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REVIEW ARTICLE

Multimodal imaging of bone metastases: From preclinical to clinical applications

Stephan Ellmann [a,*], Michael Beck [b], Torsten Kuwert [b], Michael Uder [a], Tobias Bäuerle [a]

[a] *Institute of Radiology, University Medical Centre Erlangen, Erlangen, Germany*
[b] *Institute of Nuclear Medicine, University Medical Centre Erlangen, Erlangen, Germany*

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Summary Metastases to the skeletal system are commonly observed in cancer patients, highly affecting the patients' quality of life. Imaging plays a major role in detection, follow-up, and molecular characterisation of metastatic disease. Thus, imaging techniques have been optimised and combined in a multimodal and multiparametric manner for assessment of complementary aspects in osseous metastases. This review summarises both application of the most relevant imaging techniques for bone metastasis in preclinical models and the clinical setting.

Introduction

Metastases to the skeletal system are observed in up to 70% of all cancer patients [1]. In terms of breast cancer, bony metastases are in almost one third of all patients the only site of presentation at the initial diagnosis of metastatic disease [2]. Whereas overall survival of patients with breast cancer bone-only metastases is $>$ 2 years, it is drastically reduced to approximately half a year in patients with simultaneous liver metastases [3]. Patients with bone metastases of lung cancer exhibit *per se* lower overall survival measured in months [1]. Even though bone metastases are not necessarily a life-threatening component of cancer, their complications highly compromise the patients' quality of life. Complications of osseous metastases are referred to as skeletal-related events (SRE) and include pathologic fractures, spinal cord compression, and hypercalcemia leading to renal failure.

Established localised treatments of bone metastases imply surgery and external beam radiotherapy [4—6], providing pain relief and reducing SRE [5,6]. Besides chemotherapy, systemic treatment approaches include, in particular, bisphosphonates as an integral part of bone metastases management to reduce SRE and bone pain and to improve quality of life [7]. Targeted treatment options

* Corresponding author. Institute of Radiology, University Medical Centre Erlangen, Maximiliansplatz 1, 91054 Erlangen, Germany.
E-mail address: Stephan.Ellmann@uk-erlangen.de (S. Ellmann).

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such as the monoclonal antibody denosumab binding receptor activator of nuclear factor-kappa B ligand inhibitor are increasingly applied. Beside the reduction of SRE and bone pain, the newly introduced [^{223}Ra] dichloride for the treatment of bone metastases in castration-resistant prostate cancer showed a significant improvement in overall survival [8]. Nonetheless, these systemic treatment options have to be considered palliative in most cases [9].

The standard criteria for evaluating the course of a cancer disease are the Response Evaluation Criteria In Solid Tumours (RECIST) in their current version (1.1). These criteria are only partially applicable to bone metastases as merely lytic lesions with soft tissue components $>$ 1 cm are taken into account [10]. Objective tumour response of lytic lesions is defined as the shrinkage of the soft-tissue component of $>$ 30% measured as the largest diameter, progression with growth of $\geq$ 20% or new lesions. The only nonmorphological exception for response assessment is the appearance of new metastases with fludeoxyglucose positron emission tomography (FDG-PET) [11]. Osteoblastic lesions are considered immeasurable [10].

Further sets of criteria for the evaluation of bone metastases are the International Union against Cancer (UICC) and World Health Organisation (WHO) criteria. They have been used since the 1970s and include plain radiography (UICC) or radiography along with skeletal scintigraphy (SS, WHO). The UICC criteria are only valid for lytic lesions and distinguish between stable disease (growth of $<$ 25% or decrease by $<$ 50%), progressive disease ($>$ 25%), or new lesions, complete response (disappearance of all lesions), and partial response (shrinkage $>$ 50%) [12]. The more recent MD Anderson (MDA) criteria include plain radiography, SS, computed tomography (CT), and magnetic resonance imaging (MRI) [13]. They have been shown to be superior compared with the WHO classifications in differentiating between responders and nonresponders in terms of progression-free survival and clinical response [13]. The MDA criteria describe the same four response types as UICC, but take morphological criteria such as sclerosis or fill-in of lytic lesions and normalisation of blastic lesions into account. Partial response is thus defined by the acknowledgment of a response rather than quantification [12,14].

Irrespective of the set of criteria there is a time lag of 6–12 months for reliable radiographic evidence of response in many patients [15]. Owing to this lack of adequate imaging criteria most studies define SRE as the primary endpoint. Moreover, due to this time lag patients with bone-only disease are often excluded from clinical trials, which is undesirable as they occur frequently and cause severe symptoms. Overall, early treatment response is an important determinant of survival that can currently not be measured sufficiently in patients with predominant or exclusive bone disease [16]. Obviously there is a clinical need for accurate response criteria in terms of skeletal involvement, allowing for prediction of therapy efficacy early after treatment initiation.

This review outlines current and future directions in experimental and clinical settings of bone metastasis imaging for detection and follow-up of bone metastases, with a focus on the assessment of therapy response and molecular characterisation of osseous metastases. Major animal models currently used for investigation of skeletal metastases are summarised, including preclinical imaging modalities and techniques for this purpose. Furthermore, advantages and disadvantages of current clinical imaging modalities for skeletal metastases are reported.

Preclinical imaging

Animal models and clinical relevance

In order to facilitate diagnosis and follow-up of experimental bone metastases, animal models need to closely mimic the clinical situation. For this purpose, several animal models have been developed, each with a combination of distinct advantages and disadvantages.

The primary method to study breast cancer in transgenic mice has been the overexpression of oncogenes. The transgenic mice then develop tumours spontaneously. Whereas these models have the advantage of keeping the host in an immune competent state, they suffer from the fact that in the vast majority of cases bone metastases only occur rarely [17].

To efficiently mimic and investigate bone metastases, models have been developed involving transplantation of tumour cells. The most frequently used method for this purpose is the intracardiac injection of tumour cells in immune-compromised hosts leading to disseminated metastasis to multiple organs including bone, while lacking the process of cell–cell detachment and plasma intravasation of primary tumour cells. To further select for bone tropism skeletal metastases can be isolated and grown as a bone-specific sub-cell line. The above mentioned model for example has been used to develop bone-tropic sublines of MDA-MB-231 human breast cancer cells [18]. Another model utilizes an intravenous injection of tumour cells leading to lung metastases in most cases. Nonetheless, some of the tumour cells are able to escape the lungs and metastasise further to the bone or liver [19]. Bäuerle et al [20] describe a rat model relying on injection of MDA-MB-231 breast cancer cells into the superficial epigastric artery. This leads to the induction of bone metastases exclusively in the rats' hindlegs, with a tumour take rate of 93% and no further distant metastases [20].

A more direct way to induce bone metastases is to implant tumour cells into the bone marrow cavity (e.g., tibia). Such a model also skips many early steps of metastasis, but can be used to investigate the ability of tumour cells to colonise bone. Hereby, it was possible to specify important interactions between tumour cells and bone referred to as the vicious cycle [21]. This term refers to the fact that bone resorbed by tumour cells releases factors like tumour growth factor-beta (TGF-β), which in turn positively influence tumour growth and survival. Variations of this model have also been used to test agents like bisphosphonates [22] and denosumab [23].

In a so-called orthotopic transplant model, tumour cells are injected into the primary site (e.g., the mammary fat pad). This requires the cells to undergo the full process of metastasis: development of a primary tumour, intravasation, extravasation, and colonisation. As this model is preferable in terms of fully simulating the metastatic process, many tumour cell lines are not able to metastasise to