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# Patterns of primary staging for newly diagnosed prostate cancer in the era of prostate specific membrane antigen positron emission tomography: A population-based analysis

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**Abstract:**

**Background:**

There has been a growing body of evidence highlighting the improved sensitivity and specificity for prostate specific membrane antigen (PSMA) positron emission tomography (PET) in advanced prostate cancer imaging. We aimed to assess prostate cancer staging practice patterns in Australia using population-based data.

**Subject and methods:**

We extracted data on men diagnosed with prostate cancer between October 2016 and December 2018 from the Prostate Cancer Outcomes Registry-Victoria (PCOR-Vic). We evaluated trends and comparisons between patients receiving PET/CT (with or without conventional imaging (CImg)), and CImg alone, and analysed imaging modality as predictor of clinical regional node positive disease (cN1 vs cN0/X), metastatic disease (cM1 vs cM0/X), and treatment received.

**Results**

In total, 6139 patients in the registry had either a staging PET scan (n=889, 14%), CImg without PET scan (n=2464, 40%), or no recorded PET or CImg (n=2786, 45%). The proportion of all imaged patients who received staging PET increased from 19% to 36% from the first to last three-month period, and in the high-risk category the increase was 23% to 43%. After adjustment for grade group, PET vs CImg-only patients were observed to have a higher proportion of cN1 disease (OR=2.46, 95% CI: 1.90 – 3.20) but not cM1 disease (OR=1.10, 95%CI: 0.84 – 1.44).

**Conclusions:**

Our registry data highlights the rapid uptake of PET imaging, particularly in high-risk disease. Based on this data, we highlight the increased diagnosis of nodal disease, thus potentially optimizing patient selection prior to definitive treatment for prostate cancer.

## Introduction

Novel imaging using prostate specific membrane antigen (PSMA) positron emission tomography combined with computed tomography (PET/CT) has shown high utility for staging prostate cancer in both the primary and recurrent setting [1-3]. The impact of PSMA PET on clinical management has been well-studied, leading to significant management impact in up to 50% of patients [4]. Additionally, a recent prospective randomised trial has confirmed the superior accuracy of PSMA PET/CT when compared with conventional imaging (CImg) using CT and bone scan [5], with further benefits including greater management impact, less radiation dose, and less equivocal findings in favour of PSMA PET/CT.

In patients with newly diagnosed prostate cancer, the accurate exclusion of metastatic disease allows classification of the patients with localised disease. Such patients may be managed with radical prostatectomy (RP) or radiotherapy (RT) [6]. The inability to identify metastatic disease accurately may increase the risk of disease progression post-treatment for presumed localized disease. The potential of diagnosing metastatic disease at an earlier time point is increasingly being recognised, as low-volume metastatic cancer may benefit from treatment with combined systemic and radiation therapies [7].

Imaging for patients with newly diagnosed prostate cancer is rapidly evolving with the introduction of multiparametric magnetic resonance imaging (mpMRI) [8, 9] and positron emission tomography (PET) [2, 10]. Traditionally, staging for prostate cancer is recommended in higher risk groups [11]. Staging in this setting is conventionally performed with computerised tomography (CT) and whole-body technetium bone scans. However, such imaging modalities are limited by poor sensitivity – particularly in the oligometastatic setting and at low prostate specific antigen (PSA) levels. Following early reports on $^{68}$Ga-PSMA PET [10], a growing body of evidence supporting its use in advanced prostate cancer has been published. While most studies address the use of PSMA PET in biochemically recurrent prostate cancer, numerous studies have assessed the role of PSMA PET in the primary staging setting [12].

Despite its well demonstrated success and widespread use in Europe and Australia, the uptake of PSMA PET has been limited in several countries. Several groups have suggested that PSMA PET should only occur in the setting of clinical trials [13, 14]. The regulatory environment in Australia allows relatively unregulated use of imaging agents such as $^{68}$Ga-PSMA. Thus, this imaging modality has become widely available in Australia for

paying patients. The precise practice patterns of PSMA PET in primary staging for prostate cancer in a population has not been reported in previous literature. We aimed to demonstrate the patterns of primary staging of prostate cancer in Victoria using prostate cancer registry data.

## Subjects and methods

The Prostate Cancer Outcomes Registry-Victoria (PCOR-Vic) is a population-based prospective clinical quality of enrolled men with prostate cancer who were managed across Victoria, Australia. Information pertaining to the methodology and data collection supporting the PCOR-Vic database have previously been reported [15]. This registry has been ethically approved (Ref no: HREC/16/Alfred/98). In 2017-2018 the estimated population coverage of PCOR-Vic was greater than 75%.

Men included in the analysis were those diagnosed with prostate cancer by prostate biopsy or transurethral resection of the prostate from October 2016, because this was the earliest time that dates of staging imaging were consistently collected. Conventional imaging (CImg) was defined as receiving staging CT and/or bone scan. Staging modality type "PET with or without CImg" or "CImg without PET", was assigned if the imaging was performed within 180 days before or after the diagnosing procedure. The category of neither recorded was assigned if no staging PET, CT or bone scan was recorded in the registry at any time. Patients were further subdivided into "low risk" (Grade group 1 or Grade group 2 and PSA <10 ng/ml) and "high risk" (Grade group 2 and PSA ≥10 ng/ml or Grade group 3+) for subgroup analysis. Treatments given were categorized as either systemic (ADT, chemotherapy) or interventional (surgery, radiotherapy). Abstracted patient residence location was obtained from the Victorian Cancer Registry and mapped to the Australian Statistical Geography Standard remoteness structure to allow categorisation into "Major city", "Inner regional" and "Outer regional". Comparisons between patients receiving PET/CT±CImg and CImg alone were evaluated with chi-square tests or rank sum tests as appropriate. Additional analysis of imaging modality as predictor of clinical regional node positive disease (cN1 vs cN0/X) or metastatic disease (cM1 vs cM0/X) was performed using multivariable logistic regression with grade group simultaneously entered as a factor variable. Data analysis was performed using Stata v.13.0SE with statistical significance set at $p \leq 0.05$ for a two-tailed test.

## Results

From October 2016 to December 2018 inclusive, 6139 patients in PCOR-Vic were diagnosed with prostate cancer by biopsy or TURP. A staging PET/CT scan was performed in 889 (14%) within 180 days of diagnosis; 2464 (40%) had staging with CImg but no PET scan within 180 days of diagnosis, and 2786 (45%) had no recorded PET, CT or bone scan at any time. The proportion of all patients receiving staging PET increased over the study period from 11% for men diagnosed in the first three months to 20% in the last three months. This was most pronounced for patients classified as high risk with the increase being from 19% to 33% (Figure 1). Of the patients with any recorded imaging, the proportion that underwent PET increased from 19% to 36% and from 23% to 43% for high risk men.

Comparing men undergoing PET/CT vs CImg alone, there were statistically significant differences in diagnosis method, grade group and residence ($p<0.001$) (Table 1), whereas only weak evidence of difference was observed for PSA level ($p=0.028$). PET patients were observed to have a higher proportion of cN1 disease (16% vs 6.5%) and cM1 disease (11% vs 8.3%). After adjustment for grade group, there were still significantly higher odds of cN1 vs cN0/X disease, OR=2.46 (95% CI: 1.90 – 3.20) but not cM1 vs cM0/X stage, OR=1.10 (95% CI: 0.84 – 1.44). In the high-risk subgroup, node positivity was more common in PET/CT patients (21% vs 10%, $p<0.001$) (Table 2), however the proportion of cM1 disease was similar (14% vs 12%, $p=0.36$). In the low risk subgroup, numerically few patients had either node positive (n=6) or metastatic disease (n=7) though these were proportionally more common in PET imaged men.

Subsequent treatment for regional node positive or metastatic disease varied depending on imaging type (Table 3). Interventional treatment (surgery and/or radiotherapy ± systemic therapy) vs other was more common for node positive PET/CT vs CImg only patients (56% vs 38%, $p=0.002$) and who had metastatic disease (44% vs 32%, $p=0.028$). Systemic therapy alone was prescribed less commonly for cN1 PET patients (39% vs 60%).

## Discussion

The imaging modalities used for staging for prostate cancer are changing rapidly. Using registry-based data we highlight the increasing use of PET imaging in primary staging of prostate cancer, particularly in high risk disease. Associated with this increased use of PET, there has been an increase in the diagnosis of metastatic nodal disease. Further, despite the recommendations of rationalising imaging in favorable disease, a substantial proportion of men still undergo staging prior to definitive therapy.

The findings of the current study highlight 'real-world' data regarding the use in practice of PET for the primary staging of prostate cancer in Australia, where PSMA PET/CT has been widely available for a number of years [16]. Though tracer is not recorded in the registry, in our contemporary practice, the overwhelming number of staging PET/CT scans use a PSMA tracer, hence the discussion will use PET/CT and PSMA-PET/CT interchangeably. Despite this evidence, limited data is available addressing the clinical uptake of PET/CT imaging for prostate cancer. Several groups have suggested that PSMA PET/CT should only occur in the setting of clinical trials. Our findings based on registry data quantify the rapid increase of PET/CT in routine clinical practice for primary staging of prostate cancer in Victoria, Australia, particularly for patients resident in major metropolitan areas. These results are corroborated by recent literature suggesting declining use of whole body bone scan and rising use of PSMA PET/CT in prostate cancer assessment [17]. The increased utilisation of such imaging is likely secondary to increased awareness and confidence in this imaging modality. This may be in part due to the early adoption and prolonged clinical experience of PSMA PET/CT within Australia. Indeed, soon after its initial reporting by Afshar Oromieh in 2013 [10], early series were reported in Australia from 2015 [18]. Over time, accessibility has increased, with some regional centers across Australia having satisfactory PSMA availability [19]. The familiarity and confidence in the data supporting its use and improved access to PSMA and molecular imaging in Australia have largely driven its uptake.

Our registry-based study demonstrated higher rates of diagnosis of nodal disease in patients staged with PSMA PET imaging compared with conventional imaging. Unidentified nodal metastatic disease prior to definitive treatment may increase the risk of biochemical recurrence and future oncologic compromise. The improved diagnostic utility of PSMA PET/Ct compared to computerized tomography has been well established [5, 20-22]. A recent randomized controlled cross-over trial (proPSMA) showed superiority of PSMA PET/CT compared to conventional imaging in detecting pelvic nodal disease (AUC 91% vs 59%) and distant metastases (AUC 95% vs 74%) [5]. These properties of PSMA PET/CT have clinically significant implications on the management strategies of these patients as they may no longer be suitable for local therapy and could benefit from systemic therapies such as androgen deprivation. Conversely, patients who might otherwise have benefitted from local therapy may be denied this opportunity as there is no data to demonstrate the oncological benefit, if any, of using PSMA PET/CT as a primary staging tool. Interestingly, from the current analysis, there appears to be a variation in treatment in patients identified with metastatic disease based on PET/CT and CImg. Fewer patients imaged with PET/CT who

were diagnosed with nodal disease were treated with systemic therapy alone. The reason for this is unclear, however this may be due to increased confidence in PET to identify disease not yet apparent on CImg, oligometastatic disease and thus increased use of additional metastasis-targeted therapies.

Despite recommendations by authoritative bodies, our results demonstrate that a substantial proportion of men with intermediate risk prostate cancer are undergoing systemic imaging. Current European Association of Urology (EAU) guidelines recommend systemic primary staging for prostate cancer patients with primary pattern 4 disease (ISUP 3 or higher) [11]. Similarly, the American Urological Association recommends cross-sectional imaging for staging in patients with 'unfavorable intermediate risk disease' [23]. According to our registry data, 32% of patients with 'favorable intermediate risk disease' (ISUP 1 or ISUP 2 and PSA <10) are undergoing primary staging. Of these patients that did receive imaging for staging, only 0.7% had detected metastatic disease. This finding highlights the low yield of systemic imaging in these patients. These observations support the EAU and AUA recommendations to primarily stage patients with unfavorable intermediate risk or high-risk prostate cancer.

There are limitations in the current study. Use of registry-based data is restricted by the inherent limitations in the accuracy of data collection and classification. A small number of patients without recorded PET/CT, CT or bone scan were staged as cN1, perhaps derived from mpMRI, however, imaging reports being unavailable in the medical records cannot be excluded. Additionally, 18% of patients with grade group 3+ disease had no recorded imaging. It is likely this is due to missing data; however, these patients did have a lower PSA and were more likely to have a negative DRE than the 82% with recorded imaging. In the current database, subtypes of 'PET' imaging was not defined, and thus a proportion of patients may have received alternate tracers. However, the clinical practice in our state over the time period analysed is that the overwhelming majority of PET imaging done for primary staging used a PSMA tracer. Of course, this data pertains to a part of the world where PSMA PET/CT is widely available, and these patterns are not typical for many regions. However, they do give an insight into likely patterns of use of PSMA PET/CT as it becomes more available in other regions.

## Conclusion

Our study provides a contemporary snapshot of the rapidly evolving landscape of primary staging for prostate cancer. Our registry data highlights the uptake of PSMA PET

imaging, particularly in high risk disease. We highlight the increased diagnosis of nodal disease – and thus the potential to optimizing patient selection prior to definitive treatment. We also observed different treatment patterns for men with regional node or metastatic disease, depending on the staging image modalities used. Further research, including cost-benefit analysis and impact on survival of using novel imaging, will be required in the future.

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**Contribution:**

N Papa: Project development, Data analysis

M Perera: Manuscript writing

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N Lawrentschuk: Manuscript writing/editing

M Evans: Data collection, Data analsyis

J Millar: Manuscript editing, supervision

D Bolton: Manuscript editing, supervision

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*Figure 1. Percentage split between imaging modalities over 3-month time periods for "low" and "high" risk.*

Table 1. Characteristics of the sample n=6139

| | PET ± CImg n=889 | CImg only n=2464 | Neither recorded n=2786 |
|---|---|---|---|
| Age at diagnosis, median (IQR) | 68.4 (62.9 – 73.4) | 68.7 (63.1 – 74.5) | 66.0 (60.1 – 71.1) |
| Patient residence | | | |
| Major city | 647 (73%) | 1504 (61%) | 1970 (71%) |
| Inner regional | 131 (15%) | 650 (26%) | 572 (21%) |
| Outer regional | 56 (6.3%) | 154 (6.3%) | 124 (4.5%) |
| Unavailable | 55 (6.2%) | 156 (6.3%) | 120 (4.3%) |
| Diagnosis method | | | |
| Transperineal biopsy | 711 (80%) | 1477 (60%) | 1985 (71%) |
| TRUS biopsy | 153 (17%) | 786 (32%) | 489 (18%) |
| TURP | 25 (2.8%) | 201 (8.2%) | 312 (11%) |
| PSA at diagnosis *, median (IQR) | 8.9 (6.2 – 15.2) | 8.4 (5.6 – 13.7) | 6.0 (4.5 – 8.1) |
| Biopsy/TURP grade group | | | |
| 1 | 46 (5.2%) | 179 (7.3%) | 1308 (47%) |
| 2 | 227 (26%) | 878 (36%) | 995 (36%) |
| 3 | 245 (28%) | 559 (23%) | 270 (9.7%) |
| 4 | 126 (14%) | 360 (15%) | 97 (3.5%) |
| 5 | 243 (27%) | 469 (19%) | 90 (3.2%) |
| Unrecorded | 2 (0.2%) | 19 (0.8%) | 16 (0.9%) |
| Clinical T-stage | | | |
| cT1 | 236 (27%) | 722 (29%) | 1432 (51%) |
| cT2 | 225 (25%) | 669 (27%) | 402 (14%) |
| cT3/4 | 140 (16%) | 330 (13%) | 55 (2.0%) |
| Unrecorded | 288 (32%) | 743 (30%) | 897 (32%) |
| Clinical N-stage | | | |
| cN0/X | 744 (84%) | 2303 (93%) | 2780 (99.8%) |
| cN1 | 145 (16%) | 161 (6.5%) | 6 (0.2%) |
| Clinical M-stage | | | |
| cM0/X | 790 (89%) | 2270 (92%) | 2777 (99.7%) |
| cM1 | 99 (11%) | 204 (8.3%) | 9 (0.3%) |

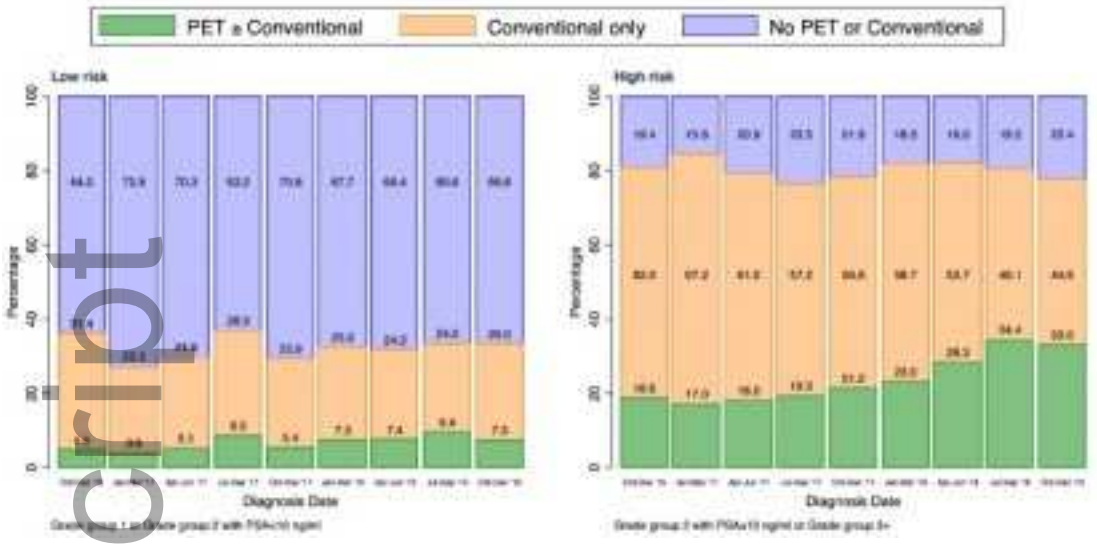
* n=341 (5.6%) no recorded diagnosis PSA

Table 2. cN and cM stage per imaging received and grade group or risk category (Patients without recorded biopsy grade or PSA level not included in risk category data)

| **Clinical Node stage** | **PET ± CImg** | | **CImg only** | |
|---|---|---|---|---|
| Grade Group | cN0/X | cN1 | cN0/X | cN1 |
| GG 1 | 45 (98%) | 1 (2.2%) | 179 (100%) | 0 |
| GG 2 | 219 (96%) | 8 (3.5%) | 872 (99%) | 6 (0.7%) |
| GG 3 | 226 (92%) | 19 (7.8%) | 549 (98%) | 10 (1.8%) |
| GG 4 | 101 (80%) | 25 (20%) | 324 (90%) | 36 (10%) |
| GG 5 | 152 (63%) | 91 (37%) | 363 (77%) | 106 (23%) |
| Risk category | cN0/X | cN1 | cN0/X | cN1 |
| Low | 203 (98%) | 4 (1.9%) | 808 (99.8%) | 2 (0.2%) |
| High | 532 (79%) | 139 (21%) | 1449 (90%) | 156 (10%) |
| **Clinical Metastasis Stage** | **PET ± CImg** | | **CImg only** | |
| Grade Group | cM0/X | cM1 | cM0/X | cM1 |
| GG 1 | 44 (96%) | 2 (4.3%) | 179 (100%) | 0 |
| GG 2 | 221 (97%) | 6 (2.6%) | 867 (99%) | 11 (1.3%) |
| GG 3 | 226 (92%) | 19 (7.8%) | 544 (97%) | 15 (2.7%) |
| GG 4 | 109 (87%) | 17 (13%) | 312 (87%) | 48 (13%) |
| GG 5 | 188 (77%) | 55 (23%) | 340 (72%) | 129 (28%) |
| Risk category | cM0/X | cM1 | cM0/X | cM1 |
| Low | 202 (98%) | 5 (2.4%) | 808 (99.8%) | 2 (0.2%) |
| High | 578 (86%) | 93 (14%) | 1405 (88%) | 200 (12%) |

Table 3. Treatment within first 12 months for regional node positive or metastatic disease

| Regional node positive | PET ± CImg<br>n=145 | CImg only<br>n=161 |
|---|---|---|
| Systemic alone | 57 (39%) | 96 (60%) |
| Interventional alone | 17 (12%) | 4 (2.4%) |
| Systemic + interventional | 64 (44%) | 57 (35%) |
| Observation/Unrecorded | 7 (4.8%) | 4 (2.4%) |
| **Metastatic** | **PET ± CImg<br>n=99** | **CImg only<br>n=204** |
| Systemic alone | 54 (55%) | 137 (67%) |
| Interventional alone | 5 (5.1%) | 5 (2.5%) |
| Systemic + interventional | 39 (39%) | 59 (29%) |
| Observation/Unrecorded | 1 (1.0%) | 2 (1.5%) |

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