Retrospective Review of Nuclear Medicine Imaging in the Staging of High-intermediate Risk to High Risk Prostate Cancer Patients at Groote Schuur Hospital

by

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Declaration

I, Justin Sven Pieterse, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

Plagiarism Declaration

This dissertation has been submitted to the Turnitin module. I confirm that my supervisor has seen my report and that any concerns revealed by such have been resolved with my supervisor.

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Format

This thesis is submitted in publication ready format.

There have been no prior publications or submissions.

Acknowledgements and contributions

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Michelle Henry – Statistician. PhD Psychology

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Abbreviations / Definitions:

[^{68}Ga]Ga-PSMA PET-CT [^{99m}Tc]Tc-HYNIC-PSMA SPECT-CT	Targeted molecular imaging techniques which localise tissues that express the PSMA transmembrane glycoprotein
ASCO	American Society of Clinical Oncology
CT	Computerised Tomography
EANM	European Association of Nuclear Medicine
EAU	European Association of Urology
GSH	Groote Schuur Hospital
High-intermediate risk	Unfavourable intermediate risk / High (tier) intermediate risk
ISUP	International Society of Urological Pathology
LN	Lymph node
MDP	Methylene diphosphonate
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NHLS	National Health Laboratory System
PET-CT	Positron Emission Tomography Computerised Tomography
PSA	Prostate Specific Antigen
PSMA	Prostate Specific Membrane Antigen
SPECT	Single Photon Emission Computerised Tomography
TNM	Tumour Nodes Metastases

Retrospective Review of Nuclear Medicine Imaging in the Staging of High-Intermediate Risk to High Risk Prostate Cancer at Groote Schuur Hospital.

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Short Title: Molecular Imaging in Prostate Cancer Staging

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Retrospective Review of Nuclear Medicine Imaging in the Staging of High-Intermediate Risk to High Risk Prostate Cancer at Groote Schuur Hospital.

Abstract:

PURPOSE: The purpose was to objectively characterise diagnostic performance of a local hospital molecular imaging protocol for staging high-intermediate and high risk prostate cancer whereby iterative molecular imaging with [^{99m}Tc]Tc-MDP bone scan, [^{99m}Tc]Tc-HYNIC-PSMA SPECT-CT and [^{68}Ga]Ga-PSMA PET-CT was performed until metastases were convincingly detected. A supplementary aim was to determine if selective use of specific modalities is justified in certain groups.

MATERIALS AND METHODS: Local patients who underwent staging with the abovementioned protocol were identified for data capturing. Overall detection rates for the presence of metastases at each iteration were calculated. Statistical analysis was performed for associations between diagnostic performance and risk stratification subcategories (clinical stage, PSA levels, histological grade; or age).

RESULTS: Detection rates for metastatic disease for those enrolled (n=88) increased from 38% to 51% to 61% with each respective imaging iteration. There was a significant association of patient age, PSA level, histological grade, and clinical stage to bone scan positivity, with a reduction in mean PSA for those demonstrating metastatic disease on subsequent [^{99m}Tc]Tc-PSMA SPECT-CT. No further significant associations were observed for the subgroup who proceeded to [^{68}Ga]Ga-PSMA PET-CT.

CONCLUSION: Bone scan or [^{99m}Tc]Tc-HYNIC-PSMA SPECT-CT proved reasonable first-line staging investigations to exclude evidence of metastases before [^{68}Ga]Ga-PSMA PET-CT, with enhanced efficiency in locally advanced disease, ISUP 5 or higher spectrum PSA/age. The findings favour [^{99m}Tc]Tc-PSMA SPECT-CT over bone scan where [^{68}Ga]Ga-PSMA PET-CT is unavailable, due to lower mean PSA threshold for detecting metastatic disease.

Keywords: prostate, adenocarcinoma, staging, PSMA, bone scan, SPECT, PET.

Introduction

In 2020 prostate cancer was rated the most common cancer affecting males in South Africa [1] and was only marginally second to lung cancer on a global scale [2].

The skeleton is the most frequent site of metastatic involvement in prostate cancer [3, 4] with notably impaired median survival rate where skeletal metastases are evident at initial diagnosis [5]. Furthermore, bone metastases contribute to morbidity with pain, fractures and impairment of mobility[6]. The incidence of bone metastases at diagnosis is variable by sample population and risk group, reports ranging 3% – 10% [3, 5, 7, 8].

Overall, adenocarcinoma of the prostate and the prognosis thereof is heterogeneous, potentially indolent in the early stages. [9].

The likelihood for biochemical recurrence, aggressive progression and adverse outcomes has been associated with various parameters; this includes histological grade, serum prostate specific antigen (PSA) levels and clinical stage (locoregional extent of disease by clinical examination) [10, 11].

Currently, prostate cancer with limited spread is amenable to therapy with curative intent, termed radical therapy [12]. Existing radical therapies, however, come with drawbacks which can negatively impact patient quality of life [13-15], as might inappropriate conservative approaches impair survival [16]. The demand of unwarranted management strategies on specialized hospital infrastructure must also be considered. Appropriate staging of patients for radical therapies is therefore crucial, as is the optimal use of resources.

Multiple non-invasive imaging modalities exist for staging in prostate cancer [17, 18]. Numerous evidence-based guidelines are therefore in contextual evolution – including those formulated by the European Association of Urology (EAU) [10], American Society of Clinical Oncology (ASCO) [19] and National Comprehensive Cancer Network (NCCN) [20], amongst others. These may, however, require local adaptation in line with particular population characteristics or resource limitations.

Nuclear medicine has historic and emerging molecular imaging options in the staging of prostate cancer.

There is a well-established role of skeletal imaging with tracers which target the hydroxyapatite matrix of bone, such as [^{99m}Tc]Tc- Methylene diphosphonate (MDP). However, prior investigation highlights non-specificity of this approach. A study by Even-Sapir et al. comparing skeletal imaging strategies (in prostate cancer patients at high risk of bone metastases) measured a specificity of [^{99m}Tc]Tc-MDP bone scan of 82%, at best (when interpreted with single photon emission computerized tomography (SPECT)), relative to [^{18}F]Fluoride PET-CT (combined interpretation with anatomical findings) [21, 22].

More current research highlights some merits of staging using molecular imaging which targets PSMA, a transmembrane glycoprotein overexpressed in prostate malignancy [23]. The allowance for detection of soft tissue metastases above bone scintigraphy is most notable [5, 24].

Data specific to the *local* population was lacking, including evidence of any possible associations between image findings and the various qualitative or quantitative risk parameters. The additional diagnostic performance of PSMA imaging over bone scan alone was also not established in our population.

To address the above, the primary aim of this study was to locally characterise diagnostic performances, and the additive value thereof, in proceeding from negative ^{99m}Tc]Tc-MDP bone scintigraphy ± SPECT (hereafter also termed bone scan) to [^{99m}Tc]Tc-HYNIC-PSMA SPECT-CT (hereafter termed [^{99m}Tc]Tc-PSMA scan); and respectively from [^{99m}Tc]Tc-PSMA scan to [^{68}Ga]Ga-PSMA positron emission tomography (PET-CT). A supplementary aim was to determine whether there might be population-specific statistically significant associations between risk profile parameters and the detection rate of each modality, as well as any association with patient age group. This data would allow for more informed local selection of initial imaging investigation and thereby more efficient resource use and delivery of care.

Materials and Methods

Imaging protocol

Molecular imaging investigations appropriate to the staging of prostate cancer available at our center between September 2018 to February 2020, listed in order of most-to-least accessible based on booking waiting periods, were: (1) bone scan, (2) [^{99m}Tc]Tc-PSMA scan, and (3) [^{68}Ga]Ga-PSMA PET-CT. The prostate cancer staging protocol implemented at the time was adapted from the existing ASCO guidelines whereby routine bone scan, if negative, was followed by [^{99m}Tc]Tc- HYNIC-PSMA scan, in lieu of a standard abdominopelvic CT [19]. More sensitive imaging with [^{68}Ga]Ga-PSMA PET-CT [25, 26] was then reserved for use in patients where metastatic disease remained undetected. Effectively, high-intermediate risk and high risk prostate cancer patients with routine bone scintigraphy negative or equivocal for evidence of metastases were subsequently investigated with [^{99m}Tc]Tc-PSMA scan, and respectively with [^{68}Ga]Ga-PSMA PET-CT imaging (see Figure 1).

Image acquisition parameters and processing

Bone scans were acquired on SIEMENS™ Symbia™ gamma cameras 3 hours after administration of approximately 740 MBq [^{99m}Tc]Tc-MDP. SPECT reconstruction parameters were as follows: OSEM method; 4 subsets; 16 iterations using HERMES™ or SIEMENS™ reconstruction software.

[^{99m}Tc]Tc-PSMA scans were acquired on SIEMENS™ Symbia™ gamma cameras 3 hours after administration of approximately 740 MBq [^{99m}Tc]Tc-HYNIC-PSMA. SPECT reconstruction parameters were as follows: OSEM method; 4 subsets; 16 iterations using HERMES™ or SIEMENS™ reconstruction software.

[^{68}Ga]Ga-PSMA PET imaging was acquired with a Philips™ Big Bore™ PET-CT camera 60 minutes after the administration of 100 – 200 MBq [^{68}Ga]Ga-PSMA (3 iterations, 33 subsets, kernel width 14.1cm).

Image interpretation

Studies were interpreted independently by qualified nuclear physicians with experience exceeding 5 years and in line with criteria established by Even-Sapir et al. [22] for bone scintigraphy; and Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria (molecular imaging PSMA expression) [27] for PSMA-targeted imaging.

Data collection

The Department of Nuclear Medicine at Groote Schuur Hospital has a database in which all radiopharmaceutical doses administered, investigations performed, and reports thereof are

recorded, as well as an electronic archive containing the raw data of all studies acquired since 2012.

A database search was performed for patients who were referred for molecular imaging of prostate cancer between 1 September 2019 and 29 February 2020.

Supplementary information for patient cancer risk profiling was obtained from the central laboratory results electronic database. Where clinical stage or reason for referral was not specified in reports, hospital folders were retrieved and reviewed to obtain this information. Patient data was captured and populated into a Microsoft ® Excel ® spreadsheet (version Part of Microsoft Office Professional Plus 2013), together with relevant dates, as follows: Hospital number, reason for referral, age at referral, clinical stage, PSA level nearest to imaging, histology grade by International Society for Urological Pathology (ISUP) at the time of referral.

Inclusion/Exclusion criteria

Patients considered for analysis were limited to those referred for (a) primary staging of (b) high-intermediate and high risk prostate cancer, as defined by European Association of Urology (EAU) 2017/2021 Guidelines [10, 28] (c) being considered for possible radical therapy (d) who completed the hospital staging protocol within the specified time period. Cases that did not meet the above criteria were excluded from further analysis (i.e. those patients with prostate cancer referred for molecular imaging in the following circumstances – ineligible for radical therapy from the onset; for watchful waiting (surveillance); with biochemical recurrence; known with metastatic disease; where reasoning for investigation was elusive; with deviations from the hospital staging protocol).

Data analysis (Primary Aim)

The number of patients with positive, negative or equivocal image findings at each iteration were tabulated. Diagnostic performance of sequential imaging was quantified for each step of the staging protocol with specific reference to any added value over preceding imaging.

The study was approved by the Human Research Ethics Committee of the University of Cape Town (HREC Reference no 715/2020).

Statistical Analysis and Methods

Data was analysed for statistically significant associations between patient risk stratification sub-categories (clinical stage, histology grade, PSA level), or age demographics, and the detection rate for metastases. For [^{99m}Tc]Tc-PSMA scan and [^{68}Ga]Ga-PSMA PET-CT, available data was limited to those who had negative or equivocal findings for metastases on preceding iterations of the hospital protocol.

Statistical analysis was performed using IBM ® SPSS ® Statistics software, version 26.

Continuous variables were described with means and standard deviations. Categorical variables were described as frequency and percentages. Continuous variables include the PSA Level an Age. Categorical variables include Clinical Stage, Histology Grade, and image findings.

Categorical variables were clustered into the following instances for analysis

- Clinical stage
    1. T1a-c Tumour not evident by physical examination
    2. T2a Tumour in no more than one half of one side of the prostate
    3. T2b Tumour is more than half of one side of the prostate
    4. T2c Tumour is in both sides of the prostate
    5. T3+ Tumour is locally invasive tumour on physical examination
- Histology grade, as per ISUP, ranging 1 to 5
- Image findings
    1. M+ positive for metastases
    2. M- negative or equivocal for metastases

The association between image findings and clinical stage/histology grade were assessed using Fisher's Exact Test. Differences in PSA level and age between image findings (testing positive vs. negative/equivocal) were assessed using independent sample t-tests. A p-value of 0.05 or less was considered statistically significant.

Results

Of the 181 patients identified, 37 were excluded from the study because they were ineligible for radical treatment from the outset, and a further 57 as they had incomplete imaging data (see Figures 2 and 3), leaving 87 eligible patients for inclusion.

Mean age of patients at baseline was 65.05 years with a mean PSA of 130.95µg/L. The majority of patients were categorised with ISUP 5 histology (42%). Seventy-six percent (76%) of patients had palpable tumours on clinical examination (see Table 1 for further patient characteristics).

Findings for the Detection of Metastatic Disease –
Thirty-three (33) of the 87 (38%) eligible patients, demonstrated bone metastases on initial bone scan, leaving 54 for further investigation.

Twenty percent (20%) (n=11) of the remaining 54 (who had negative/equivocal bone scans) were subsequently found to have evidence for metastatic disease on [^{99m}Tc]Tc-PSMA scan, equating to an absolute increase in those diagnosed with metastases of 13%, from 38% (n=33) to 51% (n=44).

Similarly, an additional 20% (n=9) of those with negative/equivocal [^{99m}Tc]Tc-PSMA scan went on to be diagnosed with metastases after [^{68}Ga]Ga-PSMA PET-CT, resulting in a further 10% absolute increase in those diagnosed with metastases, from 51% (n=44) to 61% (n=53) of the 87 patients enrolled.

This equates to a 23% increase in those diagnosed with metastases from initial bone scan to final [^{68}Ga]Ga-PSMA PET-CT, with only 39% (n=34) of the initial 87 remaining eligible for radical therapy (see Figures 2 and 3).

Association of Clinical Stage, Histology and PSA levels with Imaging Findings –
For bone scan, clinical stage was significantly associated with image findings ($p = 0.018$). Patients with a positive bone scan were more likely to have clinical stage T3/4 cancer compared to patients with a negative scan (54.5% vs 18.5%). However, in the subgroup with negative bone scans, there were no significant further associations with subsequent imaging and clinical stage; [^{99m}Tc]Tc-PSMA scan ($p = 0.154$) or [^{68}Ga]Ga-PSMA PET-CT ($p = 0.848$).

There was a statistically significant association between image findings and histology grade in both the bone scan ($p = 0.005$) and the subgroup who proceeded to a [^{99m}Tc]Tc-PSMA scan ($p = 0.009$). In both cases, patients who tested positive were more likely to have a histology grade ISUP 5 and less likely to be ISUP 3.

However, no such associations were found in the subgroup (with negative bone scan and [^{99m}Tc]Tc-PSMA scan) who further proceeded to have [^{68}Ga]Ga-PSMA PET-CT imaging ($p = 0.062$).

In both the bone scan ($p < 0.001$) and [^{99m}Tc]Tc-PSMA scan ($p = 0.026$), patients who tested positive had higher mean PSA levels compared to those who tested negative. Furthermore, patients who tested positive on bone scan had a higher mean age compared to those who tested negative ($p = 0.001$).

Discussion

For patients with high-intermediate risk to high risk prostate cancer at our centre there was incremental increase in diagnostic performance for demonstrating the presence of metastases when proceeding from molecular imaging with initial bone scan to [^{99m}Tc]Tc-PSMA scan; and then respectively to [^{68}Ga]Ga-PSMA PET-CT. Detection rates for metastatic disease for those enrolled (n=88) increased from 38% to 51% to 61% with each respective imaging iteration.

This ties in with data from published studies; bone scan and [^{99m}Tc]Tc-PSMA scan have previously shown comparable detection of skeletal metastases in the staging of prostate cancer, with additional broader capability of PSMA imaging for detecting soft tissue metastases [5, 24]. Of equal relevance, [^{68}Ga]Ga-PSMA PET-CT imaging has been shown to outperform [^{99m}Tc]Tc-PSMA scan [29] with ability to detect PSMA expressing lesions of smaller size [25]. Also, evidence exists suggesting superiority of [^{68}Ga]Ga-PSMA PET-CT in the detection of skeletal metastases when directly compared to bone scintigraphy [30, 31]. Although data available for this review did not permit *direct* comparison across all three imaging modalities, broader deductions were possible when supported by this literature. In effect, [^{68}Ga]Ga-PSMA PET-CT ought to have independently illustrated comparable diagnostic performance to that of the overall imaging protocol (i.e. 61%; n = 53 out of 87) had all qualifying patients undergone all three studies (presuming false positive bone scans [32] were not a major contributor).

Detection of metastatic disease with bone scan or [^{99m}Tc]Tc-PSMA scan was significantly linked to higher mean PSA levels, older patients, locally advanced disease (T3/4 by clinical examination) or histological ISUP 5; with lower mean PSA for [^{99m}Tc]Tc-PSMA scan (85.24 ug/L vs 275.18 ug/L). This essentially concurs with studies by Merdan et al. and Risko et al. (although with reference to diagnostic CT as oppose to [^{99m}Tc]Tc-PSMA scan) who showed PSA, histological grade and clinical stage as significant predictors for positive metastatic findings (with significance in categories ISUP grade ≥ 4 in both modalities and clinical stage ≥ T3 for diagnostic CT imaging) [33, 34]. Although, there are some conflicting results of age-significance reported across other studies/cohorts [34-37].

The role of regional epidemiology in tailoring staging protocols must be highlighted. Over a third of our sample population (38%; n = 33 out of 87) demonstrated skeletal metastases, all evident on bone scintigraphy. This equates to almost two thirds (62%; n = 33 out of 53) of those ultimately diagnosed with metastatic disease.

Some studies quote lower prevalence rates (<10%) for skeletal metastases on initial diagnosis of prostate cancer [3, 7, 38]. However, these are not representative of our context or study methods. For example, although a study by Sevcenco et al. showed only 4% (n=10 out of 236) positive bone scans in their high risk group, the mean PSA was concordantly lower than observed in our study (5.75 ug/L vs 195.3ug/L with skeletal metastases) [38]. Whilst greater prevalence of aggressive phenotype in our population might account for this, it may reflect diagnostic delay, referral bias or false positives (due to non-specificity of bone scan findings) [32]. This favours ongoing utility of bone scintigraphy where center-specific prevalence rates (or likelihood) for skeletal metastases at initial diagnosis are considered relatively high.

Based on the above, a center-specific molecular imaging algorithm tailored to our population is proposed (see Figure 4).

The study did have further limitations. Data available for retrospective review did not allow for evaluation and quantification of instances where evidence for *distant* metastases might emerge with [^{68}Ga]Ga-PSMA PET-CT imaging where undetected with [^{99m}Tc]Tc-PSMA scan. The adequacy of [^{99m}Tc]Tc-PSMA scan as a surrogate in lieu of [^{68}Ga]Ga-PSMA PET-CT, and the prognostic implications thereof, was therefore not established. In spite of this, albeit non-curative to proceed with the available radical therapies in these instances, local control has been shown to confer benefit [16] and might impact long term survival.

Also, our hospital protocol was adapted based on access and availability of molecular imaging services, to effectively limit burden on resources in line with scarcity. This is not synonymous with cost efficiency which typically plays a decisive role in patient and public healthcare.

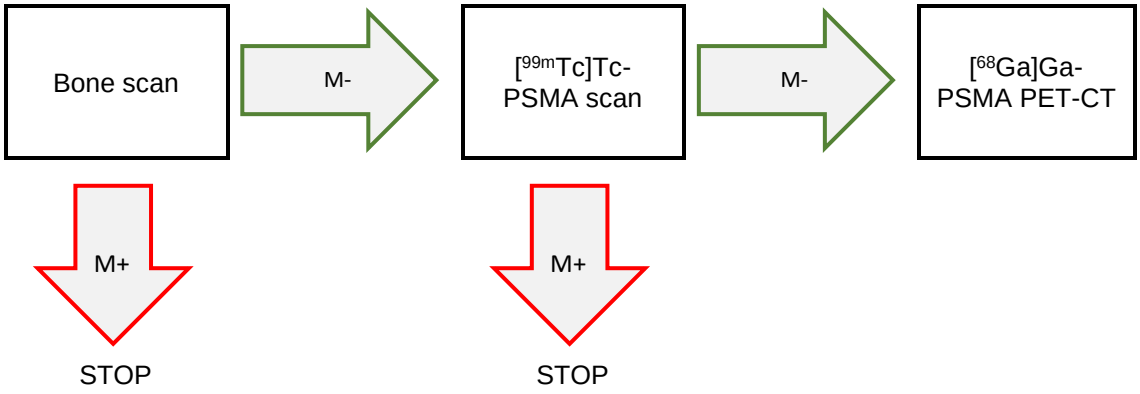
Prospective local investigation allowing for more stringent study methods, larger cohorts and cross comparison of different demographic groups might improve statistical confidence in findings and epidemiologic conclusions. Suitable cut-off thresholds of continuous variables (namely PSA and age) in specific populations can thereby be established. The role of additional variables, such as symptomatology might also be investigated. Further review of recurrence rates/dynamics in radically managed patients staged exclusively with [^{99m}Tc]Tc-PSMA scan would provide insight into clinical consequence of possible undermined disease extent in settings where [^{68}Ga]Ga-PSMA PET-CT imaging is unavailable. Concurrent cost analysis would provide a more meaningful understanding of the broader implications on health economics.

Conclusion

For local patients with high-intermediate and high risk prostate cancer undergoing staging for consideration for radical therapy, there was clear increase in detection rates for metastatic disease when sequentially proceeding from initial bone scan to [^{99m}Tc]Tc-PSMA scan imaging, and from [^{99m}Tc]Tc-PSMA scan to [^{68}Ga]Ga-PSMA PET-CT, where metastases were not evident on preceding imaging respectively.

Findings promote adaptation of the hospital protocol. First-line screening for presence of metastases with initial bone scan or [^{99m}Tc]Tc-PSMA scan is probably best reserved for routine use in cases of clinically locally advanced disease (≥T3), ISUP 5 histology grade or higher spectrum PSA/age , for greater efficiency of care; with preference for [^{99m}Tc]Tc-PSMA scan imaging due to a lower mean PSA threshold for detecting the presence of metastatic disease. In effect, patients without such characteristics can more appropriately proceed directly to [^{68}Ga]Ga-PSMA PET-CT, where available.

Figure 1. Schematic overview of molecular imaging protocol



**M+ denotes positive for evidence of metastases (locoregional or distant)*

**M- denotes negative or equivocal for evidence of metastases*

Figure 2. Schematic overview of results

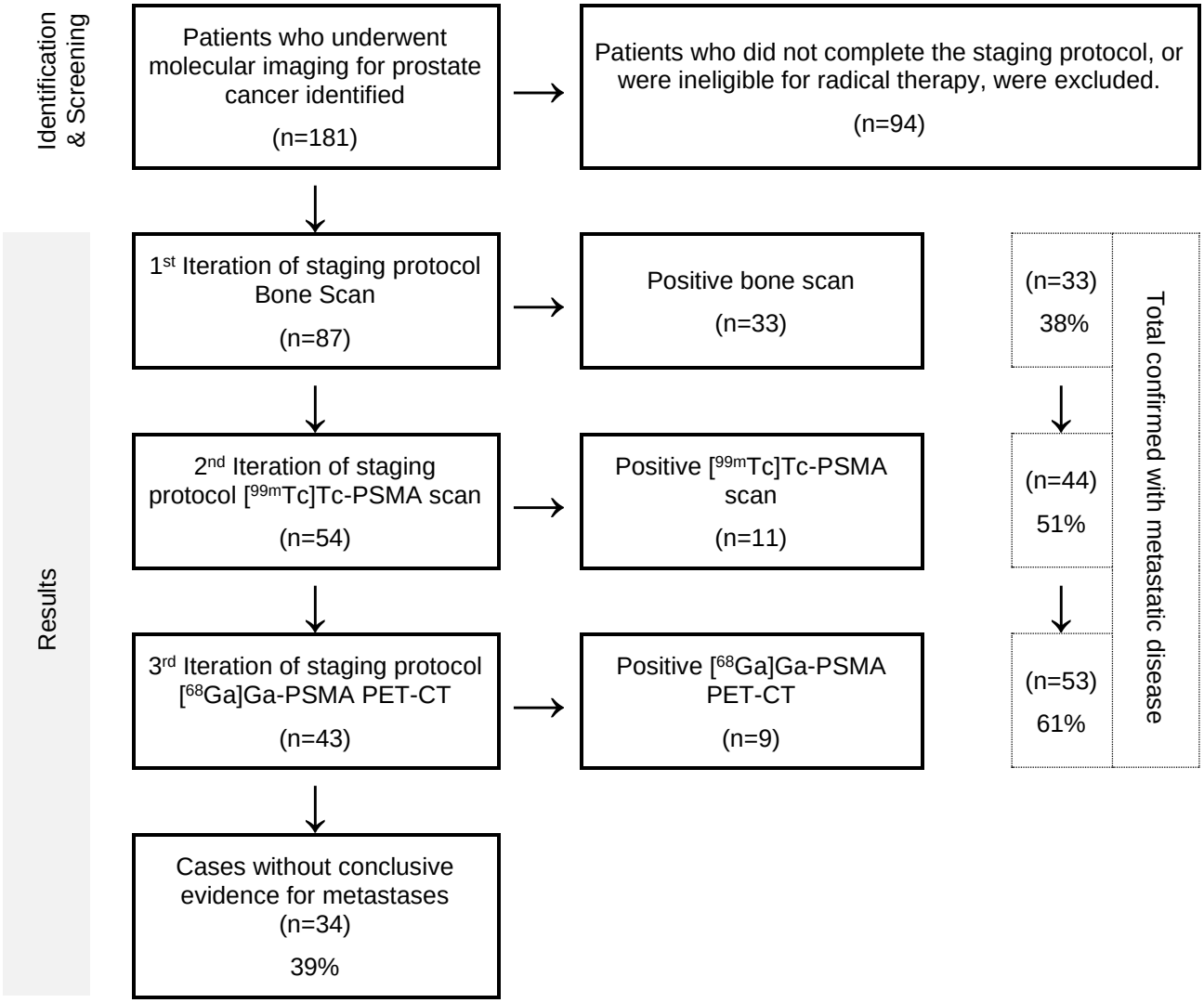
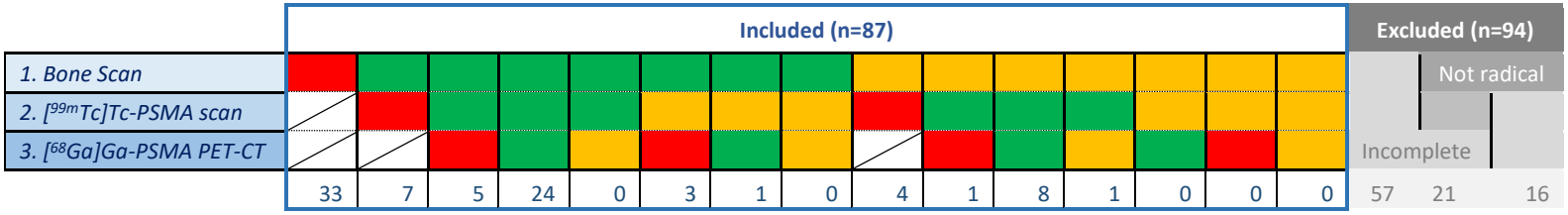


Figure 3. Image findings across the three scans



	M+ Cumulatively		M- Cumulatively	
1st Iteration	38%	33	62%	54
2nd Iteration	51%	44	49%	43
3rd Iteration	61%	53	39%	34

Key

Positive for evidence of metastases (locoregional or distant) | **Denoted M+*

Equivocal for evidence of metastases

Negative for evidence of metastases | **Denoted M-*

Metastases already evident on preceding imaging

Figure 4. Proposed clinical protocol

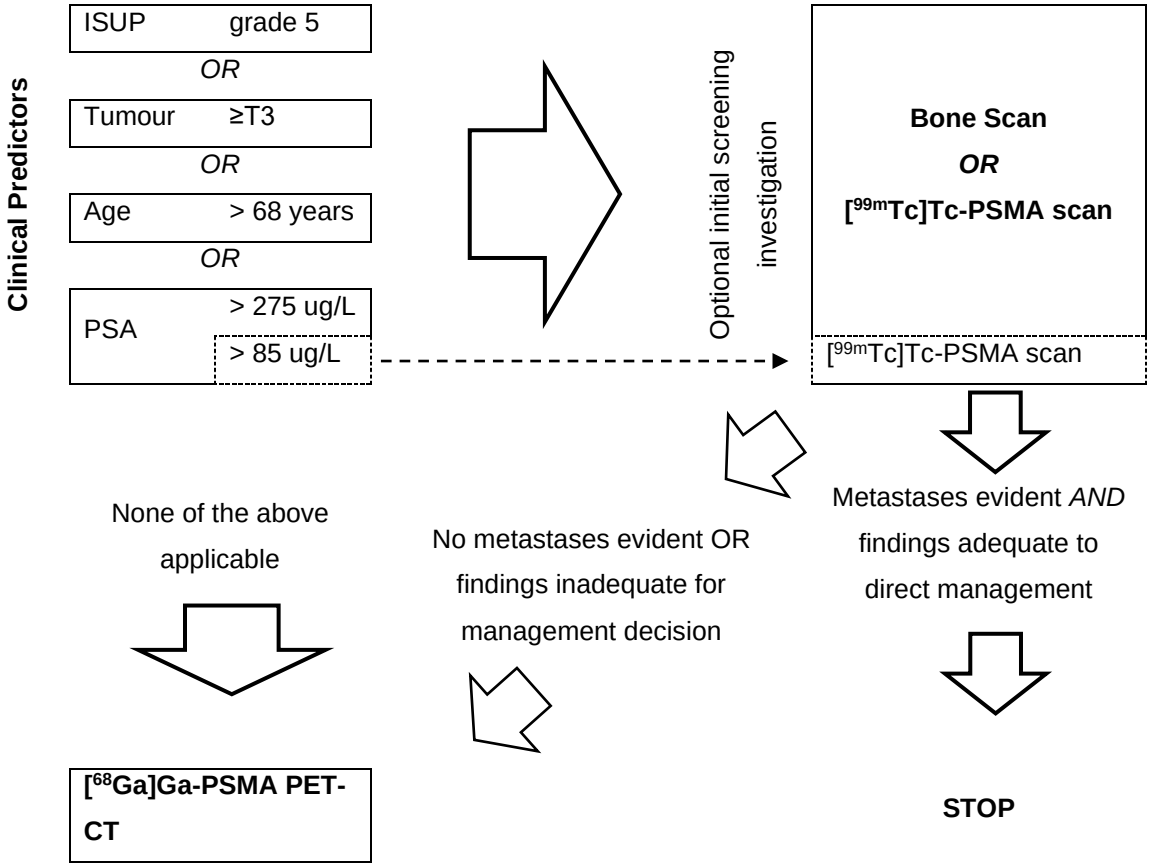


Table 1. Patient Characteristics

				M+ (n=53)	*M-* (n=33)
Age Range (years)					
48	87	**Mean**	65.05	65.8	63.8
PSA Range (µg/L)					
0.7	969	**Mean**	130.95	195.3	32.5
Histology					
ISUP	**Gleason Score**				
-	No histology	**Totals**	2	2	0
1	<7		8	2	6
2	7 (3 + 4)		11	4	7
3	7 (4 + 3)		18	8	10
4	8 (3+5 / 4+4 / 5+3)		12	6	6
5	>8		36	31	5
Clinical Stage					
T1a-c		**Totals**	21	9	12
T2a			13	6	7
T2b			14	8	6
T2c			11	6	5
T3+			28	24	4

**M+ denotes positive for evidence of metastases (locoregional or distant)*

**M- denotes negative or equivocal for evidence of metastases*

Table 2. The association between image findings at each iteration, Clinical Stage and Histology Grade.

	Bone Scan			[^{99m}Tc]Tc-PSMA scan			[68Ga]Ga-PSMA PET-CT		
Clinical Stage	**Positive 33**	**Negative/Equivocal 54**	**p-value**	**Positive 11**	**Negative/Equivocal 43**	**p-value**	**Positive 9**	**Negative/Equivocal 34**	**p-value**
T1a, b, c	6 (18.2%)	15 (27.8%)	0.018*	1 (9.1%)	14 (32.6%)	0.154	2 (22.2%)	12 (35.5%)	0.848
T2a	3 (9.1%)	10 (18.5%)		1 (9.1%)	9 (20.9%)		2 (22.2%)	7 (20.6%)	
T2b	3 (9.1%)	11 (20.4%)		4 (36.4%)	7 (16.3%)		1 (11.1%)	6 (17.6%)	
T2c	3 (9.1%)	8 (14.8%)		1 (9.1%)	7 (16.3%)		2 (22.2%)	5 (14.7%)	
T3a, b, T4	18 (54.5%)	10 (18.5%)		4 (36.4%)	6 (14%)		2 (22.2%)	4 (11.8%)	
Histology Gleason Score	**Positive 31**	**Negative/Equivocal 54**	**p-value**	**Positive 11**	**Negative/Equivocal 43**	**p-value**	**Positive 9**	**Negative/Equivocal 34**	**p-value**
G3 + 3	2 (6.5%)	6 (11.1%)	0.005**	0	6 (14%)	0.009**	0	6 (17.6%)	0.062
GI3 + 4	2 (6.5%)	9 (17%)		2 (18.2%)	7 (16.7%)		0	7 (21.2%)	
GI4 + 3	2 (6.5%)	16 (30.2%)		0	16 (38.1%)		6 (66.7%)	10 (30.3%)	
GI8	4 (12.9%)	8 (15.1%)		2 (18.2%)	6 (14.3%)		0	6 (18.2%)	
GI > 8	21 (67.7%)	15 (28.3%)		7 (63.6%)	8 (19%)		3 (33.3%)	5 (15.2%)	

Table 3. The association between image findings at each iteration, PSA Level and Age.

	n	Positive	n	Negative/Equivocal	p-value
Bone Scan					
PSA Level	32	275.18 (288.99)	54	45.49 (48.11)	< 0.001***
Age at Diagnosis	33	68.15 (7.89)	54	63.15 (6.06)	0.001**
[^{99m}Tc]Tc-PSMA scan					
PSA Level	11	85.24 (62.28)	43	35.32 (38.44)	0.026**
Age at Diagnosis	11	62.64 (7.00)	43	63.28 (5.88)	0.757
[^{68}Ga]Ga-PSMA PET-CT					
PSA Level	9	45.92 (61.17)	34	32.51 (30.57)	0.358
Age at Diagnosis	9	61.22 (5.74)	34	63.82 (5.88)	0.243

Additional Data

Table 2a.

	Bone Scan			[^{99m}Tc]Tc-PSMA scan			[^{68}Ga]Ga-PSMA PET-CT		
Clinical Stage	**Positive 33**	**Negative 40**	**Equivocal 14**	**Positive 11**	**Negative 39**	**Equivocal 4**	**Positive 9**	**Negative 33**	**Equivocal 1**
T1a, b, c	6 (18.2%)	12 (30%)	3 (21.4%)	1 (9.1%)	12 (30.8%)	2 (50%)	2 (22.2%)	12 (36.4%)	0
T2a	3 (9.1%)	9 (22.5%)	1 (7.1%)	1 (9.1%)	9 (23.1%)	0	2 (22.2%)	7 (21.2%)	0
T2b	3 (9.1%)	9 (22.5%)	2 (14.3%)	4 (36.4%)	7 (17.9%)	0	1 (11.1%)	5 (15.2%)	1 (100%)
T2c	3 (9.1%)	6 (15%)	2 (14.3%)	1 (9.1%)	5 (12.8%)	2 (50%)	2 (22.2%)	5 (15.2%)	0
T3a, b, T4	18 (54.5%)	4 (10%)	6 (42.9%)	4 (36.4%)	6 (15.4%)	0	2 (22.2%)	4 (12.1%)	0
Histology Gleason Score	**Positive 31**	**Negative 39**	**Equivocal 14**	**Positive 11**	**Negative 38**	**Equivocal 4**	**Positive 9**	**Negative 32**	**Equivocal 1**
G3 + 3	2 (6.5%)	4 (10%)	2 (14.3%)	0	6 (15.4%)	0	0	6 (18.2%)	0
GI3 + 4	2 (6.5%)	6 (15%)	3 (21.4%)	2 (18.2%)	7 (18.4%)	0	0	6 (18.8%)	1 (100%)
GI4 + 3	2 (6.5%)	13 (32.5%)	3 (21.4%)	0	13 (34.2%)	3 (75%)	6 (66.7%)	10 (31.3%)	0
GI8	4 (12.9%)	7 (17.5%)	1 (7.1%)	2 (18.2%)	6 (15.8%)	0	0	6 (18.8%)	0
GI > 8	21 (67.7%)	10 (25%)	5 (35.7%)	7 (63.6%)	7 (18.4%)	1 (25%)	3 (33.3%)	5 (15.6%)	0

Table 3a.

Bone Scan		N	Mean	SD	95% Confidence Interval for Mean		Minimum	Maximum	p-value
					Lower Bound	Upper Bound			
PSA Level	Negative	40	43.91	48.48	28.40	59.41	0.70	204.70	< 0.001***
	Equivocal	14	50.01	48.54	21.98	78.03	15.20	173.20	
	Positive	32	275.18	288.99	170.98	379.37	15.20	968.90	
	Total	86	130.95	210.65	85.79	176.12	0.70	968.90	
Age at Diagnosis	Negative	40	62.70	6.79	60.53	64.87	48.00	73.00	0.004**
	Equivocal	14	64.43	3.03	62.68	66.18	58.00	70.00	
	Positive	33	68.15	7.89	65.35	70.95	52.00	87.00	
	Total	87	65.05	7.19	63.51	66.58	48.00	87.00	

Table 3b.

[^{99m}Tc]Tc-PSMA scan		N	Mean	SD	95% Confidence Interval for Mean		Minimum	Maximum	p-value
					Lower Bound	Upper Bound			
PSA Level	Negative	39	35.31	40.26	22.26	48.36	7.40	204.70	0.007**
	Equivocal	4	35.42	12.54	15.47	55.38	17.50	45.40	
	Positive	11	85.24	62.28	43.39	127.08	0.70	173.20	
	Total	54	45.49	48.11	32.36	58.62	0.70	204.70	
Age at Diagnosis	Negative	39	63.74	5.72	61.89	65.60	48.00	73.00	0.283
	Equivocal	4	58.75	6.29	48.74	68.76	54.00	68.00	
	Positive	11	62.64	7.00	57.93	67.34	51.00	72.00	
	Total	54	63.15	6.06	61.49	64.80	48.00	73.00	

Table 3c.

[^{68}Ga]Ga-PSMA PET-CT		N	Mean	SD	95% Confidence Interval for Mean		Minimum	Maximum	p-value
					Lower Bound	Upper Bound			
PSA Level	Negative	33	32.71	31.02	21.71	43.71	7.40	137.20	0.650
	Equivocal	1	26.10				26.10	26.10	
	Positive	9	45.92	61.17	-1.10	92.94	10.00	204.70	
	Total	43	35.32	38.44	23.49	47.15	7.40	204.70	
Age at Diagnosis	Negative	33	63.64	5.87	61.56	65.72	48.00	73.00	0.289
	Equivocal	1	70.00				70.00	70.00	
	Positive	9	61.22	5.74	56.81	65.63	55.00	69.00	
	Total	43	63.28	5.88	61.47	65.09	48.00	73.00	

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