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# **Inconclusive Bone Scan in men with intermediate and high-risk prostate cancer: What next?**

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This article does not contain any studies with human participants performed by any of the authors. This article is based on clinical data that was retrospectively reviewed.

**Key words:** radionuclide scan, skeletal scintigraphy, prostatic cancer, metastatic, metastasis

## **Abstract**

### **Objective**

To evaluate the incidence of inconclusive bone scans and down-stream imaging and clinical follow-up generated, including subsequent treatment outcomes in men affected by inconclusive bone scans with intermediate and high-risk prostate cancer.

### **Data source**

Retrospective study of clinical data for a Scottish population of men diagnosed with prostate cancer in the intermediate-risk and high-risk groups.

### **Conclusion**

Of the 1246 patients included, initially 81 men were identified as having an inconclusive bone scan result following multidisciplinary team discussion. After further imaging 24 patients remained inconclusive for metastasis. Of these patients, two patients received no treatment; one due to decision of watchful waiting, and one due to death. Of the 13 patients receiving radical treatment (LRP or RT), three patients showed relapse (23%) indicating presence of microscopic disease, and failure of radical treatment alone for these patients.

### **Implications for Nursing Practice**

This paper will assist nurses and multidisciplinary team members in understanding how patients diagnosed with intermediate and high-risk prostate cancer with

inconclusive bone scan results are subsequently imaged and managed in the current healthcare system. This raises awareness amongst nursing staff of disease recurrence and possibility of downstream multimodality treatment for these men with inconclusive bone scans.

### **Introduction**

Men diagnosed with localized prostate cancer are stratified into three categories: low, intermediate or high-risk. The stratification is based on the Prostate-Specific Antigen (PSA) value, Gleason score and the clinical stage as defined by National Institute for Health and Care Excellence (NICE). These categories are: low-risk: PSA <10 ng/ml and, Gleason score  $\leq 6$  and T1 to T2a, intermediate-risk: PSA 10-20 ng/ml or, Gleason score 7 or, T2b and high-risk: >20 ng/ml or, Gleason score 8-10 or,  $\geq T2c$ .<sup>1</sup> The risk stratification guides further diagnostic pathways and treatment. Metastatic prostate cancer is commonly diagnosed by bone scintigraphy, also called isotope bone scans, or just bone scans, see **figure 1**. Bone scans remains a cornerstone of prostate cancer staging investigations and the issue of inconclusive bone scan results due to a lack of sensitivity and specificity warrants further investigation on real-world patient outcomes.

(Fig. 1 here)

Current NICE guidelines do not recommend bone scan to men with low-risk localized prostate cancer.<sup>1</sup> Multidisciplinary teams (MDTs) continues to recommend a bone scan to all men stratified to either intermediate or high-risk prostate cancer groups.<sup>1</sup> Importantly, bone scan results facilitate clinical decision-making based upon the Tumor Node Metastasis (TNM) classification.<sup>2</sup> Broadly, localized or locally advanced treatments options include prostatectomy, radiotherapy, radiotherapy and neoadjuvant/adjuvant androgen deprivation therapy, or metastatic prostate cancer has the treatment intent of palliation in the form of hormonal manipulation, chemotherapy and 2<sup>nd</sup> generation hormones such as Abiraterone + prednisolone or Enzalutamide.<sup>3</sup> The main treatment goal for a man diagnosed with metastatic prostate cancer, is disease control and optimization of quality of life.<sup>4</sup>

The main stay treatment for metastatic prostate cancer, is castration either by reducing systematic testosterone levels by surgical or chemical induced.<sup>3</sup> ADT can result in profound physical and psychological decrements in health which can negatively effect quality of life and may increased the requirement for supportive care intervention.<sup>5</sup> Side effects commonly grappled with include: body feminization, changes in sexual performance, relationship changes, cognitive and affective symptoms and fatigue, sleep disturbance, and depression.<sup>6-15</sup> Following treatment, biochemical recurrence is classified when a PSA value continues to rise (greater than 0.2 ng/mL after treatment with a second confirmatory level of greater than 0.2 ng/mL), indicating treatment failure.<sup>16</sup>

It is commonly observed in MDTs that some patients diagnosed with prostate cancer have inconclusive bone results. When clinicians receive imaging results for their patients, they must rely on interpretation by imaging experts. However, a conclusion of a bone scan may not always be definitive, and in many cases the bone scan will determine the treatment decisions for patients, recommended across all clinical urological guidelines.<sup>1,3</sup> Fundamentally, inconclusive bone scans remains a contemporary challenge for the multidisciplinary team in risk stratifying men to evidence-based treatment options. Clinicians require definitive answers from imaging about their patients, but some lesions can be difficult to interpret. Thus, the avid bone lesion may not represent per se a skeletal metastasis, which will condemn men to palliative treatment rather than curative intent. A recent systematic review of inconclusive bone scans in the clinical trial setting underscored a lack of real-world data in routine clinical practice in how this dilemma is managed.<sup>11</sup>

There are several studies describing the outcome of conclusive bone scans for metastatic status in men with prostate cancer<sup>11,17-22</sup> but seldom published clinical data exists on the clinical consequences of inconclusive bone scans on patient outcomes.<sup>12,13,15,23,24</sup> A study<sup>13</sup> reported that 58 of 459 patients (13%) affected by prostate cancer were found to have inconclusive bones scans. Furthermore, a study elsewhere<sup>23</sup> observed 50 of 366 (13%) of patients in their series had inconclusive bones scan reported. However, neither of these studies provided clarification on subsequent follow-up imaging modalities to establish whether or not these patients had metastatic or non-metastatic disease. Accurate TNM staging in men with prostate cancer has a direct causal relationship with morbidity and mortality.

However, evidence<sup>15</sup> identified 55 of 420 (13%) patients have inconclusive features in bone scan results reported, of which 40 patients (of the 55 patients) had further imaging, namely Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and x-ray to clarify metastatic status. The report of subsequent imaging identified that all 40 patients with inconclusive bone scans who had subsequent imaging were found to be consistent with non-metastatic disease. Importantly, this study did not report on the remaining 15 patients who had inconclusive bone scan with no follow-up imaging and their oncological outcomes for further imaging interventions. Clinically, this information is important to ensure correct TNM classification and evidence-based MDT treatment recommendations.<sup>1,3</sup>

Based upon the existing available research in this area, studies have consistently reported a prevalence of 13% of inconclusive bone scans being reported.<sup>13-15</sup> Importantly, data has not reported how this clinical dilemma is solved in clinical practice, or how patients are counseled in the complex treatment decision-making process in this uncertain scenario. While bone scans may be replaced with more accurate imaging methods, the experience of inconclusive bone scans remains a problem in contemporary practice. Prostate cancer specialist nurses and MDT

colleagues will encounter the occurrence of inconclusive bone scans routinely in their MDT meetings and this article provides an account of existing practice and important clinical outcomes. We used real world clinical data to report on the incidence of inconclusive bone scans, clinical interventions and subsequent patient outcomes to inform important lessons learned in prostate cancer treatment and care.

## **Patients and Methods**

**Study Design:** Retrospective case note review and electronic data linkage.

### *Data source:*

This study received local Caldecott approval (Caldicott/IGTCAL2920+). Data collection was retrospective for all patients diagnosed with prostate cancer (intermediate- or high-risk groups) between January 2010 and December 2016, within the National Health Service (NHS) Tayside in Scotland, United Kingdom (UK). The NHS Tayside health board is one of the fourteen Scottish Health authorities responsible for the delivery of healthcare in the Scottish population. Every resident in the geographical location of Tayside is registered with the health authority and has a ten-digit Community Health Index (CHI) number as a unique identifier across all health records including primary and secondary care settings. This Unique Identifier was used to link data on outcome of men with inconclusive bone scans in this study. All patients with a suspected prostate cancer are discussed in NHS Tayside's MDT and detailed documented MDT outcomes are securely managed on Tayside Urological Cancers Network Database. The cohort identified, was stratified into either intermediate- or high-risk according to EAU guidelines.<sup>3</sup> The CHI number was used to cross link electronic databases to obtain the following data: age at the time of diagnosis, PSA value, Gleason score and clinical T-stage, in addition to outcome of bone scan, results of concurrent and subsequent imaging (due to inconclusive bone scan results) and treatment decisions for patients with inconclusive bone scans.

### *Patient selection:*

**Inclusion criteria:** All consecutive histologically proven prostate cancer was included. Histological Gleason score, PSA and clinical T-stage were used to classify men as intermediate or high-risk groups during 2010 and 2016. This was based upon MDT consensus and discussion as recommended by guidelines from the National Institute for Health and Care Excellence<sup>1</sup> as defined by D'Amico.<sup>25</sup> All the included men subsequently had a bone scan performed as part of their cancer staging. **Exclusion criteria:** men in the low-risk group, and those who did not have a bone scan, outcome of bone scan, and clinical stage available for evaluation.

### *Bone scans:*

The procedure for bone scans involves <sup>99m</sup>Tc Hydroxymethylene diphosphatenate (600 MBq, 2-3 ml with NaCl 0.9%) to be injected intravenously, and imaging performed 2-5 hours post-administration. Anterior and posterior images were

obtained using a large field-of-view dual head gamma camera (NHS Tayside have three gamma cameras of the following make: GE Discovery, GE Infinia and Phillips Brighthead). Several radiologists with nuclear medicine training reported the bone scans. All bone scans were reviewed at MDT meetings and the expert (dedicated uro-radiologist with more than 5 years of experience) interpretation were documented in the Tayside Urological Cancers Network Database.

*Clinical follow-up:*

For patients who received radical prostatectomy, PSA > 0.2 ng/mL was considered as biochemical recurrence.<sup>16</sup> For patients who received radiotherapy (RT), two consecutive PSA results  $\geq 2.0$  ng/mL higher than the PSA nadir value was considered treatment failure.<sup>26</sup> For patients who received ADT, castrate resistant disease was considered when PSA values had three consecutive rises in PSA one week apart, resulting in two 50% increases over the nadir, with PSA >2 ng/mL or radiographic appearance of two or more bone lesion.<sup>3</sup>

*Statistical analysis:*

Data was entered into SPSS version 22.0. Categorical data was examined by the proportion of patients stratified into the intermediate or high-risk group. Descriptive analysis was performed and the proportion of men in each group was calculated as positive, negative or inconclusive for bone metastases.

## **Results**

Data was collected for a total of 1246 patients. The mean age was 71.8 years, (minimum 45.1 years, maximum 99.2 years). MDT consensus identified 341 patients in the intermediate-risk group and 905 in the high-risk prostate cancer group. The distribution of patients stratified into intermediate- or high-risk per annum are detailed in **Table 1**.

(Table 1 here)

A higher proportion of patients were negative for bony metastasis (90.3%, n=308, for the intermediate-risk group and 64.9%, n=587 for the high-risk group), see **figure 2**. Moreover, 28.3% (n = 256) of men were positive for metastasis in the high-risk group compared to 4.1% (n = 14) in the intermediate-risk group. The proportion of patients with inconclusive bone scans was comparable between the intermediate-risk group and the high-risk group (5.6%, n=19 vs. 6.9%, n=62), see **figure 2** and **Table 2**.

(Fig. 2 here)

(Table 2 here)

Patients with inconclusive bone scans reports (n = 81) were followed up with further imaging. Follow-up imaging included x-ray, CT or MRI scans. This identified that bone metastasis were negative for 68.4% (n = 13) for the intermediate-risk group and 48.4% (n = 30) for the high-risk group. Patients identified to have positive clinical evidence of metastatic disease was 5.3% (n = 1) for the intermediate-risk group and 21% (n = 13) for the high-risk group. Patients that remained inconclusive despite follow-up imaging were for the intermediate risk-group, 26.3% (n = 5) and for the high-risk group this were 30.6% (n = 19), see **Table 3**.

(Table 3 here)

The most frequent site location of abnormal tracer uptake, which remained inconclusive on subsequent imaging, was a single location on a rib, see **Table 4**.

(Table 4 here)

Of the 24 patients who had inconclusive bone scans, five patients had no further imaging, one patient had x-ray only, five patients had CT and eight patients had MRI as follow-up. Three patients had x-ray and MRI, one patient had both CT and MRI and lastly one patient had x-ray and CT follow-up, see **figure 3**.

(Fig. 3 here)

The 24 patients who remained inconclusive for metastatic status despite subsequent imaging were followed up to identify treatment outcomes. Five of the 24 patients had radical prostatectomy, eight patients had RT, nine patients had ADT alone and two patients had no treatment, one due to watchful wait and one due to death with unknown case, see **figure 4**.

(Fig. 4 here)

The outcome of the treatment of the 24 patients is summarized in **figure 5**. Summary of patient demographic, treatment and outcome are shown in **Table 5**. For the five patients in the intermediate-risk group, one patient was treated with LRP and had biochemical relapse (patient number 595), the remaining four were treated with RT and ADT with no biochemical relapse (patients 334, 442, 790 and 1073).

For the 19 patients in the high-risk group, eight patients received radical treatment (LRP or RT +/- ADT), of which two patients had biochemical relapse requiring salvage therapy (patients 572 and 812), and one developed metastatic castrate resistant disease and received chemotherapy (patient 622). Arguably patient number 622 already had metastatic disease to start with.

Of the remaining 11 patients, nine received indefinite ADT. Three patients developed castrate resistant disease (patients numbers: 328, 644 and 792) with the remaining six patients continued to respond to hormones (patients 637, 746, 765, 816, 1029 and 1165). Two patients received no treatment, one due to a decision of watchful waiting (patient 940), and one due to death of unrelated cause (patient 1033).

(Fig. 5 here)

(Table 5 here)

## **Discussion**

This retrospective study used real world clinical data to report on the incidence of inconclusive bone scans, clinical interventions and subsequent patient outcomes to inform important lessons learned in prostate cancer care. This study consisted of 1246 patients, 81 of which were initially diagnosed with inconclusive bone metastasis. Following further imaging, 24 patients remained inconclusive of metastatic disease. This represents a challenge in clinical practice, and handling of patients with inconclusive imaging results can vary widely. Our study provides an important contribution by detailing the frequency of inconclusive bone scan results and how these were managed in clinical practice, which to the best of our knowledge have not been accurately documented before.

The key finding of this study was that a small but clinically important proportion of men with prostate cancer in high- and intermediate-risk group show inconclusive bone scan results. These men had aggressive disease and needed further imaging to clarify appropriate treatment pathways. However, five men did not receive further imaging to accurately diagnosis the definitive TNM staging. Observations from this study underscore the importance of urgent consensus on imaging protocol in these situations including generation of further evidence.

There are several clinical implications of the study findings. Firstly, incidence of positive bone scan was higher in our cohort. A recent study<sup>17</sup> reported on men diagnosed with prostate cancer and categorized into three risk groups for the outcome of bone scans. This study showed that 31% of patients placed in the low-risk group, 48% in the intermediate risk-group and 62% in the high-risk group had a bone scan respectively. Of the patients with a bone scan that proved positive for bone metastases, the results were 0.3% in the low-risk group, 1.1% in the intermediate risk group and 14% in the high-risk group.<sup>17</sup> Despite the fact that the study by Falchook et al.<sup>17</sup> had a total patient number of 47,224 of which 23,564 individuals received a bone scan, there was no mention of patients with inconclusive bone scans. The study only mentioned those patients who are positive for metastasis. The study by Falchook et al.<sup>17</sup> concludes that bone scans are overused in the intermediate-risk group and underused in the high-risk group. Our study found a higher incidence of patients

positive for bone metastasis in both the intermediate-risk group (4.1%) and in the high-risk group (28.3%) compared to the study of Falchook et al.<sup>17</sup> As such, our study indicates that for the intermediate-risk group nearly 96% of patients potentially did not need a bone scan and for the high-risk patient group this was nearly 62%. The difference may be attributable to prevalence of screened population for prostate cancer detection.

Secondly, in contrast to our study, one study<sup>15</sup>, reported a proportion of men (55 out of 420; 13%) having inconclusive features from their bone scan, from which 40 patients received follow-up radiographic imaging to clarify metastatic status. All of these patients were from the follow-up imaging considered negative and hence this study reported no patients who remained inconclusive on the basis of their bone scan.<sup>15</sup> This underscores importance of downstream follow-up imaging to clarify lesions in men with inconclusive metastatic disease on bone scans.

Thirdly, the inconclusive bone scan generates a care pathway for men which has cost implications. The cost involved in performing a bone scan is not available for NHS Tayside as there is no treatment of private patients. Costs by hospitals conducting this investigation for private patients are set to about £363 per scan.<sup>27</sup> This means, that if patients in this cohort who was negative for metastasis (895 patients, Table 2) could avoid having a bone scan, as indicated by other predictors, then over the seven-year period a total of £324,885, or an annual cost of £55,147, could be redistributed for other use.

Fourthly, guidelines for further imaging in men with inconclusive bone scan in prostate cancer are not clear. In the present study, men with inconclusive bone scans had a variation of follow-up imaging (Figure 2), which reflects lack of consensus and guidelines in this area of clinical practice. The main follow-up imaging used was CT or MRI. Other imaging modalities for identifying bone metastasis are: Positron-emission tomography (PET), Single-photon emission computed tomography (SPECT, or hybrid imaging techniques such as SPECT/CT, PET/CT, PET/MRI. PET scanning is reported as having a sensitivity of 98% and specificity of 56%, and SPECT having a sensitivity of 87% and a specificity of 91%, as well as PET/CT having a sensitivity of 100% and specificity of 97%.<sup>12</sup> Whole body MRI was found to have a sensitivity of 91% and a specificity of 95%<sup>28</sup>, however a whole body MRI scan require a patient to be supine and not moving while strapped down by coils around head and torso including arms and lower body<sup>29</sup> for a minimum of an hour or more.<sup>30</sup> A meta-analysis comparing MRI, PET, PET/CT and bone scans found PET and PET/CT to be superior to MRI and bone scans in identifying bone metastasis.<sup>31</sup> It is acknowledged that these imaging modalities are expensive and with limited accessibility. This research shows that for this patient cohort of the seven years included, nearly 2% of patients (24 out of 1246 patients) had a bone scan of inconclusive results. This being a small population, adds to the argument that this patient group should be recommended for the more sensitive and specific imaging

modalities despite them being more expensive and lesser accessible. Recommending patients diagnosed with prostate cancer and inconclusive bones scans for more elucidatory imaging modalities will deliver an optimum treatment and care for this patient group.

Finally, the new imaging methods need further evaluation in a clinical setting of inconclusive bone scans. Prostate-specific membrane antigen (PSMA) secreted and expressed on the cell walls of almost all Prostate Carcinoma (PCa) tumors. These proteins have been targeted with gallium 68, 99mTc tracer.<sup>32</sup> The PET scan based on this tracer (Ga68-PSMA) has been shown to have better diagnostic accuracy compared to Choline and acetate PET scans in detecting extra-prostatic disease, along with lymph node and bone lesions in prostate cancer.<sup>32</sup> Furthermore, promising results are seen in staging of prostate cancer disease<sup>33</sup> and in those with recurrences following hormonal treatment.<sup>34</sup> It is essential that future studies are designed to assess the role of this new imaging modality in men with inconclusive bone scans. This study nevertheless has allowed evaluation of current practices for treatment of men diagnosed with prostate cancer with inconclusive bone scans. The challenge of dealing with inconclusive bone scans in otherwise fit and healthy men for radical treatment remains a real one.

#### *Limitations to the study:*

This is a retrospective study with its associated biases including selection of cohort. The design of exclusion introduces a minor selection bias in the study and needs to be recognized.

### **Nursing implications**

Diagnostic imaging can cause cancer-related distress, a condition known as “scanxiety”. Men are fearful of treatments, progression of disease and distress caused by the requirement for additional imaging to re-assess disease status, such as inconclusive bone scans. Men may experience sadness, anger, fear, dread, confusion and anxiety. Men affected by scanxiety can occur weeks before and follow-up scans (x-ray, CT scan, MRI). Prostate Cancer Specialist Nurses should keep an open dialogue when discussing coping strategies and feelings with their patients. The importance of routine implementation of holistic needs assessment in practice is required to identify men who are at clinical risk of scanxiety and provide appropriate person-centred supportive care interventions.

### **Conclusion**

The present study has shown nearly 2% (1.92%) incidence of inconclusive bone scan results in men with intermediate- and high-risk non-metastatic prostate cancer. Although small in number, these men do need alternate improved diagnostic

pathways and better imaging modalities in order to get a better risk stratification for further treatment. There is a need for consensus and evidence generation through further research in this area, in particular evaluation of whole body MRI and Ga68-PSMA scans.

### **Compliance with Ethical Standards**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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