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Current progress and future trends in imaging of musculoskeletal bone tumours

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ABSTRACT

Plain radiographs and MRI remains the gold standard imaging modality for bone tumour and tumour like lesions. Several imaging techniques have been developed to be used in conjunction, but doubt remains over how much additional diagnostic information they provide over and above routine MRI bone tumour sequences. Given the plethora of new modalities, this review aims to highlight some of them and how they may help in the diagnostic assessment of musculoskeletal bone tumours.

1. Introduction

While the traditional approach to radiological diagnosis of bone tumours has been focussed towards plain radiographs and magnetic resonance imaging (MRI), multi-planar and functional imaging has emerged as useful adjuncts. While certain techniques and sequences within MRI have certainly helped improve radiological diagnosis, the emergence of FDG-PET CT and PET MRI has certainly revolutionised the field by providing anatomical and morphological characteristics with a combined whole body scan in one sitting. This review aims to highlight the current state of play of most imaging techniques used for radiological diagnosis of bone tumours, with a focus on newer and emerging technologies and sequences.

2. MRI spectroscopy

While standard MRI sequences play a role in characterising bone tumours, it lacks specificity in differentiating some benign and malignant conditions. MR spectroscopy (MRS) is a form of metabolic imaging for molecular identification of malignant tumours using certain markers. The technique can be used to detect elevated levels of choline compounds, a marker of high cell membrane turnover commonly seen in malignant bony tumours.[1] The metabolic footprint of a lesion is based on the ratio of water, lipids and various metabolite contents with a high spectroscopic choline peak suggestive of malignancy.[2] A pooled analysis of MRS studies of de novo musculoskeletal lesions shows a strong association ($p < 0.0001$) between the presence of a choline peak and malignancy, with an overall sensitivity of 88% and a specificity of 68%.[3] The corresponding positive (PPV) and negative (NPV) predictive values for malignancy in the presence of a discrete choline peak are 73% and 86%.

Given the latter, the current consensus is that MRS maybe a useful tool for differentiating benign from malignant bony lesions, however some lesions are prone to giving spurious results. Low grade malignant tumours, giant cell tumours (GCT) and acute inflammatory lesions with prominent oedema can give rise to false negative and false positive results respectively. Moreover, intra osseous osteomyelitis can also lead to a high choline peak, which unfortunately is a common mimic of aggressive bone tumours usually referred for a specialist opinion. It is unclear why a choline peak is routinely seen with GCT's; possible reasons include that most lesions included in studies are hypercellular with relatively aggressive appearing on plain radiographs.[1] GCT's with an extra osseous component in particular have a strong association with a high choline peak too, with similar ratios compared to a malignant bony lesion.[1,2]

Many variables also have to be considered which can alter

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choline signal intensity. These include different coils types, magnetic field strength and size of the lesion among others.[3] Moreover, it is unclear if systemic disease can alter the normal background metabolite concentrations, yielding inaccurate proportions on MRS. The choline peaks are always given as metabolite ratios which maybe of limited use opposed to a definitive stand alone value if obtained biochemically. Voxel selection also plays a crucial role as in other parts of the body. Voxels should not be placed over necrotic or cystic areas and if contrast has been given, it should be placed over the area showing maximum enhancement. Given all the aforementioned reasons, MRS currently has no well defined role in diagnosing a bony lesion and is mainly used as an adjunct tool.

3. Diffusion weighted imaging

Diffusion weighted imaging (DWI) is a non contrast MRI technique relying on the brownian motion of water molecules within tissues and bone. The apparent diffusion coefficient (ADC) value of a lesion is a quantitative measure of brownian motion. In highly cellular lesions eg a malignant bony lesion the movement of water molecules is restricted giving rise to low ADC values. In hypocellular bony lesions, water can freely diffuse in all directions resulting in high ADC values. Areas of low ADC values will have higher signal on DWI sequences and lower signal on ADC maps. It is also important to note the phenomenon of T2 shine through, whereby high signal on DWI images corresponds to high signal on the ADC map, not due to diffusion restriction but to bright T2 signal which 'shines through,' the DWI image (Fig. 1).

The exact ADC value is calculated by calculating the change in signal of a lesion over varying diffusion gradient strengths, so called B values. The role of DWI has now been well established in the evaluation of soft tissue sarcoma, particularly regarding assessing response post chemotherapy and radiotherapy.[4]

There is relative paucity of studies looking primarily into DWI/ADC values of primary bony lesions. In most tumour centres, if the lesion appears aggressive or even indeterminate on standard MRI sequences it most often biopsied anyway, questioning the diagnostic value of DWI. In addition, the exact ADC value range for malignant lesions vary with some overlap. Ahlawat et al.[5] stated that the minimum ADC threshold of $0.9 \times 10{-}3$ mm^2/second and $1.4 \times 10{-}3$ mm^2/second (mean ADC) should be used for differentiating benign and malignant histology.

Generally speaking, malignant bone tumours show lower ADC values compared to benign lesions. However, as with MRS, certain types of benign tumours can also show lower values ($<1.0 \times 10^{-3}$ mm^2/s), such as non ossifying fibromas and GCT's due to the condensed collagen stroma of the former and high cellularity of the latter.[6] Moreover, myxoid and chondroid matrix tumours can give abberant ADC values, with Douis et al.[7] showing that ADC did not significantly differ between low and high grade chondrosarcomas. Therefore, DWI should not be used as a stand-alone tool for radiological diagnosis of a benign versus malignant lesion. Literature also shows that ADC values can be used to differentiate benign osteoporotic from malignant vertebral body

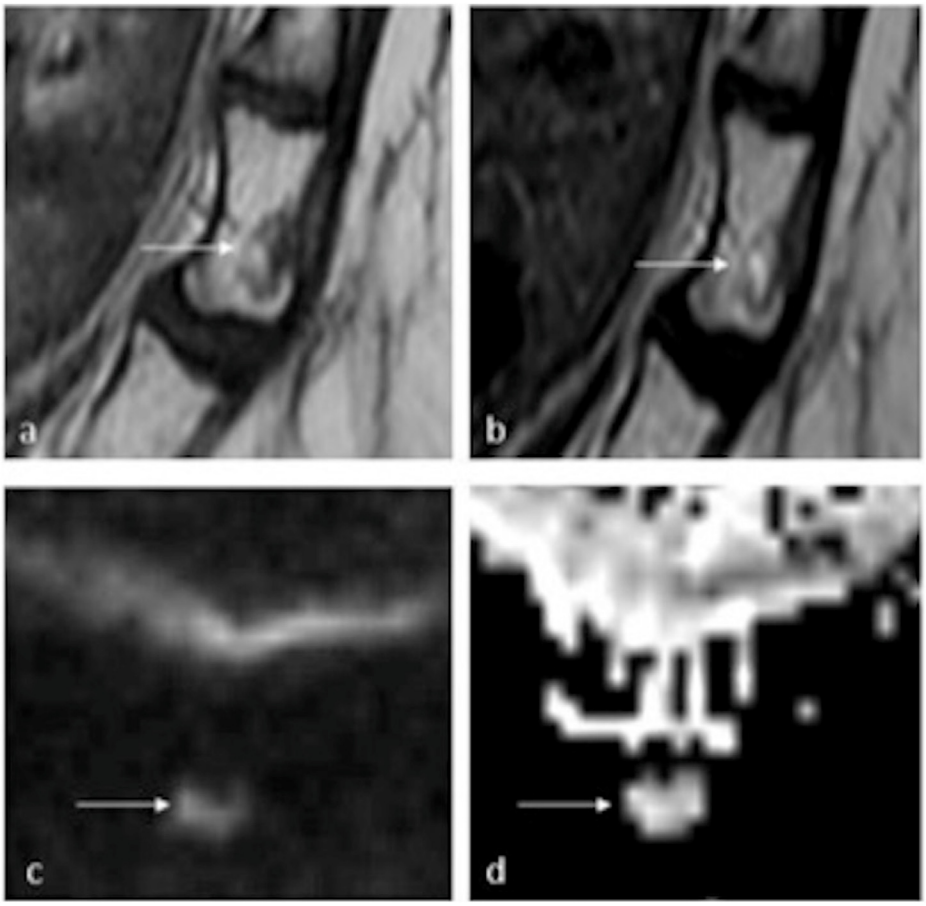

Fig. 1. Intermediate T1 (a) and heterogenous high T2 (b) weighted signal intensity lesion within the first coccygeal segment. Diffusion weighted B600 images (c) shows increased signal with corresponding high signal on the ADC (map) indicating T2 shine through with no diffusion restriction, implying a benign lesion. The appearances are in keeping with a benign notochordal cell tumour.

fractures, with the former showing higher ADC values. A threshold mean ADC of $<1.4 \times 10^{-3}$ mm^2/s has been quoted as a figure to suspect a malignant fracture.[8]

Studies analysing the ADC value to quantify response of bone tumours to chemo-radiotherapy are rare. Wang et al.[9] has shown that chemotherapy response can be predicated and evaluated by DWI/ADC values early on in the disease course, correlating well with the degree of necrosis. This is helpful as both tumoural tissue and necrosis tend to be hyperintense on T2-weighted imaging. In general, satisfactory treatment response is implied with both minimum and maximum ADC values increasing during follow up. This has been shown to be more representative of characterising a response compared to tumour volume and size on standard MRI sequences.

4. Perfusion imaging by dynamic contrast injection

Dynamic contrast-enhanced MRI (DCE-MRI) measures the perfusion properties of tissues before, during and after intravenous injection of a gadolinium contrast agent. Regarding bony lesions it is mainly used to identify areas of enhancement suitable for biopsying, monitoring chemotherapy response and staging. A region of interest (ROI) is chosen and analysed for roughly 5 min post injection. Time intensity curves are made indicating the time from bolus arrival to tumour enhancement, maximum enhancement and an enhancement slope with 5 classical curve types are produced.[9] (Fig. 2). A type 4 curve of rapid early enhancement with a washout phase is suggestive of malignant tumours. A type 2 curve of faint and gradual enhancement is rather classical for benign tumours. Other DCE parameters are using including K^{trans} and k_{ep}, the former being a transfer coefficient, measuring the amount of capillary permeability while k_{ep} represents the wash-out rate of exponential of enhancement signal within the tissue.

Generally, malignant lesions show more enhancement and higher rate of enhancement. However, there is abundant literature commenting on the significant overlap between malignant and various benign entities.[10,11] Most studies conclude that as the overlap is so large the technique is of little value. The only exception is of a slowly enhancing soft tissue mass, where malignancy can almost be definitely excluded.

DCE-MRI has also been shown to provide some value in monitoring neoadjuvant chemotherapy response in osteosarcoma patients. It is accurate in estimating residual viable and tumour necrosis in osteosarcoma patients being treated with chemotherapy before and after surgery.[12] Another study has also shown how plasma volume and vascular permeability decreased after radiation therapy in chordomas, highlighting its usefulness in monitoring response to radiation therapy.[13] Moreover, chordomas of the spine have a characteristic signal intensity time curve different to GCT's, one of the most common spine tumours. In particular, the DCE-MRI pharmacokinetic parameters K^{trans} and k_{ep} of GCTs were significantly higher than those of chordomas.[14] Moreover, most malignant tumours exhibit rapid enhancement with washout, whereas chordomas present with 'persistently,' enhancing time signal-intensity curves allowing differentiation with other aggressive spine tumours. However, this persistent pattern is also seen in chondrosarcoma and the heterogeneity of chordomas can alter the curve patterns.[13]

Recently, a combined parameter using DWI and DCE was analysed,[14] based on a earlier study where lower ADC values corresponded to increased K^{trans} in the pretreatment of breast cancer.[15] Oh et al.[14] showed that K^{trans},$k_{ep,}$ ADC and K^{trans}/ADC could help to detect malignant lesions from bone tumours with the latter proving to be the most superior variable for characterisation.

5. Chemical shift imaging

The Dixon technique is a fat suppression technique based on chemical shift imaging (CSI). Molecules of fat and water experience different magnetic effects leading to a reduced processional frequency of fat compared to water protons. CSI uses these differences to produce in-phase (IP) and out-of-phase (OOP) images. A minimum 20% drop on the OOP images implies the presence of microscopic fat, favouring a benign pathology (Fig. 3).[16] This technique has revolutionised marrow interpretation on MRI and has now become a standard technique within the bone tumour protocol in most specialist centres. It should be noted however, that a <20% drop on the OOP sequences could be due to overt sclerosis or a fracture and so a complementary CT study maybe necessary to account for the aforementioned finding.[17]

Recently, the T2w dixon sequence was found to be equivalent to standard T2 sequences in the lumbar spine for assessing degenerative disc disease, whilst taking significantly less time.[18] The study suggested that a sagittal T1, sagittal T2 and STIR sequence could all be replaced with a single T2 dixon sequence with comparable results on the in phase, opposed phase, water only and fat only images. Along these lines, another study found that the T2w dixon fat only images provided significantly more contrast than the standard T1w sagittal image for detecting multiple myeloma spinal lesions.[19] Nevertheless, Heynen et al.[20] showed that T2w dixon sequences are less sensitive than standard T1w sequences in detecting hip and pelvic occult fractures. The T1w sequence still remains as the current gold standard sequence in identifying areas of marrow infiltration, showing lower signal compared to the surrounding skeletal muscle.[20]

Chemical shift imaging also provides a useful means for identifying areas of focal nodular marrow hyperplasia (FNMH) which can mimic a bone tumour/metastases.[20] This is especially useful in the setting of known primary malignancy where the patient presents with an 'indeterminate,' lesion. The traditional approach has been to either follow up these lesions or to biopsy, carrying an unnecessary risk. With the advent of CSI, the dixon sequence can be used to triage such lesions and avoid long follow up. FNMH tends to exhibit iso-hyperintense T1 signal compared to surrounding skeletal muscle, with at least 20% signal drop on OOP sequences.[20]

6. FDG-PET CT

FDG-PET CT's role in diagnosing bone tumours has not yet been clearly defined. It however plays a more crucial in patients with no obvious primary source of malignancy upon initial staging, but have a suspected metastatic deposit (Fig. 4). It has a quoted sensitivity between 60 and 70% and specifity of around 60% for primary cancer identification.[21] Being normally the most frequent primary site, lung cancer has been detected with a high 80% sensitivity on FDG-PET CT. It should be noted that PET CT can also identify benign bone lesions which tend to be non avid, compared to malignant lesions which tend to have a SUV max>5.0.[21] However, other studies have commented that certain benign bony lesions such as histiocytic and giant-cell containing lesions can accumulate high amounts of FDG.[22]

The concept of higher SUV uptake for more malignant lesions also holds true for tumours of the same histological type, such as cartilaginous tumours. It has been shown that FDG uptake in high grade and dedifferentiated chondrosarcoma is greater than enchondromas and atypical cartilaginous lesions.[23]

As eluded to earlier however, there is significant overlap between the SUV values of malignant lesions and benign locally aggressive lesions. Schulte et al.[23] found that hypercellular lesions such as GCT, LCH, chondroblastoma and osteoblastoma commonly

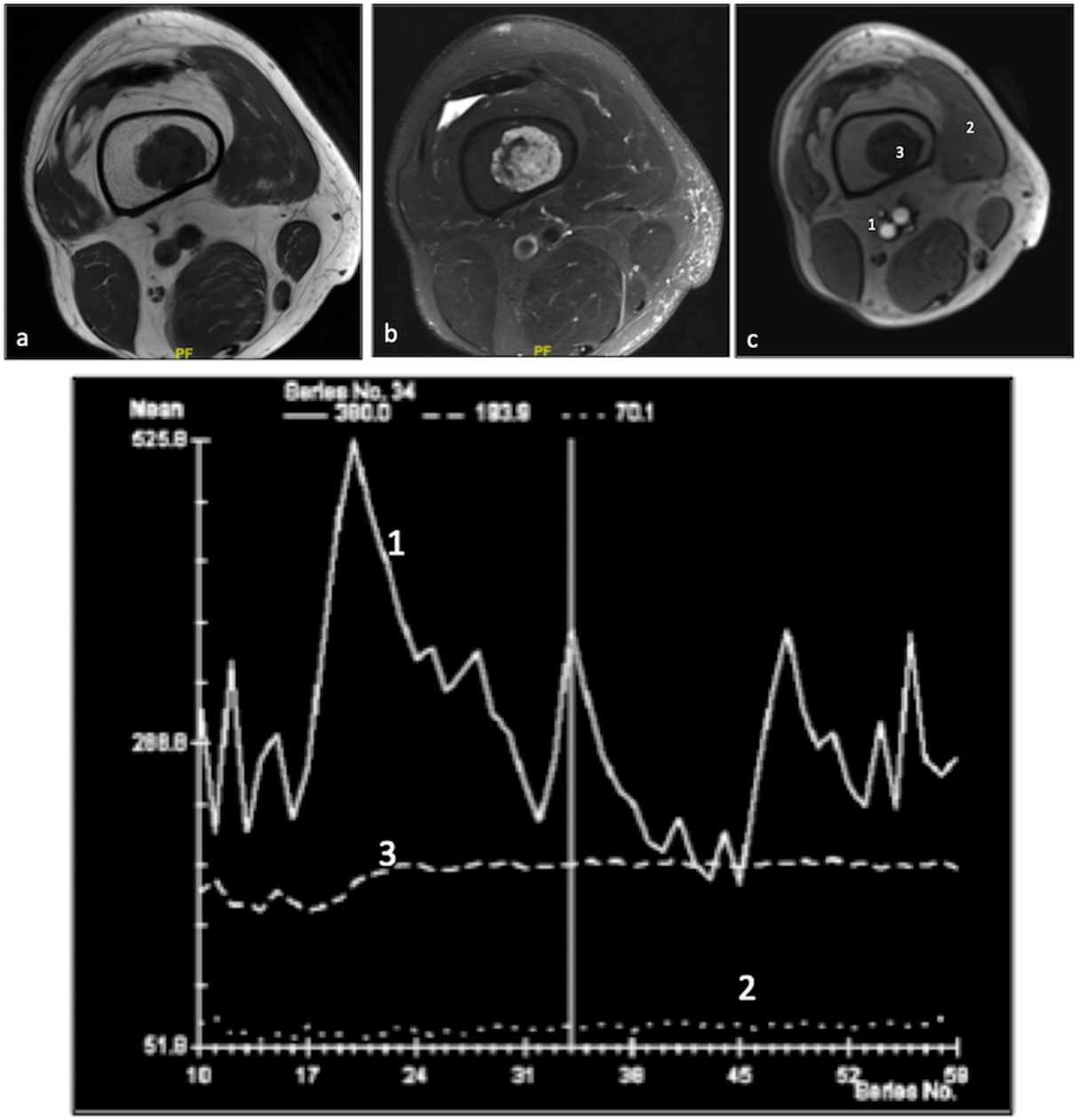

Fig. 2. 45 year old female with right knee pain. MRI axial T1 (a),T2FS (fat suppressed (b) and T1VIBE post contrast(c) with dynamic contrast enhanced imaging showing different enhancement curves for 1- artery, 2- muscle, 3- cartilage tumour.

have intense uptake. Moreover, individual tumour types can also vary with studies showing that a certain percentage of a cohort of a benign lesion (eg ABC, NOF) can be intensely avid.[23] Given the significant overlap and inconsistencies in SUV uptake, the morphological features on primary bone CT along with MRI are usually needed to come up with a final diagnosis.

The role of FDG-PET CT has shown promising results regarding follow up studies post treatment specifically related to osteosarcoma and ewing sarcoma.[24–26] Changes in FDG avidity along with morphological features are shown to be reliable in indicating the effectiveness/response of a treatment regime. Several studies have shown direct correlation of FDG avidity pre regime, post regime, between both studies with clinical outcomes in both osteosarcom and ewing sarcma patients.[24–26] Therefore rather than having a role in diagnosis, FDG-PET CT seems to have a defined role in whole body staging. It has found to identify more metastases in the skull and distant extremity lesions compared to normal CT staging studies.[27]

7. PET -MRI

PET-MRI has only been in routine use for the past ten years with no clearly defined role regarding diagnosis of bone tumours. Two approaches are commonly used. The first is a 'sequential approach,' where a MRI and PET scanner are in the same room, with a rotatable bed allowing for patient transfer. The second 'integrated approach,' has a PET detector ring within the MRI itself, allowing simultaneous MRI and PET image acquisition. The latter combines the very sensitive molecular imaging capabilities of PET with the superior characterisation of soft tissue on MRI.

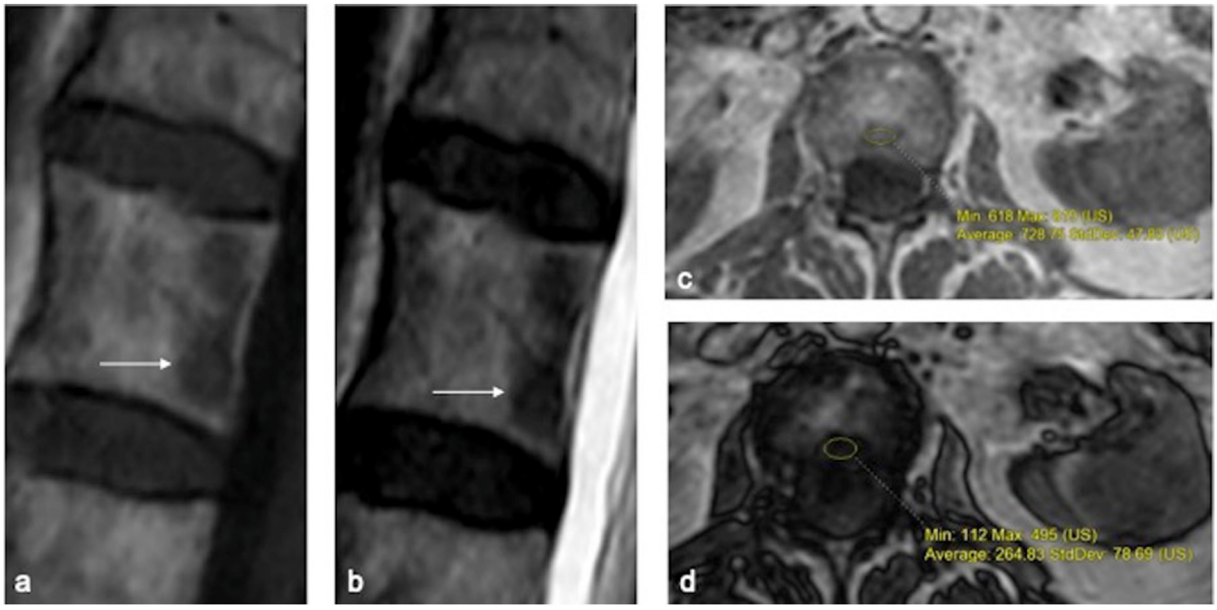

Fig. 3. Slightly isointense T1 (a) and low T2 (b) weighted signal intensity lesion within the posterior aspect of L1 in a patient with known lung cancer. Dixon CSI in-phase (c) and out of phase (d) images shows roughly 64% signal drop out on the out of phase Dixon sequences indicating microscopic fat content. The lesion most likely represents an area of focal marrow red marrow.

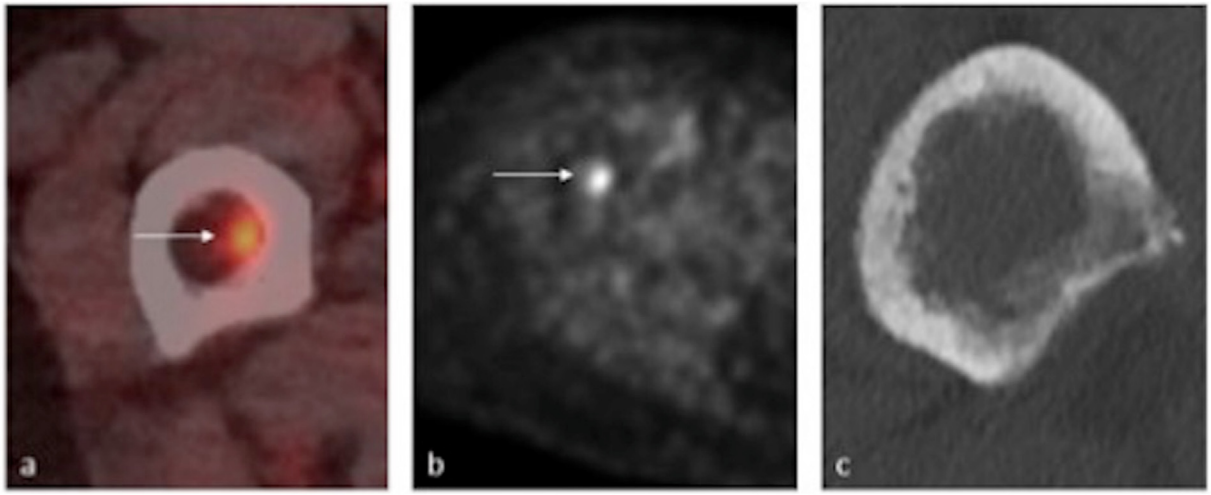

Fig. 4. A 65 year old female with right thigh pain. FDG PET CT fused axial images (a) and MIP images (b) shows avid uptake along the medial aspect of the right proximal femur. The CT component (c) showed an aggressive permeative appearance to the endosteum with expansion of the medullary cavity by a lesion. No further lesion was identified on the rest of the study. CT biopsy confirmed a metastatic deposit, with cervical cancer being the likely primary.

There are only a handful of studies looking at the role of PET MRI within a musculoskeletal oncology setting. Two studies compare PET MRI and PET CT in paedatric lymphoma patients with both reporting no statistical difference in diagnostic performance.[28,29] One study suggested that PET MRI could well be a feasible alternative to PET CT, detecting >95% of active lesions seen on PET CT.[30] As with FDG-PET CT, PET MRI appears to have more of a role in lesion follow up. Mueller et al.[31] stated that combined PET MRI was in fact a superior technique for LCH surveillance compared to MRI alone due a lower number of false positive findings related to post chemotherapy/treatment change. No study as of yet has looked into PET-MRI for whole body staging as part of the initial work up for LCH.

Loft et al.[32] showed how PET MRI was useful in 2 cases compared to MRI alone to display tumour invasion into adjacent bone and nerves, allowing for better visualisation of the surgical margins. The variable signal intensity traditionally associated with PET can be correlated with MRI and areas of suspected ill defined margins could be correlated with SUV values on the PET component. Thus, one can be accurate about the actual local extent of disease, preventing potential over treatment and more aggressive surgery. Prominent peri-lesional oedema has always been a recognised problem when interpreting MRI. Deciding if this is true oedema/inflammation or part of the lesion is not always possible and so PET MRI allows for more precise delineation.

There are however some limitations with PET MRI, namely it would take a significantly longer time for image acquisition compared to FDG-PET CT. The handling of radioactive material and fusion of data sets can also be problematic. Moreover, unlike FDG-PET CT there is no literature commenting on its role in the

surveillance and follow up of both osteosarcoma and ewing sarcoma.

8. Artificial intelligence

Plain radiographs have long been the initial imaging modality utilised to characterise suspected bone tumours. Apart from dedicated subspecialty sarcoma centres however, many radiologists will have difficulties in deciding between a benign or malignant lesion due to unfamiliarity. Artificial intelligence (AI) has been used in instances to aid the radiologist in classifying a lesion as benign or malignant, which should aid clinical care, workflow and referral patterns. Von Shacky et al.[33] had developed AI algorithms which was more accurate than radiology residents (71.2% and 64.9% respectively) and on par with experienced radiologists (83.8% and 82.9% respectively).[33] A multitask deep learning model was implemented by retrospective analysis of radiographs from 934 patients. A similar result of AI algorithms for plain radiograph analysis being more accurate compared to radiology residents was also noted in a study by He et al.[34] Despite the promising results, the main limitations of such studies are that all the data sets had a lesion. Thus, the lack of normal radiograph does not inform on the true specificity/detection rate. In addition, many bone tumour mimics are referred as potential primary bone tumours which are currently excluded from most AI studies.

While several publications describe AI in bone metastasis, only handful comment on its role in characterising primary bone tumours, specifically regarding cross sectional imaging. Regarding the latter, tumour matrix, density and transition zone may represent suitable characteristics that could be classified via deep learning techniques. In fact, one study showed that a neural network was more accurate than experienced musculoskeletal radiologists in bone tumour classification (86% vs 72% respectively).[35] In addition studies also exist analysing pixel intensity from plain radiographs using CADx software.[36] The pixel intensities vary due to differing absorption rates which directly correspond to degrees of bone destruction, cortical involvement among other radiological features and can therefore help differentiate benign and malignant lesions.

The main limitations of AI is that different algorithms can lead to a high degree of interobserver variability and therefore standardisation is mandatory to establish a robust database that can be adopted by multiple centres. For this, data input and quality check needs to be manually input by experts which is expensive and extremely time consuming. This alone has deterred most centres for adopting such algorithms until commercially available applications become readily available.

9. Conclusion

Standard MRI sequences and plain radiographs still remain as the core imaging modalities for bone tumours. Additional sequences such as dwi, spectroscopy and chemical shift imaging serve mainly as complementary roles in diagnosis, but given the significant overlap of features between benign and malignant lesions, biopsy still constitutes the gold standard. Many of the metabolic markers such as choline and FDG are not a true indicator of malignancy and are not tumour specific. Thus they cannot be considered an absolute necessity in the diagnostic work up for bony lesions, with most undergoing image guided biopsy anyway. FDG-PET CT has some use in staging and surveillance for certain bony lesions but not in primary diagnosis. This too is also the case for PET MRI which remains a novel modality mainly for the evaluation of paediatric malignancies. As of yet, all the aforementioned additional sequences and modalities still only play a complementary role in primary characterisation of bone tumours.

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Declaration of competing interest

No conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcot.2021.101622%20.

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