Original article

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Bone scan index as metastatic bone disease quantifier and predictor of radium-223-dichloride biochemical response

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Objectives **This work aims to assess whether the biochemical response of radium-223-dichloride treatment can be predicted based on the pretherapy bone scan, and consequently if bone scan index (BSI) and maximum lesion intensity have a place as alternatives or as complements to extent of bone disease (EOBD) scoring in predicting biochemical response to treatment. Many cases of advanced prostate cancer have evidence of bone metastasis. Accurate EOBD quantification could help predict the response to radium-223-dichloride therapy. Current EOBD score is simple to use but does not consider size, intensity or localisation of lesion BSI might be more suitable for stratification of bone metastases.**

Patients and methods **Bone scans ($n = 20$) preceding radium-223-dichloride treatment for prostate cancer were assessed retrospectively using automated BSI software (EXINI) and by assessing maximum counts per lesion. Results were then compared to total alkaline phosphatase (ALP) as a measure of biochemical response to therapy using linear regressions and to their EOBD scores using box plot analysis.**

Results **Moderate correlation was found between ALP response and maximum lesion intensity ($R^2 = 0.41$) and BSI ($R^2 = 0.46$). Strong correlation ($R^2 = 0.71$) was found between baseline ALP and BSI and between lesion number and BSI ($R^2 = 0.60$). Visual assessment of EOBD score was found to correlate well with baseline ALP and maximum ALP response.**

Conclusion **BSI is a useful asset in stratification of patients with metastatic bone disease. It may also have a place in prediction of biochemical response.** ***Nucl Med Commun*** **00:000–000**

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Keywords: alkaline phosphatase, bone scan index, extent of bone disease, prostate cancer, radium-223-dichloride

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Introduction

Almost 80% of advanced prostate cancer have evidence of bone metastasis [1–3]. Stratification of prostate cancer patients according to extent of bone disease (EOBD) is advantageous in informing and monitoring the course of treatment. A tool for predicting the response to therapy would lead to more accurate prognosis and ultimately aid clinicians in their therapeutic decision making [4].

Conventional bone scintigraphy remains a useful and sensitive tool for detecting bone metastasis. It is based on phosphate analogues labelled with technetium-99m that have a bone uptake proportional to bone remodelling activity. Bone lesions are areas with increased bone remodelling activity, therefore tracer uptake is increased in these regions, allowing sensitive imaging of metastatic bone involvement [5]. However, the standard visual Solway method to assess the EOBD relies solely on the number of bone lesions (EOBD 1–3) visible in a scan and metastatic 'superscan' (EOBD 4) classifies them in an ordinal scale from 1 to 4 by severity [6]. EOBD of 4 classifies as a 'superscan', the name given to bone scans that have excessive skeletal uptake, to the point where lesions are undistinguishable from each other and soft tissue activity is very faint [7]. The treatment options at these stages aim to increase overall survival and quality of life. One option, radium-223-dichloride, is a radionuclide targeted treatment used on patients with bone metastases but without visceral involvement. Radium-223-dichloride mimics calcium fixation and is therefore taken up preferentially by bone lesions. It emits alpha particles, which have a high linear energy transfer and a short range ($< 100\,\mu m$), resulting in a high capacity for killing tumour cells [8]. Despite showing improvements in overall survival and quality of life in patients with skeletal involvement of prostate cancer, there is no direct quantitative measure of treatment response. Clinically, radium-223-dichloride prognostic biomarkers such as alkaline phosphatase (ALP) and prostate-specific antigen (PSA) are routinely monitored [9]. Nonetheless, a more accurate prediction of therapy response may help in choosing the most appropriate course of treatment [4]. ALP is considered a suitable biomarker against which to assess effectiveness of treatment [10–12]. ALP's serum levels increase with osteoblatosis, being

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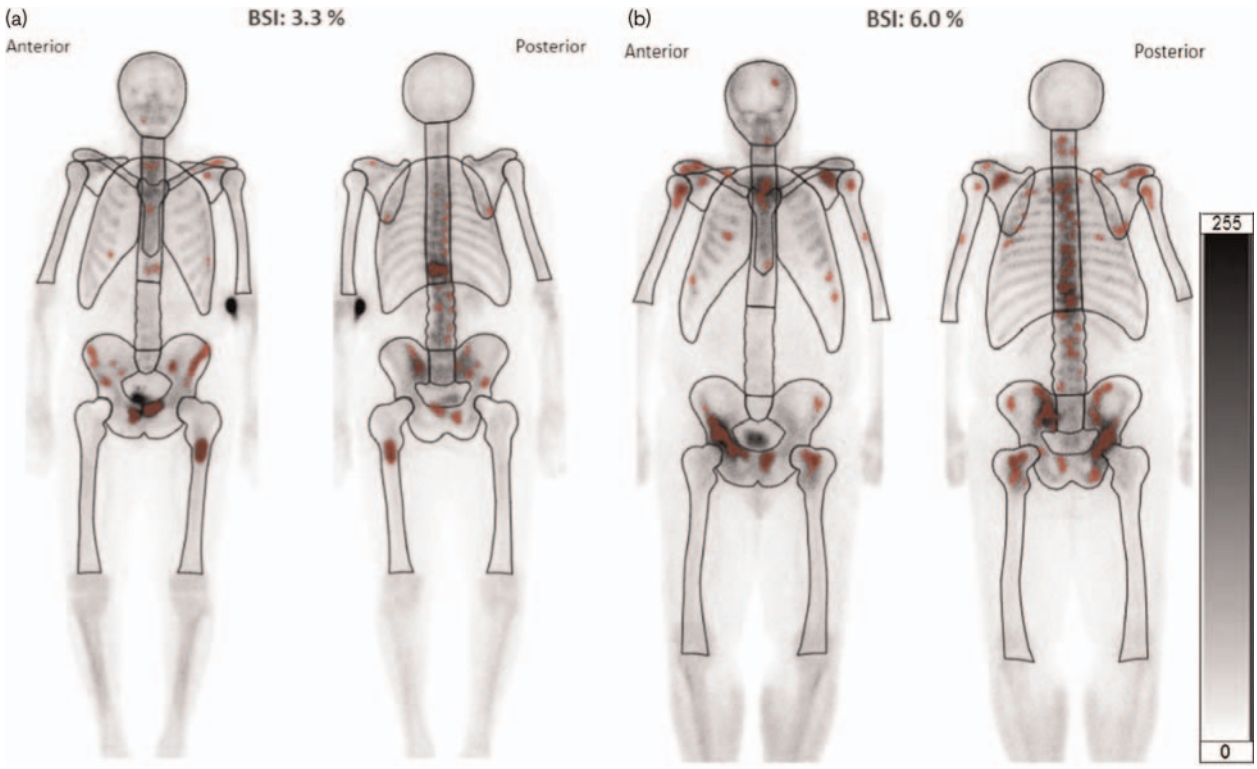
a reliable way to monitor bone metastases. Despite the usefulness of this biomarker, it is nonspecific to bone as there are ALP isoenzimes produced elsewhere in the body, such as liver and intestines. Therefore it must be taken into account that serum ALP levels might increase with heart failure, hepatobiliary disease and blood dyscrasias [13].

Bone scan index (BSI) is a measure of the percentage of total skeletal mass affected by metastases [14]. The option of calculating BSI manually has been available for several years, but it is a time-consuming technique that has not been widely adopted clinically [15]. Alternatively, there is now a software package, aBSI version 3.2.0 (EXINI Diagnostics AB, Lund, Sweden), that generates a BSI score with minimal user input, providing a more useful, objective and reproducible imaging biomarker [14,16]. This programme is based on an automated neural network, a powerful machine learning technique that mimics the way biological brains process information. They have the ability to learn from experience, meaning they can gather knowledge analysing patterns and relationships in data and adjust itself to increase the accuracy of its predictions [17]. This automated neural network follows certain steps to generate a BSI score. It starts by segmenting the skeleton into 12 anatomical regions (Fig. 1), and then thresholding what it will consider to be a hot spot and normalising healthy bone. The programme then quantifies individually the bone involvement of all eventual hot spots. After being quantified, the automated neural network classifies the hot spots in regards to features such as size, shape, intensity and distribution so that the programme can estimate the probability of metastatic lesions in those hot spots [18]. Detected hot spots can be manually selected or deselected to be counted as metastatic lesions or not (Fig. 1). The selected hot spots are used to calculate the BSI as a percentage score, being the sum of those hot spots. Figure 2 shows examples of this interface (in which example A) shows rib uptake of traumatic nature that has been deselected. Research shows that BSI can be useful for predicting survival and response to treatment, as well as correlating with various bone metabolic markers [14,16,19,20].

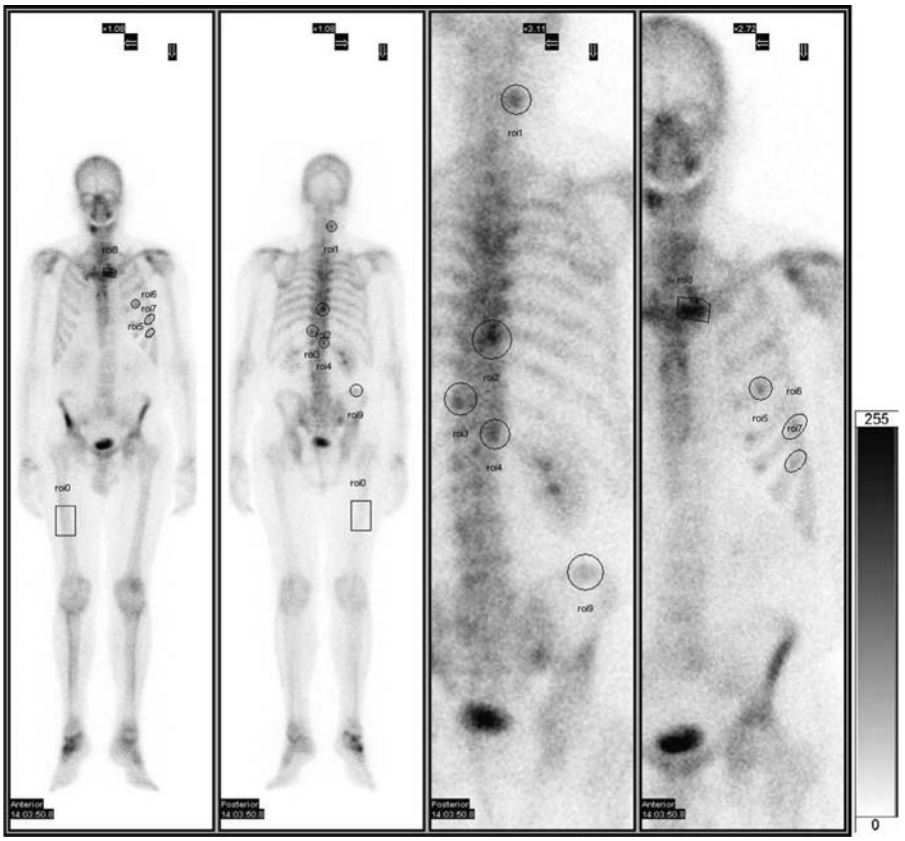
This work aims to assess whether the biochemical response of radium-223-dichloride treatment can be predicted based on information contained in a pretherapy bone scan. Specifically, testing if BSI scoring or maximum lesion intensity are predictors of biochemical treatment response.

Fig. 1



Examples of EXINI's aBSI processing display, with patient (a) showing less disease involvement than patient (b). Lines separating the bone scan into different areas are generated automatically by the programme, and hot spots are detected and used to calculate a percentage value reflecting bone disease involvement. BSI, bone scan index.

Fig. 2



Example of processing work done to retrieve maximum intensity data.

Patients and methods

Sample collection

In this pilot study, following a descriptive correlational design in a retrospective analysis, all eligible patients referred to our AQ7 centre for radium-223-dichloride (Xofigo) therapy for metastatic prostate cancer ($n = 20$) performed a bone scan before proceeding with the therapy. The therapy followed National Institute for Health and Care Excellence recommendations, which are a 55 kBq/kg dose once per month, for the duration of 6 months [21]. Chest abdominal pelvis computed tomography scan confirmed that there was no evidence of visceral disease in any of the patients. In this sample with an EOBD score of 1 there were five patients, with an EOBD score of AQ8 2 there were nine patients, with and EOBD score of 3 there were four patients, and with an EOBD score of 4 there were two patients. All scans were performed in NHS Trust Hospitals in Sussex, and were acquired according to EANM/BNMS guidelines. All patients gave written informed consent for their diagnostic and therapeutic management and follow-up.

Quantification of maximum lesion intensity

Bone scans were processed on a Xeleris processing workstation where maximum intensity, excluding bladder, was assessed manually for each patient as seen in Fig. 2. Normal bone uptake was considered as the maximum counts in a region of interest (Fig. 2) in the right central femur, as an average of anterior and posterior projections. Maximum lesion intensity was not taken as an average of anterior and posterior projections because of tissue attenuation and bone overlapping that can happen in regions of bone metastasis. This implies the highest recorded value would be the least affected by attenuation. The number used as maximum lesion intensity was the ratio between maximum lesion counts and maximum counts in the region of healthy bone. For patients with metastatic disease in the femur using mid-femur as healthy bone would be inappropriate. In a patient we found in this situation, a distal part of the femur and part of the knee was used as a standard for healthy bone.

Bone scan index data

The BSI values were calculated using EXINI aBSI v.3.2.0 software, a tool developed in Lund, Sweden based on an artificial neural network. The manual supervision of the automatically generated hot spots was performed by a senior nuclear medicine technologist.

Alkaline phosphatase data

For the purposes of this study, maximum ALP response (%) was calculated as the lowest measured ALP value for each patient during the course of therapy as a percentage of the baseline ALP value, taken before therapy began [12]. All values are based on total serum ALP.

Statistical analysis

Quantification of bone metastatic involvement with BSI and maximum lesion intensity was assessed and compared to EOBD score and ALP values. Linear regression analysis was used to calculate the coefficient of determination (R^2) between variables. Maximum ALP response and lesion number were independent variables, and BSI score together with maximum lesion intensity were dependent variables. When EOBD was one of the variables, a box plot was used since it is a discrete variable. Microsoft Excel 2016 was used in all operations.

Results

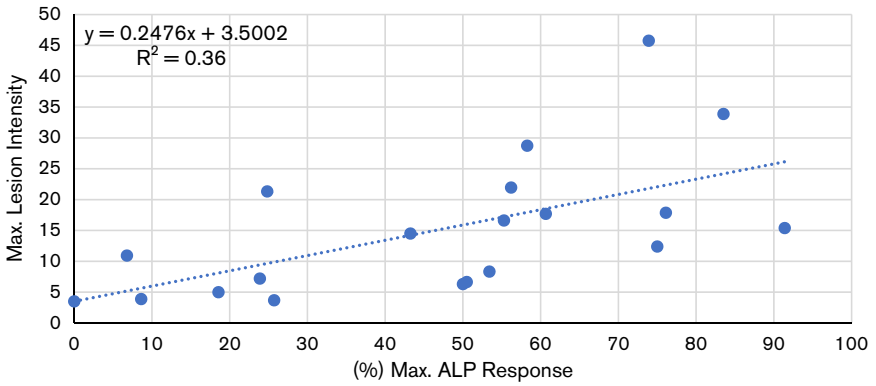
Retrieved and analysed data

Out of the 20 selected patients included in this study, only two patients have an EOBD score of 4. Lesion number was not possible to be established for patients with EOBD of 4 and for some patients with advanced stages of EOBD score of 3 that were nearly 'superscans' since lesions could not be distinguished from each other. These studies were not excluded.

The strongest linear relations found were between baseline ALP and BSI score, and between lesion number and BSI score (excluding 'superscans') and other scans were lesions could not be distinguished accurately, confirming an expected result. The maximum ALP responses were plotted against maximum lesion intensity (Fig. 3) and against BSI scores (Fig. 4).

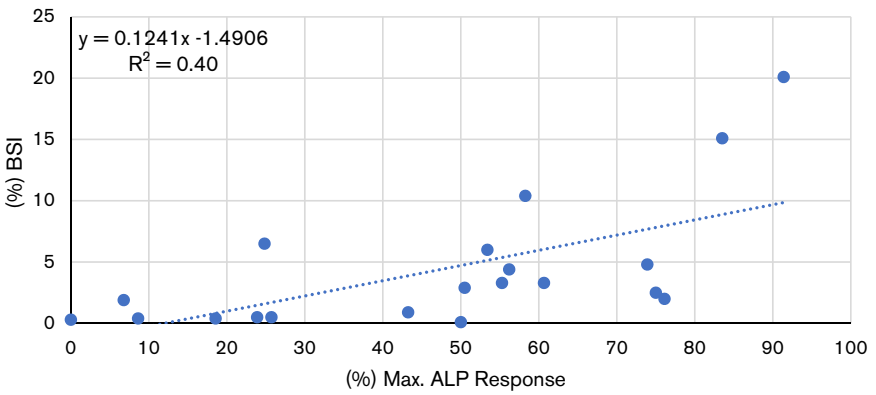
The R^2 values were 0.36 and 0.40, respectively. These both show a positive, although weak, linear relationship. However, both plots showed a very different density of data points from

Fig. 3



Maximum alkaline phosphatase (ALP) (%) response plotted against maximum lesion intensity.

Fig. 4



Maximum alkaline phosphatase (ALP) (%) response plotted against bone scan index (BSI).

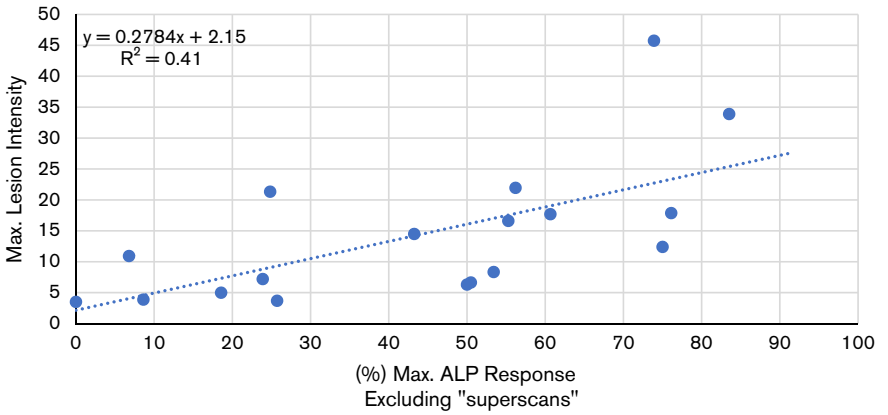
higher to lesser disease involvement. Maximum ALP response with maximum lesion intensity were plotted without including the 'superscan' data as there were too few of these scans to provide an adequate sample. Plotting the data without 'superscans' results in the correlation increasing to $R^2 = 0.41$ by excluding two studies from the initial 20 (Fig. 5).

In comparing maximum ALP response and BSI scores, the sample was also deemed inadequate for BSIs above five because of the small number of data points and how they appeared to behave differently from the rest of the distribution, so they were excluded from the data plot. Excluding these five studied from the initial 20 and therefore using 15 data points, this data improved the correlation ($R^2 = 0.46$), as seen in Fig. 6. In the plots where the inadequate datasets were removed the linearity improved, indicating a better linearity between patients in earlier stages of disease. Maximum ALP response seems to have a positive trend with maximum lesion intensity and BSI, but patients with more extensive bone disease involvement ('superscans' and BSI > 5) seemed to deviate more from the dataset. Nevertheless, with or without including patients with more extensive bone disease, maximum ALP response has a more linear correlation with BSI score than with maximum lesion intensity. Baseline ALP was found to have a stronger positive correlation to BSI ($R^2 = 0.71$), which is the highest in these findings (Fig. 7).

The number of lesions seen on a bone scan does have a moderate linear relationship with BSI (Fig. 8), to a smaller extent than baseline ALP ($R^2 = 0.60$). This analysis also excludes 'superscans', given these patients have a metastatic burden so high as to make counting individual lesions inappropriate. In all, the linear regressions that do not include patients with more advanced stages of disease show higher linear correlation.

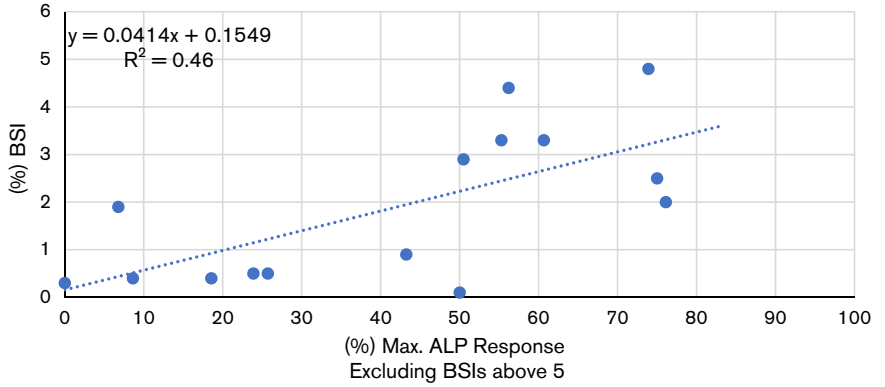
EOBD, being a discrete variable, is shown in a box plot against maximum ALP response and baseline ALP, shown in Figs 9 and 10. In both box plots it can be seen

Fig. 5



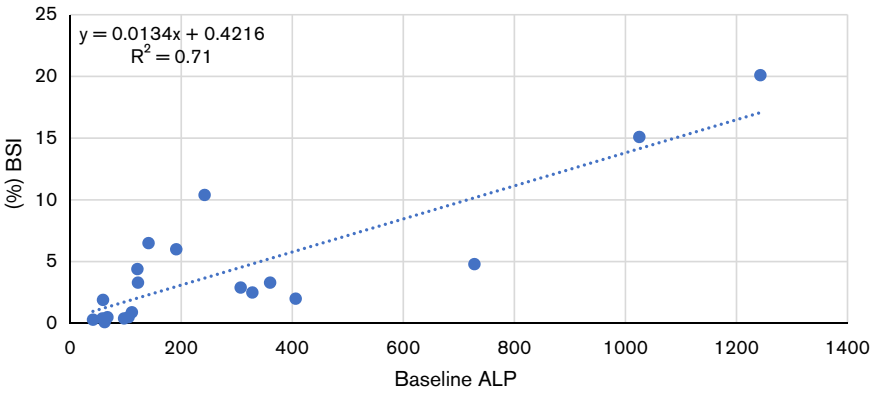
Maximum alkaline phosphatase (ALP) (%) response plotted against maximum lesion intensity, excluding data points that are classified as 'superscans'.

Fig. 6



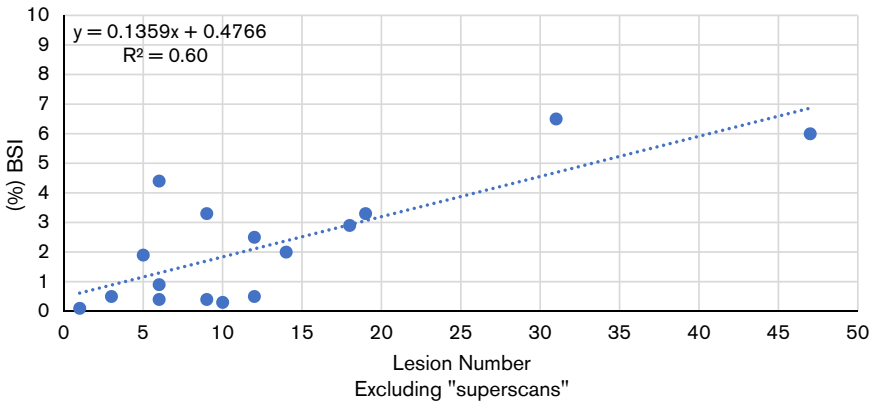
Bone scan index (BSI) plotted against (%) maximum alkaline phosphatase (ALP) response, excluding data points above 5 BSI.

Fig. 7



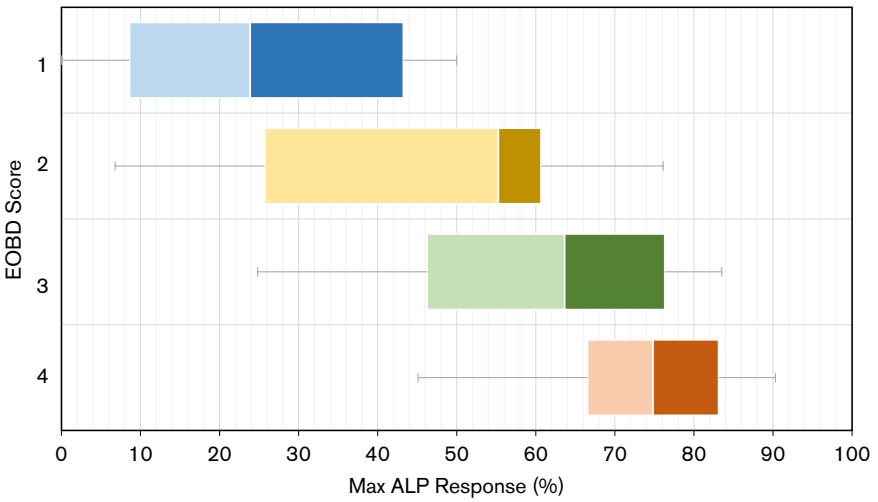
Bone scan index (BSI) plotted against baseline alkaline phosphatase (ALP).

Fig. 8



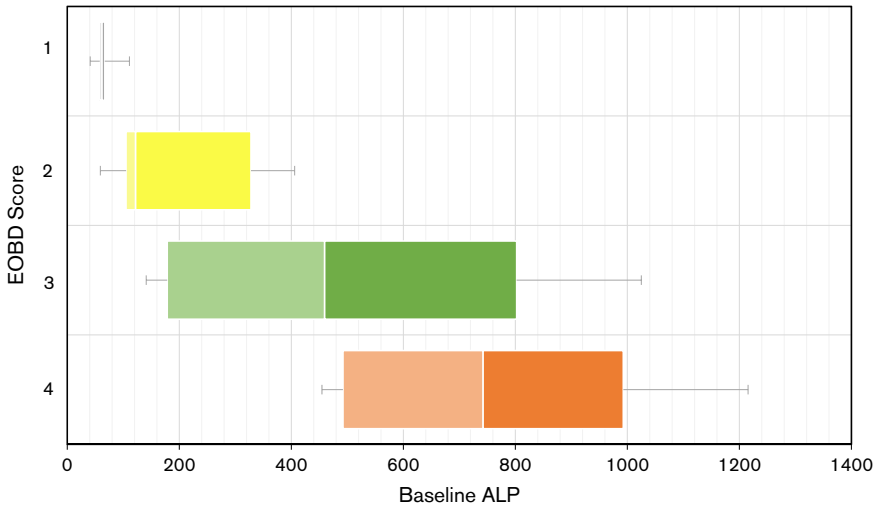
Bone scan index (BSI) plotted against lesion number.

Fig. 9



Box plot of extent of bone disease (EOBD) score and maximum alkaline phosphatase (ALP) (%) response.

Fig. 10



Box plot of extent of bone disease (EOBD) score and baseline alkaline phosphatase (ALP).

Table 1 Bone scan index range and alkaline phosphatase response range for each extent of bone disease score

EOBD	Minimum BSI	Maximum BSI	BSI range	ALP response range (%)
1	0.1	0.9	0.8	6.76
2	0.4	4.4	4	37.64
3	4.8	15.1	10.3	9.61
4	10.4	20.1	9.7	80.99

ALP, alkaline phosphatase; BSI, bone scan index; EOBD, extent of bone disease.

that as EOBD increases, baseline ALP and ALP response tend to increase as well, indicating a positive correlation. In both plots, the median increases with the EOBD score. Maximum ALP response for EOBD 1 is 33.56, 55.28 for EOBD 2, 63.65 for EOBD 3 and 74.82 for EOBD 4. In baseline ALP it is 62.0, 122.0, 459.5 and 742.5 for the same scores. In baseline ALP the interquartile range increases as EOBD score increases, indicating that the baseline ALP range for each score becomes larger with higher EOBD. In both plots, there also seems to be inconsistent skewness, which is likely due to the small dataset.

Analysis of BSI range for each EOBD score was performed to compare the respective methodologies in Table 1.

In this study, EOBD 1 had a BSI range of 0.8, EOBD 2 had a BSI range of 4, EOBD 3 had a BSI range of 10.3, and EOBD 4 had a BSI range of 9.7. The range tends to increase along with the EOBD score, except for EOBD 4. However, the range was calculated with the only two patients that had EOBD of 4 included in this study. ALP response range, in these results, does not seem to trend in any noticeable way with EOBD.

Discussion

A study by Kaboteh *et al.* [22] indicates that BSI can complement PSA to stratify high-risk prostate cancer patients. In this work, it can be seen that each EOBD score covered a wide range of BSI values, with significant overlap between the groups. This illustrates the limitations of EOBD scoring, as it reduces metastatic burden down to the simple discrete variable of lesion number. BSI also showed a positive moderate correlation to lesion number ($R^2 = 0.60$). Although, EOBD is based on lesion number, this supports the idea that BSI might be used as an alternative or in conjunction with EOBD for patient management and stratification at the time of diagnosis [22].

Wakabayashi *et al.* [14] found BSI to have a close relationship to all bone metabolic markers except PSA, and Dizdarevic *et al.* [11,12] found that maximum ALP response is a likely independent biochemical predictor of outcome in clinical practice, specifically survival. These results lend credence to the decision to use ALP in this study as a measure of treatment response. The focus of this study was to assess whether BSI has a place in predicting biochemical response to radium-223-dichloride therapy. The results from the small number of patients used in this pilot study show moderate positive correlation. This is corroborated by previous work that related BSI to treatment response and bone metabolic markers [14]. However, further research with larger study population would be required to confirm this correlation, in particular for patients with higher disease involvement. Few patients with high BSI scores are included in this work, and they may not behave in a linear fashion with lower BSI scores [14,23]. Therefore, more data points in those ranges would be needed to draw conclusions.

Previous work by Mitsui *et al.* [19] and Uemura *et al.* [24] found that BSI can be used as a predictor of chemotherapy response in metastatic prostate cancer. Other work shows BSI to be a strong prognostic survival indicator in prostate cancer patients [20,25]. In relevance to this study, BSI also was found to be a significant prognostic factor for overall survival for patients treated with radium-223-dichloride [23]. Biochemical response, the focus of this study, has previously been shown to be a predictor of overall survival [12,26]. BSI showed a strong correlation with baseline ALP ($R^2 = 0.71$) which has also been found to be a prognostic marker for overall survival as well [26,27]. This coincides with previous work that presents BSI as a useful imaging biomarker.

Maximum lesion intensity was the least accurate predictor of biochemical response measured ($R^2 = 0.36$ and 0.41) and might not be very useful on its own, especially since other parameters are more easily measured such as EOBD or BSI. Nevertheless, the small number of patients with advanced stages of disease included in this study means the conclusions that can be draw for that group are very limited. This small number might explain the inconsistent BSI range for EOBD score of 4 when compared to other EOBD scores. Another possible explanation is that some step of the BSI programme is not well optimised for 'superscans', and might lead to inconsistent results for patients in a more advanced state of the disease. However, the small number of patients with this EOBD score in this study means these results may not be reliable.

Sartor *et al.* [26] found that ALP decline correlated with overall survival and are useful to monitor, but do not serve as surrogates for survival. More recently, Dizdarevic *et al.* [12] has also found ALP response to be a good predictor of overall survival but nevertheless, the relationship between overall survival and BSI score cannot be directly inferred and should be investigated in further work.

However, BSI has with it all the limitations of a bone scan. It is very sensitive to a wide range of bone events, leading to possible false positives [16]. Given that whole-body scans are planar studies and therefore two-dimensional, it also has the possibility of overlaying anatomy making image interpretation harder [28].

The maximum intensity values may have been influenced by the partial volume effect. A lesion, if smaller than pixel size, will be averaged out over surrounding tissue. Patients in a more advanced stage of disease tend to show larger lesions, and are therefore less likely to be influenced by this effect. Mid-femur was the region of choice for background uptake, but given the unpredictable distribution of bone metastases, no single anatomical region is expected to be adequate for all patients. However, since prostate cancer tends not to metastasise to the limbs they are a better option as compared to the axial skeleton, although it misrepresents tissue attenuation that would occur for lesions in the axial skeleton. However, a patient could have a certain metastatic distribution that makes evaluating maximum intensity not feasible in this context. It also needs to be reiterated that the small number of patients involved in this study means that there can be no solid conclusion, particularly regarding the usefulness of automated BSI in advanced metastatic bone disease. Finally, the maximum count rate from each lesion is influenced by the specific attenuation between lesion and detector, which is not accounted for in this work.

Conclusion

Comparison of EOBD and BSI results confirms the hypothesis that BSI is a valuable asset in metastatic bone disease stratification. As a predictor of biochemical treatment response, BSI shows low positive correlation to ALP treatment response that could prove useful in the future. A stronger correlation to BSI was found to baseline ALP. Nonetheless, further research using a larger sample size is required, particularly for patients with more advanced disease, which in this study was inadequate to draw conclusions from. AQ9

Acknowledgements

Conflicts of interest

M. Jessop has performed occasional consultancy for Bayer. For the remaining authors there are no conflicts of interest.

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