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IMRT DOSE PAINTING FOR LOCALIZED PROSTATE CANCER USING ^{11}C-CHOLINE PET SCANS

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Dose painting using ^{11}C-choline PET

CONFLICT OF INTEREST NOTIFICATION

The authors declare that there are no conflicts of interest.

SUMMARY

^{11}C-choline PET scans can be used to identify foci of cancer within the prostate. A planning study on eight patients with localized prostate cancer compared the use of ^{11}C-choline PET-guided IMRT dose painting to 90 Gy with standard radiotherapy to 78 Gy in terms of technical feasibility and biological modeling. IMRT dose painting using ^{11}C-choline PET is technically feasible, results in higher tumor control probability, and does not raise the rectal normal tissue complication probability.

ABSTRACT

Purpose: To demonstrate the technical feasibility of IMRT dose painting using ^{11}C-choline PET scans in patients with localized prostate cancer.

Methods and materials: This was a radiotherapy planning study of eight patients with prostate cancer who had ^{11}C-choline PET scans prior to radical prostatectomy. Two contours were semi-automatically generated on the basis of the PET scans for each patient: 60% and 70% of the maximum standardized uptake values ($SUV_{60\%}$ and $SUV_{70\%}$). Three IMRT plans were generated for each patient: $PLAN_{78}$ which consisted of whole prostate radiotherapy to 78 Gy; $PLAN_{78\text{-}90}$ which consisted of whole prostate radiotherapy to 78 Gy, a boost to the $SUV_{60\%}$ to 84 Gy and a further boost to the $SUV_{70\%}$ to 90 Gy; and $PLAN_{72\text{-}90}$ which consisted of whole prostate radiotherapy to 72 Gy, a boost to the $SUV_{60\%}$ to 84 Gy and a further boost to the $SUV_{70\%}$ to 90 Gy. The feasibility of these plans was judged by their ability to reach prescription doses while adhering to published dose constraints. Tumor control probabilities based on PET scan-defined volumes (TCP_{PET}) and on prostatectomy-defined volumes (TCP_{path}), and rectal normal tissue complication probabilities (NTCP) were compared between the plans.

Results: All plans for all patients reached prescription doses while adhering to dose constraints. The TCP_{PET} values for $PLAN_{78}$, $PLAN_{78\text{-}90}$ and $PLAN_{72\text{-}90}$ were 65%, 97% and 96%, respectively. The TCP_{path} values were 71%, 97% and 89%, respectively. Both $PLAN_{78\text{-}90}$ and $PLAN_{72\text{-}90}$ had significantly higher TCP_{PET} ($p = 0.002$ and 0.001) and TCP_{path} ($p < 0.001$ and 0.014) than $PLAN_{78}$. $PLAN_{78\text{-}90}$ and

$PLAN_{72\text{-}90}$ were not significantly different in terms of TCP_{PET} or TCP_{path}. There were no significant differences in rectal NTCPs between the three plans.

Conclusions: IMRT dose painting for localized prostate cancer using ^{11}C-choline PET scans is technically feasible. Dose painting results in higher TCPs without higher NTCPs.

Keywords:

Dose painting

^{11}C-choline

Positron emission tomography

Prostate cancer

IMRT

INTRODUCTION

There is a clear dose-response relationship between radiation dose and biochemical tumor control rates in prostate cancer. A meta-analysis (1) shows that an increase of radiotherapy dose from 70 Gy to 80 Gy results in an increase in biochemical prostate specific antigen (PSA) control rates by 19% in patients with high risk prostate cancer. An extrapolation of that data suggests that in this population, doses higher than 90 Gy may be necessary to maximize tumor control rates. However, such high doses are impossible to deliver using conventional external beam radiotherapy without an unacceptably high risk of severe toxicity (1, 2).

"Dose painting" (3) is a strategy that has been proposed to enable the delivery of such high radiotherapy doses without giving an unacceptably high risk of toxicity. This is the concept of using functional imaging to identify regions within the conventional target volumes that may have different biology and thus may require escalated doses of radiation to achieve tumor control.

Previous studies of local recurrence patterns indicate that strategies such as dose painting may be beneficial. Pucar *et al.* showed that dominant intraprostatic lesions (DILs) identified on pre-treatment MRI are the main sites of local recurrence following whole-prostate radiotherapy (4). It is reasonable then to hypothesize that if higher doses of radiation are delivered to DILs, lower local recurrence rates may result.

Previous studies have examined the use of dose painting in prostate cancer using various imaging modalities ranging from dynamic contrast enhanced (DCE) MRI (5), magnetic resonance spectroscopy (MRS) (5), ^{18}F-fluorocholine PET (6), and ^{11}C-acetate PET (7). This study examines the use of dose painting in prostate cancer using ^{11}C-choline PET scans.

This study is an extension of a previous study performed at Austin Health (8). In the previous study, ^{11}C-choline PET scans were compared with prostatectomy specimens to quantify the degree of correlation for the purposes of target volume definition for prostate radiotherapy. The current study uses the contouring methods developed from that study to determine the technical feasibility of using ^{11}C-choline PET for dose painting by contours.

METHODS AND MATERIALS

Study design

The radiotherapy planning study cohort consisted of eight patients with intermediate to very high risk prostate cancer who had ^{11}C-choline PET scans prior to radical prostatectomy. Their characteristics are described in Table 1.

Image co-registration

^{11}C-choline PET scans and CT scans were acquired and co-registered. Following radical prostatectomy, transverse sections were taken of the prostate. A single pathologist outlined each tumor focus on the histological sections and then scanned the sections directly on a flat-bed scanner. The JPEG images of the prostatectomy transverse sections were manually deformed to account for shrinkage and distortion of the prostate ex-vivo (Fig. 1). These deformed prostatectomy images were then co-registered with the CT scan. The image acquisition, histopathological preparation and co-registration protocols have previously been described in detail (8).

Generation of contours

Contours for the prostate, seminal vesicles, and the surrounding normal structures were generated as per the RTOG 0126 protocol (9). According to our previous study (8), the contour of ^{11}C-choline PET resulting in the best correlation with the prostatectomy-defined DIL was $SUV_{60\%}$. $SUV_{70\%}$ had higher specificity at the expense of lower sensitivity. As such, for the current study, $SUV_{60\%}$ and $SUV_{70\%}$ were used as the volumes for dose painting (Fig. 1F).

Four PTV volumes were generated for each patient. PTV1 was defined as the prostate and seminal vesicles with a 6 mm isotropic expansion margin. PTV2 was defined as the prostate alone with a 6 mm isotropic expansion margin. PTV_{S60} was defined as the $SUV_{60\%}$ volume with a 6 mm isotropic expansion margin with 6 mm exclusions from the rectum and bladder. PTV_{S70} was defined as the $SUV_{70\%}$ volume with a 6 mm isotropic expansion margin and 6-8 mm exclusions from the rectum and bladder.

Using the co-registered prostatectomy specimen images, DILs were contoured and designated “PathDIL” (Fig. 1F). These were used as the “gold standard” contours for the true location of the tumor for the biological modeling calculations.

Radiotherapy Treatment Planning

All of the images and contours were imported into a treatment planning system, CMS Monaco 2.03 (Elekta CMS Software, St Louis, MO, USA). Step-and-shoot IMRT treatment plans were created using seven equally spaced fields.

All plans had a dose of 60 Gy prescribed to the PTV1. Three radiotherapy plans were generated for each patient: a standard whole-prostate radiotherapy plan ($PLAN_{78}$) with a dose of 78 Gy prescribed to the PTV2; a dose escalation plan ($PLAN_{78\text{-}90}$) with a dose of 78 Gy prescribed to the PTV2, 84 Gy to the PTV_{S60} and 90 Gy to the PTV_{S70}; and a dose escalation / de-escalation plan ($PLAN_{72\text{-}90}$) with 72 Gy prescribed to the PTV2, 84 Gy to the PTV_{S60} and 90 Gy to the PTV_{S70}. All of the treatment plans were based on schedules with 39 fractions.

The prescribed dose for each PTV was defined as the median dose within the volume (D_{50}). In addition, the D_{98} within each PTV had to exceed 95% of the prescription dose, and the D_2 within the highest dose PTV could not exceed 107% of the prescription dose.

Dose constraints for OARs were combined from the QUANTEC review (2) and the RTOG 0126 protocol (9), taking the more conservative values from each. These constraints are listed in Table 2.

Biological modeling

TCP was calculated using the modified (10) Zaider and Minnerbo (11) formula. The following parameters were used: $\alpha/\beta = 3.1$, $\alpha = 0.15$, $\beta = 0.048$, $\lambda = 0.0165$ and tumor cell density = 10^7 clonogens/cm^3 (12). Two different TCP calculations were calculated for each plan for each patient, according to two different ways of defining the actual tumor volume: TCP_{PET} was calculated using the above parameters, using $SUV_{60\%}$ as the tumor volume; and TCP_{path} was calculated using the above parameters, using the prostatectomy-defined DIL volume as the tumor volume.

The TCP_{PET} metric (which takes $SUV_{60\%}$ as the tumor volume) follows the methodology of most previous planning studies (5-7), which assume that the imaging-defined volume is representative of the actual tumor with 100% accuracy. This is almost without exception an overestimation of the accuracy of imaging in prostate cancer. However, this metric was included as it allows comparisons with previous planning studies. The TCP_{path} metric, which takes the prostatectomy specimen-defined DIL volume as the tumor volume is a more novel way of calculating TCP. Since PET scans do not always correlate well with the actual tumor location, this may be more representative of real world scenarios.

NTCP was calculated for the rectum using the Lyman-Kutcher-Burman formula (13). The following parameters were used for rectal NTCP (for Grade ≥ 2 late rectal toxicity): n = 0.09, m = 0.13 and TD_{50} = 76.9 Gy (14). Doses were normalized to 2 Gy per fraction using α/β ratios of 3 Gy for the rectum (14).

RESULTS

In all 24 radiotherapy plans generated, the target volume objectives as well as the OAR dose constraints were met without exception. The dose distributions for the three plans for a representative patient (Patient 8) are shown in Fig. 2. The TCP_{PET} and TCP_{path} values for each patient for each plan are shown in Table 3.

The mean TCP_{PET} values for $PLAN_{78}$, $PLAN_{78\text{-}90}$ and $PLAN_{72\text{-}90}$ were 65%, 97% and 96%, respectively. $PLAN_{78\text{-}90}$ had a 49% higher TCP_{PET} than $PLAN_{78}$ and this difference was statistically significant ($p = 0.002$). $PLAN_{72\text{-}90}$ had a 48% higher TCP_{PET} than $PLAN_{78}$ and this difference was statistically significant ($p = 0.001$). There was no statistically significant difference between $PLAN_{78\text{-}90}$ and $PLAN_{72\text{-}90}$ ($p = 0.673$). For $PLAN_{78\text{-}90}$, every single patient's TCP_{PET} was improved compared with $PLAN_{78}$. Similarly, for $PLAN_{72\text{-}90}$, every single patient's TCP_{PET} was improved compared with $PLAN_{78}$.

The mean TCP_{path} values for $PLAN_{78}$, $PLAN_{78\text{-}90}$ and $PLAN_{72\text{-}90}$ were 71%, 97% and 89%, respectively. $PLAN_{78\text{-}90}$ had a 37% higher TCP_{path} than $PLAN_{78}$.and this difference was statistically significant ($p < 0.001$). $PLAN_{72\text{-}90}$ had a 26% higher TCP_{path} than $PLAN_{78}$ and this difference was statistically significant ($p = 0.014$). There was no statistically significant difference between $PLAN_{78\text{-}90}$ and $PLAN_{72\text{-}90}$ (p

= 0.15). For $PLAN_{78\text{-}90}$, every single patient's TCP_{path} was improved compared with $PLAN_{78}$. For $PLAN_{72\text{-}90}$, however, one patient (Patient 8 on Table 3) actually had a drop in TCP_{path} compared with $PLAN_{78}$. This patient's DIL contours and dose distributions are shown in Fig. 2.

The mean rectal NTCP values for $PLAN_{78}$, $PLAN_{78\text{-}90}$ and $PLAN_{72\text{-}90}$ were 4.6%, 3.7% and 3.2%, respectively. There were no statistically significant differences between the three plans ($p = 0.082$).

DISCUSSION

This study demonstrates the technical feasibility of dose painting for localized prostate cancer. Two dose painting approaches were compared with standard radiotherapy and both were found to be achievable while staying within published dose constraints. Both dose painting approaches had superior TCPs to standard radiotherapy, while not having significantly different NTCPs. There was also no significant difference in the TCPs and NTCPs between the two dose painting strategies; however, worryingly, one patient's TCP_{path} decreased when comparing $PLAN_{78}$ with $PLAN_{72\text{-}90}$.

In this particular case, the drop in TCP_{path} with $PLAN_{72\text{-}90}$ is not surprising. While ^{11}C-choline PET has excellent overall accuracy for defining DILs in the entire patient cohort, in some individual patients the extent of disease may not be accurately defined (Fig. 2). With the $PLAN_{72\text{-}90}$ approach, the region outside of the ^{11}C-choline PET-defined PTV volume is dose de-escalated to 72 Gy. Therefore, in a patient where ^{11}C-

choline PET does not accurately define the entire DIL volume, a large proportion of the DIL may be under-dosed, leading to a lower TCP_{path}.

The strategy of dose escalation to the imaging-defined DILs and dose de-escalation to the rest of the prostate has been advocated by a number of previous studies. van Lin *et al.* (5) performed a radiotherapy planning study on five patients who had DILs defined using DCE-MRI and MRS. Two plans were generated for each patient: a standard whole prostate radiotherapy plan to 78 Gy, and an experimental plan with DIL dose escalation to 90 Gy and rest of the prostate dose de-escalation to 70 Gy. The two plans had similar TCPs, however the experimental plans had lower NTCPs. The authors concluded that the experimental plan had a higher therapeutic ratio and therefore may be preferable. Seppala *et al.* (7) performed a planning study on 12 patients who had DILs defined using ^{11}C-acetate PET scans. Six plans were compared for each patient: a whole prostate radiotherapy plan to 77.9 Gy, and DIL dose escalations to 77.9 Gy, 81 Gy, 84 Gy, 87 Gy and 90 Gy with rest-of-prostate dose de-escalations to 72 Gy. They found that all of the DIL dose escalation approaches had superior TCP compared with the standard whole prostate radiotherapy plan, and that the highest probability of uncomplicated control was achieved with an average dose of 82.1 Gy to the dose-escalated volume.

All of these studies calculated TCPs according to the way that we calculated TCP_{PET}; meaning that they calculated the TCP based on imaging data alone. For the purposes of calculating TCP, these studies assumed that imaging has 100% sensitivity for defining the DIL, which is almost without exception an overestimation. As such, these studies assumed that their dose escalation volumes contained the DILs in their

entirety, and that their dose de-escalation volumes did not contain any portions of the DILs. It was therefore a foregone conclusion that dose de-escalation to volumes containing no DILs would not degrade the overall TCPs according to this method of calculation. In fact, that is what we found with our TCP_{PET} calculation – even $PLAN_{72\text{-}90}$, which contains a dose de-escalation volume resulted in higher TCPs for every single patient.

The reason these previous studies calculated their TCPs based on imaging data alone is that they did not have histopathological data available for comparison. Our study is unique in that all patients underwent radical prostatectomy, therefore we could use the histopathological sections to correlate with the imaging data for calculating TCP_{path}. TCP_{path} takes into consideration scenarios where the imaging and the true location of the tumor do not correlate well, and therefore is a more appropriate metric for estimating differences in TCPs between plans.

The drop in TCP_{path} for that single case calls into question the safety of the $PLAN_{72\text{-}90}$ approach, or in fact any dose escalation / de-escalation approach where the sensitivity of imaging is not close to 100%. This is consistent with the findings of the study by Niyazi *et al.* (15), which demonstrated that a low PET sensitivity along with small variations in other parameters such as α/β ratio, $\gamma 50$ and dose may completely abrogate the benefits of a ^{11}C-choline PET-based dose escalation.

Our study does have a number of limitations, however. Firstly, like most previous planning studies, the effects of inter- and intra-fractional movements are not simulated.

It is therefore unknown how well our dose painted PTVs would cover the DILs, or how much additional dose the OARs may receive in real world scenarios.
Secondly, none of the biological models have been clinically validated. Markedly different results can be obtained if different models are used, or if different parameters are applied to these models (2). As such, the values obtained from these models should be interpreted with caution, and be used only to compare the relative differences between the plans.

It must also be borne in mind that the ^{11}C-choline PET scan itself has a number of limitations. The accuracy is not perfect, with our previous study (8) reporting a sensitivity of 79% for the $SUV_{60\%}$ contouring method, and other studies indicating sensitivities as low as 66% (16). Previous studies have demonstrated that prostatic disorders other than cancer (such as prostatitis, benign prostatic hypertrophy and high grade prostatic intraepithelial neoplasia) may accumulate ^{11}C-choline, which can affect its specificity (16, 17). Furthermore, the tumor configuration affects the sensitivity, with small lesions being poorly visualized (17).
Other imaging modalities such as multiparametric MRI have already been successfully employed to guide prostate dose painting in clinical trials. A prospective study of 230 patients with prostate cancer treated with MRI and MRS-guided radiotherapy dose painting showed that the treatment was feasible and resulted in low acute toxicities (18). In this context, it would be an interesting direction for future research to directly compare dose painting strategies using the more well-established multiparametric MRI with ^{11}C-choline PET.

The central premise of our study is that higher radiotherapy doses delivered to the tumor will result in higher local control rates. Higher local control rates may then lead to decreased metastatic dissemination (19). The ultimate aim of this study however, is to evaluate strategies that can one day potentially improve survival in patients with prostate cancer. This is most likely not achievable with dose-escalation alone, due to factors such as the high prevalence of micrometastatic disease already present at the time of treatment (19). Systemic therapies such as androgen deprivation and other emerging therapies (20) will probably need to be used in conjunction with dose escalation to lead to meaningful improvements in outcomes.

CONCLUSIONS

Dose painting by contours using ^{11}C-choline PET scans is technically feasible. This study evaluated biological modeling based on both PET-defined DILs and pathologically defined DILs, showing that both $PLAN_{78\text{-}90}$ and $PLAN_{72\text{-}90}$ resulted in higher TCPs than $PLAN_{78}$, while having similar NTCPs. As such, both $PLAN_{78\text{-}90}$ and $PLAN_{72\text{-}90}$ have higher therapeutic ratios. Caution should be applied in using the dose escalation / de-escalation strategy as evidenced by the drop in TCP_{path} for a single patient when $PLAN_{72\text{-}90}$ is compared with $PLAN_{78}$.

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REFERENCES

1. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* 2009;74:1405-1418.
2. Marks LB, Yorke ED, Jackson A, *et al.* Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010;76:S10-19.
3. 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.
4. Pucar D, Hricak H, Shukla-Dave A, *et al.* Clinically significant prostate cancer local recurrence after radiation therapy occurs at the site of primary tumor: magnetic resonance imaging and step-section pathology evidence. *Int J Radiat Oncol Biol Phys* 2007;69:62-69.
5. van Lin EN, Futterer JJ, Heijmink SW, *et al.* IMRT boost dose planning on dominant intraprostatic lesions: gold marker-based three-dimensional fusion of CT with dynamic contrast-enhanced and 1H-spectroscopic MRI. *Int J Radiat Oncol Biol Phys* 2006;65:291-303.
6. Pinkawa M, Attieh C, Piroth MD, *et al.* Dose-escalation using intensity-modulated radiotherapy for prostate cancer--evaluation of the dose distribution with and without 18F-choline PET-CT detected simultaneous integrated boost. *Radiother Oncol* 2009;93:213-219.
7. Seppala J, Seppanen M, Arponen E, *et al.* Carbon-11 acetate PET/CT based dose escalated IMRT in prostate cancer. *Radiother Oncol* 2009;93:234-240.
8. Chang JH, Lim Joon D, Lee ST, *et al.* Histopathological correlation of 11C-choline PET scans for target volume definition in radical prostate radiotherapy. *Radiother Oncol* 2011;99:187-192.
9. Michalski JM, Purdy J, Bruner DW, *et al.* A phase III randomized study of high dose 3D-CRT/IMRT versus standard dose 3D-CRT/IMRT in patients treated for localized prostate cancer. RTOG 0126 [Internet]. [updated 2004 Oct 18; cited 2010 Dec 19]; Available from: www.rtog.org/members/protocols/0126/p0126.pdf.
10. Warkentin B, Stavrev P, Stavreva N, *et al.* A TCP-NTCP estimation module using DVHs and known radiobiological models and parameter sets. *J Appl Clin Med Phys* 2004;5:50-63.
11. Zaider M, Minerbo GN. Tumour control probability: a formulation applicable to any temporal protocol of dose delivery. *Phys Med Biol* 2000;45:279-293.
12. Wang JZ, Guerrero M, Li XA. How low is the alpha/beta ratio for prostate cancer? *Int J Radiat Oncol Biol Phys* 2003;55:194-203.
13. Kutcher GJ, Burman C, Brewster L, *et al.* Histogram reduction method for calculating complication probabilities for three-dimensional treatment planning evaluations. *Int J Radiat Oncol Biol Phys* 1991;21:137-146.
14. Michalski JM, Gay H, Jackson A, *et al.* Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys* 2010;76:S123-129.
15. Niyazi M, Bartenstein P, Belka C, *et al.* Choline PET based dose-painting in prostate cancer--modelling of dose effects. *Radiat Oncol* 2010;5:23.

16. Farsad M, Schiavina R, Castellucci P, *et al.* Detection and localization of prostate cancer: correlation of (11)C-choline PET/CT with histopathologic step-section analysis. *J Nucl Med* 2005;46:1642-1649.
17. Souvatzoglou M, Weirich G, Schwarzenboeck S, *et al.* The sensitivity of [11C]choline PET/CT to localize prostate cancer depends on the tumor configuration. *Clin Cancer Res* 2011;17:3751-3759.
18. Fonteyne V, Villeirs G, Speleers B, *et al.* Intensity-modulated radiotherapy as primary therapy for prostate cancer: report on acute toxicity after dose escalation with simultaneous integrated boost to intraprostatic lesion. *Int J Radiat Oncol Biol Phys* 2008;72:799-807.
19. Morgan PB, Hanlon AL, Horwitz EM, *et al.* Timing of biochemical failure and distant metastatic disease for low-, intermediate-, and high-risk prostate cancer after radiotherapy. *Cancer* 2007;110:68-80.
20. Longo DL. New therapies for castration-resistant prostate cancer. *N Engl J Med* 2010;363:479-481.