Incorporating multi-parametric MRI staging and the new histological Grade Group system improves risk-stratified detection of bone metastasis in prostate cancer.

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Abstract

Background:
There remains uncertainty on the need for bone staging in men with intermediate-risk prostate cancer. Current guidelines do not use mpMRI-staging information and rely on historic pathology grading.
Methods:
We investigated the ability of mpMRI and the new Grade Group system to better predict bone metastasis status in a retrospective cohort-study of 438 men with prostate cancer undergoing baseline mpMRI and isotope bone scintigraphy(BS).
Results:
Including mpMRI-staging information significantly increased the specificity of bone metastasis detection from 3.0% to 24.2%($p<0.01$) and sensitivity from 89.2% to 97.3%. The new Grade Group score demonstrated progressive increase in bone metastasis rates($p<0.001$). A novel risk-stratification model combining Grade Groups, PSA and mpMRI-staging shows promise in predicting bone metastasis and could potentially reduce BS usage by 22.4%-34.7%.
Conclusions:
Incorporating the new Grade Group system and mpMRI-staging more accurately identified bone metastatic risk and suggests men with Grade Group ≤2 and/or without radiological T3 disease could safely avoid routine bone-staging.

Introduction

Assessment of bone metastasis status is key for the management of prostate cancer (PCa)(NICE 2014a, Fizazi et al. 2015). Clear evidence exists for staging investigations such as isotope bone scintigrams (BS) in patients with high-risk PCa whilst precluding its routine use in low-risk disease(NICE 2014a). However, the utility of BS in intermediate-risk disease is unclear with EAU, AUA and NICE offering conflicting guidance(Heidenreich et al. 2014, NICE 2014a).

The International Society of Uro-Pathology (ISUP) have recently approved a new PCa 'Grade Group' classification system to improve correlation of Gleason grade to biochemical recurrence(Epstein et al. 2016). Concurrently, multiparametric (mp)-MRI has emerged as a crucial tool in local staging of PCa, allowing improved discrimination between T2 and T3 disease compared to clinical nomograms(Turkbey et al. 2013, Lawrence et al. 2014). However, current guidelines on bone staging do not mandate use of mpMRI information or Grade Groups(NICE 2014a). Therefore, we investigated the ability of mpMRI-staging information or the new Grade Group system to help predict bone metastatic status and refine the use of bone staging investigations.

Methods

A radiology database was searched for all PCa patients undergoing baseline mpMRI prostate and BS from January 2010 - May 2015 in our tertiary centre(study registration CUH/3927). In cases of equivocal BS, the final status was recorded using a combination of clinical follow-up and/or any further radiological investigations. mpMRI was performed on a 3T Discovery MR750-HDx or 1.5T MR450 system (GE Healthcare, Waukesha, USA) with a surface phased-array coil, including standard anatomical and functional diffusion-weighted imaging using multiple b-values, as previously described(Lawrence et al. 2014). All studies were reported by expert uro-radiologists and reviewed in a multi-disciplinary team (MDT) setting.

Gleason score was assessed according to the ISUP 2005 recommendations (Epstein et al. 2005) and recorded alongside the number of positive cores and percentage involvement of tissue. All cases were reported by a specialist uropathologist, and reviewed a second time by another uropatholigist prior to discussion at a specialist MDT. The core with the highest grade was used to devise the Grade Group.

Patients were first categorised to low-(T1–T2a, Gleason ≤6 and PSA <10 ng/mL), intermediate-(T2b-c, and/or Gleason = 7 and/or PSA 10–20 ng/mL) and high-risk(T3-T4, or Gleason 8-10 or PSA level >20 ng/mL) according to NICE 2008 guidelines(NICE 2014b). Patients were subsequently re-categorised according to the new Grade Group system(Epstein et al. 2016) and a novel 5 stratum Risk Group system developed in our centre integrating PSA, Grade Group, and mpMRI staging (Gnanapragasam et al. 2016) (table 1).

Contingency tables were constructed with expected frequency for bone metastasis and adjusted residuals calculated for each risk system. Pearson's chi-squared test was used to examine the differences in observations. Comparison of sensitivities and specificities of bone metastasis between systems was made using McNemar's test. To compare positive and negative predictive values, we used a generalised score statistic in R 3.1.2 (Leisenring et al. 2000, Stock and Hieschler 2014). All other statistical analysis was performed in Stata®14 (StataCorp LP, Texas, USA).

Results

438 patients underwent mpMRI and BS. Mean age (±SD) was 67.1 years (±6.7) and mean PSA 21.3 ng/ml (±48.1). In this cohort 37 patients had bone metastases (8.4%); **Table 2**. The specificity of BS was 86.5%. 14/37 (37.8%) men with bone metastases also had evidence of pelvic metastasis on prostate MRI. Using NICE intermediate-risk as a threshold for performing BS, 426 BS would have been performed. Assessing this risk-stratification as if it were a diagnostic test demonstrated a sensitivity of 100% but specificity of only 3.0%. Comparisons of other decision models were made against this standard (**Table 3**).

Adding mpMRI to current NICE risk groups:

The distribution of patients by NICE classification is shown in **Table 2A**. By these categories 33/37 men with bone metastases were classified as high-risk and 4 as intermediate-risk. All 4 intermediate-risk patients had PSA <20.0ng/mL but Gleason 4+3 disease. mpMRI staging re-categorised 3 of these patients to high-risk (**eFigure 1&2**), improving the sensitivity of high-risk for detecting bone metastases to 97.3% from 89.2%, and specificity compared to intermediate-risk to 24.2% from 3.0% ($p<0.01$). Using mpMRI-defined high-risk disease as a threshold for BS would have reduced the number of scintigrams performed by 98 (22.4%), with a single missed diagnosis.

Applying the new Grade Group scores to predict bone metastases:

Using the new Grade Group scores in isolation, there was a progressive increase in bone metastases detection from 0/43(0%) for Grade Group 1 to 20/121 (16.5%) for Grade Group 5 (Gleason 9-10); $p<0.001$, **Table 2B**. Using BS only for patients with Grade Group scores ≥3 significantly improved sensitivity to 97.3% and significantly improved specificity to 37.7% ($p<0.01$); **Table 3**. Using this cut-off would have reduced the number of BS by 152 (34.7%), with a single missed diagnosis.

Combining mpMRI and Grade Group scores in a novel risk-stratification system:

This model defines 5 prognostic risk strata for prostate cancer (**Table 1**)(Gnanapragasam et al. 2016). Within this model, no men in Risk Groups 1 or 2 had bone metastasis. Bone metastasis rate increased progressively in Risk Groups 3 (2.13%), 4 (5.8%) and 5 (13.7%); $p=0.004$. Using Risk Group 4 as a threshold for bone staging, demonstrated improvement in specificity to 23.9% ($p<0.01$) and 97.3% sensitivity, with a 22.1% reduction in the need for BS.

Discussion

Detection of bone metastasis confers a significantly worse prognosis in men with PCa and is thus an important part of the staging work-up(Fizazi et al. 2015). In our study we showed that only 8.4% of men had bone metastasis out of 438 men scanned, emphasising the need to refine use of this resource-intensive investigation. Of note, we did not find that a high PSA alone was a good discriminator; in our cohort we identified 4 men with bone metastases and a PSA <20ng/mL which is at odds with other reports(McArthur et al. 2012).

In this study we have demonstrated evidence that mpMRI-staging provides a useful adjunct in appropriately identifying men who will benefit most from BS. The integration of mpMRI alongside traditional biochemical and pathological markers, to re-categorise patients as

high-risk disease, would have led to a 99.0% NPV for bone metastases at this threshold, alongside a significant increase in specificity to 24.2% and reduction in BS use. We also provide early validation of the new histological Grade Group system, with BS yield being higher in Grade Group 3 (bone metastasis rate of 5.8%) compared to Grade Group 2 (0.6%). Setting a threshold for BS of Grade Group ≥3 would have reduced the number of BS performed by 152 (34.7%), with a single false negative. This correlates with data used to inform the 2015 update to EAU guidelines(Heidenreich et al. 2014) and should encourage adoption of these proposed grading groups(Epstein et al. 2016).

It should be noted that grade and stage data are not used in isolation in clinical management. We therefore tested the proof-of-principle of a new risk model incorporating the new Grade Group system, mpMRI and biochemical information. This refinement demonstrated promising results with a NPV of 100% for Risk Groups 1 and 2. Taken together, our data demonstrate that the combined use of more accurate mpMRI-staging and histological grade stratification better defines men who benefit most from bone staging investigations. These promising results show potential for reductions in the use of BS by up to a third while maintaining sensitivity and NPV above 97% and 99% respectively.

The main limitation of our study is its retrospective nature and a selected population, only including men undergoing both mpMRI and BS. The relatively small absolute numbers of men with intermediate risk disease, or men with bone metastases in this cohort should lead to caution when interpreting sensitivity or specificity values in isolation. Additionally, bone scintigraphy can be questioned as an ideal standard for diagnosing bone metastases, however, our data reflects current clinical practice and should be useful in guiding clinical management. PET-CT using fluorine or choline tracers has been shown to be a superior, albeit more expensive option for assessing metastatic bone involvement(Fuccio et al. 2012). Our results would require further validation in external cohorts in a prospective study and preferably using these modalities.

Conclusion

We demonstrate for the first time that the new histological Grade Group system and mpMRI staging more accurately identified men at risk of harbouring bone metastases. Importantly, our data strongly suggests that men without histology in Grade Group ≥3 and/or radiological T3 disease could safely avoid routine bone staging.

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Conflict of Interest Statement

We, the authors, have read and understood the BJC policy on declaration of interests and declare that we have no conflict of interest.

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Table 1: Proposed new prostate cancer Risk group criteria taken from Gnanapragasam et al 2016(Gnanapragasam et al. 2016) and using the new Grade Group system(Epstein et al. 2016).

New Risk Group	Criteria
1	Gleason 6 (Grade Group 1) **AND** PSA <10ng/ml **AND** Stage T1-2
2	Gleason 3+4=7 (Grade Group 2) **OR** PSA 10-20ng/ml **AND** Stage T1-T2
3	A combination of: Gleason 3+4=7 (Grade Group 2), PSA 10-20ng/ml, Stage T1-T2 **OR** Gleason 4+3=7 (Grade Group 3) **AND** Stage T1-T2
4	Any one of: Gleason 8 (Grade Group 4) **OR** PSA >20ng/ml **OR** Stage T3
5	Any combination of: Gleason 8 (Grade Group 4), PSA >20ng/ml, Stage T3 **OR** Any Gleason 9-10 (Grade Group 5) **OR** Any Stage T4

Table 2A. The distribution and bone metastasis status of men categorised according to NICE classification, by clinical parameters alone and with mpMRI staging information integrated. P values are calculated with Pearson's Chi-Squared tests using full contingency tables (eTable 1). n=438.

	Clinical (NICE)			Clinical (NICE) + mpMRI		
NICE risk group	**No bone mets**	**Bone mets**	**Bone mets rate (%)**	**No bone mets**	**Bone mets**	**Bone mets rate (%)**
Low	12	0	0	4	0	0
Int.	143	4	2.7	93	1	1.1
High	246	33	11.8	304	36	10.6
P Value			0.003			<0.001

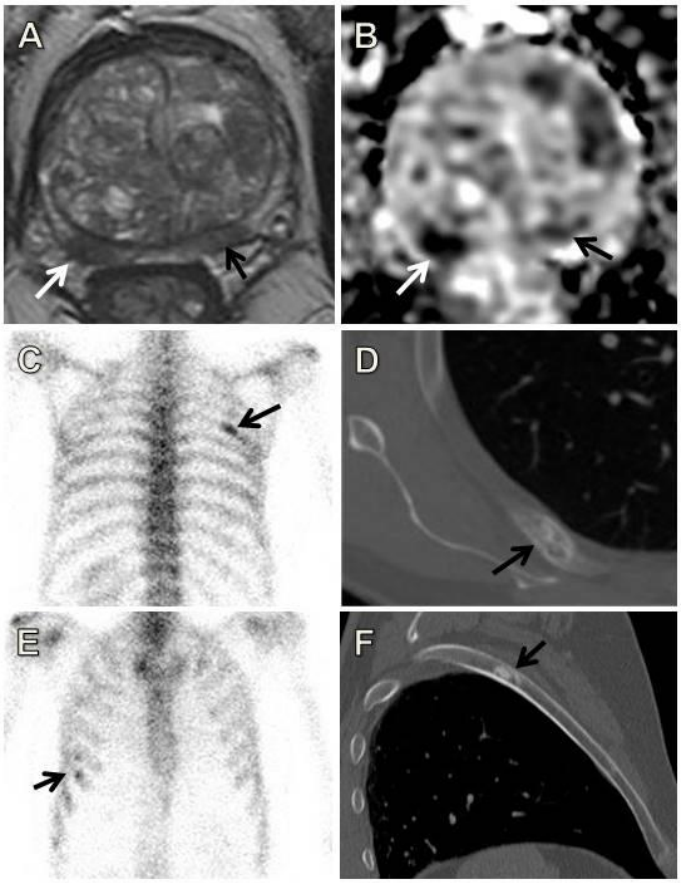
Table 2B. The distribution and bone metastasis status of men categorised by the new Grade Group score and the proposed Cambridge Risk score. P values are calculated with Pearson's Chi-Squared tests using full contingency tables (eTable 1). n=438.

	Grade Group score			New Risk model		
Grade/ Risk Group	**No none mets**	**Bone mets**	**Bone mets rate (%)**	**No bone mets**	**Bone mets**	**Bone mets rate (%)**
1	43	0	0	10	0	0
2	108	1	0.9	40	0	0
3	67	7	9.6	46	1	2.1
4	82	9	9.9	129	8	5.8
5	101	20	16.5	176	28	13.7
			<0.001			0.004

Table 3. Summary statistics for each stratification system and risk group using the stated cut-offs, as if it were a diagnostic test for bone metastasis. Comparisons (p values) are made against the current NICE classification (column 1), using McNemar's test. The number of patients requiring BS using each classification is recorded in the first row.

	NICE (BS for ≥ Intermediate-risk)	**NICE +mpMRI (BS for High-Risk men only)**		**Grade Group (BS for Score ≥ 3)**		**Grade Group (BS for Score ≥ 4)**		**New risk model (BS for Risk Group ≥ 3)**		**New risk model (BS for Risk Group ≥ 4)**	
			P value		P value		P value		P value		P value
BS performed	426	340	-	286	-	212	-	388	-	341	-
Sensitivity (%) (95% CI)	100 (90.5, 100)	97.3 (85.8, 99.9)	0.32	97.3 (85.8, 99.9)	0.32	78.4 (61.8, 90.2)	<0.01	100 (90.5, 100)	-	97.3 (85.8, 99.9)	0.32
Specificity (%) (95% CI)	3.0 (1.6, 5.2)	24.2 (20.1, 28.7)	<0.01	37.7 (32.9, 42.6)	<0.01	54.4 (49.3, 59.3)	<0.01	12.5 (9.4, 16.1)	<0.01	23.9 (19.8, 28.4)	<0.01
PPV (%) (95% CI)	8.69 (6.2, 11.8)	10.6 (7.5, 14.4)	<0.01	12.6 (9.0, 17.0)	<0.01	13.7 (9.4, 19.1)	<0.01	9.5 (6.8, 12.9)	<0.01	10.6 (7.5, 14.3)	<0.01
NPV (%) (95%CI)	100 (73.5, 100)	99.0 (94.4, 100)	0.33	99.3 (96.4, 100)	0.33	96.5 (93.1, 98.5)	0.02	100 (92.9, 100)	-	99.0 (94.4, 100)	0.33

eFigure 1: 71 year old patient with clinically intermediate risk prostate cancer on 2008 guidelines, up-risked by MRI.
PSA 11.57, transperineal biopsy showed right side Grade Group 3 (Gleason 4+3=7) in 7 cores (5-25%) and left side Grade Group 2 (Gleason 3+4=7) in 6 cores (5-80%). A, B: MRI confirms bilateral tumour in the mid gland peripheral zone (arrows) with matching restricted diffusion (B), and irregularity consistent with early T3a disease on the right (white arrow in A), confirming high-risk disease. C-F: Subsequent bone scintigraphy shows focal tracer uptake in the right 5th posterior rib (arrow in C) and adjacent right anterior ribs (arrow in E), confirmed as sclerotic metastases on CT (D and F, respectively).



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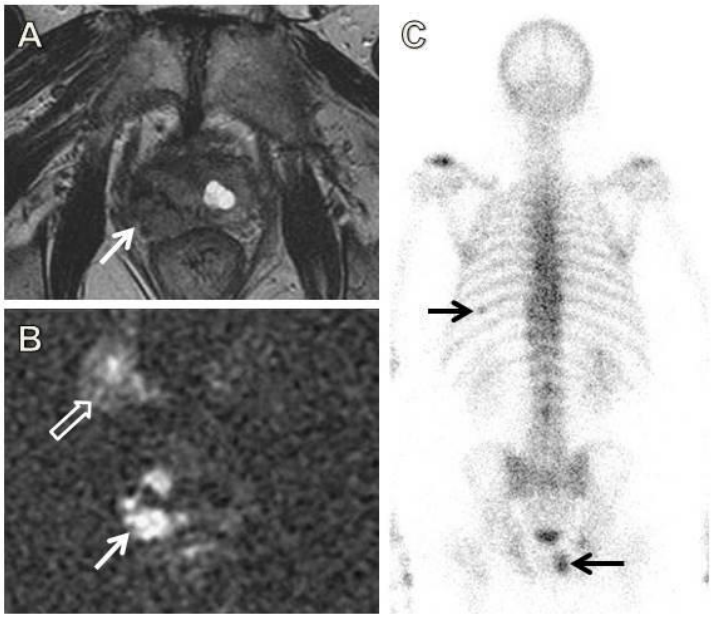

eFigure 2: 73 year old patient with clinically intermediate risk prostate cancer on updated guidelines, up-risked by MRI.
PSA 12.25, transrectal ultrasound (TRUS) guided-biopsy showed right side Grade Group 3 (Gleason 4+3=7) in 1/6 cores (5%), left side benign. A: MRI demonstrates a large tumour at the right apex (arrow), likely under-sampled at TRUS with filling in of the retro-prostatic angle and capsular irregularity, consistent with T3a high-risk disease. B: high b-value diffusion-weighted imaging shows a suspicious area of high signal adjacent to the right pubic symphysis (open arrow). C: bone scintigraphy (posterior view) confirms pubic metastasis and demonstrates additional area suspicious for metastasis in the posterior left 9th rib (arrows).

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eTable 1. Contingency table showing the observed, expected and adjusted residual of bone metastasis in each of the grading and risk systems. P-Values calculated with Pearson's Chi-Squared tests.

	Grade Group			'Cambridge' Risk Score			Clinical NICE (PSA & Gleason)			
Grade/Risk Group	No Bone Mets	Bone Mets	Bone Mets Rate (%)	No Bone Mets	Bone Mets	Bone Mets Rate (%)	NICE Group	No Bone Mets	Bone Mets	Bone Mets Rate (%)
1 Obs	43	0	0	10	0	0	Low	12	0	0
1 Exp	39.37	3.63		9.16	0.85			10.99	1.01	
1 Column %	10.72	0		2.49	0			2.99	0	
1 Adj. residual	2.1	-2.1		0.97	-0.97			1.07	-1.07	
2 Obs	108	1	0.92	40	0	0				
2 Exp	99.79	9.21		36.62	3.38					
2 Column %	26.93	2.7		9.98	0					
2 Adj. residual	3.26	-3.26		2.02	-2.02					
3 Obs	67	7	9.56	46	1	2.13	Int.	143	4	2.72
3 Exp	67.75	6.25		43.03	3.97			134.58	12.42	
3 Column %	16.71	18.92		11.47	2.79			35.66	10.81	
3 Adj. residual	-0.34	0.34		1.65	-1.65			3.06	-3.06	
4 Obs	82	9	9.89	129	8	5.84				
4 Exp	83.31	7.69		125.43	11.57					
4 Column %	20.45	24.32		32.17	21.62					
4 Adj. residual	-0.56	0.56		1.32	-1.32					
5 Obs	101	20	16.53	176	28	13.73	High	246	33	11.83
5 Exp	110.78	10.22		186.77	17.23			255.43	2357	
5 Column %	25.19	54.05		43.89	75.68			61.35	89.19	
5 Adj. residual	-3.76	3.76		-3.71	3.71			-3.37	3.37	
p Value		<0.001			0.004				0.003	