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**Histopathological correlation of 11C-choline PET scans for target volume definition in radical prostate radiotherapy**

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# IMRT DOSE PAINTING FOR LOCALIZED PROSTATE CANCER USING <sup>11</sup>C-CHOLINE PET SCANS

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## **CONFLICT OF INTEREST NOTIFICATION**

The authors declare that there are no conflicts of interest.

## ABSTRACT

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

**Methods and materials:** This was a radiotherapy planning study of eight patients with intermediate to high risk prostate cancer who had  $^{11}\text{C}$ -choline PET scans prior to radical prostatectomy. Two different contours were semi-automatically generated on the basis of the PET scans for each patient: 60% and 70% of the maximum standardized uptake values ( $\text{SUV}_{60\%}$  and  $\text{SUV}_{70\%}$ ). Three IMRT plans were generated for each patient:  $\text{PLAN}_{78}$  which consisted of whole prostate radiotherapy to 78 Gy;  $\text{PLAN}_{78-90}$  which consisted of whole prostate radiotherapy to 78 Gy, a boost to the  $\text{SUV}_{60\%}$  to 84 Gy and a further boost to the  $\text{SUV}_{70\%}$  to 90 Gy; and  $\text{PLAN}_{72-90}$  which consisted of whole prostate radiotherapy to 72 Gy, a boost to the  $\text{SUV}_{60\%}$  to 84 Gy and a further boost to the  $\text{SUV}_{70\%}$  to 90 Gy. The technical 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 ( $\text{TCP}_{\text{PET}}$ ) and on prostatectomy-defined volumes ( $\text{TCP}_{\text{path}}$ ), and rectal normal tissue complication probabilities (NTCP) were compared between the plans.

**Results:** All plans for all patients reached prescription doses while adhering to published dose constraints. The  $\text{TCP}_{\text{PET}}$  values for  $\text{PLAN}_{78}$ ,  $\text{PLAN}_{78-90}$  and  $\text{PLAN}_{72-90}$  were 65%, 97% and 97%, respectively. The  $\text{TCP}_{\text{path}}$  values were 71%, 97% and 89%, respectively. Both  $\text{PLAN}_{78-90}$  and  $\text{PLAN}_{72-90}$  had significantly higher  $\text{TCP}_{\text{PET}}$  ( $p = 0.002$  and  $0.001$ ) and  $\text{TCP}_{\text{path}}$  ( $p < 0.001$  and  $0.014$ ) than  $\text{PLAN}_{78}$ .  $\text{PLAN}_{78-90}$  and  $\text{PLAN}_{72-90}$  were not significantly different in terms of  $\text{TCP}_{\text{PET}}$  or  $\text{TCP}_{\text{path}}$ . There were no significant differences in rectal NTCPs between the three plans.

**Conclusions:** IMRT dose painting for localized prostate cancer using  $^{11}\text{C}$ -choline PET scans is technically feasible. Dose painting results in higher TCPs without higher NTCPs and therefore higher therapeutic ratios.

## INTRODUCTION

There is a clear dose-response relationship between radiation dose and biochemical tumor control rates in prostate cancer (1). A meta-analysis (1) shows that an increase of radiotherapy dose from 70 Gy to 80 Gy results in an increase in biochemical control (BC) 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, 4) 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 support the use of dose painting in prostate cancer (5, 6). These studies show that dominant intraprostatic lesions (DILs) identified on pre-treatment imaging are the main sites of local recurrence following radiotherapy. 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 including  $^{18}\text{F}$ -fluorocholine PET (7),  $^{11}\text{C}$ -acetate PET (8), dynamic contrast enhanced (DCE) MRI (9), magnetic resonance spectroscopy (MRS) (9, 10), and endorectal coil MRI (11).

This study examines the use of dose painting in prostate cancer using  $^{11}\text{C}$ -choline PET scans.  $^{11}\text{C}$ -choline is a radiotracer based on choline, an essential component of the cell membrane (12, 13). Choline is taken up into cells via the choline transport system. Intracellularly, it is phosphorylated by choline kinase to phosphorylcholine and integrated into cell membrane phospholipids. Prostate cancer cells show increased transport as well as increased expression of choline kinase compared with normal cells, providing the rationale for the use of  $^{11}\text{C}$ -choline as a radiotracer in prostate cancer.

This study is an extension of a previous study performed at Austin Health (14). In the previous study, eight men with intermediate to high risk prostate cancer who had  $^{11}\text{C}$ -choline PET scans prior to radical prostatectomies were studied. The patients'  $^{11}\text{C}$ -choline PET scans were compared with their prostatectomy specimens to quantify the degree of correlation for the purposes of target volume definition for prostate radiotherapy. Several contouring methodologies were developed which could accurately define DILs. The current study uses the same patient cohort and the contouring methods developed from that study to determine the technical feasibility of using  $^{11}\text{C}$ -choline PET for dose painting by contours.

## **METHODS AND MATERIALS**

### *Study design*

This is a radiotherapy planning study designed to confirm the technical feasibility of delivering radiotherapy according to the “dose painting by contours” approach (4). The study cohort consisted of eight patients with intermediate to very high risk (15) prostate cancer who had  $^{11}\text{C}$ -choline PET scans prior to radical prostatectomy. Their characteristics are described in Table 1.

The patients' pre-prostatectomy  $^{11}\text{C}$ -choline PET and CT scans as well as their prostatectomy specimens were analyzed. The Austin Health Human Research Ethics committee granted approval for this study. All patients consented to the collection and use of their data for research purposes.

### *Imaging*

$^{11}\text{C}$ -choline PET scans were performed on an Allegro PET scanner (Philips Healthcare, Cleveland, OH, USA). 30-second transmission scans covering the prostate and lower abdominal regions were performed using a single 740 MBq  $^{137}\text{Cs}$  point source for accurate patient positioning and attenuation correction. List-mode emission scans were acquired immediately after intravenous injection of approximately 370 MBq of  $^{11}\text{C}$ -choline and continued for 60 minutes. Scans were acquired in a single bed position, with only the pelvis imaged. All images were reconstructed using a 3D row action maximum likelihood iterative algorithm (RAMLA).

CT scans were obtained separately at 5 mm slice thickness.  $^{11}\text{C}$ -choline PET scans were aligned and fused with the CT scans.

### *Histopathology*

Following radical prostatectomy, the prostate was fixed overnight in 4% neutral buffered formalin. Transverse sections were taken of the prostate perpendicular to its posterior surface at 3-5mm intervals. Sections were then stained with hematoxylin and eosin. A single pathologist reviewed the specimen and outlined each tumor focus on the histological sections. Marked specimens were scanned directly on a flat-bed scanner.

### *Image co-registration*

All images were co-registered and analyzed using MIMvista (MIM Software Inc., Cleveland, OH, USA). The  $^{11}\text{C}$ -choline PET scan was manually co-registered with the CT scan using rigid body transformation (Fig. 1). The JPEG images of the prostatectomy transverse sections were divided up, stacked, and reoriented to match the CT scan slices. In order to account for shrinkage and distortion of the prostate ex-vivo, these images were manually deformed using a mesh in Adobe Illustrator CS5 (Adobe Systems Incorporated, San Jose, CA, USA) to match anatomical landmarks on the CT scan (e.g. urethra, seminal vesicle tissue in superior slices, edges of prostate) (Fig. 2). This was then co-registered with the CT scan. This stack of prostatectomy slice images (3-5 mm slice thickness) was then co-registered with the CT scan (5 mm slice thickness). Both the prostatectomy images and the CT scan images represented averages across the thicknesses of the slices. The similar slice thicknesses and averaging effect through the slices allowed easy registration.

### *Generation of contours*

Contours for the prostate, seminal vesicles, and the surrounding normal structures were generated as per the RTOG 0126 protocol (16). Contours for the dose painting volumes were generated using MIMvista.

According to our previous study (14), the contour of  $^{11}\text{C}$ -choline PET resulting in the best correlation with the prostatectomy-defined DIL was  $\text{SUV}_{60\%}$  (60% of the maximum standardized uptake value), which had a dice similarity coefficient,

sensitivity and specificity of 0.64, 79% and 72% respectively.  $SUV_{70\%}$  (70% of the maximum standardized uptake value) had higher specificity at the expense of lower sensitivity, with a dice similarity coefficient, sensitivity and specificity of 0.59, 56% and 88% respectively. As such, for the current study,  $SUV_{60\%}$  and  $SUV_{70\%}$  were used as the volumes for dose painting (Fig. 3).

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. PTV60 was defined as the  $SUV_{60\%}$  volume with a 6 mm isotropic expansion margin with 6 mm exclusions from the rectum and bladder. PTV70 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 for the biological modeling calculations and designated “PathDIL” (Fig. 3).

### *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. Inhomogeneity corrections were calculated using X-ray Voxel Monte Carlo algorithms. A minimum of 5 monitor units was set for each segment.

Three radiotherapy plans were generated for each patient: a standard whole-prostate radiotherapy plan (PLAN<sub>78</sub>) with a dose of 78 Gy prescribed to the PTV2; a dose escalation plan (PLAN<sub>78-90</sub>) with a dose of 78 Gy prescribed to the PTV2, 84 Gy to the PTV60 and 90 Gy to the PTV70; and a dose escalation/de-escalation plan (PLAN<sub>72-90</sub>) with 72 Gy prescribed to the PTV2, 84 Gy to the PTV60 and 90 Gy to the PTV70. All plans also had a dose of 60 Gy prescribed to the PTV1 (which includes the seminal vesicles). All of the treatment plans were based on schedules with 39 fractions. The normalized total doses in 2 Gy fractions (NTD<sub>2Gy</sub>) are listed in Table 2.

As per ICRU 83 recommendations (17), 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 (16), taking the more conservative values from each. As per the RTOG 0126 protocol, dose constraints were calculated on the basis of rectums including contents and bladders including contents. These constraints are listed in Table 3.

### *Biological modeling*

The tumor control probability (TCP) and normal tissue complication probability (NTCP) were calculated for each plan for each patient.

TCP was calculated using the modified (18) Zaider and Minnerbo (19) 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<sup>3</sup> (20). Two different TCP calculations were calculated for each plan for each patient, according to two different ways of defining the actual tumor volume: TCP<sub>PET</sub> was calculated using the above parameters, using SUV<sub>60%</sub> as the tumor volume; and TCP<sub>path</sub> was calculated using the above parameters, using the prostatectomy-defined DIL volume as the tumor volume.

The TCP<sub>PET</sub> metric, which takes SUV<sub>60%</sub> as the tumor volume follows the methodology of most previous planning studies (7-9), 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<sub>path</sub> 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.

A TCP calculation for microscopic extension of disease was also performed. This calculation takes account of clonogens that may be present in the prostate outside of the prostatectomy-defined DIL volume or the PET scan-defined volume. This used the same parameters as described above, except used a tumor cell density of  $10^5$  clonogens/cm<sup>3</sup> and used the prostate volume excluding either the prostatectomy-defined DIL volume or the PET scan-defined volume. Even at the lowest dose of 72 Gy, the TCP for this region did not significantly affect the overall TCP, therefore was not included in the final analysis.

NTCP was calculated for the rectum using the previously defined “rectum including contents” volume. NTCP was calculated using the Lyman-Kutcher-Burman formula (21). The following parameters were used for rectal NTCP (for Grade  $\geq 2$  late rectal toxicity):  $n = 0.09$ ,  $m = 0.13$  and  $TD_{50} = 76.9$  Gy (22). Doses were normalized to 2 Gy per fraction using  $\alpha/\beta$  ratios of 3 Gy for the rectum (22).

### *Statistical analyses*

Statistical analyses were performed using SPSS version 17 (IBM, Armonk, NY, USA). Biological modeling calculations were compared between the three plans (PLAN<sub>78</sub>, PLAN<sub>78-90</sub>, PLAN<sub>72-90</sub>) using ANOVA and paired t-tests.

## **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. 4. The TCP<sub>PET</sub> and TCP<sub>path</sub> values for each patient for each plan are shown in Table 4.



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

The mean TCP<sub>path</sub> values for PLAN<sub>78</sub>, PLAN<sub>78-90</sub> and PLAN<sub>72-90</sub> were 71%, 97% and 89%, respectively. PLAN<sub>78-90</sub> had a 37% higher TCP<sub>path</sub> than PLAN<sub>78</sub> and this difference was statistically significant ( $p < 0.001$ ). PLAN<sub>72-90</sub> had a 26% higher TCP<sub>path</sub> than PLAN<sub>78</sub> and this difference was statistically significant ( $p = 0.014$ ). There was no statistically significant difference between PLAN<sub>78-90</sub> and PLAN<sub>72-90</sub> ( $p = 0.15$ ). For PLAN<sub>78-90</sub>, every single patient's TCP<sub>path</sub> was improved compared with PLAN<sub>78</sub>. For PLAN<sub>72-90</sub>, however, one patient (Patient 8 on Table 4) actually had a drop in TCP<sub>path</sub> compared with PLAN<sub>78</sub>. This patient's DIL contours and dose distributions are shown in Fig. 4.

The mean rectal NTCP values for PLAN<sub>78</sub>, PLAN<sub>78-90</sub> and PLAN<sub>72-90</sub> 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. Overall, there was no significant difference in the TCPs and NTCPs between the two dose painting strategies; however, worryingly, one patient's TCP<sub>path</sub> actually decreased when comparing PLAN<sub>78</sub> with PLAN<sub>72-90</sub>.

This patient's drop in TCP<sub>path</sub> with PLAN<sub>72-90</sub> is not surprising. While <sup>11</sup>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. 4). With the PLAN<sub>72-90</sub> approach, the region outside of the <sup>11</sup>C-choline PET-defined PTV volume is dose de-escalated to 72 Gy. Therefore, in a patient where <sup>11</sup>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<sub>path</sub>.

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.* (9) 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. Pinkawa *et al.* (7) performed a radiotherapy planning study on 12 patients who had DILs defined using  $^{18}\text{F}$ -fluorocholine PET scans. Two comparisons were made: whole prostate irradiation to 76 Gy with or without a boost to the DIL to 80 Gy, or 66.6 Gy to the whole prostate with or without a boost to 83.25 Gy. Both comparisons resulted in increases in the EUDs of the DILs with only minor changes to the bladder and rectum EUDs. Seppala *et al.* (8) performed a planning study on 12 patients who had DILs defined using  $^{11}\text{C}$ -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 we calculated  $\text{TCP}_{\text{PET}}$ ; meaning 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  $\text{TCP}_{\text{PET}}$  calculation – even PLAN72-90, 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. In our study, all patients underwent radical prostatectomy, therefore we could use the histopathological sections to correlate with the imaging data for calculating  $\text{TCP}_{\text{path}}$ .  $\text{TCP}_{\text{path}}$  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  $\text{TCP}_{\text{path}}$  for that single patient calls into question the safety of the PLAN72-90 approach, or in fact any dose escalation / de-escalation approach where the sensitivity of imaging is not close to 100%. While the overall  $\text{TCP}_{\text{path}}$  for the entire patient cohort is improved with PLAN72-90 as compared with PLAN78, it is unacceptable that a dose painting strategy may result in poorer tumor control rates for some patients. The PLAN78-90 approach however does not have a dose de-escalation component and thus ensures that the  $\text{TCP}_{\text{path}}$  is improved. Additionally, the NTCPs associated with PLAN78-90 are non-statistically significantly different from the other two plans, so theoretically should not result in higher toxicity rates. For this reason, the PLAN78-90 dose escalation strategy may be more preferable than the PLAN72-90 dose escalation / de-escalation strategy.

The magnitude of the improvement in TCPs with our dose painting strategies is comparable to the improvements in 5 year BC rates noted in previous studies. Miralbell *et al.* (11) studied 50 patients who received radiotherapy to the whole prostate to a dose of 64 Gy followed by a hypofractionated boost of two fractions of 5,

6, 7 or 8 Gy to the DIL. This corresponds to  $NTD_{2Gy}$  values of 82 – 104 Gy ( $\alpha/\beta = 2$ ). The 5 year biochemical disease-free survival and disease-specific survival were 98% and 100%, respectively. Vianni *et al.* (1) performed a meta-analysis of randomized controlled trials on prostate radiotherapy dose-escalation and developed a linear correlation model between radiotherapy dose and biochemical failure. According to this model, high risk prostate cancer patients who receive a dose of 78 Gy are predicted to have 5 year BC rates of approximately 66%. We prescribed two dose escalation levels – one at 84 Gy in 39 fractions ( $NTD_{2Gy}(\alpha/\beta = 2) = 87.2$  Gy), and another at 90 Gy in 39 fractions ( $NTD_{2Gy}(\alpha/\beta = 2) = 96.9$  Gy). According to Vianni *et al.*'s linear correlation model, these two dose levels are predicted to result in 5 year BC rates of 84% and 100% respectively. In our study, the mean  $TCP_{path}$  with  $PLAN_{78}$  and  $PLAN_{78-90}$  are 71% and 98% respectively, which are very close to the results found in both the Miralbell *et al.* study (11) and the Viani *et al.* linear correlation model (1).

Additionally, the values of the rectal NTCPs are comparable to that predicted by the QUANTEC review (16). The QUANTEC review estimates the risk of grade 2 or higher late rectal toxicity to be less than 15% if none of the dose constraints are exceeded. From our calculations, the mean rectal NTCPs range from 3.2% to 4.6%. The highest rectal NTCP for any patient was 6.7%.

More important than the biological modeling calculations however, is the fact that both  $PLAN_{78-90}$  and  $PLAN_{72-90}$  can be deemed “technically feasible” according to published criteria. Our prescription reporting complies with what is suggested by ICRU 83 (17) and our dose constraints comply with both the QUANTEC review (2) and the RTOG 0126 randomized controlled trial (16). Previous prostate planning studies recorded their prescription doses according to a variety of criteria, and either did not include dose constraint data or used their own “in house” constraints. Seeing that our data complies with contemporary standards, the “technical feasibility” of our plans should be easier to judge.

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. In fact, because the PTV60 and PTV70 volumes had 6-8mm exclusions from the bladder and rectum (in order to meet dose constraints), these volumes may not give the DILs the same level of coverage as predicted by these plans in the face of significant antero-posterior movement. This is a similar issue to that experienced by clinicians giving prostate PTVs a reduced posterior margin. However, because the PTV2 volume is isotropic without any exclusions in our study, the DILs should at least receive the PTV2 prescription dose.

A second limitation is that we used the same patient cohort that we used to validate our contouring strategy. Using the same contouring strategy on a different set of patients will not necessarily give the same degree of accuracy that we found in the original study. However, our methodology is still preferable to previous radiotherapy planning studies which used unvalidated contouring strategies (7, 8).

A third limitation, common to many planning studies, is the fact that 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.

The central premise of our study is that higher radiotherapy doses delivered to the tumor will result in higher local control rates (23). Higher local control rates may then lead to decreased metastatic dissemination (24-26). The ultimate aim of this study however, is to lead to work that can one day 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 (26). Systemic therapies such as androgen deprivation (27) and other emerging systemic therapies (28) will probably need to be used in conjunction with dose escalation to lead to meaningful improvements in outcomes.

## CONCLUSIONS

Dose painting by contours using  $^{11}\text{C}$ -choline PET scans is technically feasible. Both PLAN<sub>78-90</sub> and PLAN<sub>72-90</sub> resulted in higher TCPs than PLAN<sub>78</sub>, while having similar NTCPs. As such, both PLAN<sub>78-90</sub> and PLAN<sub>72-90</sub> have higher therapeutic ratios. Caution should be applied in using the dose escalation / de-escalation strategy as evidenced by the drop in TCP<sub>path</sub> for a single patient when PLAN<sub>72-90</sub> is compared with PLAN<sub>78</sub>.

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Tables/Figs Refs: to NCCN ([15](#)), QUANTEC review ([2](#)) RTOG 0126 protocol ([16](#))

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