

A Farewell to Arms - An Institutional Review of Conventional Staging for Intermediate-Risk Prostate Cancer

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Abstract

Background

EAU guidelines advise patients with intermediate risk Gleason 4+3=7 prostate cancer undergo cross-sectional abdominopelvic imaging and bone scan for metastatic screening. We hypothesised detection rate of extra-prostatic disease in this cohort is low using conventional CT/bone scans and could potentially be avoided.

Materials and Methods

Patients with overall Gleason 4+3 histology were identified over 69 months at East Kent University Hospitals NHS Trust. Patients were excluded if PSA >20ng/mL and/or MRI prostate >T3b stage. Primary outcomes were: (a) detection rates of metastatic disease using conventional CT and bone scan and b) the proportion of fully-staged patients with positive lymph nodes at dissection or biochemical recurrence following robotic-assisted laparoscopic prostatectomy (RALP).

Results

A total of 134 patients were identified. Median age was 72 (range 45-83), PSA 7.8ng/mL (range 1.8-19.3) and prostate volume 40cc (range 10-129). 130/134(97%) had MRI scans prior to staging. 124/134(93%) had bone scans and 83/134(62%) had CT scans, of which 77/134(57%) had both. 0/124(0%) bone scans identified metastatic disease and only 2/83(2%) CT scans identified nodal disease not detected by MRI. 0/134(0%) had management changes from staging. 57/134(43%) patients negatively-staged proceeded to RALP. 19/57(32%) had lymph node dissections. 6(11%) had missed metastatic disease at 19 months median follow-up.

Conclusion

Detection of metastatic disease by conventional CT and bone scan was poor in this cohort, despite their presence, and their recommendation by EAU seems unwarranted. Patients could safely avoid these scans and proceed directly to radical treatment, due to the theoretical benefit of treating despite oligometastatic disease.

Keywords

bone scans • prostate cancer • staging scans • intermediate risk • PSMA PET/CT

Introduction

Accurate staging of prostate cancer with imaging is crucial for diagnosis and forming appropriate treatment plans for patients. EAU guidelines currently recommend all patients with high-risk prostate cancer, and those with intermediate-risk and Gleason 4+3=7 histology, undergo cross-sectional abdominopelvic imaging and bone scan (1). This recommendation is based on two single-centre retrospective studies, that included just 40 and 13 patients respectively with ISUP Grade 3 histology (2,3), and pre-date the multiparametric MRI prostate era.

Conventionally, this staging is performed using CT and nuclear medicine bone scans. However, there is concern that conventional imaging techniques have insufficient sensitivity and specificity to accurately detect extra-prostatic disease in high-risk patients (4,5). We aimed to identify the

detection rates of metastatic disease, specifically for patients with intermediate-risk prostate cancer with Gleason 4+3=7 histology, using CT and bone scan. We also aimed to identify the oncological outcomes of these patients who subsequently proceeded to robot-assisted laparoscopic prostatectomy (RALP) to help determine whether distant metastatic disease was missed on imaging.

Materials and Methods

We performed an institutional retrospective analysis of patients using a study population of patients at East Kent University Hospitals NHS Foundation Trust (eKUFT) in Kent, UK

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who underwent prostate biopsy between 2017 and 2023. The catchment area of eKUFT is approximately 700,000 people. The study design was a retrospective cohort study. The study aims were to:

- Identify the detection rates of metastatic disease using conventional staging scans (CT and Bone Scan) in patients diagnosed with Gleason 4+3=7 prostate cancer.
- To identify the proportion of Gleason 4+3=7 patients who developed metastatic disease post RALP in this cohort, who had negative staging beforehand, to demonstrate missed metastatic disease on imaging.

The study protocol was designed to retrospectively identify any new diagnosis of Gleason 4+3=7 between 2017 and 2023 from our InfoFlex® hospital database. Hospital databases were also interrogated to determine any relationship between PSA values, patient demographics and MRI results following multidisciplinary team (MDT) review (specifically prostate volume and PIRADS scoring) with positive staging scans. Other parameters checked included overall histology, including laterality of disease, maximum core length, percentage of cores involved, median number of cores and percentage of pattern 4. Inclusion criteria was any patient with new diagnosis of Gleason 4+3=7 overall histology on prostate biopsy between 2017 and 2023. Exclusion criteria was a Prostate Specific Antigen (PSA) >20ng/mL and/or MRI prostate >T3b stage or patients with missing data.

Radiological exam results after multidisciplinary team (MDT) review were assessed. From the MRI, prostate volume and Prostate Imaging Reporting and Data System (PIRADS) scoring were analysed for demographic data. CT scans and bone scans were considered either positive, negative or equivocal depending on findings as reported. Equivocal results were subsequently determined to be positive or negative after either MDT discussion or further imaging. No statistical analysis was required.

Any patient who proceeded to RALP after negative staging scans were included for sub-analysis to assess if metastatic disease was missed on imaging. Patients were excluded if they had positive surgical margins at final histology. Missed metastatic disease on imaging was defined as any patient with positive lymph nodes at dissection or biochemical recurrence (defined as PSA >0.2ng/mL on two consecutive measurements) in those with negative surgical margins. Median follow up was included for each patient.

Results

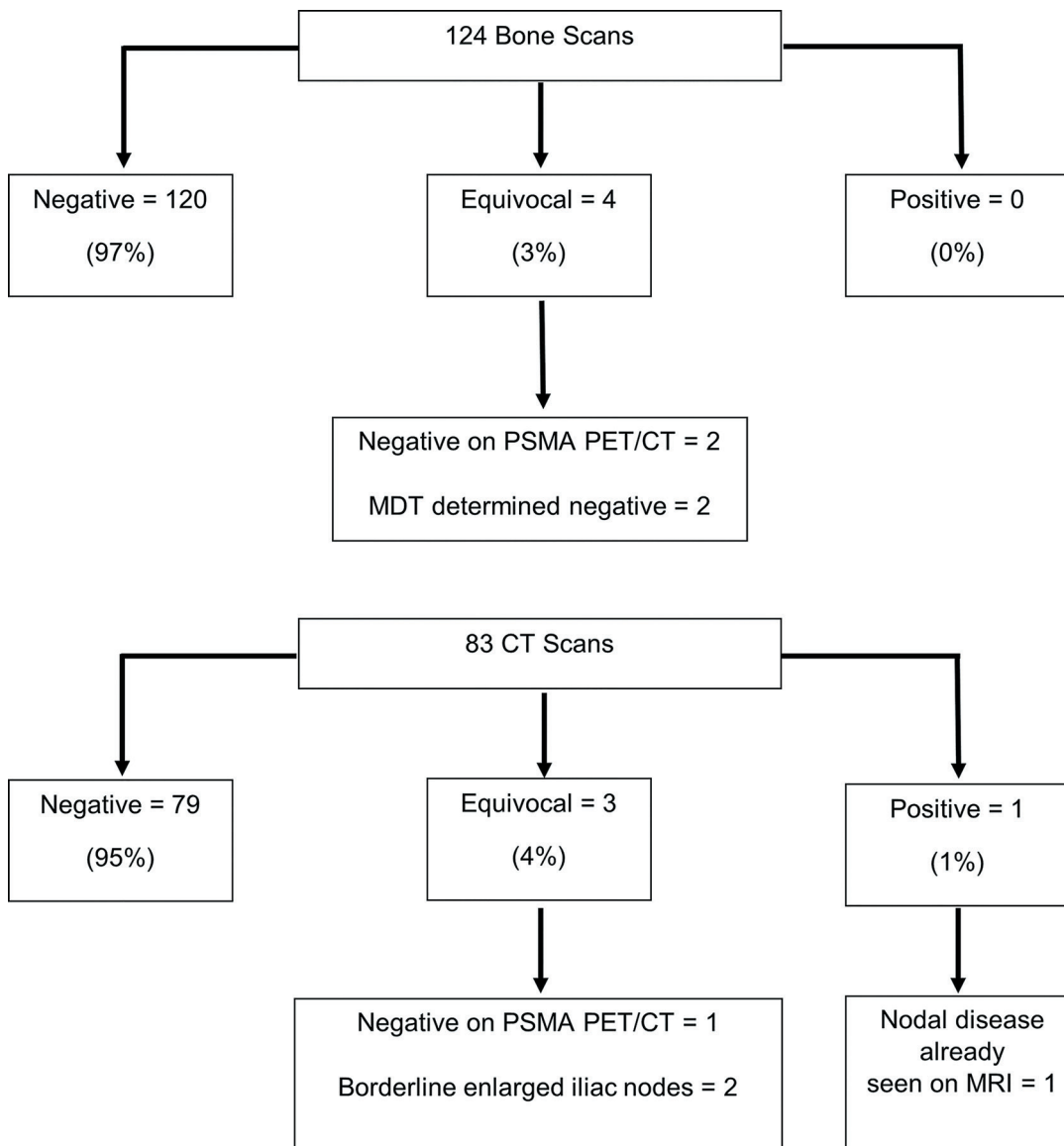
A total of 169 patients were initially identified. Sixteen patients had PSA ≥ 20 ng/mL, four had MRI stage $\geq T3b$ and three had

Table 1. Patient demographics and staging scans for patients with Gleason 4+3 intermediate risk disease.

Patient demographics (n=134)	Median (range or %)
Age	72 (45 - 83)
PSA (ng/mL)	7.8 (1.8 – 19.3)
Prostate volume (mL)	40 (10 - 129)
Biopsy type	
TRUS	14 (10)
Transperineal	120 (90)
MRI prostate (n=130)	
PIRADS 2	15 (11)
PIRADS 3	9 (7)
PIRADS 4	66 (51)
PIRADS 5	40 (31)
MRI T stage	
T1	8 (6)
T2	74 (57)
T3a	48 (37)
MRI N Stage	
N0	128 (98)
N1	2 (2)
MRI M stage	
M0	130 (100)
Bone scan (n=124)	
NM Bone scan	121 (98)
SPECT CT	3 (2)
CT scan (n=83)	
CT chest / abdomen / pelvis	77 (93)
CT Urogram	4 (5)
CTKUB	1 (1)
CT abdomen / pelvis	1 (1)
Both CT & Bone scan (n=77)	77 (53)

both. Twelve patients had neither CT or bone scans and were excluded, leaving 134 patients for analysis (**Table 1**). Median age was 72 (range 45-83), PSA 7.8ng/mL (range 1.8-19.3) and prostate volume 40cc (range 10-129). 130/134(97%) had MRI scans prior to staging. 124/134(93%) patients had bone scans and 83/134(62%) had CT scans, of which 77/134 (57%) had both.

120/134(90%) prostate biopsies were transperineal rather than transrectal. Median cores involved were 8 (range 1-20), percentage of cores involved was 24 (range 3-100), percentage of Pattern 4 was 75 (<5-90) and maximum tumour length 9mm

Figure 1. Detection of metastatic disease using both bone scan and CT in Gleason 4+3 intermediate risk disease.

(range 1-17). 70/134 (52%) patients had bilateral Gleason 4+3=7 disease.

0/124(0%) bone scans identified metastatic disease (**Figure 1**). 4/124(3%) were initially deemed equivocal; two were determined negative at MDT discussion and two confirmed negative on PSMA PET/CT. 1/83(1%) CT scans identified clear metastatic disease, which was already seen on MRI prostate. Three equivocal scans were found; 2/83(2%) showed borderline enlarged iliac lymph nodes and were deemed indeterminate at MDT and thus considered positive. One scan showed a rib abnormality, subsequently proved negative with PSMA PET/CT. Management changes as a result of imaging occurred in 0/134(0%) of all patients.

59/134(44%) patients proceeded to RALP, of which 19(32%) patients had lymph node dissections. 57/59(97%) had staging with bone scan and abdominopelvic imaging using either MRI or CT, of which 32/59(54%) had MRI, CT and bone scan. In the 57 patients staged with bone scan & either CT or MRI, 6(11%) patients had metastatic disease missed on conventional staging scans; 3(5%) had biochemical recurrence despite negative surgical margins and 3(5%) had positive lymph nodes at dissection (**Table 2**). In the 32 patients staged with all three modalities of MRI, CT and bone scan, 2(6%) had missed disease; 1(3%) biochemical recurrence and 1(3%) positive lymph nodes at dissection. Median length of follow up was 18.7 months (range 2.3 – 49.1). Final histopathology at RALP showed

Table 2. Staging scans performed in patients with missed metastatic disease prior to RALP.

	PSA ng/mL	MRI T stage	Bone Scan	CT CAP	Lymph node dissection	Biochemical recurrence	Post-op PSMA PET/CT
Patient 1	18.0	T3a	Negative	Negative	Negative	Yes	Positive
Patient 2	6.4	T2c	Negative	Not performed	Not performed	Yes	Negative
Patient 3	5.3	T3a	Negative	Not performed	Negative	Yes	Not performed
Patient 4	5.5	Not performed	Negative	Negative	Positive	No	n/a
Patient 5	3.9	T3a	Negative	Negative	Positive	No	n/a
Patient 6	4.7	T3a	Negative	Not performed	Positive	No	n/a

31/59 (51%) were ISUP Grade 3; 20/59 (34%) were downgraded to ISUP Grade 2 and 8/59 (14%) were upgraded to ISUP Grade 5.

Discussion

Our study found the ability of bone and CT scans to detect metastatic disease in intermediate risk disease with overall Gleason 4+3=7 histology was poor. This finding is in contrast to previous retrospective studies (2,3) on which the EAU recommendation was made. The EAU recommendations are almost twenty years old, are based on a small number of ISUP Grade 3 patients, and pre-date routine use of multi-parametric MRI scans.

Consensus on when to stage patients with CT and bone scan is also lacking. NICE has cited an absence of evidence regarding when bone scans should be performed and recommended for research in this area (6). Their use in high-risk disease groups is also questionable: one study involving 125 patients with T3a disease, no patients had positive bone scans when excluded for PSA ≥ 20 ng/mL or ISUP group Grade ≥ 3 (7). CT scans too have shown poor detection rates of visceral metastases, with studies showing initial prostate MRI scan confers adequate staging information in itself (8). Despite this, a significant proportion of fully-staged patients will have positive lymph nodes at dissection or future biochemical recurrence, as evidenced by our own results. This number is likely to increase as length of follow up increases also.

The use of Prostate Specific Membrane Antigen (PSMA) PET/CT as alternative staging to CT and bone scan has increased in popularity in recent years. This follows several retrospective studies showing improved diagnostic accuracy compared to CT and bone scan (9,10). These were validated in the ProPSMA trial; a multi-centre prospective randomised controlled trial, which demonstrated greater sensitivity and specificity for distant and nodal metastases in high-risk prostate cancer when directly compared to CT and bone scan, as well as fewer equivocal findings (11). Earlier detection with PSMA PET/CT has the potential to facilitate radiologically guided lymph node dissection at RALP (12). Negative scans could also obviate the

need for lymph node dissection and its associated morbidity, although this is not a consensus in guidelines as yet, reflecting both the uncertainty in the ability of PSMA PET/CT to exclude nodal disease and furthermore the clinical utility of node dissection in terms of prognostic impact.

However, most evidence for PSMA PET/CT currently relates to detection of metastatic disease in high-risk prostate cancer, rather than specifically in intermediate risk and primary pattern Gleason 4. Furthermore, the high cost of PSMA PET/CT precludes its routine use in clinical practice, although the access to PSMA PET/CT is steadily improving. In the 2023 guidelines, the National Comprehensive Cancer Network (NCCN) recommend the use of PSMA PET/CT as the first-line imaging option for primary staging of Prostate cancer, based on its higher sensitivity and specificity, compared to CT and bone scan (13,14). EAU is yet to endorse this recommendation although as of 2024, it has modified its stance of 2023 from "Treatment should not be changed based on PSMA PET/CT findings, in view of currently available data," to "Results from RCTs (...) are awaited before a recommendation can be made to treat patients based on the results of these tests" (15). This reflects the current paucity of evidence demonstrating improved survival benefit from early detection and treatment of oligometastatic disease (16,17) compared to proceeding directly to radical treatment. Our study's strengths include larger numbers of intermediate-risk ISUP Grade 3 patients than the studies cited by the EAU for performing staging scans in this cohort (2,3). It also helps redefine the role of traditional staging scans in the modern diagnostic work-up of prostate cancer, given the widespread use of multi-parametric MRI for accurate staging and more accurate histology with MRI targeted biopsies. Its limitations include its single-centre retrospective nature and further evidence would be required to validate its results.

Detection of metastatic disease by conventional CT and bone scan was low in patients with intermediate risk prostate cancer and Gleason 4+3=7 histology. Patients should either undergo more sensitive staging with PSMA PET/CT or proceed directly to radical treatment due to the theoretical benefit of treating patients with oligometastatic disease. Further large scale multicentred studies are warranted.

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Conceived and designed the analysis: RK, ES

Collected the data: RK, PS, VB, OT

Contributed data or analysis tools: RK, SK, HB, ES

Performed the analysis: RK, HB, ES

Wrote the paper: RK, HB, ES

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