Should Lutetium-prostate specific membrane antigen radioligand therapy for metastatic prostate cancer be used earlier in men with lymph node only metastatic prostate cancer?

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Purpose: Lutetium-labelled prostate-specific membrane antigen radioligand therapy (Lu-PSMA RLT) has shown pleasing early results in management of high-volume metastatic castration resistant prostate cancer (mCRPC), but its role in the early treatment of men with only lymph node metastasis (LNM) is unknown. The aim was to assess the outcome of Lu-PSMA RLT earlier in the treatment of men with only LNM.

Materials and Methods: Single institution retrospective review of men with only LNM on staging Ga-PSMA PET PSMA who proceeded with Lu-PSMA RLT.

Results: There were 17 men with only LNM, including 13 with mCRPC and 3 who were both hormone and chemotherapy naïve. The median PSA was 3.7 (0.46–120 ng/mL). A PSA decline of ≥50% occurred in 10/17 (58.8%), decreasing to <0.2 ng/mL in 35.3% (6/17). The PSA continues to decline or remain stable in 10/17 (58.8%) with a median follow-up of 13 months, and 8/17 (47.1%) have not reached their pre-treatment levels. There were no significant side effects. There was a better PSA response in men without prior chemotherapy (p=0.05). The prostate cancer specific and overall survival is 82.4% (14/17).

Conclusions: Our results identify improved PSA response to Lu-PSMA RLT in men with only LNM, especially in the chemotherapy naïve cohort, compared to previous series with more advanced mCRPC. These findings provide important proof of principle to aid with planning of future prospective randomized trials evaluating the role of Lu-PSMA RLT earlier in the management of node metastatic prostate cancer, including men naïve of ADT and chemotherapy.

Keywords: Lutetium-177; Lymphatic metastasis; Prostate cancer; PSMA-617

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INTRODUCTION

The role of Lutetium labelled prostate-specific membrane antigen radioligand therapy (Lu-PSMA RLT) in management of lymph node only metastatic prostate cancer has not been established. Most reports on the oncological outcome of Lu-PSMA RLT are from treatment of metastatic castration resistant prostate cancer (mCRPC) with multiple sites of metastasis including bone and soft tissue, and following chemotherapy and/or other third line antiandrogen therapies. Although the presence of visceral metastases is associated with poor response and survival outcomes in men with mCRPC [1], the outcomes following treatment with Lu-PSMA RLT for lymph node only metastatic prostate cancer are poorly defined in the literature, particularly with pre-treatment prostate-specific antigen (PSA) levels <20 ng/mL.

PSMA is a non-secreted type II transmembrane protein produced by prostate tissue and up regulated in high-grade prostate cancer [2]. The 177Lu is rapidly internalised by malignant cells. The internalisation and retention within the cancer cell has the advantage of selectively targeting multiple metastases [3]. Lu-PSMA RLT has shown promising early therapeutic outcomes. PSA levels decreased in 68% of the 369 men with mCRPC in a pooled sample meta-analysis, including 39.1% with a >50% decline in PSA level, although survival outcomes were not assessed [4].

An initial case report in 2017 identified a patient with pathological lymph node metastasis (LNM) at radical prostatectomy who developed unrecordable PSA levels following a dose of Lu-PSMA for recurrent LNM despite prior androgen deprivation therapy (ADT), abiraterone, and pelvic lymph node radiotherapy [5]. A subsequent small series identified that men with only LNM had a better overall survival following Lu-PSMA RLT than men who had LNM associated with 1-2 oligometastatic bone metastases [6].

I-Med Radiology Network, Wesley Hospital previously reported our initial experience of Lu-PSMA RLT in 50 men with mCRPC, with a PSA decline of ≥50% identified in 44.9% [7]. We aim to evaluate if the outcomes of Lu-PSMA RLT in men with lymph node only metastasis treated at lower PSA levels at our institution had improved and sustained PSA responses compared to more extensive disease. We also aimed to investigate whether Lu-PSMA results are improved in chemotherapy or ADT naïve men.

MATERIALS AND METHODS

Before commencing LuPSMA therapy all patients sign a detailed informed consent form. This consent form includes an ‘opt-in’ option for a theranostics research database developed at I-Med Radiology Network, Wesley Hospital. A retrospective review of our institutions Lu-PSMA RLT database was performed to evaluate men with only LNM as identified on 68Ga-PSMA PET/CT PSMA imaging. Ethics approval was granted by the Uniting Care Ethics Committee (approval number: 2017.20.234). The hospital Medical Advisory Committee authorized the use of Lu-PSMA RLT at our institution in 2017.

Our Lu-PSMA RLT program commenced in August 2017. All men referred for Lu-PSMA RLT are discussed at the institutional Uro-radiology multidisciplinary team meeting to confirm consensus on the appropriateness of Lu-PSMA RLT. Lu-PSMA synthesis is performed on site with the Modular-Lab eazy automated synthesizer (Eckert & Ziegler, Berlin, Germany) using initially a disposable synthesis cassette (177Lu DOTA conjugated PSMA-617 with CM cartridge post purification, product number: C0-LUDOTAPSMA-CM) and reagent kit (90Y/177Lu DOTA components, product number: EZ-103). Subsequently PSMA-I&T was used due to lack of availability of PSMA-617. The Lu-PSMA (40–80 +/-10% GBq activity) is administered via a dedicated radionuclide therapy pump (RadInject; Tema Sinergie, Faenza, Italy) over 10 minutes under the supervision of a dual-trained Radiologist/Nuclear Medicine Specialist (DW). All patients undergo whole-body and two-bed single-photon emission computed tomography imaging to check the distribution of activity, typically 4 hours after Lu-PSMA administration. Patients are monitored for adverse events to the point of discharge, and subsequently via phone in the 1 to 2 weeks following treatment and then at subsequent routine consultations.

PSA progression was defined as a PSA increase above nadir. We also analysed PSA progression as per the Prostate Cancer Trials Working Group 2 (PCWG2) criteria (a PSA increase being ≥25% and ≥2 µg/L above the nadir for patients with initial PSA decline and ≥25% and ≥2 µg/L above baseline for patients without PSA decline) [8]. A Fisher’s exact test was used to calculate significance of the maximum standard uptake value (SUVmax) of metastases on baseline 68Ga-PSMA PET/CT PSMA and reduction in PSA levels post treatment, although due to the small sample size the results should only be considered indicative.

RESULTS

Of the 120 consecutive men treated with Lu-PSMA RLT between August 2017 and December 2020, there were 17 men with only LNM. The patient characteristics are shown in Table 1. There were 13 men with mCRPC and 3 hormone
 naïve men with primary treatment failure who had not received ADT, chemotherapy or any other salvage therapies. The final patient had neoadjuvant Lu-PSMA before and after a radical prostatectomy for LNM. The median follow-up is 13 months (2–39 months). The median time between diagnosis and Lu-PSMA RLT was 8 years (3–18 years) in the mCRPC group and 5 years (3 months–11 years) in hormone naïve prostate cancer. LNM were found in the pelvis and retroperitoneum +/- supradiaphragmatic areas in 11 men, pelvic nodes alone in 4 and retroperitoneal or supradiaphragmatic nodes alone in one each.

The median PSA at referral for Lu-PSMA RLT was 3.7 ng/mL (0.46–120 ng/mL) and the median number of Lu-PSMA RLT treatments was 3 (1–7 infusions). A PSA decline occurred in 15 of 17 men (88.2%) and a PSA decline of ≥50% in 10 of 17 (58.8%). Using the PCWG2 criteria, 7 of 17 (41.2%) patients had PSA progression. The PSA continues to decline or remain stable in 10 of 17 (58.8%).

The median time to PSA nadir was 5 months (2–16 months). In 6 of 17 men (35.3%) the PSA declined to <0.2 ng/mL. Eight men (47.1%) have not reached their pre-treatment PSA level.

The median SUVmax of the LNM on baseline imaging was 25 (7.1–104, median=23). Of men with available data, 5 of 7 (71.4%) with pre-treatment node SUVmax >25 had a ≥50% reduction in PSA levels, compared to 4 of 8 (50%) with node SUVmax <25 (p=0.067). Of the 12 men with surveillance post-treatment 68Ga-PSMA PET/CT scans, complete radiological resolution of disease was identified in 1 of 12 (see Fig. 1), partial resolution in 7 of 12, stable disease in 1 of 12 and progression in 3 of 12. Excluding the patient with neoadjuvant Lu-PSMA, 6 of 7 men with complete or partial radiological resolution had an associated ≥50% reduction in PSA level. The prostate cancer specific and overall survival

### Table 1. Patient characteristics at baseline and response to Lu-PSMA RLT

| Characteristic                                      | Total cohort (n=17) | Any PSA decline cohort (n=15) | PSA ≥50% decline cohort (n=10) |
|-----------------------------------------------------|--------------------|-------------------------------|-------------------------------|
| Pre-treatment PSA (ng/mL)                           |                    |                               |                               |
| <10                                                  | 12                 | 10                            | 7                             |
| >10                                                  | 5                  | 5                             | 3                             |
| Prior treatments                                    |                    |                               |                               |
| ADT                                                  | 13                 | 11                            | 8                             |
| Chemotherapy                                         | 9                  | 7                             | 3                             |
| Site of lymph node metastasis at baseline           |                    |                               |                               |
| Pelvis and retroperitoneum +/− supradiaphragmatic nodes | 11                 | 10                            | 7                             |
| Pelvic nodes only                                    | 4                  | 3                             | 1                             |
| Retroperitoneal nodes only                          | 1                  | 1                             | 1                             |
| Supradiaphragmatic nodes only                       | 1                  | 1                             | 1                             |

Values are presented as number only.

Lu-PSMA RLT, Lutetium labelled prostate-specific membrane antigen radioligand therapy; PSA, prostate-specific antigen; ADT, androgen deprivation therapy.

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A

B

**Fig. 1.** Complete radiological resolution of retroperitoneal lymph node metastasis after Lu-PSMA RLT. Prior to Lu-PSMA RLT imaging (A) compared to post Lu-PSMA RLT imaging (B). Lu-PSMA RLT, Lutetium labelled prostate-specific membrane antigen radioligand therapy.
is 82.4% (14/17), at a median follow-up of 13 months (Fig. 2).

Chemotherapy was administered in 9 of 17 men prior to Lu-PSMA, including 8 men with mCRPC. Of the mCRPC group 8 of 13 had received prior docetaxel chemotherapy, 4 also had carbazitaxel and 6 of 13 men had enzalutamide +/- abiraterone. A PSA decline was seen in 7 of 9 (77.8%) with prior chemotherapy and 8 of 8 (100%) with no prior chemotherapy. A PSA decline of ≥50% was identified in 3 of 9 (33.3%) of the prior chemotherapy cohort compared with 7 of 8 (87.5%) without prior exposure to chemotherapy (p=0.05). The post-treatment PSA results are shown in Fig. 3 and Fig. 4. When using the definition of PSA rise above nadir, freedom from biochemical progression was identified in 4 of 8 (50%) of the chemotherapy-naïve cohort (progression free period since Lu-PSMA 5–16 months), but all but two men with prior chemotherapy progressed with a median time to biochemical rise above nadir of 55 months (1–11 months). Based on the PCWG2 definition, 3 of 9 of the chemotherapy group and 7 of 8 of the chemotherapy-naive group are free of progression (Fig. 5).

Of the 8 men without prior chemotherapy, 5 had mCRPC, of which three remain free from PSA progression above nadir at 5, 13, and 16 months. The two men with PSA progressions above nadir occurred at 14 and 8 months, respectively. In the 3 men both ADT and chemotherapy naïve, the mean follow-up is 9 months (6–15 months). The PSA at Lu-PSMA ranged from 0.86 to 25 ng/mL. The first patient had a single cycle of Lu-PSMA for a PSA of 25 at 13 years post high dose rate brachytherapy. His PSA nadir was 0.04 at 9 months and a plan for a second cycle following a PSA rise to 0.73 at 15 months. Two men post radical prostatectomy 3 and 5 years earlier had 2 cycles of Lu-PSMA with pre-treatment PSA of 0.86 and 1.8 respectively. The first had nodes above and below the pelvis and the second pelvic node recurrence after prior salvage robot PLND then salvage pelvic radiotherapy. Their PSA levels are low at 0.5 and 0.47 respectively at 6 months follow-up.

As classified using the Common Terminology Criteria
for Adverse Events (version 5), all side effects were grade I, with fatigue (4/17) and dry mouth (3/17) the most common symptom. There were no haematological or renal complications related to the Lu-PSMA RLT.

**DISCUSSION**

There is very little data on the outcome of Lu-PSMA radioligand therapy in men with lymph node only metastatic prostate cancer. We have demonstrated a significant response to Lu-PSMA theranostics in heavily pre-treated node positive patients and even better responses in systemic treatment naïve patients. Given the known toxicities of both ADT and/or chemotherapy there is impetus to consider Lu-PSMA theranostics earlier in the treatment paradigm of LNM. In an experienced German centre treating 119 men with Lu-PSMA RLT over a 3-year period, 19 men were identified with only LNM disease [9]. Although the outcomes of the node only group were not specifically stated, it was noted that in general, men with mCRPC and only LNM responded better to Lu-PSMA RLT than men with bone metastases. This finding could be explained by the higher radiation dose absorbed by LNM, which generally exhibited higher uptake (SUVmax) on the $^{68}$Ga-PSMA PET/CT than bone metastases. We also identified high SUVmax levels in the LNM in our cohort, with a median of 25, which is more than double the SUVmax of the primary tumour in men with LNM at our institution [10]. In a previous publication from our institution, the overall 18 month survival after Lu-PSMA RLT in our cohort with lymph node only metastasis was higher (79%) compared to men with bone only (61%) or visceral (52%) metastases [11]. Our survival in the LNM cohort is also superior to the median overall survival of 16 months in the systematic review of mCRPC by von Eyben et al. [12].

In our cohort with only LNM, treating at lower PSA levels resulted in a PSA nadir <0.2 in 35.3%. Even in the heavily pre-treated mCRPC group, 33.3% of men had a ≥50% reduction in PSA level. Of particular interest, all 3 (100%) chemotherapy/ADT naïve men in our study had a reduction in PSA following Lu-PSMA RLT.

The von Eyben series is the largest study to assess the outcomes of Lu-PSMA RLT in men with lymph node only mCRPC [6], comparing 35 men with only LNM to 10 men with LNM and also one or two bone oligometastasis. Although a PSA decline of >50% was seen more frequently in their cohort compared to our series (89% vs. 58.8%), the freedom from biochemical recurrence was almost identical based on the definition of PSA failure (≥25% above nadir) in the von Eyben series (29% vs 29.4%).

The mean SUVmax (avidity) of the tumour was a prognostic indicator of survival in the LuPSMA phase 2 trial [13]. In the Bad Berka German experience, the complete or partial radiological response to Lu-PSMA RLT in 58 men with mCRPC in both soft tissue and bone was 29.3% [9]. In our LNM only cohort a complete or partial response was seen in 66.7%, with radiological progression in only 25% during the median follow-up period of 13 months. There appeared to be a better PSA response in men with a lymph node SUVmax >25, although the patient numbers are too small for statistical significance (p=0.067).

Lu-PSMA-617 and Lu-PSMA-I&T in general have minimal renal toxicity and only a 2% to 3.4% risk of haematological toxicity [14] Similar to other published series, we had very few complications from Lu-PSMA RLT, which were all grade 1. Dry mouth and fatigue are common symptoms but there were no haematological complications or changes in renal function related to the Lu-PSMA RLT, similar to our previous outcomes [7].

Management of LNM at diagnosis, or recurrence following primary prostate cancer treatment remains controversial. The current main aim of treatment is to extend prostate cancer specific survival while minimising side-effects. There are no randomized trials for clinical node only positive patients. The introduction of ADT is not without complications, including a decline in cognitive function [15,16], hot flushes, lack of libido/impotence, long-term risk of osteoporosis and a slightly increased risk of cardiac and thromboembolic events. The inference regarding the benefit of chemotherapy in LNM is made from analysis of the node positive populations in prospective randomised trials. The GETUG-12 trial identi-
fied improved relapse free, but not prostate cancer specific or overall survival [17]. Similar findings were noted in the STAMPEDE trial, although the Kaplan–Meier curves separated in favour of a combination of ADT and abiraterone over ADT alone [18]. In the mCRPC setting the improvement in long-term survival with chemotherapy is measured in months, although occasional anecdotal long-term suppression of cancer is well known to clinicians.

A systematic review comparing third-line treatment of mCRPC against Lu-PSMA RLT identified a higher decline of PSA ≥50% following Lu-PSMA RLT compared to enzalutamide and carbazitaxel (44% vs. 22%) and a lower risk of adverse events causing discontinuation of treatment (p<0.001) [14]. There was no significant difference in median survival (14 vs. 12 months, p=0.32) [14]. This issue was addressed in the Therap phase 2 randomized trial of Lu-PSMA lutetium vs. carbazitaxel. After 13 months follow-up the ≥50% decline in PSA level was improved for the Lu-PSMA cohort (66% vs. 37%, p<0.0001) [19]. In our series we commenced Lu-PSMA RLT at much lower median PSA levels than Therap (37 ng/mL vs. 94 ng/mL). However, our high overall and prostate cancer specific survival could be due to the better prognosis of men with only LNM, rather than earlier introduction of Lu-PSMA RLT at lower PSA levels.

One of our patients had 2 cycles of neoadjuvant Lu-PSMA RLT prior and after a radical prostatectomy for common iliac and pelvic node metastatic prostate cancer in the context of his radical prostatectomy initially being cancelled at the start of the COVID-19 pandemic. We have subsequently obtained approval for a pilot study on neoadjuvant Lu-PSMA RLT prior and after a radical prostatectomy [20]. The role of neoadjuvant Lu-PSMA is also being assessed in the non-randomised open label LuTectomy trial [21].

The limitations of our study include the retrospective review and small patient numbers. It is also possible that our pleasing results just reflect an overall favourable outcome of treating men with node only disease compared with bone and visceral metastases. However, our encouraging finding with earlier treatment of LNM will be of value in planning future clinical trials. We have identified that all men with mCRPC obtained a ≥50% decline in PSA levels if they were chemotherapy naïve and 60% (3/5) had not progressed above PSA nadir over a follow-up period of 5 to 16 months. A randomized trial to assess whether Lu-PSMA prior to, or in combination with docetaxel improves long term relapse free or prostate cancer specific survival in lymph node only mCRPC is an obvious exploration of our findings. The excellent initial PSA response with Lu-PSMA RLT in hormone and chemotherapy naïve men with only LNM suggests at the very least, earlier introduction of Lu-PSMA RLT in this cohort could potentially delay the introduction of ADT or chemotherapy, with few side effects. This is in contrast to Radium 223, which is not introduced early in a treatment pathway due to potential irreversible toxicities. It has been shown that PSMA is up regulated by ADT [22]. Therefore, in the hormone naïve setting, future studies will be required to investigate the role Lu-PSMA RLT with or without ADT. Finally, our findings in the hormone naïve cohort confirm the appropriateness of trials such as the UpFrontPSMA trial [23] of Lu-PSMA 467 and docetaxel versus docetaxel in hormone naïve bone or visceral metastatic prostate cancer, however a similar trial in men with node only metastases would identify if there is an incremental long-term oncological value in the cohort.

CONCLUSIONS

This study provides evidence of improved PSA response to Lu-PSMA RLT in men with only LNM, especially in the chemotherapy naïve cohort, compared to previous series with more advanced mCRPC. Although this is a retrospective review of a small series, the results are important proof of principle to aid with planning of future prospective randomised trials looking at the role of Lu-PSMA RLT earlier in the management paradigms of the management of men with only lymph node metastases on staging 68Ga-PSMA PET/CT.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS’ CONTRIBUTIONS

William John Yaxley – Data acquisition, data analysis and interpretation, drafting of the manuscript, approval of the final manuscript. Rhiannon McBean – Data acquisition, data analysis and interpretation, approval of the final manuscript. David Wong – Data acquisition, data analysis and interpretation, approval of the final manuscript. David Grimes – Data acquisition, data analysis and interpretation, approval of the final manuscript. Paul Vasey – Data acquisition, data analysis and interpretation, approval of the final manuscript.
REFERENCES

1. Satapathy S, Mittal BR, Sood A. Visceral metastases as predictors of response and survival outcomes in patients of castration-resistant prostate cancer treated with 177Lu-labeled prostate-specific membrane antigen radioligand therapy: a systematic review and meta-analysis. Clin Nucl Med 2020;45:935-42.

2. Baum RP, Kulkarni HR, Schuchardt C, Singh A, Wirtz M, Wissalla S, et al. 177Lu-labeled prostate-specific membrane antigen radioligand therapy of metastatic castration-resistant prostate cancer: safety and efficacy. J Nucl Med 2016;57:1006-13.

3. Weinisein M, Schöttelius M, Simecek J, Baum RP, Yildiz A, Beyer K, et al. 68Ga- and 177Lu-labeled PSMA & T: optimization of a PSMA-targeted therapeutic concept and first proof-of-concept human studies. J Nucl Med 2015;56:1169-76.

4. Calopedos RJS, Chalasani V, Asher R, Emmett L, Woo HH. Lutetium-177-labelled anti-prostate-specific membrane antigen antibody and ligands for the treatment of metastatic castration-resistant prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2017;20:352-60.

5. von Eyben FE, Kiljunen T, Kairemo K, Virgolini I, Virgolini I. 177Lu-PSMA-617 radioligand therapy for a patient with lymph node metastatic prostate cancer. Oncotarget 2017;8:66112-6.

6. von Eyben FE, Singh A, Zhang J, Nipsch K, Meyrick D, Lenzo N, et al. 177 Lu-PSMA radioligand therapy of predominant lymph node metastatic prostate cancer. Oncotarget 2019;10:2451-61.

7. McBean R, O’Kane B, Parsons R, Wong D. Lu177-PSMA therapy for men with advanced prostate cancer: initial 18 months experience at a single Australian tertiary institution. J Med Imaging Radiat Oncol 2019;63:538-45.

8. Scher HI, Morris MJ, Basch E, Heller G. End points and outcomes in castration-resistant prostate cancer: from clinical trials to clinical practice. J Clin Oncol 2011;29:3695-704.

9. Kulkarni HR, Singh A, Schuchardt C, Nipsch K, Sayeg M, Leshch Y, et al. PSMA-based radioligand therapy for metastatic castration-resistant prostate cancer: the Bad Berka experience since 2013. J Nucl Med 2016;57(Suppl 3):978-104S.

10. Franklin A, Yaxley WJ, Raveenthiran S, Coughlin G, Ganduzzo T, Kua B, et al. Histological comparison between predictive value of preoperative 3-T multiparametric MRI and $^{68}$Ga-PSMA PET/CT scan for pathological outcomes at radical prostatectomy and pelvic lymph node dissection for prostate cancer. BJU Int 2021;127:71-9.

11. Tatkovic A, McBean R, Wong D. Lu177-PSMA therapy for men with advanced prostate cancer: 18 months survival analysis in a single Australian tertiary institution. J Med Imaging Radiat Oncol 2021 Apr 22 [Epub]. https://doi.org/10.1111/1754-9485.13182.

12. von Eyben FE, Bauman G, von Eyben R, Rahbar K, Soydal C, Haug AR, et al. Optimizing PSMA radioligand therapy for patients with metastatic castration-resistant prostate cancer. A systematic review and meta-analysis. Int J Mol Sci 2020;21:9054.

13. Ferdinandus J, Violet J, Sandhu S, Hicks RJ, Ravi Kumar AS, Iravani A, et al. Prognostic biomarkers in men with metastatic castration-resistant prostate cancer receiving [177Lu]-PSMA-617. Eur J Nucl Med Mol Imaging 2020;47:2322-7.

14. von Eyben FE, Roviello G, Kiljunen T, Uprimny C, Virgolini I, Kairemo K, et al. Third-line treatment and 177Lu-PSMA radioligand therapy of metastatic castration-resistant prostate cancer: a systematic review. Eur J Nucl Med Mol Imaging 2018;45:496-508.

15. Green HJ, Pakenham KI, Headley BC, Yaxley J, Nicol DL, MacTaggart PN, et al. Altered cognitive function in men treated for prostate cancer with luteinizing hormone-releasing hormone analogues and cyproterone acetate: a randomized controlled trial. BJU Int 2002;90:427-32.

16. Gonzalez BD, Jim HS, Booth-Jones M, Small BJ, Sutton SK, Lin HY, et al. Course and predictors of cognitive function in patients with prostate cancer receiving androgen-deprivation therapy: a controlled comparison. J Clin Oncol 2015;33:2021-7.

17. Fizazi K, Faivre L, Lesaunier F, Delva R, Gravis G, Rolland F, et al. Androgen deprivation therapy plus docetaxel and estramus-tine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial. Lancet Oncol 2015;16:787-94.

18. James ND, Ingleby FC, Clarke NW, Amos C, Attard G, Cross W, et al. 855PD - Docetaxel for hormone-naive prostate cancer (PCA): results from long-term follow-up of non-metastatic (M0) patients in the STAMPEDE randomised trial. Ann Oncol 2019;30(Suppl 5):v331.

19. Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, et al. [177Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet 2021;397:797-804.

20. Emerging digital prostate specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT)
guided Lutetium-177-PSMA therapy pre- and post-prostatectomy in newly diagnosed high risk prostate cancer patients: a feasibility study [Internet]. Camperdown: Australian New Zealand Clinical Trials Registry; 2020 Dec 17 [cited 2021 Jan 25]. Available from: https://www.anzctr.org.au/TrialSearch.aspx#&conditionCode=&dateOfRegistrationFrom=&interventionDescription=&interventionCodeOperator=OR&primarySponsorType=&gender=&distance=&postcode=&pageSize=20&ageGroup=&recruitmentCountryOperator=OR&recruitmentRegion=&ethicsReview=&countryOfRecruitment=&registry=&searchTxt=ACTRN12620001358932&studyType=&allocationToIntervention=&dateOfRegistrationTo=&recruitmentStatus=&interventionCode=&healthCondition=&healthyVolunteers=&page=1&conditionCategory=&fundingSource=&trialStartDateTo=&trialStartDateFrom=&phase=.

21. Dhiantravan N, Violet J, Eapen R, Alghazo O, Scalzo M, Jackson P, et al. Clinical trial protocol for lutectomy: a single-arm study of the dosimetry, safety, and potential benefit of 177Lu-PSMA-617 prior to prostatectomy. Eur Urol Focus 2021;7:234-7.

22. Wright GL Jr, Grob BM, Haley C, Grossman K, Newhall K, Petrylak D, et al. Upregulation of prostate-specific membrane antigen after androgen-deprivation therapy. Urology 1996;48:326-34.

23. Dhiantravan N, Emmett L, Joshua AM, Pattison DA, Francis RJ, Williams S, et al. UpFrontPSMA: a randomized phase 2 study of sequential 177 Lu-PSMA-617 and docetaxel vs docetaxel in metastatic hormone-naïve prostate cancer (clinical trial protocol). BJU Int 2021 Mar 7 [Epub]. https://doi.org/10.1111/bju.15384.