Metastatic tumours of bone

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Abstract

Metastatic tumours of the bone are the most common types of bone cancer. Autopsy studies have shown that 70% of patients with breast and prostate carcinoma develop skeletal metastases. The most commonly involved bone sites are those with persistent red marrow, such as the vertebrae, proximal femur, ribs, sternum, pelvis and skull. The precise mechanism of metastases to bone is unclear, however, the understanding of the molecular biology of metastases is becoming increasingly important in providing new therapeutic targets. Treatment of bone metastases is multimodal and may include medications, radiotherapy or surgery. Bone metastases can cause many complications and have significant morbidity. Traditionally, the presence of a metastatic bone deposit has been seen as a terminal event. With the increased survival and improved treatment of patients with carcinoma, long-term survival with metastatic bone disease is possible and treatment can prolong life, or even be curative. Implants used in reconstruction need to be sufficiently robust to survive the patient, and the expertise of reconstruction available within tertiary bone tumour units is increasingly required.

Keywords Bone; carcinoma; metastasis; outcome; secondaries; treatment

Metastatic tumours of bone are tumours that spread to bone from another primary site in the body. Histologically, they often resemble the cells of the tumour from which they originated, but sometimes they are poorly differentiated and the primary tumour site cannot be determined. Metastasis is the ultimate phase in the multistage process of tumour progression and is the major cause of death in cancer; however, improvements in treatment are allowing long-term survival of patients with metastatic bone disease, and may even be curative.

In view of increased survivorship following surgery, the implants used in reconstruction need to be sufficiently robust to out-live the patient, and the expertise within tertiary bone tumour units on the gold standard reconstructive techniques is increasingly required.

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The investigation and staging of secondary tumours has been dealt with in a previous article by the authors on primary tumours of bone; this article specifically deals with the basic science, clinical features and treatment of metastases.

Epidemiology

Metastases affecting bone are far more common than primary bone tumours. In the UK in 2011, 331,000 new cases of cancer were diagnosed, and it is thought that up to 70% of these patients will develop metastatic bone tumours. Bone metastases are common in late-stage disease but certain cancers are 'osteotropic' (have an affiliation to bone). Autopsy studies have shown that 70% of patients with breast and prostate carcinoma develop skeletal metastases, numbers are less but still significant in thyroid (40%), renal (35%), bronchus (35%) and rectal (10%) carcinoma. Although bowel, rectal and bladder carcinoma have a lower rate of metastasis to bone, due to the much higher incidence of these cancers, bone metastases from these tumours are common.

The skeletal system is the third most common site for metastatic tumour spread, after the lungs and liver. Most secondary bone tumours are found in middle-aged and older patients, with 75% of metastases affecting those over the age of 50 years.

The most commonly involved bone sites are those with persistent red marrow, such as the vertebrae, proximal femur, ribs, sternum, pelvis and skull. The vertebrae are affected by 50–70% of metastases, but only 10% of these ever become symptomatic. About 70% vertebral deposits occur in the thoracic spine (T4–7), 20% are found in the lumbar spine and rest in the cervical spine. Multiple spinal deposits are found in half of patients, with the anterior portion of the vertebral body being most commonly affected, followed by the pedicle or lamina.

The site prevalence depends, in part, on the primary source of the tumour. For example, widespread skeletal metastases are common in lung cancer primary due to its tendency to spread via the systemic arterial blood supply.

Breast carcinoma is the most common cause of metastatic deposits, and causes 50% of pathological fractures that are due to metastases. Prostate carcinoma is the second most common site of origin, but is less likely to cause pathological fractures, as metastases tend to be osteosclerotic. Renal cell carcinoma metastases can occur many years after the primary tumour, necessitating long-term follow-up, and bone metastases are the presenting feature in 15% of renal tumours.

Pathogenesis of bone metastases

The precise mechanism of metastases to bone is unclear but consists of a multistep process that involves interaction between tumour cells and normal host cells. The biology of bone metastases is complex and involves: breaking free from the extracellular matrix of the primary tumour; being transported in the blood or lymphatic system; avoiding detection and destruction by the immune system; exiting the blood or lymphatic system; and proliferating in an environment which is removed from their original location. The host environment has to be rich in nutrients and oxygen and so the metastatic cells must recruit blood vessels (neoangiogenesis) in order to allow continued growth of the secondary tumour.

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Tumours can spread by direct tumour invasion (e.g. soft tissue sarcoma directly invading bone), via the bloodstream or via the lymphatics.

Theories of mechanisms of macroscopic tumour spread

Two main theories exist to explain possible mechanisms of distant spread of tumour and it is most likely that a combination of factors are responsible.

Soil hypothesis (Paget): in 1889 British surgeon Stephen Paget (son of Sir James Paget) popularized a theory published previously by Fuchs, of 'the seed and the soil' hypothesis. This suggested that malignant cells escaping from the tumour (the 'seeds') colonize those tissues (the 'soils') that are favourable for them because of mutual compatibilities. Paget imagined that breast tumours metastasize to bones and liver, rather than the spleen, because bone marrow and liver tissues provide optimal conditions for the multiplication of breast cancer cells.

Circulation theory (Ewing): proposed in 1928 by James Ewing, of the New York Memorial Hospital, stating that the distribution of metastases depends principally on the routes of dissemination of the tumour. He observed that colonic tumours metastasize principally to the liver because the liver is the first organ visited by the circulating blood coming from the intestines. The preferential deposition of primary tumour cells in the vertebrae, with relatively scarce visceral involvement, was also noted. This can be explained by Batson's valveless venous plexus from around the vertebrae that communicates with the pelvis and proximal halves of the upper and lower extremities, but excludes the chest, portal and caval systems. It is postulated that the spread of malignant cells through this plexus is likely to occur through retrograde spread, as a result of a Valsalva manoeuvre, from the sites of primary tumours.

The unique ability of lung lesions to shed tumour cells directly into the arterial circulation causes the spread of tumour cells to tissues far and wide in the body, including to the bones of the hands and feet, with 50% of all metastases to the hands coming from primary lung tumours.

Molecular mechanisms in bone metastases

The bone matrix provides a unique and fertile microenvironment for the proliferation of tumour cells. The interaction between tumour cells and bone stroma that initiate the cycle of bone destruction and tumour growth are critical aspects of the metastatic process. The exact pathogenesis or biology of bone metastasis is still not well understood.

There are several important factors in the development of osteolytic bone metastases. Some of the major contributors are: parathyroid hormone-related protein (PTHrP – which is an important cause of hypercalcaemia of malignancy and bone resorption); transforming growth factor β (TGF β); interleukin-11 and interleukin-6 (which have been shown to simulate bone resorption and may induce osteolysis). Other factors include calcitonin receptors, osteopontin and silo protein, tumour necrosis factor α, prostaglandins, receptor activator of nuclear factor-K B ligand (RANKL), macrophage colony-stimulating factor (M-CSF) and human platelet-derived growth factor (PDGF).

Osteoblastic metastatic lesions arise from uncoupled increase in bone formation and reduced bone resorption. TGF β, bone morphogenetic protein (BMP), and insulin growth factors stimulate the differentiation and activity of osteoblasts, leading to increased bone formation. Mixed lesions are caused by a combination of both osteolytic and osteoblastic processes. Several other factors are also involved in the metastatic process, but are not specific to bone metastasis, such as matrix metalloproteinase (MMP) maspin, integrin, e-cadherin and vascular endothelial growth factor (VEGF).

In metastatic bone disease the normal balance of formation of new bone by osteoblasts and resorption of old bone by osteoclasts becomes imbalanced, leading to the development of lesions that are osteolytic, osteoblastic or a combination of both. Analysis of osteolytic bone metastases indicates that the bone destruction is mediated by the osteoclast rather than directly by the tumour cells. These observations suggest a vicious cycle driving the formation of osteolytic metastases: tumour cells secrete factors stimulating osteoclasts through adjacent bone marrow stromal cells; osteoclastic resorption in turn releases growth factors from the bone matrix; finally, locally released growth factors activate the tumour cells. This vicious cycle model has now been confirmed at the molecular level. In particular, TGF β is abundant in bone matrix and released as a consequence of osteoclastic bone resorption. Bone-derived TGF β plays an integral role in promoting the development and progression of osteolytic bone metastases by inducing tumour production of PTHrP, a known stimulator of osteoclastic bone resorption. In breast cancer cells TGF β appears to stimulate PTHrP secretion by a post-transcriptional mechanism through both Smad and p38 mitogen-activated protein (MAP) kinase signalling pathways. Osteolytic metastases can be suppressed in vivo by inhibition of bone resorption, blockade of TGF β signalling in tumour cells, and by neutralization of PTHrP. Other factors released from bone matrix may also act on tumour cells in bone, and in turn stimulate bone resorption, following the vicious cycle paradigm established for TGF β and PTHrP.

Studies have shown that tumour cancer cells interact with osteoblasts or stromal cells to induce osteoclast formation by increasing RANKL expression in several ways. RANK, RANKL and osteoprotegerin (OPG) are the regulatory triad in the differentiation, activation and survival of osteoclasts. RANK is a receptor on the surface of the osteoclast and RANKL is a member of the tumour necrosis factor (TNF) family of cytokines that binds to its receptor RANK to stimulate osteoclast differentiation and activation. RANKL and OPG form a ligand–ligand inhibitory pair which modulates RANK signalling in osteoclasts and their precursors. It is likely that increased bone resorption around cancer cells in the bone results from increased RANKL expression.

Mice studies have shown that in-vivo neutralization of RANKL by OPG results in complete protection from paralysis and marked reduction in tumour burden in bones, but not in other organs. Factors such as PTHrP regulate the expression of OPG and RANKL. Cancer cells can express or upregulate the expression of these factors, of which OPG and RANKL will lead to bone resorption. In this process, treatment possibilities arise, for example, by blocking RANKL signalling within OPG treatment. This can protect against bone destruction, and may inhibit tumour growth in bone. The clinical application of this is the

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