Original research

Evaluating the role of a ^{99m}Tc-HYNIC-PSMA SPECT scan following a negative bone scan in men with prostate cancer: a single-centre, retrospective cohort study

By

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OPPCLE001

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Master of Medicine (MMed) Urology
(Minor Dissertation)
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UNIVERSITY OF CAPE TOWN

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DECLARATION

I, *Cleve Desmore Oppel*, hereby declare that the work on which this dissertation/thesis 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.

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Abstract

Purpose: This study aimed to review the management of patients with high-risk and unfavourable intermediate-risk prostate cancer, who had a ^{99m}Tc-HYNIC-PSMA SPECT (technetium-99m hydrazine nicotinamide prostate-specific membrane antigen single-photon emission computerised tomography) scan following a negative ^{99m}Tc-MDP (technetium-99m methylene diphosphonate) bone scan.

Materials and methods: This study is a retrospective review of patients with high-risk and unfavourable intermediate-risk prostate cancer, who underwent a ^{99m}Tc-PSMA SPECT scan after a negative/equivocal bone scan between January 2018 and December 2020. Patients with a life expectancy of less than 10 years were excluded.

Results: A total of 64 patients were investigated. The mean age was 63 years and the mean prostate-specific antigen (PSA) level was 40 ng/mL. The International Society of Urological Pathology (ISUP) scores were as follows: ISUP 1 in six patients, ISUP 2 in eight patients, ISUP 3 in 13 patients, and ISUP > 4 in 37 patients. A positive ^{99m}Tc-PSMA SPECT scan for disease metastases occurred in 20% of the patients who had a negative bone scan. Seven of the patients with a positive ^{99m}Tc-PSMA SPECT scan received a bilateral orchiectomy, while four patients received treatment with radical intent. Management of patients with both scans negative included external beam radiotherapy (EBRT) and androgen deprivation therapy (ADT) (*n* = 47), and radical prostatectomy with or without lymph node (LN) dissection (*n* = 4). A limiting factor was that not every patient underwent conventional cross-sectional imaging of the pelvis and prostate prior to intervention.

Conclusion: A ^{99m}Tc-PSMA SPECT scan is a valuable diagnostic tool and was able to identify one in five men (20%) who are understaged by bone scan, allowing for their management plan to be tailored and sparing them morbid intervention.

Keywords: prostate cancer, bone scan, ^{99m}Tc-PSMA SPECT scan, staging, management

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Abbreviations

LN: Lymph Node

EBRT: External beam radiotherapy

EAU: European Association of Urology

NCCN: National Comprehensive Cancer Network

MRI: Magnetic Resonance Imaging

CT: Computed tomography

PET: Positron emission tomography

PSMA: Prostate specific membrane antigen

68Ga-PSMA PET/CT: gallium-68 prostate-specific membrane antigen positron emission tomography/computed tomography

99mTc-PSMA SPECT: technetium-99m Prostate specific membrane antigen single-photon emission computerised tomography

Introduction

Prostate cancer is the second most common cause of cancer deaths among men. It is estimated that one in seven (15.3%) men will be diagnosed with prostate cancer, and one in 38 (2.6%) will die from this disease.[1] Prostate cancer can be risk stratified into low risk, intermediate risk (favourable and unfavourable), and high risk for disease progression per modified Epstein criteria.[2] These stratifications are based on the PSA level, digital rectal examination, and Gleason score from a prostate biopsy.

For intermediate-risk and high-risk patients, imaging plays an important role in the management of prostate cancer with curative intent. Investigations help plan treatment selection, including radical prostatectomy and level of LN dissection or EBRT. Current European Association of Urology (EAU) guidelines recommend abdominopelvic imaging and bone scan for patients with high-risk diseases.[3] The 2022 National Comprehensive Cancer Network (NCCN) guidelines indicate that for patients with high-risk prostate cancer, next-generation imaging – whole-body magnetic resonance imaging (MRI), prostate-specific membrane antigen positron emission tomography (PSMA PET) – should be performed if results from conventional imaging modalities – computed tomography (CT), multiparametric MRI, or bone scan – are negative or equivocal.

The ^{68}Ga-PSMA PET/CT (gallium-68 prostate-specific membrane antigen positron emission tomography/computed tomography) is a non-invasive diagnostic technique to image prostate cancer with increased Prostate Specific Membrane Antigen (PSMA) expression. Nearly all adenocarcinomas of the prostate demonstrate PSMA expression in the majority of primary and metastatic lesions.[4,5] Research has shown that PSMA expression is a significant prognosticator for disease outcomes.[6] Several studies demonstrate the superiority of the ^{68}Ga-PSMA PET/CT compared to CT, MRI, or a bone scan for the detection of metastases at initial staging at primary diagnosis.[7–11] However, the ^{68}Ga-PSMA PET/CT is more expensive and not always readily available. Our study involves the ^{99m}Tc-HYNIC-PSMA, which is more readily available and significantly cheaper.

This study reviewed how patients were managed (radical prostatectomy, radiotherapy, or bilateral orchiectomy) following a ^{99m}Tc-PSMA SPECT scan after a previously negative ^{99m}Tc-MDP bone scan.

Materials and methods

This study was a retrospective review of the imaging and staging protocols implemented and how they affected management decisions at the Groote Schuur Hospital in Cape Town, South Africa, between January 2018 and December 2020. The study population consisted of patients with high-risk and high-tier (unfavourable) intermediate-risk prostate cancer, with high-risk defined as greater than or equal to clinical stage T2c, or a PSA level ≥ 20 ng/mL, or Gleason score 8–10.[12] High-tier (unfavourable) intermediate-risk prostate cancer was defined as Gleason score 4 + 3, or more than one intermediate risk factor (T2b and/or Gleason score = 7 and/or PSA > 10–20 ng/mL not low-risk), or greater than 50% positive biopsy cores.[13] All patients were staged at a prostate cancer multi-disciplinary team meeting, where decisions regarding whether or not a patient is eligible for radical therapy are made.

Inclusion and exclusion criteria

Inclusion criteria consisted of high-risk and high-tier intermediate-risk prostate cancer patients who had a bone scan and a ^{99m}Tc-PSMA SPECT scan between October 2018 and January 2020.
The exclusion criteria consisted of:

- patients who are not candidates for radical treatment (life expectancy less than 10 years, multiple comorbidities);
- low-risk and low-tier (favourable) intermediate-risk prostate cancer patients; and
- confirmed metastases on previous plain film, CT or MRI.

Recruitment and enrolment

All patients enrolled in the study had been recruited from the combined Urology and Oncology multidisciplinary team, which took place at LE34 at the Groote Schuur Hospital. Figure 1 illustrates the patient recruitment and enrolment process. All the enrolled patients would have had both a ^{99m}Tc-MDP bone scan as well as a ^{99m}Tc-PSMA SPECT scan performed at the Nuclear Medicine Department. Results from these studies were provided by Nuclear Medicine physicians. Upon enrolment into the study, the patients were assigned a patient number, and this number was included in the patient data sheet. Patient folders were reviewed, and the management they underwent was evaluated – whether it was curative (radical prostatectomy or radiotherapy) or alternate.

Research procedures and data collection methods

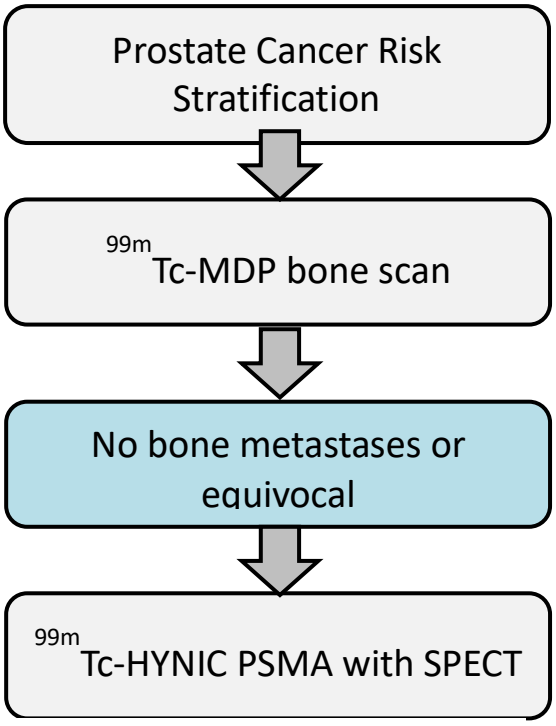

Figure 1: Patient recruitment and enrolment

A protocol based on the NCCN guidelines was agreed upon between the Nuclear Medicine and Oncology Departments, which stated that all high-risk and high-tier intermediate-risk prostate cancer patients who are candidates for radical treatment will undergo a bone scan followed by a ^{99m}Tc-PSMA SPECT scan if the bone scan was negative or equivocal. The folders of patients eligible for the study were reviewed, and management was examined.

Results

A total of 64 patients underwent both a bone scan and a ^{99m}Tc-PSMA SPECT scan. Their baseline characteristics are summarised in Table I. The majority, 50 patients, were risk stratified as having high-risk prostate cancer, while the remaining 14 patients had unfavourable intermediate-risk cancer. There were 13 patients with a negative bone scan and a positive ^{99m}Tc-PSMA SPECT scan for disease metastases, with six having disease at more than one metastatic site. Sites of metastases included LN (*n* = 12), bone (*n* = 3), and visceral organs (*n* = 3).

Eight of the patients with a positive ^{99m}Tc-PSMA SPECT scan received a bilateral orchiectomy. Five patients received treatment with radical intent, including EBRT and ADT (*n* = 4), and radical prostatectomy with extended pelvic LN dissection (*n* = 1). Management of those patients with both a negative bone scan and a ^{99m}Tc-PSMA SPECT scan included EBRT and ADT (*n* = 47) and radical prostatectomy with or without LN dissection (*n* = 4). A total of five patients underwent radical prostatectomy (including one with a positive ^{99m}Tc-PSMA SPECT scan for metastases). Of these, only two received a pelvic LN dissection. Histology findings correlated with preoperative ^{99m}Tc-PSMA SPECT scan findings in one of the two cases, at a sensitivity of 50%. Figure 2 illustrates the difference in patient management between the two groups.

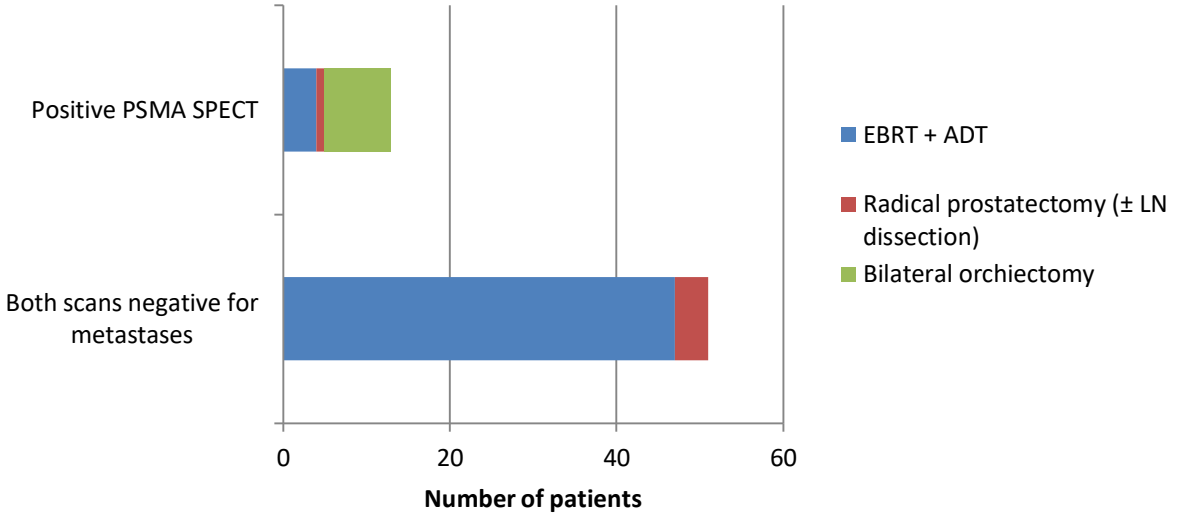

Figure 2: Bar graph illustrating the differences in patient management between the two groups

Table I:

Characteristics		Value (*n*)
Number of patients		64
Age		63.6 (mean) (47–70)
PSA level (ng/mL)		40.2 (mean) (0.2–229)
	< 10	10
	10–20	18
	> 20	36
Gleason score	3 + 3	6
	3 + 4	8
	4 + 3	13
	> 4 + 4	37
Clinical stage	T1	15
	T2a	19
	T2b	13
	T2c	8
	> T3	9

Discussion

An estimated 15% of men alive today will be diagnosed with prostate cancer.[14] Prostate cancer is responsible for 13% of all cancer deaths among men in South Africa and is the second leading cause of cancer deaths in males globally.[15] The disease can be risk-stratified according to its risk of progression and need for intervention, based on serum PSA level, clinical findings on a digital rectal exam, and a Gleason score from a prostate biopsy. Imaging plays an important role in the management and decision-making of patients diagnosed with intermediate- and high-risk diseases. The 2022 NCCN guidelines indicate that for patients with high-risk prostate cancer, next-generation imaging (whole-body MRI, PSMA PET) should be performed if results from conventional imaging modalities (CT, multiparametric MRI, or bone scan) are negative or equivocal.[16]

In 80% of prostate cancer patients, metastases to the bone represent the initial and main metastatic site, making it one of the most important prognostic factors.[17] The clinical importance of early detection of bone metastases in patients with prostate cancer is to determine the overall survival of the patients and their quality of life. Patients who only

have localised disease and no metastases may be offered radical treatment with curative intent. However, patients who have proven bone metastases should be offered less invasive treatment options to avoid unnecessary side effects.

^{99m}Tc-MDP is a nonspecific marker of osteoblastic activity that accumulates in response not only to tumours but also to degenerative joint disease, benign fractures, and inflammation.[18] Although bone metastases from prostate cancers are very heterogenic, the majority are described as "osteoblastic", while pure "osteolytic" metastases are very rare. A bone scan only detects metastases at an advanced stage of tumour infiltration when an osteoblastic reaction to metastatic cell deposit has occurred. Studies have shown that a bone scan can be avoided with a serum PSA level less than or equal to 20 ng/ml.[19] The main problem with a bone scan has been its lack of sensitivity and specificity, leading to questions raised regarding its diagnostic effectiveness.[20,21]

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) guidelines on bone scan state that bone scintigraphy is usually appropriate for initial staging in patients for:

- determining intermediate-risk disease (stage T2, PSA level 10 ng/mL, or Gleason score ≥ 7);
- initial evaluation of patients with high-risk disease (stage T3, PSA level 20 ng/mL, or Gleason score 8);
- evaluation of patients with symptoms referable to the bones regardless of stage or risk;
- evaluation of patients in whom a change in treatment is anticipated;
- evaluation of patients presenting with a pathologic fracture; and
- evaluation of patients who are to undergo radium or other radionuclide bone therapy.

The guideline further states that bone scintigraphy is usually not appropriate for initial staging in patients with a low risk of metastatic disease (PSA level 10 ng/mL, Gleason score 6, and no other clinical signs or symptoms of disease).[20] In many cases, the region of interest cannot be definitively characterised as negative or positive for malignancy, and will routinely end up being characterised as equivocal, suspicious, or likely. Guidelines do not provide any technical recommendations for bone scans, and in many centres, a bone scan is limited to anterior and posterior planar images. A standard planar bone scan can be improved by single-photon emission computerised tomography (SPECT) on selected areas, enhancing both sensitivity and specificity for the detection of metastases.

PSMA has emerged as the pre-eminent prostate cancer target for diagnostic imaging, monitoring disease recurrence, and tracking disease progression. Nearly all adenocarcinomas of the prostate demonstrate PSMA expression in the majority of primary and metastatic lesions.[4,5] Studies have shown that PSMA expression is a significant prognosticator for disease outcomes.[668]Ga-PSMA PET/CT is superior to conventional imaging in the identification of nodal disease in patients with moderate- to high-risk prostate cancer.[7] [68]Ga-PSMA PET/CT has also been found to be superior to a bone scan in detecting bone metastases in prostate cancer.

However, ^{68}Ga-PSMA has significant shortcomings. Gallium-68 is obtained from a ^{68}Germinium/^{68}Gallium generator. As the generator reaches its end, it allows for a limited number of elutions per day, with each elution being sufficient for imaging up to two patients at a time. For institutions with limited access to gallium-68, this results in a barrier to patient workup. There are fewer PET cameras installed worldwide than most other imaging machines, which also limits the utility of this modality in daily clinical practice. This significantly limits the ability of ^{68}Ga-PSMA to meet the demand for imaging in prostate

cancer. Another issue is the high cost of ^{68}Ga-PSMA, readily impeding accessibility to the study.

These shortcomings have led to research into technetium-99m-labelled PSMA with HYNIC used as a chelator molecule. Technetium-99m is developed from a molybdenum-99 generator, which is capable of producing a large activity sufficient to prepare radiotracer for a large number of patients daily. The imaging is done with a gamma camera, which is also more readily available worldwide than PET cameras. The average cost per ^{99m}Tc-PSMA SPECT scan is R4 000.

Studies have shown that ^{99m}Tc-PSMA has a lower sensitivity for lesion detection compared to ^{68}Ga-PSMA PET/CT and recommend its use when ^{68}Ga-PSMA PET/CT is not available, or as part of monitoring the response to radioligand therapy in patients with lesions with known PSMA expression.[10] Furthermore, a comparison of these two types of imaging has shown that there is no significant difference between their detection of LN and bone metastases despite differences in spatial resolution.

There are studies that compare the ^{99m}Tc-PSMA scan with a bone scan. Rathke et al. found that PSMA scintigraphy demonstrated a reduced number of equivocal findings compared to a bone scan.[22] PSMA resulted more often in tumour-typical appearance, while MDP bone scan lesions were scored as equivocal or presumably benign. The sensitivity of PSMA in detecting bone lesions was 92%, compared to 76% for the MDP bone scan. Kabunda et al. concluded that the ^{99m}Tc-PSMA scan was comparable to a bone scan in the detection of bone metastases with the additional benefit of providing information on visceral disease.[23]

Available literature indicates that PSMA-targeted radiotracers are superior to conventional imaging, including a bone scan, in the workup of patients with prostate cancer. It has a higher pick-up rate for both skeletal and non-skeletal metastases. Given the limited diagnostic effectiveness of bone scans used in isolation, specifically their poor detection rate in the setting of men considered for radical treatment of organ-confined prostate cancer, and the aforementioned advantages of PSMA, this study sought to review the management of patients with high-risk and high-tier intermediate-risk prostate cancer, who have had a less well-studied form of the PSMA scan – the ^{99m}Tc-PSMA SPECT – following a negative ^{99m}Tc-MDP bone scan. We retrospectively reviewed whether or not these patients still underwent radical treatment after these findings or were offered alternate management modalities instead.

The discussion highlights that a bone scan is considered the gold standard imaging modality in the workup for metastases in this patient cohort, as per guideline recommendations, and is still being used worldwide. The problem with a bone scan is that it lacks sensitivity at lower PSA levels, and studies are often "indeterminate". PSMA has emerged as a far more sensitive and specific modality in the workup of metastases but is not yet standard practice. Furthermore, most studies supporting PSMA have looked at ^{68}Ga-PSMA PET/CT, whereas our study looked at the slightly less sensitive yet much more cost-effective and readily available alternative – the ^{99m}Tc-PSMA SPECT.

This study aimed to compare ^{99m}Tc-PSMA SPECT to bone scans, as there is a paucity of data comparing these two modalities head-to-head. Only one study made such a comparison, but in that setting, patients were already known to have bone metastases. This study involves patients who are workup naïve.

The results from this study confirm that ^{99m}Tc-PSMA SPECT is more sensitive and specific than a bone scan in detecting metastases. The major drawback of completely switching from bone scans to PSMA-based studies has been the cost and availability of ^{68}Ga-PSMA

PET/CT, whereas ^{99m}Tc-PSMA SPECT is a less expensive and more readily available alternative that can overcome this issue. Consequently, it is recommended for clinical use for staging.

Conclusion

PSMA-targeted radiotracers are superior to conventional imaging, including a bone scan, in the workup of patients with prostate cancer. It has a higher pick-up rate for both skeletal and non-skeletal metastases. The major shortcomings are cost and availability. ^{99m}Tc-labelled PSMA is more cost-effective and readily available than ^{68}Ga-ligands targeting PSMA, at the expense of diagnostic sensitivity. There is only one published study comparing PSMA scintigraphy with an MDP bone scan, although this was in a setting of known prostate cancer metastases. There are no studies available that compare the diagnostic accuracy of these modalities in the staging of patients with high-risk diseases. This is an area that has not yet been sufficiently explored, and it could potentially open up the possibility of incorporating PSMA scintigraphy as a standard modality in prostate cancer workup, and not only in the setting where conventional imaging is equivocal.

This study confirms that a ^{99m}Tc-PSMA SPECT scan is a valuable diagnostic tool in the workup of patients with high-risk and unfavourable intermediate-risk prostate cancer. Amongst the group of patients reviewed, this scan was able to identify 20% who are understaged by bone scan. This enabled a tailored approach to their management plan, and unnecessary morbid intervention could be avoided.

Conflict of interest

The authors declare no conflict of interest.

Funding source

This study was self-funded.

Ethical approval

The University of Cape Town HREC REF Number 526/2020.

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22 September 2020

HREC REF:526/2020

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Dear Dr Rachelle Steyn

PROJECT TITLE: ***THE MANAGEMENT OF HIGH RISK AND UNFAVOURABLE INTERMEDIATE RISK PROSTATE CANCER PATIENTS WHO HAVE UNDERGONE A PSMA SPECT CT FOLLOWING A NEGATIVE BONE SCAN: A SINGLE-CENTRE, RETROSPECTIVE COHORT STUDY. MMED CANDIDATE: DR. C OPPEL***

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID-19, dated 17 March 2020 and 6 July 2020.

Approval is granted for one year until the 30 September 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Please also note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/03/2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	16/2/2023

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Comments to PI from the HREC
Thank you for your Study Deviation HREC Chair Signature 16/2/2023 Date:

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	14/02/2023		
HREC REF Number	526/2020	Current Ethics Approval was granted until	30/09/2022
Protocol title	The management of high risk and unfavourable intermediate risk prostate cancer patients who have undergone a PSMA SPECT CT following a negative bone scan: a single-centre, retrospective cohort study		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		☐ Yes	x No
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			

(Note: Please complete the Closure form (FHS019) if the study is completed within the approval period)

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AFRICAN UROLOGY

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2. Submissions

Submissions

Make a new submission or view your pending submissions.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

- The submission has not been previously published, nor is it before another journal for consideration.
- The submission file is in Microsoft Word file format.
- The text is 1½-spaced; uses a 12-point font.
- All illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end. Figures and images should also be uploaded as high resolution png/jpg supplementary files.
- The text adheres to the requirements outlined in the Author Guidelines.

Author Guidelines

African Urology Author Guidelines

African Urology is a multilingual journal. English, French and Portuguese submissions will be considered. The objective of the *African Urology* is to provide an exceptional source of current and clinically relevant research in the discipline of urology.

Review process

All submitted manuscripts undergo extensive peer review by at least 2 recognised authorities in the field prior to their acceptance for publication. Reviewers' and authors' identities are kept confidential. The Editorial Board strives to reply to a submission within 2 weeks.

Submission of Manuscripts

1. Manuscripts are submitted via the online submission system only. You should register/log in and select your role as "Author" to start submission of your manuscript.
2. Please upload the following material via the online submission system:

- **Cover letter** - this should include the title of the manuscript, authors details, including initials, surname, department and place of work, email address and ORCID number. Declarations should also be included here.
- **Manuscript file**(this should include the title, abstract, main text and references [organised with subheadings of *Introduction, Materials and Methods, Results, Discussion, Conclusion, References,* tables and figures with legends).
- **Figures** should be uploaded as part of the main manuscript and should also be uploaded a high resolution png/jpg images, as supplementary files.

3. The journal editors are unable to undertake major language corrections. The Editor has the right to make editorial corrections and additional changes with the knowledge and approval of corresponding author.
4. Proofs will be sent to the corresponding author by email as a PDF file. Corrections should be kept to a minimum. Authors are asked to return their corrected proofs within 3 days of receipt.
5. The preferred word processing format is Microsoft Word.

Submission Types

Original articles

Original articles on research relevant to urology should not exceed 3 000 words, no more than 30 references, with up to 6 tables or figures. A structured abstract under the following headings, Purpose, Materials and Methods, Results, and Conclusions, is a requirement and should not exceed 250 words. Please provide 5 keywords.

Scientific letters/short reports

Short reports should not exceed 1 500 words with a maximum of 10 references. Only one table or illustration is permissible. A structured abstract under the following headings, Purpose, Materials and Methods, Results, and Conclusions, is a requirement and should not exceed 250 words. Please provide 5 keywords.

Case reports

Case reports should not exceed 1 500 words with no more than 10 references. Figures are limited to 2 figures and may include images or photographs. The case report should have three headings: Summary (not exceeding 100 words), Case report (with no introduction) and Discussion. Case reports will be published online only. Please provide 5 keywords.

Video case reports (AUJ-VIDEO)

Video case reports should not exceed 1 500 words with 10 references and 6 figures. Heading should include Summary (not exceeding 100 words) and Case description (with three subheadings: Introduction, Case presentation and Discussion). Please provide 5 keywords. The video file format must be only MP4 or MOV and should not exceed 300 MB and 8 minutes. Video case reports will be published online only. The summary and the URL will appear in the printed version.

Review articles

Review articles relevant to surgery should not exceed 5 000 words, with a maximum of 50 references and no more than 6 tables or figures. A summary of 250 words or less is required. Please provide 5 keywords.

Letters to the editor

Letters to the editor should be 400 words or less with only one image or table.

Submission Guidance

1. **Abstract:** A structured abstract (with the subheadings Purpose, Materials and Methods, Results, and Conclusion) should appear on the second page of the manuscript and should not exceed 300 words. As far as possible, abbreviations should be avoided in the abstract.
2. **Manuscript Text:**

- **The INTRODUCTION** should state concisely the purpose and rationale for the study and cite only the most pertinent references as background.
- **The MATERIALS AND METHODS** section should describe briefly (but in sufficient detail to permit other workers to repeat the study) the plan, patients, experimental

animals or other species, material, controls, methods, procedures, and statistical method(s) used.

- **The RESULTS** section should present the detailed findings. Refer to all tables and/or figures in this section. Figures and tables should supplement, not duplicate, the text - presentation of data in either one or the other will suffice.
- In the **DISCUSSION** section, state the importance and significance of your findings, but do not repeat the details given in the Results section. Compare your findings with those of others. No new data should be presented in this section. The paper should conclude with a brief section that summarises the clinical and research implications of the work, as appropriate.
- The **CONCLUSIONS** section should provide a brief summary of the main findings of the study.
- **REFERENCES** should appear in the text as superscript number that corresponds to the reference in the references list. References should be formatted as follows:

1. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002;347:284-7.

- **FIGURES AND TABLES** should be placed in the manuscript, not at the end of the manuscript with their legend below each figure or table. All computer-generated images and photographs must have acceptable quality (at 300 dpi or higher) and should be submitted as high resolution png/jpg images, as supplementary files.

The following declarations statements are required:

Authorship

The authors confirm that all authors have made substantial contributions to all of the following:

- The conception and design of the study, or acquisition of data, or analysis and interpretation of data.
- Drafting the article or revising it critically for important intellectual content.
- Final approval of the version to be submitted.
- Sound scientific research practice

The authors further confirm that:

- The manuscript, including related data, figures and tables has not been previously published and is not under consideration elsewhere
- No data have been fabricated or manipulated (including images) to support your conclusions
- This submission does not represent a part of single study that has been split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (e.g. “salami-publishing”).

Plagiarism:

- The authors confirm that the work submitted is original and does not transgress the plagiarism policy of the journal.
- No data, text, or theories by others are presented as if they were the author’s own.
- Proper acknowledgements of other’s work has been given (this includes material that is closely copied, summarized and/or paraphrased), quotation marks are used for verbatim copying of material.
- Permissions have been secured for material that is copyrighted.

Conflict of interest statement

A conflicting interest exists when professional judgement concerning a primary interest (such as patient's welfare or the validity of research) may be influenced by a secondary interest (such as financial gain or personal rivalry). It represents a situation in which financial or other personal considerations from authors, reviewers or editors have the potential to compromise or bias professional judgment and objectivity. It may arise for the authors when they have financial interest that may influence their interpretation of their results or those of others. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. All potential conflicts of interest need to be declared. The conflict of interest statement should list each author separately by name, i.e.

"John Smith declares that he has no conflict of interest. Paula Taylor has received research grants from Drug Company A. Mike Schultz has received a speaker honorarium from Drug Company B and owns stock in Drug Company C."

If there is no conflict of interest to declare please include the following: The authors declare no conflict of interest.

Funding sources

All sources of funding should be declared. Also define the involvement of study sponsors in the study design, collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication. If the study sponsors had no such involvement, this should be stated as follows: No funding source to be declared.

Compliance with ethical guidelines

For all publications:

"The author/s declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010."

Available from: http://publicationethics.org/resources/international-standards-for-editors-and-authors

Institutional Review Board (IRB) ethical approval must have been given if the study involves human subjects or animals. **Please provide the IRB approval letter.**

"Prior to commencement of the study ethical approval was obtained from the following ethical review board: *Provide name and reference number"*

For studies with human subjects include the following:

"All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008."

"Informed written consent was or was not obtained from all patients for being included in the study."

For studies with animals include the following sentence:

"All institutional and national guidelines for the care and use of laboratory animals were followed."

For articles that do not contain studies with human or animal subjects:

"This article does not contain any studies with human or animal subjects."

If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach, and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study. If any identifying information about patients is included in the article, the following sentence

should also be included: Additional informed consent was obtained from all patients for which identifying information is included in this article. The Helsinki Declaration 2008 can be found at http://www.wma.net/en/30publications/10policies/b3/
The submitting author must provide written confirmation of Research Ethics Committee approval for all studies including case reports. The ethics committee as well as the approval number should be included.