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FULL PAPER

Effect of androgen deprivation therapy on intraprostatic tumour volume identified on ^{18}F choline PET/CT for prostate dose painting radiotherapy

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Objective: Prostate dose painting radiotherapy requires the accurate identification of dominant intraprostatic lesions (DILs) to be used as boost volumes; these can be identified on multiparametric MRI (mpMRI) or choline positron emission tomography (PET)/CT. Planning scans are usually performed after 2–3 months of androgen deprivation therapy (ADT). We examine the effect of ADT on choline tracer uptake and boost volumes identified on choline PET/CT.

Methods: Fluoroethylcholine (^{18}F choline) PET/CT was performed for dose painting radiotherapy planning in patients with intermediate- to high-risk prostate cancer. Initially, they were performed at planning. Owing to low visual tracer uptake, PET/CT for subsequent patients was performed at staging. We compared these two approaches on intraprostatic lesions obtained on PET using both visual and automatic threshold methods [prostate maximum standardized uptake value (SUV_{max}) 60%] when compared with mpMRI.

Results: PET/CT was performed during ADT in 11 patients (median duration of 85 days) and before ADT in 29 patients. ADT significantly reduced overall prostate volume by 17%. During ADT, prostate SUV_{max} was lower although it did not reach statistical significance (4.2 vs

6.6, $p = 0.06$); three patients had no visually identifiable PET DIL; and visually defined PET DILs were significantly smaller than corresponding mpMRI DILs ($p = 0.03$). However, all patients scanned before ADT had at least one visually identifiable PET DIL, with no significant size difference between MRI and visually defined PET DILs. In both groups, threshold PET produced larger DILs than visual PET. Both PET methods have moderate sensitivity (0.50–0.68) and high specificity (0.85–0.98) for identifying MRI-defined disease.

Conclusion: For visual contouring of boost volumes in prostate dose painting radiotherapy, ^{18}F choline PET/CT should be performed before ADT. For threshold contouring of boost volumes using our PET/CT scanning protocol, threshold levels of above 60% prostate SUV_{max} may be more suitable. Additional use of PET with MRI for radiotherapy planning can significantly change the overall boost volumes compared with using MRI alone.

Advances in knowledge: For prostate dose painting radiotherapy, the additional use of ^{18}F choline PET with MRI can significantly change the overall boost volumes, and PET should be performed before hormone therapy, especially if boost volumes are visually identified.

INTRODUCTION

Higher radiation doses to the whole prostate have been shown to improve biochemical relapse free survival for prostate cancer but at the cost of increased rectal toxicity.¹ Dose painting radiotherapy boosts tumour volumes [dominant intraprostatic lesions (DILs)] whilst delivering the standard dose to the rest of the prostate. Cohort studies have demonstrated outcomes without increased toxicity.^{2–5} These DILs have been contoured using a co-registered multiparametric MRI (mpMRI) in several studies such as Dose Escalation to Intraprostatic tumour Nodules in localised prostate Cancer

(DELINEATE) (ISRCTN04483921), Hypofractionated External beam Image-Guided Highly Targeted radiotherapy (HEIGHT) (NCT01411332) and Focal Lesion Ablation Microboost In Prostate Cancer (FLAME) trials.⁶

An alternative imaging modality for identifying lesions is the positron emission tomography CT scan (PET/CT). The standard treatment protocol for patients of intermediate and high risks combines several months of neoadjuvant androgen deprivation therapy (ADT) prior to radiotherapy. One option is for the PET/CT scan to be performed before

ADT (*i.e.* at staging), which will allow outlining of the original boost volume. However, this can complicate co-registration of the PET with planning CT since 2–3 months of ADT can reduce the overall prostate size by around 10–20%. Another option is for the PET/CT to be performed during ADT. This would allow the CT component of the scan to be used for planning, reducing the requirement for image co-registration and the number of scans performed. Studies have used this second option, but there are no data available to quantify the effects of ADT on the intraprostatic tracer uptake and boost volume sizes.²

Different isotopes have been used to radiolabel choline as a tracer for prostate cancer.⁷ There is more evidence for the use of ¹¹C choline, where automatic contouring by using the threshold of SUV_{60%} was found to result in the best correlation with pathology in the only study that has systematically analysed different threshold methods.⁸ However, fluoroethylcholine (¹⁸F choline) has the advantage of a longer half-life which allows its use at centres without an onsite cyclotron and permits use of imaging protocols involving prolonged uptake times.⁹ Currently, there is no available evidence for the best threshold to use for ¹⁸F choline.

The Biologically Optimised Intensity Modulated Radiotherapy for Prostate Radiotherapy clinical trial (NCT02125175) investigating dose painting by contours used both MRI [staging mpMRI and

planning T₂ weighted MRI (T2w MRI)] and ¹⁸F choline PET/CT to define the boost volumes.⁵ In the study development phase, patients had PET/CT imaging at planning whilst on ADT (“ADT group”). As visual tracer uptake was noted to be low for the first 10 patients, subsequent patients had PET/CT imaging at staging before ADT (“ADT-naïve group”). By using the tumour volumes defined on MRI as the reference standard, we have retrospectively analysed these scans to quantify the effect of ADT on the tumour volumes on PET, identified either by manual contouring (visual method) or automatic contouring (threshold method of 60% of prostate maximum SUV).

METHODS AND MATERIALS

Patient groups

The Biologically Optimised Intensity Modulated Radiotherapy for Prostate Radiotherapy clinical trial had been approved by the local ethics committee, and all patients had provided written informed consent. All patients had histologically confirmed intermediate- or high-risk prostate adenocarcinoma, T2a–T4 N0 disease on staging mpMRI, and a negative bone scan. Patients who had received ¹⁸F choline PET/CT were identified and separated into either the ADT group or the ADT-naïve group (Figure 1). The only difference in protocol between the two groups was whether ADT was started before or after the PET/CT. In all patients, fiducial markers were inserted in the prostate prior to PET/CT, planning MRI and planning CT.

Imaging protocol

All patients were scanned with the same PET/CT imaging protocol. The patients fasted for at least 4 hours before imaging and were asked to drink 500 ml of water before an intravenous injection of 370 MBq of ¹⁸F choline. A static pelvic scan performed at 90 min post injection in a single bed position over 10 min with a GE Discovery™ 690 PET/CT scanner (GE Medical Systems, Milwaukee, WI) was used. Images were reconstructed using the iterative line of response algorithm. Standardized uptake values (SUVs) were corrected for body weight. Prior to planning T2w MRI and planning CT, patients emptied their bowels with a mini enema and drank 300 ml of water. These scans were acquired with an indwelling 12-gauge soft Foley urethral catheter. The planning MRI was performed with turbo spin echo thin slice acquisition using a Philips Intera 1.5-T MRI scanner with phased array coils. The planning CT was performed by a Philips Brilliance wide-bore scanner, giving a 3-mm slice width.

Boost volume outlining protocol

On ProSoma (OSL Oncology Systems Limited, UK), the PET/CT and planning T2w MRI images were rigidly co-registered to the planning CT using fiducial markers and catheter. The whole prostate was contoured on both PET/CT and planning CT. The identification of DILs on MRI was performed by two radiation oncologists together by contouring on the planning T2w MRI whilst using the staging MRI (anatomical T2w and functional diffusion-weighted imaging) for reference. The identification of DILs on PET was performed visually (“visual PET”) by the two radiation oncologists on ProSoma and automatically using the threshold method [“threshold PET”—threshold was 60% of prostate maximum SUV (SUV_{max})] on Mirada (Mirada Medical

Figure 1. Sequence of imaging in both groups. ¹⁸F choline, fluoroethylcholine; ADT, androgen deprivation therapy; PET, positron emission tomography; T2w, T₂ weighted.

Table 1. Patient demographics

		ADT group	ADT-naïve group
Number of patients		11	29
Age (years) ^a		63 (49–76)	68 (50–77)
PSA (ng ml ⁻¹) ^a		16.6 (10.9–28.6)	9.0 (3.6–39.4)
ADT duration before PET/CT (days) ^a		85 (42–193)	–
High risk ^b		11	25
Gleason score	6	0	1
	7	7	21
	8, 9	4	7
TNM staging	T2a	0	5
	T2b, c	4	6
	T3a, b	7	18

ADT, androgen deprivation therapy; PET, positron emission tomography; PSA, prostate-specific antigen.

^aMedian and range.

^bRisk stratification as per prostate cancer: diagnosis and management (2014), the National Institute for Health and Care Excellence guidelines CG175.

Limited, Oxford, UK) where SUV_{max} uptake data was also collected. All information was available at the time of contouring (including pathology and other imaging).

Boost volume analysis

To unite the structures from both ProSoma and Mirada systems, the contours were imported into ARIA v. 11 (Varian Medical Systems, Palo Alto, CA) which displayed the registered images along with all structures. Data on DIL volumes were collected from ARIA. In order to account for registration errors between the primary data set (planning CT) and the secondary data sets (MRI or PET), a 5-mm isotropic expansion margin was performed around the prostate contours and the DIL contours within ARIA. Correlation analyses were used with these expanded volumes, with four different metrics used.⁸ Dice similarity coefficient (DSC) was defined according to the following formula: $\text{DSC} = 2 \times A \cap B / (A + B)$, where A and B are the volumes of the MRI-defined and PET-defined DIL contours and $A \cap B$ is the volume of the overlapping volumes. Sensitivity, specificity and Youden index were calculated according to the following formulas: sensitivity = $\text{TP} / (\text{TP} + \text{FN})$; specificity = $\text{TN} / (\text{TN} + \text{FP})$; Youden index = sensitivity + specificity – 1, where TP is the overlapping volume between MRI and PET

contours; FP is the PET contour excluding the MRI contour; FN is the MRI contour excluding the PET contour; and TN is the planning CT prostate contour excluding MRI and PET contours.

Statistical analysis

SPSS® v. 22.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) was used for statistical analysis. Owing to the skewed distribution of the contour volumes and SUV uptake values (kurtosis of up to 8.5 and 5.2, respectively), they were reported by median and range, with two-tailed significance testing using Wilcoxon signed-rank test. As the distribution of the correlation analyses tended to normal distribution (kurtosis were all well below 3 except for DSC between MRI and threshold PET during ADT which was 3.3), they were reported by mean $\pm$ standard deviation with two-tailed significance testing using independent t -test.

RESULTS

There were 11 patients in the ADT group (all were on 150 mg of bicalutamide once a day orally) and 29 patients in the ADT-naïve group (Table 1). Within the groups, the number of patients who were already on concomitant medications that may affect prostate volume was one and two, respectively (doxazosin only).

Table 2. Prostate and dominant intraprostatic lesion (DIL) volumes.

		ADT group		ADT-naïve group	
		Median	Range	Median	Range
Prostate volumes/ml	PET/CT	38.02	26.01 to 60.30	47.02	25.92 to 84.38
	Planning CT	36.92	25.63 to 64.96	39.07	18.07 to 82.96
	% change	0.03%	–5.79 to 7.73	–16.94%	–50.86 to 9.67
DIL volumes/ml	MRI	1.98	0.53 to 17.83	2.17	0.68 to 10.45
	Visual PET	1.34	0.36 to 6.41	2.62	0.65 to 8.77
	Threshold PET	4.81	1.12 to 10.68	3.71	0.20 to 18.35

ADT, androgen deprivation therapy; PET, positron emission tomography.

Table 3. Number of dominant intraprostatic lesions (DILs) identified

	<i>n</i>	ADT group	ADT-naïve group
Number of patients with <i>n</i> MRI DILs	0	0	1
	1	11	25
	2	0	3
Number of patients with <i>n</i> visual PET DILs	0	3	0
	1	7	20
	2	1	9
Number of patients with <i>n</i> threshold PET DILs	0	0	0
	1	10	21
	2	1	6
	3	0	1
	4	0	1

ADT, androgen deprivation therapy; PET, positron emission tomography.

There was no significant change in prostate volume between PET/CT and planning CT scans for the ADT group (median 0.03%, $p = 0.89$), but there was a significant reduction in the ADT-naïve group (median -16.9% , $p < 0.01$, Table 2).

The prostate SUV_{max} was lower in the ADT group (median 4.2, range 2.7–12.0) than in the ADT-naïve group (median 6.6, range 4.1–18.6), although it did not reach statistical significance (Mann–Whitney U test; $p = 0.06$).

In the ADT group, all patients had one MRI lesion, but three patients had no visually identifiable PET lesions. In the ADT-naïve group, 28 patients had at least 1 MRI lesion, 1 patient had no MRI lesions that could be confidently contoured and all patients had at least one visually identifiable PET lesion (Table 3).

In both groups, the median DIL volumes on MRI were small (1.98 and 2.17 ml), but there was a large variation between patients (0.53–17.83 ml, Table 2). Per individual patient, the

visual PET lesions were significantly smaller than the MRI lesions in the ADT group (median reduction of 63%, $p = 0.03$) but not in the ADT-naïve group (median reduction of 5%, $p = 0.84$). The threshold PET lesions were generally larger than the MRI lesions in both groups, but this varied between patients and was not statistically significant (median increase of 60%, $p = 0.33$ and median increase of 20%, $p = 0.19$).

The correlation analyses showed that both visual and threshold PET have a moderate sensitivity (0.50–0.68) and a high specificity (0.85–0.98) for identifying MRI-defined disease (Table 4). There was a trend for the PET DILs (especially visually defined) to correlate better with the MRI DILs in the ADT-naïve group.

DISCUSSION

Although the observation of reduced tracer uptake in patients on ADT has previously been described, our article is the first to have quantified this effect.¹⁰ If the PET/CT was performed during ADT, the prostate SUV_{max} was lower although it did not

Table 4. Comparison between dominant intraprostatic lesions (DILs) and prostate (with 5-mm margin)

		ADT group ^a	ADT-naïve group ^a	<i>p</i> -value ^b
PET/CT vs planning CT prostate (+5 mm)	DSC	0.86 ± 0.05	0.86 ± 0.06	–
MRI vs visual PET DIL (+5 mm)	DSC	0.56 ± 0.11	0.61 ± 0.15	0.41
	Sensitivity	0.50 ± 0.11	0.68 ± 0.18	0.12
	Specificity	0.98 ± 0.03	0.92 ± 0.08	<0.05
	Youden	0.48 ± 0.10	0.60 ± 0.20	0.11
MRI vs threshold PET DIL (+5 mm)	DSC	0.49 ± 0.15	0.51 ± 0.15	0.72
	Sensitivity	0.64 ± 0.22	0.63 ± 0.25	0.99
	Specificity	0.85 ± 0.14	0.87 ± 0.11	0.63
	Youden	0.48 ± 0.20	0.50 ± 0.21	0.80

ADT, androgen deprivation therapy; DSC, dice similarity coefficient; PET, positron emission tomography.

^aMean ± standard deviation.

^bIndependent t test (two-tailed).

Figure 2. A patient who had positron emission tomography/CT during androgen deprivation therapy. No dominant intraprostatic lesion could be identified visually.

reach statistical significance, and over a quarter of patients had no visually identifiable PET boost volumes (Figure 2). If PET/CT was performed when ADT-naïve, all patients had at least one visually identifiable PET boost volume and two patients had three to four threshold-identified PET boost volumes. These additional volumes tended to be small (0.1–0.3 ml) and, in practice, would be omitted from the total boost volume.

For the patients who were ADT-naïve at PET/CT imaging, visually identified PET boost volumes were similar in size to those seen on MRI, whilst those identified in patients who were on ADT were significantly smaller (Figures 3 and 4). This suggests that choline tracer uptake in malignant lesions is reduced by ADT on PET imaging, and therefore, ADT should ideally be commenced after imaging has been performed. This effect might also be found for PET imaging with other tracers such as prostate-specific membrane antigen, which is increasingly used for identifying sites of recurrence following radical treatment.

Although it would be expected that a similar effect should be found for boost volumes contoured by the threshold PET method, our results have not shown this. This may be because the threshold level of SUV_{max} 60% is too low for our PET imaging protocol, resulting in generally larger boost volumes which may have obscured any effect from ADT.

Although it did not reach statistical significance, the correlation between threshold PET boost volumes and MRI boost volumes were generally poorer than with the visual PET method. This is likely to be because clinicians had access to all relevant clinic details at the time of visual contouring, as per real life clinical

practice. The overall DSC values were the highest for visual PET in the ADT-naïve group (Figure 5).

Our data have also shown that around two and a half months of ADT can reduce the overall prostate volume by 17%, albeit with significant interpatient variation. When both PET/CT and planning CT were performed during ADT, the prostate volumes were similar although there were differences of up to 7.7%, which reflects the difficulty in contouring pelvic soft tissue on CT. Despite the reduction in prostate size from ADT, the DSC between the prostate volumes were the same between the two groups (0.86) which may suggest that the variation due to the change in size is on the same scale as the variation due to difficulty contouring on CT. Rigid co-registration of the PET/CT and planning CT using the fiducial markers and catheter was generally uncomplicated.

The duration of ADT before PET/CT was performed varied from 42 to 193 days, in part due to the busy clinical schedule of our nuclear medicine department. Although it is not clear in the literature the duration of ADT at which the effect on prostate volume size is maximal, this variability may have influenced volume reduction. The ADT used in this study was bicalutamide, an antiandrogen. Other ADTs commonly used in clinical practice include luteinizing hormone-releasing hormone agonists which may be expected to have a larger effect on SUV_{max} and intraprostatic lesion reduction.

For this study, we had used a standard injected activity of 370 MBq of ^{18}F choline, as opposed to a dose calibrated to the patient's weight. This is because when we first introduced

Figure 3. A patient who had positron emission tomography (PET)/CT during androgen deprivation therapy. The dominant intraprostatic lesion identified visually by PET is smaller than the corresponding lesion identified by MRI.

Figure 4. A patient who had positron emission tomography (PET)/CT before androgen deprivation therapy. The dominant intraprostatic lesion identified visually on PET overlaps the corresponding lesion identified on MRI.

^{18}F choline imaging in our department, we were unsure about the optimum time of imaging, *i.e.* whether delayed imaging at 90 min would be appropriate. Hence, we injected the maximum activity possible under the regulations. Since this study was conducted, there is more evidence for weight-based reduction of injected activity which we have now adopted.

MRI and nuclear medicine specialists were not directly involved in contouring for this study, as radiotherapy contouring is principally performed by radiation oncologists in the UK. Therefore, our results are directly relevant to potential clinical practice.

There are differing views about the benefit of the addition of ^{11}C choline PET/CT with MRI to detect intraprostatic tumours.^{11,12} However, Hartenbach *et al*¹³ showed the increased accuracy of using ^{18}F choline PET/MRI (a scanning protocol with a comparatively prolonged tracer uptake time) for identifying intraprostatic tumour compared with MRI alone. It may be the prolonged uptake time possible with using ^{18}F choline which allows better differentiation between malignant and benign prostate tissue.

Owing to the lack of available literature identifying the optimal threshold level for ^{18}F choline PET/CT, we used the threshold

Figure 5. Distribution of dice similarity coefficient (DSC) values between (a) MRI and visual positron emission tomography (PET) and (b) MRI and threshold PET (the red line depicts the maximum DSC achievable with the given differences between the MRI and PET dominant intraprostatic lesion volumes). ADT, androgen deprivation therapy.

level of SUV_{max} 60% which was identified by Chang et al.⁸ to provide the best correlation between ^{11}C choline PET and pathology. However, there are key differences between their methodology and ours, including the radioisotope used, registration method and the defined standard (histology vs MRI) for comparison.

It is acknowledged that there is a substantial difference in the number of patients between the two groups in our retrospective study and that each group individually constitutes a small sample size. However, the DIL correlation methodology deployed here followed that in the published work (involving a smaller number of subjects than in either of our groups) of Chang et al.⁸

A limitation of our retrospective study is that the patients were not randomized into the two groups, but instead the groups were recruited in sequence. This should not have resulted in differing group characteristics as the inclusion criteria were constant throughout. However, subjective visual identification of DILs may have changed over time with increasing experience in analysing choline PET/CT imaging. Furthermore, there was a lack of the gold standard comparison with cross-sectional histology. It should be noted that surgical series may often include patients with lower risk, and histology samples distort

significantly after preparation and mounting. An alternative to cross sectional histology is template biopsies, which would have offered an accurate assessment of the location and size of significant high-grade tumour. Overall, any visual method is by definition subjective, and therefore the conclusions from this article will ideally be confirmed by other research groups using different PET/CT imaging protocols. Further studies are required to determine whether the addition of PET for the planning process will ultimately improve clinical treatment outcomes.

CONCLUSION

For visual contouring of boost volumes in prostate dose painting radiotherapy, ^{18}F choline PET/CT should be performed before ADT. For threshold contouring of boost volumes using our PET/CT scanning protocol, threshold levels of $>60\%$ of prostate SUV_{max} may be more suitable. The location and size of PET boost volumes can vary to that of the MRI boost volumes, and therefore the additional use of PET with MRI for radiotherapy planning can significantly change the overall boost volumes compared with using MRI alone. However, further studies are required to determine whether the addition of PET for the planning process will ultimately improve clinical treatment outcomes. Similar effects of ADT on PET/CT using other tracers, such as prostate-specific membrane antigen, may exist.

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