risk tumor as low risk tumor (a loss of sensitivity) we have considered the scenario of very high-risk DILs (considering TD50 = 82.3 Gy or 95 Gy) embedded in a lower-risk tumor PTV (excluding PTVDIL, considering TD50 = 57.3 Gy or 68.3 Gy). The TD50 values were reasonably assessed from literature data as likely ranges for highly and moderately resistant tumors [22,23].

Moreover, two different value of the normalized slope of the dose–response curve around a TCP of 50%, $\gamma 50$ (8 and 4) were used; these values were reported in literature and were chosen as consistent with the hypothesis that inter-patient dose-effect variability is mainly due to the presence of resistant DILs [23]. Different combinations of these parameters were tested with the aim of maximizing TCP while constraining each NTCPs below 5%.

In total, 16 combinations of parameters were obtained when varying TD50 of DIL and CTV and $\gamma 50$; then, 16 optimization were carried out for each patients for a total of 112 plans.

A coplanar 6 MV equi-spaced 9-field arrangement was used for each patients.

The number of fractions was fixed to 28, following our hypofractionated protocol and previous planning investigation based on physical constraints optimization [9]. The biological optimization was performed by assessing the objective function as the product of the probability for tumor control of the DIL and of CTV in the hypothesis that the more radioresistant cells were confined within the DILs. Then, biological and physical constraints for the OARs were defined, based on our experience and on literature evidence. For each biological constraint it was necessary to assign a bound value that represents the maximum probability for a complication which one can tolerate; the dose-volume constraints do not have bounds. A summary of the optimization constraints for OARs is reported in Table 2: the LKB model was used for rectal NTCP [24,25] while the relative seriality model was used for bladder and femoral heads [26].

For PTVDIL and PTV we also introduced a special physical constraint called uniformity in order to limit the standard deviation of dose distribution inside the tumor to 5% in order to avoid dose distributions too far from the clinical experience, excepting the delivery of a higher, possibly homogeneous dose within the DIL. During the optimization it was possible interactively to see, on the views, patient structures, isodoses superimposed on the CT images, the cumulative dose-volume histogram of structures selected, the displays of the score function values and a progress optimization graph to monitor the convergence of the optimization process.

The prescribed doses to DIL and CTV were optimized by the system, with a real biological-based customization of the prescribed dose (i.e.: without any "physical dose prescription").

Table 2
Biological and physical optimization parameters used (LKB model used for rectal end-points; relative seriality model used for bladder and femoral heads).

Organ	End-point	Reference	TD50 (Gy)	*n*	*s*	*m*	γ	α/β	Bound (%)
Anal Canal	Incontinence	Peeters 2006	105	1	–	0.43	–	3	3
Rectum	Late rectal Bleeding ≥ G2	Michalski 2010	76.9	0.09	–	0.13	–	3	5
Bladder	Contracture	Agren 1995	80	–	0.18	–	3	3	5
Femoral Heads	Necrosis	Agren 1995	65	–	1	–	2.7	3	1

The fraction of PTV/PTVDIL and CTV/DIL receiving at least 95% and 98% of the mean dose (V95%, V98%), mean and median dose to PTV and PTVDIL and DVH was used to evaluate the target coverage and the dose distribution. Rectal, bladder, femoral heads NTCP was calculated using the Eclipse biological evaluation.

Results

The risk-adaptive optimization allows one to significantly increase the dose in the high-risk tumor sub-volumes above minimal peripheral dose without violating normal tissue constraints. A summary of the results is reported in Tables 3 and 4 and Figs. 1–4.

The biologically optimized physical dose to the tumor varied from patient to patient: median doses were in the range of 94–116 Gy and 69–77 Gy for DIL and CTV respectively, depending on the parameters applied (Fig. 1).

The median TCP Total (the composite TCPs, referred to DIL + CTV) averaged on the whole group ranged between 65.6% and 98.5% when changing the parameters (Table 3); for all combinations and patients, the TCP Total value ranged between 38.4% and 99.9% and strongly depended on the patient and on the optimization parameters (Fig. 2 and Table 3) while the median TCP Total averaged on individual patient data ranged between 71.3% and 99.9% (Table 4).

TCP values were correlated with both the overlap PTV-rectum and the minimum distance between rectum and DIL (Figs. 3 and 4): in four favorable patients, values were generally larger than 85–90% even in case of very high radioresistance (TD50 = 95 Gy and 68.3 Gy for DIL and CTV respectively) while for three unfavorable patients TCP values were reduced of about 5–20%. For two of these (pt. 2, pt. 7 in Fig. 2) the TCP value decrease was due to greater overlap PTV-rectum and/or smaller distance rectum-DIL. For one of the three unfavorable patients (pt. 4), the dose limiting organs were urethra and bladder despite the relatively large overlap between PTV and rectum; this patient is visible in the Figs. 3 and 4 as it appears well outside from the linear fit.

Higher is the gamma and better are the results in the favorable patients while an opposite effect is seen in the unfavorable patients.

Concerning the sparing of OARs, NTCP constraints for rectum (bleeding), anal canal (fecal incontinence), bladder and femoral heads were respected with median values equal to 3.7%, 3.3%, 0.4% and <0.1% respectively; constraints on urethra were also respected.

Discussion

The concept of “ultra-high” dose escalation to intra-prostatic dominant lesions is based on the Cellini et al. [1] study that revealed that all the observed recurrences in their patient population originated in the primary tumor site. More recently, other investigators [27,28] corroborated this statement. On the other hand, a number of planning studies demonstrated the possibility to safely escalate the dose; typical investigated values ranged between 80 and 90 Gy [5–8] with few other exploring the feasibility of dose as high as 100–150 Gy [3,9].

In particular, in a previous study, we showed the ability of Tomotherapy in safely escalating the dose to 100 Gy to most of the DIL, although some limit was evident for patients with a larger overlap between rectum and PTV [9].

The inherent limitations of dose-volume-based optimization become an issue when it is employed in selective boosting strategies based on biological information that require highly inhomogeneous dose patterns.

It is for instance possible to reduce the large number of dose-volume constraints for each organ at risk by one single NTCP function. Biological models can be used to control the necessary trade-off between high tumor dose and low normal tissue dose, as long as the biologically optimized plan is subsequently evaluated

Table 3
Median % TCP and NTCP values for all parameter combinations (of note: NTCP values for femoral heads were always <0.1%); the ranges of variation for TCP DIL and TCP Total values were also added, considering all patients.

DIL		CTV		TCP DIL	TCP CTV	TCP Total	Rectum (bleeding)	Anal canal (incontinence)	Bladder
TD50	γ50	TD50	γ50						
82.3	8	68.3	8	97.85 (84.36; 99.98)	98.49	96.37 (68.42; 99.55)	3.39	3.26	0.61
82.3	8	68.3	4	97.61 (96.21; 99.96)	92.69	90.48 (77.07; 95.68)	3.28	3.29	0.46
82.3	4	68.3	8	98.07 (82.86; 99.90)	96.20	93.64 (67.41; 99.30)	3.96	3.37	0.75
82.3	4	68.3	4	98.15 (93.94; 99.83)	93.47	90.37 (75.81; 96.75)	4.00	3.26	0.85
95	8	68.3	8	75.34 (52.69; 99.95)	95.02	71.59 (38.35; 99.51)	4.05	3.35	0.46
95	8	68.3	4	77.58 (54.28; 99.94)	84.53	65.58 (39.03; 96.57)	3.98	3.42	0.63
95	4	68.3	8	93.30 (64.65; 99.83)	96.81	83.88 (49.07; 99.03)	4.00	3.37	0.43
95	4	68.3	4	93.60 (78.43; 99.78)	90.50	78.53 (59.46; 95.82)	4.09	3.38	0.73
82.3	8	57.3	8	98.57 (96.46; 99.96)	99.88	98.48 (95.29; 99.89)	3.38	3.17	0.14
82.3	8	57.3	4	98.36 (97.00; 99.97)	99.00	97.34 (94.12; 99.81)	3.13	3.19	0.57
82.3	4	57.3	8	98.44 (93.71; 99.92)	99.86	97.58 (92.40; 99.87)	3.80	3.08	0.46
82.3	4	57.3	4	97.90 (93.86; 99.93)	98.88	94.29 (91.76; 99.44)	4.16	3.09	0.90
95	8	57.3	8	77.39 (58.49; 99.96)	99.50	77.01 (57.71; 99.91)	3.92	3.34	0.27
95	8	57.3	4	77.96 (59.21; 99.98)	96.89	75.22 (56.04; 99.51)	4.12	3.35	0.42
95	4	57.3	8	95.48 (75.77; 99.94)	99.83	92.95 (74.19; 99.88)	3.53	3.29	0.38
95	4	57.3	4	95.08 (80.41; 99.88)	98.29	88.18 (76.20; 99.31)	3.75	3.32	0.56

Table 4
The median % values and the ranges of variation for TCP DIL and TCP Total for different patients.

Pt	TCP DIL	TCP Total
1	99.93 (99.56; 99.98)	99.28 (93.63; 99.91)
2	91.69 (53.31; 97.00)	86.16 (42.36; 96.69)
3	99.84 (99.44; 99.95)	99.43 (94.78; 99.91)
4	81.64 (71.62; 97.96)	71.31 (38.35; 95.29)
5	90.84 (75.34; 98.57)	88.89 (65.58; 98.48)
6	99.90 (99.72; 99.97)	98.84 (92.13; 99.89)
7	96.31 (69.86; 98.57)	84.14 (39.03; 97.58)

in the dose domain. If the resulting dose distribution is not satisfactory it can be tuned further by adding dose-volume functions.

The results reported in current work confirms that biological optimization has the potential to personalize the dose prescription to each single patient with the potential advantage to avoid the delivery of doses higher than the necessary or, at the opposite, to minimize any risk for the adjacent OARs.

In the extreme hypothetic case of very resistant clonogens within the DIL (TD50 according to Nahum et al. [23] equal to 95 Gy for fully hypoxic tumors), our study confirms the possibility of obtaining high TCP values for most patients while the intrinsic geometric limitations reduced the obtainable TCP values for patients whose DILs are very near to the rectum.

Not surprisingly, in one patient the limiting organ was the urethra and secondarily the bladder, although this result could be affected by the "safe" constraints used, likely due to our lack of knowledge of dose-volume relationships for bladder and urethra, as recently reviewed [29]. Anyway, the evidence that severe genitourinary toxicity seems to be mainly correlated to the dose received by the portion of bladder included in the PTV [29], highly correlated with the prescribed dose, suggests that the reduction of the dose in the bladder-PTV overlap with the proposed DIL boost approach, could be of paramount importance in likely reducing the genitourinary toxicity while largely escalating the dose to the DILs for most patients. It is obvious that the large dose escalation to DIL once applied biological optimization should be performed with caution within Phase I controlled studies.

An interesting finding of our investigation is the large variation of TCP (and optimized physical dose) values when applying a TD50 value around 82 or 95 Gy to the DIL; in the second case, there would be some intrinsic limitation in safely escalating the dose to

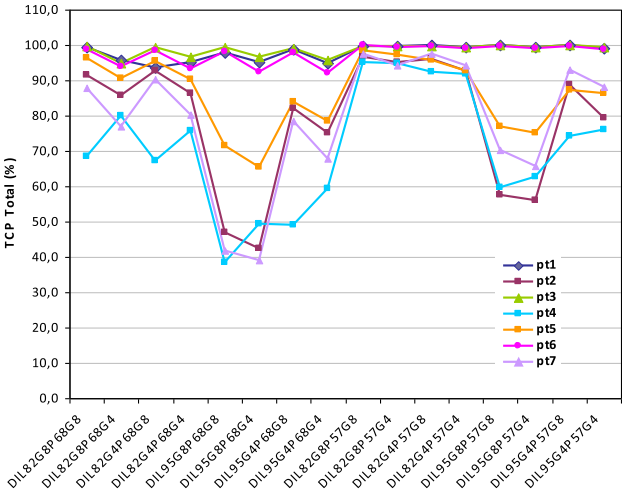

Figure 2. The TCP Total values (referred to DIL + CTV) for all patients with various combinations of all parameters.

"acceptable" TCP values (>80%) to a number of patients, just due to the proximity of the OAR to the DILs. On the other hand a so large value of TD50 has been assessed in radiobiological models postulating highly hypoxic region confined into the DIL, a hypothesis that remains to be demonstrated. The recently reported good results of the biochemical relapse-free survival in cohorts of high-risk patients treated with hypofractionation or with >80 Gy dose [30], conventionally fractionated, seem to suggest that such a high value of TD50 could be unlikely. It is worthy mentioning that, when considering TD50 = 82.3 Gy for DIL, the system was always able to find solutions corresponding to TCP values higher than 85%, excepting one patient where a minimum value of 67% was obtained for one of the parameter combinations; the average TCP values on the seven patients were always larger than 90%, suggesting that the biological optimized simultaneous boost technique on the DIL could be a very efficient technique.

Loss of tumor control due to cold spots is an important question in the context of IMRT where DVHs of targets that abut a critical structure often exhibit a cold dose tail. For instance, cold spots in a very small volume of the tumor would not have a significant effect on the objective value of a physical plan; however, the tumor control probability would be greatly diminished as a result of the

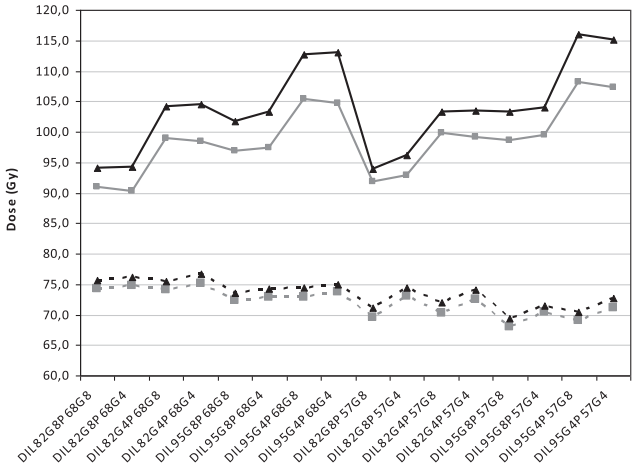

Figure 1. Median physical doses for DIL (black), PTVDIL (gray), CTV (black dotted) and PTV (gray dotted) for all parameter combinations (named as: DIL-TD50-γ; PTV-TD50-γ).

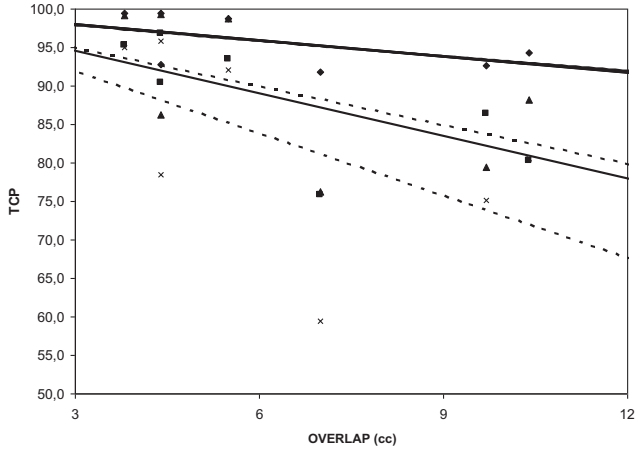

Figure 3. Plot of TCP values vs overlap PTV-rectum volume for γ = 4. The continuous lines correspond to TD50 = 82.3 Gy for the DIL (TD50 = 68.3 and 57 Gy for CTV); the dotted lines correspond to TD50 = 95 Gy for the DIL (TD50 = 68.3 or 57 Gy for CTV).

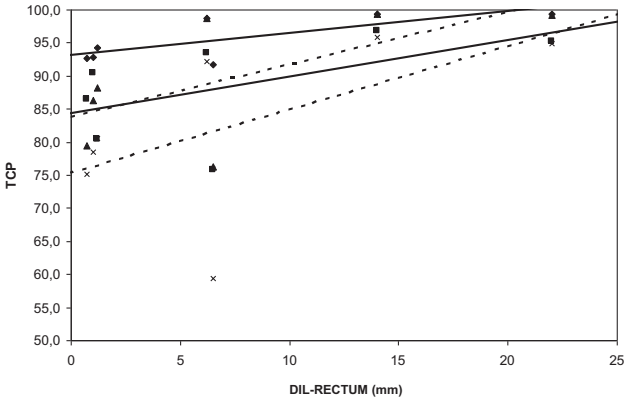

Figure 4. Plot of TCP values vs minimum DIL-rectum distance for $\gamma = 4$. The continuous lines correspond to TD50 = 82.3 Gy for the DIL (TD50 = 68.3 and 57 Gy for CTV); the dotted lines correspond to TD50 = 95 Gy for the DIL (TD50 = 68.3 or 57 Gy for CTV).

cold spot [31]. Biological optimization permits to take into account these estimates directly into the optimization through Equation (4) and to counteract these effects.

An important point of DIL escalation approaches is the reliability of the imaging technique used to identify the intra-prostatic lesions. The combined MRI technique used in our study was reported to be highly sensitive [10,12]. However, the impact of the intrinsic accuracy limitation of imaging techniques (namely sensitivity and specificity) should be investigated in order to understand its influence on DIL dose escalation strategies. The ADC measurements from DWI sequences performed with diffusion gradient value $b = 0$ and 1200 mm^2/s showed that the ADC value measured inside DILs was significantly lower than that inside the prostate [9], consistently with the values recently obtained by Woodfield et al. [10].

An Image-Guided Radiotherapy (IGRT) technique is clearly required in order to accurately deliver these treatments. The accuracy of the IGRT techniques as well as intra-fraction motion should be incorporated into the margin around the DIL. In a previously investigated Tomotherapy scenario it was shown that the margin could difficultly be reduced to less than 5 mm [9]: for this reason we avoided applying a smaller margin for PTVDIL, which could introduce a significant risk of missing the target.

A limit of our study is the relatively low number of patients; however, the group of seven patients investigated in this study may be well considered to be a representative sample of the high-risk population, due to the presence of peripheral prostate cancer lesions. The distance between rectum and DIL in our patients is consistent with data reported in literature for larger populations [2]; the large inter-patient variability of TCP values shows a large variability of patient characteristics from the point of view of dimension and location of DILs. As the purpose of the current sensitivity study is to explore the impact of radiobiological parameters uncertainty on biologically optimized dose escalation to DILs, it is unlikely that the addition of other patients would significantly change the major results of the study.

Conclusions

As conclusion, we can state that the use of biological optimization in IMRT treatment planning holds tremendous promise for improving tumor cell killing while minimizing normal tissue damage. Generally, plan quality for an IMRT plan can be affected by the overall planning time used to generate the plan that depends on many factors including the complexity of the plan and planners' experience. Once becoming familiar with the system, the biologically based optimization allows us to obtain the desirable solution more easily and in a quicker way as compared to the physical optimization planning.

Caution should be taken in choosing appropriate models and/or model parameters and in evaluating the plan obtained when using the biologically based treatment planning system.

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