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On Voxel based Iso-Tumor Control Probability and Iso-Complication Maps for Selective Boosting and Selective Avoidance Intensity Modulated Radiotherapy

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Summary

Voxel based iso-Tumor Control Probability (TCP) maps and iso-Complication maps are proposed as a plan-review tool especially for functional image-guided intensity-modulated radiotherapy (IMRT) strategies such as selective boosting (dose painting) and conformal avoidance IMRT. The maps employ voxel-based phenomenological biological dose-response models for target volumes and normal organs. Two IMRT strategies for prostate cancer, namely conventional uniform IMRT delivering an EUD = 84 Gy (equivalent uniform dose) to the entire PTV and selective boosting delivering an EUD = 82 Gy to the entire PTV, are investigated, to illustrate the advantages of this approach over iso-dose maps. Conventional uniform IMRT did yield a more uniform isodose map to the entire PTV while selective boosting did result in a nonuniform isodose map. However, when employing voxel based iso-TCP maps selective boosting exhibited a more uniform tumor control probability map compared to what could be achieved using conventional uniform IMRT, which showed TCP cold spots in high-risk tumor subvolumes despite delivering a higher EUD to the entire PTV. Voxel based iso-Complication maps are presented for rectum and bladder, and their utilization for selective avoidance IMRT strategies are discussed. We believe as the need for functional image guided treatment planning grows, voxel based iso-TCP and iso-Complication maps will become an important tool to assess the integrity of such treatment plans.

Keywords

selective boosting; dose painting; tumor control probability (TCP); normal tissue complication probability (NTCP); dose map

I. INTRODUCTION

The conventional standard for a well-designed radiotherapy (RT) treatment plan has been to require ‘uniform’ dose-coverage of target volumes while minimizing the volume of normal tissue that is irradiated to high dose. This central dogma of RT rests on the following two assumptions: First it is assumed that the physiologic makeup of the gross tumor volume (GTV) is reasonably similar throughout and secondly that functional subunits (FSU) in normal tissues are uniformly distributed and that each FSU is of the same importance. Since

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intensity-modulated radiotherapy (IMRT) leads to steep dose gradients between target volumes and organs at risk chances are higher that a shift in patient position could bring some region of the target volume outside the high-dose volume and Webb and Nahum therefore stated as a general rule of RT that only small inhomogeneities in dose could be tolerated (1). However, the advent of image guided RT affords one the ability to guard against shifts in patient position on a fraction-to-fraction bases opening the door for delivery of highly non-uniform dose distributions. However, the effectiveness of such inhomogeneous dose distributions arrived at using either physical or biological optimization can no longer be judged using isodose maps and different concepts such as iso-tumor control probability (TCP) maps and iso-Complication-maps should be used instead to judge the fidelity of such inhomogeneous dose distributions.

Furthermore, the incorporation of functional imaging techniques showing a nonuniform physiological make-up of the GTV into IMRT treatment planning has clearly challenged the assumption of uniform make-up of the GTV, which has been instrumental to the central dogma of RT. Two pathways can be followed when implementing functional imaging into RT treatment planning to improve outcome of RT— one can either use boosting by itself to increase local tumor control or one can combine it with a strategy in which one aggressively avoids functional subvolumes within critical structures and irradiates nonfunctioning subvolumes within these critical structures to higher doses. The first is to selectively boost dose in high-risk tumor subvolumes that are strongly associated with tumor recurrence, especially for locally advanced tumor sites. This concept has been called either ‘selective boosting’ (2,3,4) or ‘dose painting’ (5,6). The second is intra critical organ conformal avoidance; which has recently been suggested with the aim of selectively reducing radiation dose in functionally and/or clinically-more-important critical organ subvolumes (7,8), to potentially reduce normal tissue toxicity, allowing one to boost the dose to target volumes at equal or lower expected normal tissue complication probability (NTCP). In essence ‘selective avoidance’ is the normal tissue counterpart to selective boosting of high-risk tumor subvolumes, since functionally and/or clinically more important critical organ subvolumes are more aggressively spared. Therefore, a lot of interest is currently devoted to the integration of specific physiologic information into RT treatment planning with the aim of selective boosting of high-risk tumor subvolumes and selective avoidance of functional normal tissue volumes.

Dose distributions resulting from functional image-guided IMRT are, therefore, non-uniform rather by design than by ones inability to achieve a uniform dose distribution. Hence, conventional plan evaluation measures either for target volumes or organs at risk are clearly not adequate to assess the integrity of functional image-guided IMRT treatment plans. In an effort to extend currently used physical dose-volume-histogram (DVH) to deal with an inhomogeneous IMRT plan, Yang and Xing (9) proposed the use of effective-DVH for target volumes which are obtained by replacing the dose for individual voxels with an effective dose – obtained by normalizing the physical dose in a voxel by the desired dose. Regarding an extended DVH for selective avoidance IMRT, Marks and coworkers have suggested the use of functional DVH (10) to incorporate the inhomogeneous distribution of FSU into dose volume histograms. However, even though use of extended dose volume histograms such as effective and/or functional DVH provide a tool to assess the uniformity level of a dose distribution they still ignore the spatial information of where the dose within the target volume or normal tissue volume is placed, and therefore identical dose volume histograms with different spatial distribution of dose within the target or normal tissue volumes can lead to different RT outcomes — in terms of expected TCP or NTCP. For this reason we propose a plan-review tool that is uniquely suited for the spatial evaluation of the nonuniform dose distributions. Voxel based iso-TCP map are designed to allow one to

evaluate tumor-control uniformity of target volumes, while voxel based iso-Complication maps allow one to evaluate the spatial variations of NTCP for normal organs.

II. METHODS AND MATERIALS

IMRT Treatment Planning for Two Different Scenarios

We have used the model of prostate cancer as our vehicle to explore the usefulness of voxel based iso-TCP and iso-Complication maps in showing expected tumor-control uniformity and predicted regions of increased NTCP. All investigated treatment plans were generated using the Philips Pinnacle³ treatment planning system (Philips Medical Systems, Fitchburg, Wisconsin), version 8.1s. An equiangular beam arrangement consisting of seven coplanar fields, a dose grid of 0.4 cm × 0.4 cm × 0.4 cm, and reference fraction size of 2 Gy were employed for all plans. Furthermore, a 0.5 cm volumetric margin was added to the clinical target volume to obtain the planning target volume (PTV) and a similar margin was added to the high-risk tumor subvolumes when contracting from PTV to the remaining low-risk PTV without a high-risk tumor subvolume (rPTV). Figure 1(A) shows a simulated high-risk tumor subvolume, which in the case of prostate cancer is the dominant intraprostatic lesion, which has been constructed in the peripheral zone of the prostate (11).

A conventional prostate IMRT plan and a selective boosting plan were generated. For the selective boosting plan a high-risk tumor subvolume identified using functional imaging, as constructed above, has been postulated. The conventional IMRT plan delivers an equivalent uniform dose (EUD) of 84 Gy to the whole PTV using a conventional schedule of thirty-nine 2 Gy fractions prescribed to 100 % of the PTV (12). While, the selective boosting plan delivers in 39 fractions a minimal peripheral dose of 2 Gy to 98 % of the entire PTV yielding a total EUD of 82Gy, where the high-risk tumor subvolume receives an EUD of 91 Gy and the rPTV receives an EUD of 81 Gy. Note that the selective boosting plan delivers a lower EUD to the entire PTV than the conventional IMRT plan, and should, therefore, be judged inferior using classical EUD ranking. The organs at risk constraints of both strategies were obtained from the Memorial Sloan Kettering dose-escalation trial (13).

When comparing competing treatment plans obtained using different optimization strategies it would be desirable to have a treatment planning evaluation tool that allows one to effectively differentiate between plans in terms of biological effective parameter vs volume histograms or biological isoeffect parameter distributions. In what follows we describe two such biological isoeffect parameter distributions that can be used to compare and rank competing treatment plans in terms of their expected biological effectiveness.

Voxel-based Iso-TCP map

Due to its computational simplicity, we have chosen to work with the phenomenological Logistic TCP model (14) to estimate the expected TCP for individual voxels within a voxel-based iso-TCP map:

$$TCP(D_i) = \frac{1}{1 + \left(\frac{D_{50}}{D_i}\right)^{4\gamma_{50}}}, \quad (1)$$

where the two parameters D_{50} and γ_{50} are determined from clinical data. D_{50} is the dose which yields a tumor control probability of 50% and γ_{50} refers to the normalized dose-response gradient of the tumor response curve at D_{50} . As mentioned by Bentzen (15), the Logistic TCP model has been extensively used to evaluate tumor-dose response, along with the Poisson TCP model. Due to its computational simplicity and flexibility for estimating

tumor response probabilities the Logistic TCP model is a more practical model for assessing tumor dose response than the Poisson TCP model (15). The Logistic TCP model clearly applies to a tumor voxel that receives a uniform voxel dose D_i . We assume that D_{50} and γ_{50} can be determined for different physiological tumor types using functional imaging techniques combined with information from tumor biopsies, or from functional imaging alone.

Strictly speaking, the parameters D_{50} and γ_{50} only apply to the reference fractionation schedule (f_s, f_x) to which they were fitted, hence if the fraction-size changes these parameters cannot be used for dose response prediction (i.e. TCP and NTCP) without appropriate adjustments. Therefore, to incorporate the change in fraction-size into voxel-based iso-TCP maps, we have utilized the fraction-size equivalent dose (FED) concept introduced by Tomé and Fenwick (16) to obtain a normalized dose map using the reference fraction-size from which the dose response parameters have been derived:

$$FED_{\alpha/\beta}^{f_s} \equiv nd \frac{\left(1 + \frac{d}{\alpha/\beta}\right)}{\left(1 + \frac{f_s}{\alpha/\beta}\right)}, \quad (2)$$

where f_s is the reference fraction-size which is the dose per fraction delivered to the prescription point using the fractionation schedule (f_s, f_x) from which the TCP and NTCP data was derived, d denotes the physical dose per fraction at some point of interest, n denotes the total number of fractions, and α/β is the usual ratio of the linear-quadratic model parameters for the organ under consideration and a given radiobiological end point.

As the first step in the construction of voxel-based iso-TCP maps, the dose maps of target volumes having a different fraction-size from the reference fraction-size are transformed into $FED_{\alpha/\beta}^{f_s}$ dose-maps, and the expected TCP is then estimated for each voxel using Eq. (3):

$$TCP\left(FED_{\alpha/\beta}^{f_s}\right)_i = \frac{1}{1 + \left(\frac{D_{50}}{(FED_{\alpha/\beta}^{f_s})_i}\right)^{4\gamma_{50}}} \quad (3)$$

Additionally, an overall TCP estimate for the entire PTV consisting of tumor subvolumes having different risk-levels, is then given by (cf. Ref. 4):

$$TCP(\{D\}) = \prod_{j=1}^R \left[TCP_j \left(\left\{ (FED_{\alpha/\beta}^{f_s})_i^j, v_i^j \right\} \right)^{v_j} \right] = \prod_{j=1}^R \left[\prod_{i=1}^k \left[\frac{1}{1 + \left(\frac{D_{50}^j}{(FED_{\alpha/\beta}^{f_s})_i^j}\right)^{4\gamma_{50}^j}} \right]^{v_i^j} \right]^{v_j}, \text{ where } \sum_{i=1}^k v_i^j = 1, \text{ and } \sum_{j=1}^R v_j = 1 \quad (4)$$

where $\{D\}$ denotes the inhomogeneous dose distribution in the entire tumor. v_i^j , v_j , k , and R represent a fractional volume of i^{th} -tumor voxel, the fractional volume of the j^{th} -subvolume of the tumor, total number of tumor voxels within the j^{th} -subvolume, and the total number of tumor subvolume. In this TCP model, it is assumed that each of the R -tumor subvolumes has different D_{50}^j and γ_{50}^j values that are based on the physiological make-up of the tumor

subvolume and that these values can be obtained from functional imaging combined with biopsy, or from functional imaging alone.

Motivated by the recently published clinical data for prostate cancer by Levegrün *et al.* (17), we have used the tumor risk classifications listed on Table 1 for the high-risk tumor subvolume and the rPTV.

Voxel-based Iso-Complication Map

Again for simplicity, we have chosen to work with the phenomenological NTCP model given by the Logistic expression (14) to calculate the predicted NTCP for individual voxels within a voxel-based iso-Complication map. To employ the clinical data fitted to the

classical Lyman-NTCP model (18), γ_{50} is simply replaced by $\frac{1}{\sqrt{2\pi m}}$, which can be straightforwardly derived from the Lyman-NTCP model by simply evaluating the dose gradient at $D = D_{50}$. We have assumed no volume effect for individual normal tissue voxels so that our phenomenological Logistic NTCP is given by

$$NTCP(D_i) = \frac{1}{1 + \left(\frac{D_{50}}{D_i} \right)^{\frac{1}{\sqrt{2\pi m}}}} \quad (5)$$

where D_{50} is the dose to the whole organ that leads to a complication probability of 50% and m denotes the parameter relating to the slope of the NTCP curve. D_{50} and m are determined from clinical parameters fitted using the classical Lyman-NTCP model. Table 1 shows the NTCP model parameters employed in this study. It is of course well known that with this substitution for γ_{50} the phenomenological Logistic NTCP model in equation (5) closely approximates the classic Lyman-NTCP model with no volume effect, i.e., $n = 0$ (cf. Ref.

19). Substituting $FED_{\alpha/\beta}^{fs}$ into Eq. (5) yields the NTCP estimate for individual voxels within an organ at risk, which is given by:

$$NTCP\left(FED_{\alpha/\beta}^{fs}\right) = \frac{1}{1 + \left(\frac{D_{50}}{(FED_{\alpha/\beta}^{fs})_i} \right)^{\frac{4}{\sqrt{2\pi m}}}} \quad (6)$$

The iso-NTCP complication map is then formed by evaluating equation (6) for each organ at risk voxel. Since, our phenomenological NTCP does exclude a possible volume effect we have chosen to calculate the overall expected NTCP estimate for an organ at risk using the Lyman-NTCP model (18). Therefore, in reaching a clinical decision regarding selective avoidance IMRT plans one goes through a two-step process. In the first step, one evaluates the spatial variations of expected NTCP values for functional and/or clinically more important subregions using the information obtained from a voxel-based iso-Complication maps. Note that the volume effect is not included in this map and it therefore represents a conservative estimate of the expected NTCP. In a second step, one uses the organ at risk DVH to obtain an overall estimate for the expected NTCP that includes the volume effect using the Lyman NTCP model. We have employed the generalized equivalent uniform dose (gEUD) concept (20) as our DVH reduction method when employing the Lyman-model to evaluate expected NTCP values. This gEUD-based Lyman-NTCP model is mathematically equivalent to the classical Lyman-Kutcher-Burman NTCP model (cf., Appendix A. of Ref. 21), and is given by:

$$NTCP(gEUD) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t \exp\left(-\frac{x^2}{2}\right) dx \quad (7)$$

$$\text{where, } t = \frac{(gEUD - D_{50})}{m D_{50}} \text{ and } gEUD = \left(\sum_i v_i D_i^{\frac{1}{n}} \right)^n.$$

The parameter v_i denotes the fractional volume of the i^{th} dose bin whose dose value is denoted by D_i . Where the dose-response parameters (D_{50} , m , and n) are obtained from available population based clinical data.

III. RESULTS

As shown in Figure 1(A), the conventional uniform prostate IMRT plan shows a uniform dose distribution across the entire PTV (rPTV plus high-risk tumor subvolume) representing a well-designed plan in terms of the classical RT dogma. The selective boosting IMRT plan shown in Figure 1(B) yielded non-uniform dose distribution within the entire PTV, in which high doses are focused on the tumor subvolume that is at highest risk for tumor recurrence. Therefore, when employing isodose maps (cf., Figure 1(A) and 1(B)) the conventional uniform prostate IMRT will be judged as superior to the selective boosting IMRT in terms of dose uniformity. However, when using the metric of tumor-control uniformity instead of a dose-uniformity, as in Figure 1(C) and (D), the selective boosting IMRT plan clearly depicts a more uniform iso-TCP map while the uniform plan yields a considerable deficit of expected TCP in the high risk tumor subvolume. Hence, despite the fact that the uniform IMRT plan delivers an EUD of 84 Gy to the entire prostate which is higher than the EUD of the selective boosting plan (EUD = 82Gy), it results in an inferior treatment outcome in terms of expected TCP. This result was confirmed by the fact that the expected TCP values for a high-risk subvolume were 75.6% for conventional uniform prostate IMRT and 95.1% for selective boosting IMRT. In order to achieve an iso-TCP map for uniform IMRT that is equivalent to the one achieved for selective boosting the EUD of the entire PTV would need to be raised from an EUD of 84 Gy to an EUD of 91 Gy. Hence, the dose delivered to the entire prostate would have to be escalated by an Δ EUD of 7 Gy; however, escalating the dose to the entire prostate above 90Gy has been deemed as not clinically feasible by Zelefsky and colleagues, since they could not achieve sufficient sparing of rectum and urethra in the inverse planning process when prescribing 91.8 Gy to entire prostate (13).

More importantly, to compare the expected tumor-control levels between different treatment plans, clinicians typically evaluate the overall expected TCP for the entire PTV (cf. Ref. 23). However, in this study the overall expected TCP estimates for the entire PTV were 96.2% for uniform IMRT and 97.4% for selective boosting. The difference of 1.2% in TCP for the entire PTV for the two plans appears to be clinically insignificant. However, local recurrence is associated with high-risk tumor subvolumes such as hypoxic tumor subvolumes (24,25) and regions that contain a large number of highly proliferation capable clonogens (25,26). Hence, the highest-risk tumor subvolume having the lowest TCP value will drive the expected local tumor control, and plan evaluation tools should reflect this tumor biology. As can be seen from Figure 1, voxel-based iso-TCP maps clearly provide the spatial variations of expected local TCPs, showing possible cold tumor-control subregions. Therefore, the use of voxel-based iso-TCP maps will allow clinicians to effectively assess the integrity of an IMRT treatment plan, especially in cases where high-risk tumor subvolumes can be identified using either functional imaging in combination with biopsy or functional imaging alone.

Figure 2 portrays the voxel-based iso-Complication maps for both plans in which each organ at risk voxel (assumed to have no volume effect) represents predicted NTCP estimates according to the total physical dose it has received. As shown in Figure 2, the voxel-based iso-Complication map obtained from the selective boosting IMRT plan yielded slightly better NTCP distributions. This result is however not all that surprising, since the selective boosting plan delivers an EUD of 82 Gy to the entire PTV while the uniform IMRT plan delivers an EUD of 84 Gy. Hence, a lower dose to the entire PTV affords more favorable normal tissue sparing. However, the selective boosting IMRT plan delivering a lower EUD affords not only more favorable rectum and bladder sparing but also affords a significantly more uniform tumor-control probability distribution—which would not be clearly perceived using physical iso-dose maps, physical DVH, and overall TCP estimates, but is clearly appreciated employing voxel-based iso-TCP map and iso-NTCP maps.

The overall NTCP estimates of the entire rectum calculated by the Lyman NTCP model were 8.5% and 7.8% for the uniform prostate IMRT plan and the selective boosting, respectively. While bladder NTCP estimates were less than $10^{-4}\%$ for both plans. Note however, that when computing these NTCP estimates using the Lyman NTCP model given in Eq. (7) we are assuming that all FSU are of equal importance for organ function preservation and that they are uniformly distributed. Hence, for the case in which there are both functional and non-functional subregions within a normal organ, i.e. when there exists an asymmetry between the importance of different FSU, a metric such as iso-NTCP maps may prove to be useful in the evaluation of treatment plans to assess their impact on functional subregions within normal organs.

IV. DISCUSSION

Locoregional tumor control for locally advanced cancers treated with RT has been less than satisfactory. Most early-stage cancers can be cured with either RT or surgery; however, tumor control for locally advanced tumors has been unsatisfactory in spite of combined-modality treatments. This resistance to therapy is in part due to the fact that tumor cells in high-risk tumor subvolumes, such as hypoxic or highly proliferating tumor cells, are likely to have unusually high repair capacity (27). In an effort to overcome local recurrence, boosting techniques have been widely studied, since there exists firm clinical evidence that tumor control can be enhanced using boost techniques (27–29). Moreover, increased locoregional tumor control is associated with an increased survival rate (30). However, it was found for breast cancer patients that only 1 in 34 patients would have benefited from an additional boost above baseline in terms of increased locoregional control (31). Applying a boost technique indiscriminately to all patients carries the risk that many patients incur added side effects due to the more aggressive treatment, while only a few might derive a benefit from it. An alternative way of boosting is selective boosting (dose painting) where the boost dose is focused on patient-specific, high-risk tumor subvolumes determined employing a functional imaging technique and/or biopsy.

As far as the methods for deciding on the boosting level for patient-specific, high-risk tumor subvolume are concerned, the majority of present approaches determine a boosting level based on clinical experience, i.e., a radiation oncologist decides on the boosting level (32). To determine the boosting level for patient-specific high-risk tumor subvolumes based on patient-specific information, two routes have been explored: (1) to prescribe a baseline minimal peripheral physical dose and to add on top of it a nonuniform boosting component that corresponds to a companion, physiologically based risk image intensity—called *dose painting by number* (cf. Ref. 6); and (2) to use radiobiological parameters (cf. Ref. 4), such as TCP, NTCP, and uncomplicated tumor control probability (UTCP) (33) to arrive at the

maximal tolerable boost level within high-risk tumor subvolumes without violating normal tissue constraints, while maintaining an adequate minimal peripheral dose.

Even though different methods for determining a boosting level based on patient-specific high-risk subregions exist, voxel-based iso-TCP maps represent an excellent plan-evaluation tool for the approaches described above. Voxel-based iso-TCP maps presented in this study are based on tumor risk levels, specified using different D_{50} and γ_{50} values for on the different tumor subvolumes (cf. Figure 1(C) & (D) and Table 1). However, the map can also be based on risk levels for individual tumor voxels, as it consists of TCP estimates for individual tumor voxels. Hence, voxel-based iso-TCP maps are also applicable to the dose painting by number strategy.

With regard to selective avoidance IMRT, interest has focused on its impact on normal tissue function preservation. Particular treatment sites in which this technique has been successfully applied include the selective boosting of brain metastasis in combination with hippocampal sparing whole-brain radiotherapy and the treatment of locally advanced, non-small-cell lung cancer (NSCLC). For instance in the treatment of NSCLC, three functional imaging modalities have been investigated that potentially allow the integration of ventilation- and/or pulmonary perfusion-competent lung subregions into RT treatment planning—single photon emission tomography (SPECT) (34), magnetic resonance imaging (MRI) with hyperpolarized helium (35), and four-dimensional computed tomography (4D-CT) data sets (7). The results reported from these studies, promise reduced lung toxicity and therefore allow for a wider therapeutic window to increase tumor dose—showing a FV_{5Gy} (the functional lung volume receiving dose above 5Gy) reduction of 9.6% (7), FV_{20Gy} reduction of 13.6% (34), and a predicted reduction in the incidence of Grade 3+ radiation pneumonitis (NTCP) from 12% to 4% (35) when compared to the conventional baseline plan. Regarding its application to hippocampal sparing whole-brain RT in combination with the simultaneous boosting of brain metastases, Gutiérrez and coworkers (8) suggested a selective avoidance IMRT strategy for the hippocampus while simultaneously selectively boosting existing brain metastases to more than twice the dose given to whole brain CTV—promising both a reduction in the risk of memory decline and improvement in intracranial tumor control. As we go towards selective avoidance IMRT coupled with selective boosting of high-risk tumor sub volumes, voxel-based iso-Complication maps may prove to be a useful supplement to physical iso-dose maps and overall NTCP estimates; since in a voxel-based iso-Complication map, functional and nonfunctional subvolumes are differentiated in terms of complication risk (D_{50} and m). It therefore, allows clinicians to assess the integrity of selective avoidance treatment plans in which functional and/or clinically more important subregions within ‘parallel’ organs are selectively avoided. A voxel-based iso-Complication map has the potential to reflect the inhomogeneous distribution of functional subregions within organs at risk. Additionally, voxel-based iso-Complication maps allow one to compare the spatial variations of NTCP for different IMRT strategies.

Note that voxel-based iso-TCP and iso-Complication maps are strongly dependent on the dose-response parameters (D_{50} and γ_{50}) employed for TCP and NTCP evaluations in individual voxels. Hence, in the absence of hard clinical data, voxel-based iso-TCP and iso-Complication maps should only be employed as a guide along with classical plan-evaluation tools such as physical iso-dose maps and dose volume histograms.

Functional image-guided IMRT with the aim of selective boosting of high-risk tumor subvolumes and/or the selective avoidance of functional subregions within organs at risk remains very much a work in progress. Efforts to determine the microscopic spread of high-risk tumor, changes within high-risk subregions throughout RT treatment using treatment response monitoring, and a methodology to obtain patient-specific, dose-response

parameters for high-risk tumor-subvolumes and functional subvolumes within organs at risk, remain critical. Many endeavors are currently underway to evaluate the impact of functional image-guided IMRT on local tumor control. For example, Thorwarth and coworkers have proposed a phenomenologic TCP model (cf., Figure 4 in Reference 36) for head-and-neck cancer. Their model incorporates patient-specific levels for hypoxia and reoxygenation determined using a hypoxic imaging employing the functional imaging ^{18}F -FMISO-PET (18F-fluoromisonidazole positron emission tomography) that could potentially provide patient-specific dose-response parameters (D_{50} and γ_{50}) for these regions (36).

V. CONCLUSION

In recent years, functional imaging modalities have provided an increasing amount of information on high-risk tumor subvolumes and/or functional subregions in normal organs and advanced image-guided IMRT technologies such as helical tomotherapy make it possible to deliver functional image-guided IMRT such as selective boosting and/or selective avoidance IMRT. However, conventional treatment planning evaluation tools are inadequate to evaluate the quality and potential impact of functional image-guided IMRT dose distributions on the expected outcome of therapy, and the present study has therefore focused on the development of new radiobiological and dosimetrical plan evaluation tools for functional image-guided IMRT. We found that conventional IMRT optimization did result in a more uniform dose distribution across the entire PTV while selective boosting employing biological objective functions resulted in a non-uniform dose distribution across the entire PTV having a lower EUD than the conventional IMRT plan. Using conventional plan evaluation and plan ranking paradigms we would have to choose the conventional IMRT treatment plan over the selective boosting treatment plan since it delivers a higher EUD and a more uniform dose distribution to the entire PTV. However, using voxel-based iso-TCP maps, we found cold spots of tumor-control in the high-risk tumor subvolume for the conventional IMRT plan while the selective boosting plan did deliver a more uniform tumor-control probability distribution despite delivering a lower equivalent uniform dose to the entire PTV. We believe as the need for a functional image-guided treatment planning grows, voxel-based iso-TCP and iso-Complication maps will become an important assessment tool of such treatment plans.

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Figure 1.

Diagrams in the upper row show the physical isodose distribution for both the conventional intensity modulated radiotherapy (IMRT) (Panel A) and the selective boosting IMRT plan (Panel B). In terms of the physical dose uniformity achievable the conventional IMRT plan having a higher EUD appears to be superior. In the lower row, tumor-control uniformity for both plans is compared using voxel based iso-TCP maps, and the selective boosting IMRT plan (Panel C) yields considerably better tumor-control uniformity than the conventional IMRT (Panel D) showing that it is clearly superior in terms of the expected tumor control probability.

Figure 2.

Voxel based iso-Complication maps for the organs at risk: rectum and bladder. The panel on the left shows the iso-Complication map obtained for the conventional prostate IMRT plan, while the one on the right shows the iso-Complication map obtained for the selective boosting IMRT plan.

Table 1

NTCP and TCP model parameters used in the construction of voxel based iso- Complication map and iso-TCP map, respectively.

Structures	D_{50} [Gy]	m & n or γ_{50}	References
Organs-at-risk (OAR): $\alpha/\beta=3$			
Bladder	80.0	$m = 0.11$ & $n = 0.5$	Burman <i>et al.</i> ²²
Unspecific Pelvic Normal tissue	55.0	$m = 0.13$ & $n = 0.15$	Burman <i>et al.</i> ²²
Rectum	81.9	$m = 0.19$ & $n = 0.23$	Rancati <i>et al.</i> ²¹
Tumor Risk Classifications: $\alpha/\beta=10$			
High-Risk Tumor Subvolume	82.3	$\gamma_{50} = 8$	Levegrün <i>et al.</i> ¹⁷
Low Risk remaining PTV	72.8	$\gamma_{50} = 8$	

Abbreviations: D_{50} = the dose yielding a 50% dose-response for a specific end point to either normal tissue complications or tumor control, γ_{50} = the normalized dose-response gradient, m = the parameter is related to the slope of the dose-response curve, n = a volume effect parameter, and no volume effect (i.e. $n = 0$) is assumed within a voxel in a voxel based iso-Complication map.