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HOW DOES PERFORMANCE OF ULTRASOUND TISSUE TYPING AFFECT DESIGN OF PROSTATE IMRT DOSE-PAINTING PROTOCOLS?

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Abstract

Purpose—To investigate how the performance characteristics of ultrasound tissue typing (UTT) affect the design of a population-based prostate dose-painting protocol.

Methods and Materials—The performance of UTT is evaluated using the receiver operating characteristic curve. As the imager's sensitivity increases, more tumors are detected, but the specificity worsens, causing more false-positive results. The UTT tumor map, obtained with a specific sensitivity and specificity setup, was used with the patient's CT image to guide intensity-modulated radiotherapy (IMRT) planning. The optimal escalation dose to the UTT positive region, as well as the safe dose to the negative background, was obtained by maximizing the uncomplicated control (*i.e.*, a combination of tumor control probability and weighted normal tissue complication probability). For high- and low-risk tumors, IMRT plans guided by conventional ultrasound or UTT with a one-dimensional or two-dimensional spectrum analysis technique were compared with an IMRT plan in which the whole prostate was dose escalated.

Results—For all imaging modalities, the specificity of 0.9 was chosen to reduce complications resulting from high false-positive results. If the primary tumors were low risk, the IMRT plans guided by all imaging modalities achieved high tumor control probability and reduced the normal tissue complication probability significantly compared with the plan with whole gland dose escalation. However, if the primary tumors were high risk, the accuracy of the imaging modality was critical to maintain the tumor control probability and normal tissue complication probability at acceptable levels.

Conclusion—The performance characteristics of an imager have important implications in dose painting and should be considered in the design of dose-painting protocols.

Keywords

Receiver operating characteristic; Dose painting; Radiation biologic model; Treatment planning; Prostate cancer

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INTRODUCTION

Recent developments in biologic and spectroscopic imaging, such as magnetic resonance spectroscopic imaging (MRSI) (1–8) and ultrasound tissue typing (UTT) (9–12), provide clinicians with information on the heterogeneous distribution of metabolic, physiologic, and physical properties inside the prostate gland. After these images have been co-registered with traditional anatomic CT images, the fused images can provide guidance during intensity-modulated radiotherapy (IMRT)-based dose painting (13). Xing *et al.* (14) designed an inverse optimization algorithm for MRSI-guided IMRT treatment planning that escalates the dose in the suspected cancerous region according to an index of abnormality obtained from MRSI. By choosing to dose escalate more heavily in more suspicious regions and less heavily in “normal” areas, they implicitly incorporated the diagnostic uncertainty of MRSI into their dose-escalation scheme (15). However, the uncertainty in imaging can have an effect on dose escalation and must be accounted for. In this report, we explicitly and quantitatively include the imaging uncertainty into a biologically based model of tumor control under conditions of inhomogeneous dosing.

The quality and the performance of the imaging modalities are evaluated using the receiver operating characteristic (ROC) curve (16). The ROC curve is a plot of the imaging modality’s sensitivity (true-positive fraction) vs. its false-positive fraction (equal to $1 - \text{specificity}$). The ROC curve describes the imaging modality’s ability to correctly classify tumors and the surrounding normal tissues. Although an ideal imager would have both sensitivity and specificity at 1, in reality, as the sensitivity of an imager increases, the operation threshold slides along the ROC curve and the specificity worsens (decreases) as a compromise.

When an imager is operated with a low-sensitivity setup, the amount of tumor identified is small. The small dose-escalation target volume would result in a low normal tissue complication probability (NTCP). However, because some real tumors are missed, following the localized dose-escalation scheme guided by this imaging with low sensitivity, would result in a treatment plan with low tumor control probability (TCP) because lots of tumors are located in the non-dose-escalation region. When an imager is operated with high sensitivity, most tumors are detected, but an increasing percentage of normal tissue is misclassified as cancerous as a compromise. This greater false-positive ratio results in a larger target volume for escalation, and the increased dose can result in a greater NTCP.

Advanced imaging modalities such as UTT and MRSI offer improvement compared with standard imaging such as conventional B-mode ultrasonography and MRI by increasing the amount of true tumor detected without compromising the specificity (8,12). The NTCP resulting from dose escalation is directly linked to the specificity of an imager. When the advanced imaging modalities use the same specificity setup as the standard imaging techniques to limit NTCP, the advanced imaging modalities result in better TCP because of their greater sensitivity.

The choice of imaging and the selection of its operation criterion influences the balance between cancer cure and treatment toxicity. We evaluated the possible risks and benefits associated with heterogeneous dosing of the prostate for high- and low-risk populations using the four performance criteria: no imaging, conventional B-mode ultrasonography, UTT using a one-dimensional spectrum (1D) analysis technique, and UTT using a two-dimensional (2D) spectrum analysis technique. We presented a systematic framework to explicitly investigate the interplay between sensitivity/specificity and local control/complications for high- and low-risk populations in the scenario of prostate dose painting.

METHODS AND MATERIALS

In this report, we used a probability approach to design the UTT image-guided prostate dose-painting protocols. The optimal escalation dose to the tumor-positive region identified by UTT imaging, as well as the safe dose to the imaging negative background prostate but suspicious for microscopic disease, was obtained by optimizing a radiobiologic model-based objective function. For both high- and low-risk tumors, IMRT plans guided by conventional ultrasound and UTT with a 1D or 2D spectrum analysis technique were compared with an IMRT plan in which the whole prostate gland was dose escalated.

Four operation situations

In our consideration of the design of an image-guided dose-painting protocol, we included four tumor screening scenarios that, together, meet a range of image performance criteria. In the first simulation, no tumor-specific imaging was used, and we assumed that the whole prostate would be uniformly dose escalated. This is equivalent to assuming a sensitivity of 1 and specificity of 0 (*i.e.*, the entire prostate is identified as tumor). In the other three simulations, we assumed that an imaging modality, one capable of differentiating between tumorous and nontumorous regions, was available.

A predefined normal tissue complication rate (or tolerance dose) is generally used to restrict treatment toxicities in dose-escalation protocols. Because of the requirement of the imager, an appropriate specificity is set to limit the amount of false-positive tissues detected and unnecessary boosting to tissues with a low cancerous burden. Therefore, for all three of the following imaging modalities, we assumed they operated at a high specificity level of 0.9. However, we allowed the sensitivity of the imagers to vary depending on their performance. In the first instance, we assumed the imager was a conventional B-mode ultrasound scanner. As indicated by the ROC curve generated by Feleppa *et al.* (10), at a specificity of 0.9, the ability to detect tumor using the B-mode ultrasound scanner is poor, with a sensitivity of approximately 0.3. If the imager operation uses a 1D-UTT spectrum analysis technique, the ability to identify tumor is greatly improved; the area under the ROC curve can reach 0.85, and, with a specificity of 0.9, the sensitivity can increase to 0.6 (10). This currently available imaging technique served as our third simulation situation. As an improvement on the 1D-UTT, a cutting-edge 2D-UTT spectrum analysis technique has been developed by Liu *et al.* (11). Their initial investigation demonstrated a substantial improvement in terms of gathering more diagnostically significant features regarding tissue microstructures. The preliminary results from the 2D-UTT study were extremely encouraging, suggesting that the sensitivity might be as great as 0.9, with a specificity of 0.9. This advanced technique was used as the last scenario.

Effect of imaging uncertainty on tumor detection

Generally, an imager classifies the regions within the prostate gland into two categories: the detected primary tumor zone, with a volume of v_t , and the detected tumor negative zone, with a volume of v_n . However, if a whole mount pathology study were done, it would reveal that the volume of the true primary tumor and the true nonprimary tumor were V_t and V_n , respectively. The discrepancy is due to the uncertainty of the imager. Given the true-positive fraction (sensitivity) and false-positive fraction ($1 - \text{specificity}$) of the imaging modality, on a patient population basis, v_t and v_n can be expressed in combinations of V_t and V_n :

$$\begin{cases} v_t = V_t \times TPF + V_n \times FPF \\ v_n = V_t \times (1 - TPF) + V_n \times (1 - FPF) \end{cases} \quad (1)$$

In practice, v_t and v_n are revealed by way of the imaging modality, but V_t and V_n are unknown, because a whole mount pathology study is not done for radiotherapy patients. Therefore, V_t and V_n can be calculated as follows:

$$\begin{cases} V_t = \frac{FPF \times v_n - (1 - FPF) \times v_t}{FPF - TPF} \\ V_n = v_t + v_n - V_t \end{cases} \quad (2)$$

For each voxel inside the diseased organ that is identified as tumor by the imager, the probability that it is truly a tumor, P_{tt} , is

$$P_{tt} = V_t \times TPF / v_t \quad (3)$$

If a voxel is identified as nonprimary tumor, the probability that it is misidentified, P_{nt} , is

$$P_{nt} = V_t \times (1 - TPF) / v_n \quad (4)$$

As the imaging modality improves, P_{tt} and P_{nt} approach 1 and 0, respectively. The tumor identification uncertainty expressed in these two probabilities should be taken into account in the design of prostate dose-painting protocols.

IMRT planning

From our prostate image database, a patient with a prostate volume of 44 cm³ was chosen as the subject of the IMRT planning study. Because the tumor inside the prostate of this patient was mainly located in the peripheral zone and the distribution was similar to the average tumor map obtained in the whole mount pathology study done by Chen *et al.* (17), this case was a general representation of prostate cancer patients. The tumor distributions obtained by way of different imaging methods were digitized into the patient's CT image set and imported into an in-house IMRT planning system based on Eclipse (Varian Medical System, Palo Alto, CA) along with critical organs such as the bladder, urethra, and rectum. To account for organ motion and setup error, the entire prostate was expanded with a uniform 1 cm margin to form the prostate planning target volume (PTV). Gold markers implanted right into the imaging-defined tumor-positive region using ultrasound guidance were used to correct setup error during prostate treatment. We expanded the imaging-defined tumor positive region by a reduced 5-mm margin to form the PTV for dose escalation (EPTV), the target for dose escalation. We emphasize that dose escalation needs accurate target localization using this reduced margin. Subtracting the EPTV from the prostate PTV resulted in the background planning target volume (BPTV), which still needed to be covered with a safe background dose.

The purpose of our study was to obtain the optimal escalating dose to the EPTV (D_{EPTV}), as well as the safe background dose to the BPTV (D_{BPTV}) to cover the microscopic disease, as a function of the imaging findings. We defined the D_{EPTV} or D_{BPTV} as the dose to the 97% target volume. For IMRT plan optimization, we constructed an objective function defined as uncomplicated tumor control:

$$E = TCP \times \prod_{i \in (GU, GI)} (1 - NTCP_i)^{w_i} \quad (5)$$

where w_i is the weight for each organ system at risk, including genitourinary and gastrointestinal organs. We weighted prostate cure and organ at risk toxicity equally and assigned each w_i as 0.5. For each treatment plan, the TCP was calculated as

$$TCP = TCP(v_n \times P_{it}, R_t, D_{EPTV}) \times TCP(v_n \times P_{nt}, R_n, D_{BPTV}) \times TCP(v_t \times (1 - P_{it}), R_n, D_{EPTV}) \times TCP(v_n \times (1 - P_{nt}), R_n, D_{BPTV})$$

where R_t and R_n represent the stage of the primary and background tumors, respectively. The first term in Eq. 6 calculates the TCP for the true tumor that is correctly identified by imaging and receives the escalated dose, the second term is the TCP for the true tumor that is misidentified and receives the background dose, and the third and fourth term calculate the TCP for the nonprimary tumor zone. We used a TCP model proposed by Webb and Nahum (18). The prostate tumor stage was classified into categories according to the Gleason grading system (19,20). For prostate tumors of different stages, the radiosensitivity and tumor density were suggested by Levegrün *et al.* (21–23). However, their data were based on the assumption that the tumor is evenly distributed within the entire prostate. In our investigations, we assumed an inhomogeneous tumor distribution, with the primary tumor at either high or low risk and the nonprimary tumor zone always at very low risk. On the basis of this assumption, we adjusted the original tumor density and radiosensitivity parameters in the TCP model so that the same dose distribution resulted in the same TCP for homogeneous and inhomogeneous tumor distributions. The results are listed in Table 1.

We calculated the NTCP using a model proposed by Kutcher and Burman (24). For organs at risk, we used the fitting parameters suggested by Burman *et al.* (25) (Table 2). We combined the urethra and bladder complications into genitourinary complications using the histogram reduction method proposed by Kutcher and Burman (26).

Dose-escalation experiment design

For each combination of tumor screening scenario and tumor stage, the optimal escalation and background dose was determined by maximizing the uncomplicated tumor control using biologic models. The TCPs and NTCPs resulting from optimized IMRT plans for different imaging scenarios are generally different. To directly compare how different imaging guidance systems affects IMRT planning with the tumor stage fixed, we chose the lowest NTCP in all the IMRT plans as a limit, and reoptimized the other image-guided IMRT plans to achieve their greatest TCP with respect to this NTCP limit. The percentage of gain/loss of TCP then served as a direct measure of the effect of the imaging uncertainty on IMRT planning. Similarly, the percentage of gain/loss of NTCP with respect to a fixed TCP was used as another direct measure.

RESULTS

Tumor at high-risk stage

In our first experiment, we assumed the primary tumor was at the high-risk stage and the rest of the prostate was at the very-low-risk stage. The map of uncomplicated tumor control vs. D_{EPTV} and D_{BPTV} for 2D-UTT imaging is shown in Fig. 1. The optimal uncomplicated tumor control occurred when D_{EPTV} was at 88.3 Gy and D_{BPTV} was at 81.8 Gy. The resulting TCP and genitourinary and gastrointestinal NTCP was 0.89, 0.18, and 0.17, respectively. Similarly, the optimal escalation dose to the primary tumor and background, as well as the resulting TCP and NTCP, was obtained for the other three image-guided scenarios. As shown in Fig. 2, when more advanced imaging modalities (greater sensitivity with fixed specificity) were used, the optimal escalation dose to the primary tumor increased and the necessary safe background dose to the remaining prostate decreased. Because the increased sensitivity leaves less unidentified

true tumor in the background area, the TCP improves even though the magnitude of the increasing escalation dose is less than that of the decreasing background dose. A whole mount pathology study done by Chen *et al.* (17) revealed that the primary tumor only occupies a small portion of the prostate volume. Therefore, on a population basis, it would seem that the NTCP of critical organs depends more on the safe background dose than on the escalation dose to the primary tumor. As the dose distribution becomes more inhomogeneous with more accurate image guidance, treatment toxicity modeled as the NTCP is predicted to decrease significantly.

The 2D-UTT-guided IMRT plan produced the best tumor control and normal tissue complication of all the image-guided dose-painting plans. Using the resulting genitourinary and gastrointestinal NTCP from this plan as the complication limit (about 17–18%), we reoptimized the IMRT plans from the other three image-guidance scenarios. Compared with the best TCP (0.89) from the 2D-UTT-guided plan, the TCP dropped by 5%, 9%, and 10% for the 1D-UTT, B-mode ultrasound, and no-imaging-guided plans, respectively. Low objective complication rates limited the tumor control, especially for the poorer imaging modalities. Using the TCP from the 2D-UTT-guided plan (0.89) as the norm, the resulting genitourinary NTCP of the reoptimized plans from the other three scenarios increased by 4%, 9%, and 14% for the 1D-UTT, B-mode ultrasound, and noimaging-guided plans, respectively. The corresponding values for gastrointestinal NTCP increased 3%, 7%, and 13%. The NTCP increased significantly if a high TCP was desired in dose painting performed in conjunction with a suboptimal imaging quality.

Tumor at low-risk stage

In our second experiment, we assumed the primary tumor was low risk and the rest of the prostate was very low risk. The optimal dosages, TCP, and NTCP for the best treatment plan from each imaging scenario are shown in Fig. 3. Both tumor control and normal tissue complication improved with improved image guidance. The 2D-UTT-guided IMRT plan again had the best tumor control and normal tissue complication. Using the resulting genitourinary and gastrointestinal NTCP from this plan as the complication limit (about 7–8%), we reoptimized the IMRT plans from the other three image-guidance scenarios. Compared with the best TCP of 0.93 from the 2D-UTT-guided plan, the TCP dropped by 3%, 5%, and 6% using 1D-UTT, B-mode ultrasound, and no-image guidance, respectively. Setting the TCP from the 2D-UTT-guided plan (0.93) as the objective, the resulting genitourinary and gastrointestinal NTCP of the reoptimized plans from the other three scenarios increased a few percentage points. The NTCP only increased moderately if a high TCP was desired in dose painting in conjunction with the suboptimal imaging modalities.

DISCUSSION

In this report, we framed image guidance into a probability approach in the design of dose-painting protocols. We have demonstrated the importance of incorporating *a priori* knowledge of tumor stage into the selection of an appropriate imaging method and dose-escalation strategy. First, we found that improved imaging always resulted in better probabilities of tumor control and a lower complication rate. More importantly, our results demonstrated that the outcome of the dose-painting technique tended to be more sensitive to the quality of the imaging modality when the primary tumor was categorized at high, rather than low, risk. When the primary tumor is low risk, optimal IMRT plans guided by all imaging strategies were sufficient to maintain a low toxicity level (no >10%) and an acceptable tumor control (>90%). Therefore, introducing imaging guidance in these tumors is beneficial, but not critical. When the primary tumor was modeled as high risk, the quality of the imaging modality became essential for an acceptable outcome. Dose escalation was hindered without image guidance or with traditional B-mode ultrasound, regardless of the dose-painting optimization strategy adopted (*i.e.*, keeping

a limited complication rate or maintaining a high tumor control rate). The advanced 2D-UTT imaging technique with both superior sensitivity and specificity was clearly better.

The uncertainty inherent in the imaging modalities requires a probabilistic approach. Likewise, organ motion and setup error may be taken into account with localization probabilities throughout the treatment course (27). Therefore, a model that combines these two probabilities, target motion and operation uncertainty, with the static tumor distribution image may serve to define the planning target. Instead of prescribing a uniform margin and uniform dose, IMRT dose painting or dose sculpting could be used with this new multidimensional probability image set (28).

In our investigation, we used the Webb model to calculate the TCP and $1 - \text{NTCP}$, multiplying TCP as the plan evaluation criterion. The Webb model assumes that the radiosensitivity parameters (such as α/β) obey gaussian distributions. In our experiment, we found that the results were fairly robust with respect to the choice of the radiosensitivity values and tumor density parameters. The trend that guidance with better imaging improves the treatment objective defined by Eq. 5 holds for a wide range of parameter values. However, different biologic models, such as those proposed by Niemierko and Goitein (29), or an alternative objective function using the equivalent uniform dose (30) will result in different optimal doses and different TCP and NTCP values. We intended to demonstrate the concept of integrating the operational setting of imaging into the treatment planning process, and we realized that the TCP and NTCP values we obtained were subject to a number of assumptions. Furthermore, the detailed design of the treatment plan may depend on advancing our knowledge about imaging and plan outcome assessment. Although the numeric values have limited meanings, we believe that the relative effects we have demonstrated and the systematic framework merit consideration in the use of imaging in the clinic. Our approach can be adapted to other functional imaging modalities and modified numerically as the radiation biologic effect parameter values evolve and become better understood.

In our simulation, we modeled the patient's anatomic geometry, the radiosensitivity parameters, and the technological ability to shape the dose conformally to the target using a population-based approach. For each individual patient, these parameters will vary, especially the geometric parameters, including the size and location of the targets and related organs. As explored by Nutting *et al.* (31), the location of tumor nodules can significantly influence whether the dose escalation will, or will not, lead to improved outcomes. When the tumor borders with a critical organ, dose escalation may not be possible. As we continue our ultrasound-guided prostate dose escalation project, we will be able to collect more patient data and address this issue more specifically. However, we expect that the results of our investigation represent a class solution for a population of patients because the tumor distribution emulated the average tumor map obtained in the comprehensive whole mount pathology study by Chen *et al.* (17).

CONCLUSION

Performance of an imager characterized by its sensitivity and specificity has important implications in prostate dose painting. The affect of imager quality can be quantified using a systematic approach and should be considered in the future design of dose-painting protocols.

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REFERENCES

1. Chao KS, Mutic S, Gerber RL, et al. A novel approach to overcome hypoxic tumor resistance: Cu-ATSM-guided intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2001;49:1171–1182. [PubMed: 11240261]
2. Zaider M, Zelefsky MJ, Lee EK, et al. Treatment planning for prostate implants using magnetic-resonance spectroscopy imaging. *Int J Radiat Oncol Biol Phys* 2000;47:1085–1096. [PubMed: 10863082]
3. Zakian K, Kutcher J, Ballon D, et al. Developments in nuclear magnetic resonance imaging and spectroscopy: Application to radiation oncology. *Semin Radiat Oncol* 2001;11:3–15. [PubMed: 11146038]
4. Menard C, Smith ICP, Somorjai RL, et al. Magnetic resonance spectroscopy of the malignant prostate gland after radiotherapy: A histopathologic study of diagnostic validity. *Int J Radiat Oncol Biol Phys* 2001;50:317–323. [PubMed: 11380217]
5. Aoyama H, Shirato H, Nishioka T, et al. Magnetic resonance imaging system for three-dimensional conformal radiotherapy and its impact on gross tumor volume delineation of central nervous system tumors. *Int J Radiat Oncol Biol Phys* 2001;50:821–827. [PubMed: 11395252]
6. Pirzkall A, McNight TR, Graves EE, et al. MR-spectroscopy guided target delineation for high-grade gliomas. *Int J Radiat Oncol Biol Phys* 2001;50:915–928. [PubMed: 11429219]
7. DiBiase SJ, Hosseinzadeh K, Gullapalli RP, et al. Magnetic resonance spectroscopic imaging-guided brachytherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;52:429–438. [PubMed: 11872289]
8. Hasumi M, Suzuki K, Oya N, et al. MR spectroscopy as a reliable diagnostic tool for localization of prostate cancer. *Anticancer Res* 2002;22:1205–1208. [PubMed: 12168926]
9. Feleppa EJ, Liu T, Kalisz A, et al. Ultrasonic spectral parameter imaging of the prostate. *Int J Imag Sys Tech* 1997;8:11–25.
10. Feleppa EJ, Fair WR, Liu T, et al. Three-dimensional ultrasound analyses of the prostate. *Mol Urol* 2000;4:133–141. [PubMed: 11062367]
11. Liu, T.; Lizzi, FL.; Silverman, RH., et al. Ultrasonic tissue microstructure characterization using two-dimensional spectral analysis and the potential role in conformal radiation therapy. Presented at the Annual Meeting of ASTRO; New Orleans, LA. 2002.
12. Gefen S, Tretiak OJ, Piccoli CW, et al. ROC analysis of ultrasound tissue characterization classifiers for breast cancer diagnosis. *IEEE TMI* 2003;22:170–177.
13. Ling CC, Humm J, Larson S, et al. Towards multidimensional radiotherapy (MD-CRT): Biological imaging and biological conformality. *Int J Radiat Oncol Biol Phys* 2000;47:551–560. [PubMed: 10837935]
14. Xing, L.; Cotrutz, C.; Hunjan, S., et al. Inverse planning for functional image-guided IMRT. Presented at the Annual Meeting of ASTRO; New Orleans, LA. 2002.
15. Cotrutz C, Xing L. IMRT dose shaping with regionally variable penalty scheme. *Med Phys* 2003;30:544–551. [PubMed: 12722806]
16. Zhou, X.; Obuchowski, N.; McClish, D. Statistical methods in diagnostic medicine. New York: Wiley; 2002.
17. Chen ME, Johnston DA, Tang K, et al. Detailed mapping of prostate carcinoma foci: Biopsy strategy implications. *Cancer* 2000;89:1800–1809. [PubMed: 11042576]
18. Webb S, Nahum AE. A model for calculating tumor control probability in radiotherapy including the effects of inhomogeneous distribution of dose and clonogenic cell density. *Phys Med Biol* 1993;38:653–656. [PubMed: 8346278]
19. Beahrs, OH.; Henson, DE.; Hutter, RVP., et al. American Joint Committee on Cancer manual for staging of cancer. 4th ed.. Philadelphia: JB Lippincott; 1992. p. 181-183.
20. Gleason, DF. Histologic grading and clinical staging of prostatic adenocarcinoma. In: Tannenbaum, M., editor. Urologic pathology: The prostate. Philadelphia: Lea & Febiger; 1977. p. 171-197.
21. Levegrün S, Jackson A, Zelefsky M, et al. Analysis of biopsy outcome after three-dimensional conformal radiation therapy of prostate cancer using dose-distribution variables and tumor control probability model. *Int J Radiat Oncol Biol Phys* 2000;47:1245–1260. [PubMed: 10889378]

22. Levegrün S, Jackson A, Zelefsky M, et al. Risk group dependence of dose-response for biopsy outcome after three-dimensional conformal radiation therapy of prostate cancer. *Radiother Oncol* 2002;63:11–26. [PubMed: 12065099]
23. Levegrün S, Jackson A, Zelefsky M, et al. Fitting tumor control probability models to biopsy outcome after three-dimensional radiation therapy of prostate cancer: Pitfalls in deducing radiobiological parameters for tumor from clinical data. *Int J Radiat Oncol Biol Phys* 2001;51:1064–1080. [PubMed: 11704332]
24. Kutcher GJ, Burman C. Calculation of complication probability factors for non-uniform normal tissue radiation: The effective volume method. *Int J Radiat Oncol Biol Phys* 1989;16:1623–1630. [PubMed: 2722599]
25. Burman C, Kutcher GJ, Emami B, et al. Fitting of normal tissue tolerance data to an analytic function. *Int J Radiat Oncol Biol Phys* 1991;21:123–135. [PubMed: 2032883]
26. Kutcher GJ, Burman C. Histogram reduction method for calculating complication probability for three-dimensional treatment planning evaluations. *Int J Radiat Oncol Biol Phys* 1991;21:137–146. [PubMed: 2032884]
27. Remeijer P, Rasch C, Lebesque JV, et al. Margins for translational and rotational uncertainties: A probability-based approach. *Int J Radiat Oncol Biol Phys* 2002;53:464–474. [PubMed: 12023151]
28. Mageras GS, Fuks Z, Leibel SA, et al. Computerized design of target margins for treatment uncertainties in conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 1999;43:437–445. [PubMed: 10030273]
29. Niemierko A, Goitein M. Implementation of a model for estimating tumor control probability for an inhomogeneously irradiated tumor. *Radiother Oncol* 1993;29:140–147. [PubMed: 8310139]
30. Niemierko A. Reporting and analyzing dose distributions: A concept of equivalent uniform dose. *Med Phys* 1997;24:103–110. [PubMed: 9029544]
31. Nutting CM, Corbishley CM, Sancheznieto B, et al. Potential improvements in the therapeutic ratio of prostate cancer irradiation: Dose escalation of pathologically identified tumor nodules using intensity modulated radiotherapy. *Br J Radiol* 2002;75:151–161. [PubMed: 11893639]

Fig. 1.

Map of uncomplicated control vs. dose to primary tumor and background. Primary tumor is at high risk and advanced 2-dimensional ultrasound tissue typing imaging was applied. Optimal uncomplicated control occurred when dose to primary tumor was 88.3 Gy and dose to background was 81.8 Gy. Resulting tumor control probability and genitourinary and gastrointestinal normal tissue complication probability was 0.89, 0.18, and 0.17, respectively. D_{EPTV} = optimal escalating dose to planning target volume; D_{BPTV} = safe dose to background planning target volume.

Fig. 2.

Impact of imager quality on dose painting for high-risk prostate cancer patient at fixed specificity (0.9). Normal tissue control probability (NTCP) increased significantly if high tumor control probability (TCP) was desired in dose painting performed in conjunction with suboptimal imaging quality. (a) Optimal dose to dose-escalating target and prostate background. (b) Corresponding TCP and NTCP. NTCP_{GI} = gastrointestinal NTCP; NTCP_{GU} = genitourinary NTCP.

Fig. 3. Treatment outcome modeled as tissue control probability (TCP) and normal tissue complication probability (NTCP) was not sensitive to imager quality in scenario of dose painting for low-risk prostate cancer patient. (a) Optimal dose to dose-escalating target and prostate background. (b) Corresponding TCP and NTCP. NTCP_{GI} = gastrointestinal NTCP; NTCP_{GU} = genitourinary NTCP.

Table 1

Parameters used in Webb TCP model

Tumor stage	Tumor density ρ	α	α/β	σ
Very low risk	10^4	0.197	10	0.027
Low risk	10^5	0.230	10	0.036
High risk	10^7	0.248	10	0.040

Abbreviation: TCP = tumor control probability.

Table 2

Parameters used in NTCP model

Organ at risk	TD ₅₀	n	M
Urinary	80	0.5	0.11
Rectum	80	0.12	0.15

Abbreviation: NTCP = normal tissue complication probability.