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Original Article

PSMA-PET guided dose-escalated volumetric arc therapy (VMAT) for newly diagnosed lymph node positive prostate cancer: Efficacy and toxicity outcomes at two years

Thomas Philip Shakespeare [a,*], Elizabeth Eggert [b], Maree Wood [a], Justin Westhuyzen [a], Kirsty Turnbull [a], Natalie Rutherford [c], Noel Aherne [a,d]

[a] Department of Radiation Oncology, Mid-North Coast Cancer Institute, Coffs Harbour; [b] Department of Radiation Oncology, Mid-North Coast Cancer Institute, Port Macquarie; [c] Nuclear Medicine and PET Department, John Hunter Hospital, Newcastle; and [d] Faculty of Medicine, University of New South Wales, Australia

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ABSTRACT

Purpose/objectives: There are no published reports of prostate specific membrane antigen (PSMA) positron emission tomography (PET) guided dose-escalated intensity-modulated radiation therapy (DE-IMRT) in newly diagnosed lymph node (LN) positive prostate cancer. We report early toxicity and efficacy outcomes with this approach.

Materials/methods: Patients with newly diagnosed high-risk prostate cancer were staged using PSMA PET, computed tomography (CT) and bone scans. Patients with LN positive-only metastases were offered curative therapy using 3 months androgen deprivation therapy (ADT) followed by DE-IMRT (using volumetric arc therapy), and 3 years adjuvant ADT. All patients had fiducial marker insertion, with privately insured patients having spacer hydrogel insertion. PET and prostate magnetic resonance imaging were fused with the planning CT. We aimed to deliver 81 Gy in 45 fractions (Fx) to the prostate and PET-positive LNs, and 60 Gy in 45Fx to bilateral elective pelvic LNs.

Results: In all, 46 patients were treated, with 83% Gleason 8–10, 67% T3/T4, median number of LNs 2 (range 1–6), and median PET-positive LN volume 1.14 cc (range 0.15–4.14). LNs were outside of standard contouring guidelines in 37% of patients. The mean PET-positive LN clinical target volume dose ranged from 73.3 to 85.9 Gy (median 83.6 Gy). With 24 months median follow-up, two year failure-free survival was 100%, and 2 year overall survival 95.7%. Acute grade 1 and 2 GI toxicity occurred in 48 and 11% of patients, and GU toxicity in 72 and 24%. Late grade 1, 2 and 3 GI toxicity occurred in 13, 2 and 0%, and GU toxicity 28, 13 and 4%. No toxicity was attributable to the high dose LN boost.

Conclusions: PSMA PET-guided DE-IMRT up to 81 Gy to the prostate and involved LNs, and long term ADT, is a promising approach for newly diagnosed LN positive prostate cancer. LN contouring guidelines require re-evaluation in the era of PSMA PET imaging.

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The management of patients with lymph node (LN) positive prostate cancer remains controversial, with some authors advocating systemic therapy [1], and others recommending the use of radiation therapy [2]. With the advent of prostate specific membrane antigen (PSMA) positron emission tomography (PET), LN metastases are being detected early, and curative approaches appear more promising. New guidelines have recommended that LN positive prostate cancer be staged with PSMA PET imaging, and if locoregional disease exists, that dose-escalated intensity-modulated radiation therapy (DE-IMRT) be used [3]. These guidelines recommend treating elective pelvic LNs, and dose escalating PET positive LNs and the prostate to high doses. Long term androgen deprivation therapy (ADT) is also recommended.

We could find no reports of PSMA PET guided DE-IMRT for newly diagnosed men with node positive prostate cancer. In the present series we report on our early experience in terms of toxicity and efficacy.

Methods

Since the availability of PSMA PET imaging in 2015, all patients with newly diagnosed high risk prostate cancer attending our cancer centres have been staged using PSMA PET, computed tomography (CT) and bone scans. PSMA PET procedures are summarised in

* Corresponding author at: Department of Radiation Oncology, Mid North Coast Cancer Institute, Coffs Harbour Health Campus, Coffs Harbour, New South Wales 2450, Australia.
E-mail address: Thomas.Shakespeare@health.nsw.gov.au (T.P. Shakespeare).

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Appendix A – Supplementary materials. Patients with LN positive-only metastases from the level of the fourth lumbar vertebrae (L4) or below, were offered curative intent therapy using 3 months of neoadjuvant ADT followed by DE-IMRT, followed by 3 years of adjuvant ADT. IMRT was delivered using volumetric arc therapy (VMAT) on our institutional protocol. We report on patients accrued over a 3 year period from July 2015 until July 2018.

All patients had fiducial marker insertion with privately insured patients also having spacer hydrogel inserted [4]. PSMA PET and prostate magnetic resonance imaging (MRI) were fused with the planning CT using our department protocols [5]. Elective LNs were volumed based on the PIVOTAL guidelines [6], with volumes modified in cases where PET positive LNs were outside of the elective LN volume specified by PIVOTAL. Involved LNs on PSMA PET were volumed as the boost clinical target volume (CTV) and expanded 7 mm for a boost planning target volume (PTV). The boost PTV was allowed into the rectum by 4 mm, however was cropped at the junction with any other bowel volume.

Our protocol aimed to deliver 81 Gy in 45 fractions (Fx) to the prostate and PET positive LNs, and 60 Gy in 45Fx to bilateral elective pelvic LNs. Planning constraint aims and those actually achieved are displayed in Table 1. If planning constraints could not be met, dose de-escalation was permitted, based on previous evaluations showing that in the presence of ADT, there is no significant difference in 5 year biochemical disease-free survival (bDFS) in patients with intermediate [7] or high risk [8] prostate cancer.

During the treatment course, patients took biomagnesium each day to reduce bowel gas [9], had antiemetic prophylaxis, and followed bowel and bladder protocols as previously reported [10,11]. Daily cone beam CT (CBCT) was performed prior to each fraction, with matching to the fiducial markers, and ensuring appropriate pelvic bony anatomy match, bladder filling, and lack of bowel gas. Where bladder filling or rectal gas was not adequate, patients were taken off the treatment couch and problems rectified with further water intake (verified by bladder ultrasound scanning), passing bowel motions, use of enemas etc. The radiation oncologist reviewed every CBCT to ensure nodal regions were being adequately covered. Where patients had consistent problems with nodal regions being underdosed, patients were re-simulated and replanned.

Patients were seen weekly during treatment by the RT nursing staff, and saw the treating doctor mid-way and at the end of treatment. Following IMRT, patients were reviewed at 3 months, then annually, with more frequent follow-ups scheduled if patients were experiencing significant problems. Prostate specific antigen (PSA) measurements were performed 3 monthly until 2 years after the end of adjuvant ADT, then 6 monthly. Based on our previous experience [12], annual faecal occult blood tests (FOBTs) were monitored post IMRT; patients with positive FOBTs or bowel symptoms persisting beyond 3 months underwent colonoscopy. Patient information including toxicity and outcome data were prospectively entered into our electronic medical record (Mosaiq, Version: 2.64, Elekta Pty Ltd., North Sydney, Australia). Acute toxicity was reported by noting the worst genitourinary (GU) or gastrointestinal (GI) toxicity scored using CTCAE v3.0. Late toxicity was reported using the latest toxicity assessment. This data was collected as an institution approved quality assurance project (QA220).

Results were analysed by SPSS v 25 (IBM Corp., Armonk, New York, USA). Due to the small number of events, univariate and multivariate analyses were not performed as initially planned.

Results

In all, 46 patients were treated, with no patient lost to follow-up. Patient demographics are displayed in Table 2. The median age was 70 (range 51–81), median PSA 13 μg/L (range 1.33–190), 67% were T3 or T4, and 83% were Gleason 8–10. The median number of PET positive LNs involved was 2 (range 1–6), and the median PET positive LN volume was 1.14 cc (range 0.15–4.14).

Of note, 17 of the 46 patients (37.0%) had PSMA PET positive lymph nodes outside of the PIVOTAL contouring guidelines (Table 2). Eight patients had PET positive mesorectal nodes, 4 had low presacral nodes below S3, 4 patients had involved high common iliac nodes (above the lower border of L5), and 3 had para-aortic (PA) nodes at L4 or L5.

Forty-two of 46 (91%) patients were prescribed 81 Gy to the PET positive LNs, with the other 4 receiving 72–74 Gy due to high volumes of surrounding small bowel. The prostate received 81 Gy in 45 patients (with one patient receiving 73.8 Gy due to severe pre-existing urinary symptoms). The mean dose to the PET positive LN CTV ranged from 73.3-85.9 Gy (median 83.6 Gy).

With a median follow up of 24 months (range 10–50 months), the two year failure-free survival was 100%, and 2 year overall survival 95.7%. One patient had a PSA failure at 30 months and distant bone failure at 31 months, with repeat PSMA PET showing no residual prostate or LN avid disease. One patient died of multiple myeloma at 24 months. This was a pre-existing condition thought to be in remission at the time of prostate therapy, with the treating haematologist recommending the prostate cancer be treated on its

Table 1
Organ at risk (OAR) planning constraints and actual planned parameters in 46 patients.

Organ at risk	OAR criteria	No violation	Major violation	Actual planned parameters in 46 patients median (range)
Rectum	Volume receiving 40 Gy	<35%	>60%	39% (16–74%)
	Volume receiving 65 Gy	<17%	>21%	12% (2–24%)
	Volume receiving 75 Gy	<10%	>15%	6% (0–12%)
	Volume receiving 83 Gy	<2cc		0.02 cc (0–0.97 cc)
	Maximum dose	<84 Gy	>85 Gy	83 Gy (74–86 Gy)
Sigmoid	Volume receiving 40 Gy	<35%	>60%	42% (16–99%)
	Volume receiving 65 Gy	<17%	>21%	0.2% (0–18%)
	Maximum dose	<74 Gy	>78 Gy	66 Gy (47–84 Gy)
Bladder	Volume receiving 50 Gy	<50%	>60%	34% (15–58%)
	Volume receiving 83 Gy	<2cc		1.4 cc (0–12 cc)
Small Bowel	Volume receiving 45 Gy	<195 cc	>250 cc	73 cc (0–333 cc)
	Volume receiving 60 Gy	<2cc		0 cc (0–11 cc)
	Maximum dose	<70 Gy	>74 Gy	62 Gy (45–75 Gy)
Right Femoral head	Volume receiving 45 Gy		V45 > 60%	3% (0–14%)
Left Femoral Head	Volume receiving 45 Gy		V45 > 60%	4% (0–16%)
Spinal Canal	Maximum Dose	<47 Gy	>50 Gy	47 Gy (34–70 Gy)

Table 2
Patient demographics.

	Median	Range	N (%)
Age (years)	70	51–81	
PSA (μg/L)	13	1.33–190	
T stage			
T2			15 (32.6)
T3a			8 (17.4)
T3b			17 (37.0)
T4			6 (13.0)
Gleason 6			1 (2.2)
Gleason 7			7 (15.2)
Gleason 8			12 (26.1)
Gleason 9			25 (54.3)
Gleason 10			1 (2.2)
Number of nodes	2	1–6	
1			20 (43.5)
2			10 (21.7)
3			7 (15.2)
4			5 (10.9)
5			2 (4.3)
6			2 (4.3)
Highest node			
Obturator/pararectal			4 (8.7)
Internal/external iliac/presacral			32 (69.6)
Common iliac			7 (15.2)
PA			3 (6.5)
Nodes outside of PIVOTAL guidelines			17 (37.0)
Mesorectal			8 (17.4)
Low presacral (below S3)			4 (8.7)
Common iliac above lower border of L5			4 (8.7)
Para-aortic nodes			3 (6.5)
Node volume (cc)	1.14	0.15–4.14	
Dose prescribed to involved nodes (Gy)			
72			1 (2.2)
73.8			1 (2.2)
74			2 (4.3)
81			42 (91.3)
Dose to prostate (Gy)			
73.8			1 (2.2)
81			45 (97.8)

own merits. Unfortunately this patient's myeloma failed shortly after IMRT.

Acute grade 1 and 2 GI toxicity occurred in 48 and 11% of patients, and GU toxicity in 72 and 24%, with no grade 3 acute toxicity. Late grade 1, 2 and 3 GI toxicity occurred in 13, 2 and 0% of patients, and GU toxicity in 28, 13 and 4%. The grade 3 GU toxicities were bulbar stricture requiring dilatation (1 patient), and poor flow requiring transurethral resection of the prostate (1 patient). There was no toxicity attributable to the high dose LN boost.

Discussion

The management of patients with newly diagnosed prostate cancer and LN-only metastases is controversial [13]. There are no randomised trials investigating the role of adding radiation therapy to ADT, however there are several retrospective evaluations [14–17]. One example is the Stampede study [14], whose authors' analysed the node positive cohort of 157 patients, demonstrating that radiation to the prostate and nodal regions plus systemic therapy improved 2 year failure-free survival (FFS) from 64 to 89%, compared to systemic therapy alone. An analysis of the Surveillance, Epidemiology and End-Results (SEER) database [15,16] showed that radiation plus ADT improved overall survival compared to ADT alone. Another evaluation of LN positive patients in the National Cancer Database showed that radiation plus ADT improved 5 year overall survival from 53 to 72% [17], compared to ADT alone. It is noted that none of the patients in the above studies were staged using PSMA PET imaging, and details about doses to involved LNs is generally lacking. We have found that the use of PSMA PET changes clinical decision-making in 53.7% of patients [18]. We consider it a vital component of patient management, and is particularly useful for identifying involved LNs.

Despite the lack of good evidence, several guidelines recommend the use of pelvic radiation and ADT in the management of clinically LN positive prostate cancer [2,3,19–21]. Nodal dose-escalation is recommended variably, including "as dose-volume histogram parameters allow" [2], up to 79.2 Gy [20], and above 60 Gy [3,21]. Our institutional protocol indicated that lymph nodes should be treated to the same dose as the prostate, with the rationale being that gross disease would require the same dose regardless of its location in the prostate, seminal vesicles, or lymph nodes. Our intact prostate protocol uses 81 Gy to the prostate, and thus the lymph nodes were also given 81 Gy where possible.

Some of these guidelines recommend the use of PSMA PET to guide treatment [3,21], due to the evidence that PSMA PET is more accurate than CT and bone scan for nodal staging [22–24]. A meta-analysis has shown that for lymph node metastases at diagnosis, PSMA PET has a sensitivity of 75%, and specificity of 99% [25], and thus both false positives and false negatives can occur. It is not certain what the best radioisotope is for PET imaging, however a review of the literature comparing PSMA with four other tracers (^{11}C- or ^{18}F-choline, ^{11}C-acetate, anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid, and ^{18}F-fluorodeoxyglucose) in the detection of prostate cancer found that PSMA had a greater likelihood of detecting lymph node and bone lesions [26]. This is an area for ongoing research.

We have identified no reports using PSMA PET-guided radiation for newly diagnosed node positive disease, although there are studies focussing on lymph node recurrence after primary curative therapy [27–31]. As might be expected, these series have limited follow-up, and vary in their radiation techniques, doses and use of ADT. Our own results for newly diagnosed LN positive disease appear promising. With a median follow-up of 2 years, we found a 2 year FFS of 100%. This compares well to the Stampede node positive analysis [14] with a 2 year FFS of 89%, and only 17 months median FU. The Stampede cohort did not have the benefit of PSMA PET, and LN dose escalation was not mandated or reported. Our toxicity profile was also very acceptable, and in particular, despite our LN boost dose up to 81 Gy, no toxicity was attributable to the high LN boost doses. We note that 4 patients received a lower dose to the PET positive LNs (ranging from 72 to 74 Gy), and one patient received a lower dose to the prostate (73.8 Gy). It is uncertain whether this will have any effect on local or nodal failures. Based on our own experience, dose de-escalation for localized intermediate and high risk prostate cancer does not affect 5 year biochemical disease-free survival in patients receiving ADT [7,8], although it is uncertain whether these findings are applicable to node boost doses. Further research is obviously required to define the optimal boost dose for PET positive LNs.

Other limitations of our evaluation are the small number of patients (46 in our series), and a median follow-up of only 2 years. However, our series compares favourably against other published evaluations [27–31]. Reports of PSMA PET-guided radiation to lymph nodes in the salvage setting include between 11 and 37 patients (median 17 patients), with median follow-ups ranging from 7 to 23 months (median 12 months). As previously mentioned, the Stampede report [14] (without PET guidance) consisted of 71 node positive patients treated with radiation, with only 17 months follow-up. It is clear that further evaluations of large numbers of patients treated in a homogenous fashion, with longer term follow-up, are required.

Due to the small number of events we were not able to evaluate associated factors such as patient demographics and tumour characteristics. In particular, effect of PSA, T stage, Gleason score, and number, volume and location of lymph node metastases would all be of interest. As data matures and late failures occur, these factors will become amenable to investigation. Another limitation of our series is that elective LN contouring could not be standardized, due to PSMA PET positive lymph nodes often falling outside of standard contouring guidelines. Seventeen of 46 (37%) of our patients were in this category, with 8 patients having mesorectal nodes, 4 with low presacral nodes (below S3), 4 with high common iliac nodes (above L5/S1), and 3 with para-aortic (PA) nodes at L4 or below. There were several additional patients with PA LNs at L1-L3 excluded from our protocol due to concerns about kidney dose as well as boost doses affecting the duodenum. It is clear that in the era of PSMA PET imaging, contouring guidelines require re-evaluation.

In conclusion, this appears to be the first report of the efficacy and toxicity of patients treated with PSMA PET-guided DE-IMRT for patients with newly diagnosed LN positive prostate cancer. Efficacy and toxicity appear promising utilizing this technique, and further research is required.

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None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.09.027.

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