

# Bone Metastasis – an overview

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## Abstract

Bone metastases are associated with high level of morbidity and compromised quality of life .It often leads to wide variety of unpleasant or sometimes life threatening complications. The probability of bone metastasis originating from a primary site can be assessed only by knowing the prevalence of the cancer in that community and its predilection for bone. Therefore, the frequency of bone metastases depends on the prevalence of the cancer in a particular community. Investigations most commonly include 99mTc radionuclide bone scan. It is regarded as the most cost-effective and available whole-body screening test for the assessment of bone metastases. Bone metastases can present to different specialties and the success of treatment depends on the coordination between multiple disciplines. The team approach should be always considered. Surgery, external radiation, radioactive pharmaceuticals, bisphosphonates and chemotherapy all are reasonable treatment options and should individualized as per clinical picture.

## INTRODUCTION

Bone metastases are associated with high level of morbidity and compromised quality of life .It often leads to wide variety of unpleasant or sometimes life threatening complications. Unfortunately the true incidence of bone metastases is the subject of controversy, thus not truly known. The probability of bone metastasis originating from a primary site can be assessed only by knowing the prevalence of the cancer in that community and its predilection for bone. Therefore, the frequency of bone metastases depends on the prevalence of the cancer in a particular community. The incidence of bone metastases also depends on the source of the data and how it was collected. In literature it is a known fact that bones are one of the most common sites for malignant circulating cells to settle and start growing<sup>1</sup>. Metastases can occur in bones anywhere in the body and is different from cancer that starts in the bone, which is called primary bone cancer. Bone metastasis is one of the most frequent causes of pain in people with known malignancy. It can cause fractures, hypercalcemia and often results in reduced ability to maintain normal quality of life including day today daily activities.

There is now a much greater understanding of the mechanisms underlying the development of bone metastases and the interdependence between cancer cells and the micro environment of bone matrix. Tumor cells have tendency to secrete a variety of cytokines in the matrix of bone marrow

which has tendency to stimulate the bone cell. This chronic stimulation of osteoclast results in osteolysis which causes disruption of the normal coupling signals between osteoblasts and osteoclast. This imbalance leads to changes in internal bone metabolism. The relative degree of resultant bone resorption or deposition is highly variable and depends on the type and location of the tumor. The relationship between the osteoclastic and osteoblastic remodeling processes determines whether a predominant lesion is lytic, sclerotic, or mixed pattern<sup>2</sup>. The bone metastases can occur by direct extension, retrograde venous flow, and or tumor emboli via the blood or lymphatic circulation. Seeding occurs initially in the red marrow; this process accounts for the predominant distribution of metastatic lesions in the red marrow. Retrograde venous embolism is probably the major mechanism when there is spread from the peritoneal cavity or tumor invading the bony vertebrae. Increased intra-abdominal pressure causes blood to be diverted from the systemic caval system to the valve less vertebral venous plexus of Batson; this diversion allows the caudal and cranial flow of blood<sup>3</sup>. In patients with a known primary carcinoma, the development of bone pain usually is considered to be highly suggestive of bone metastases.

However, Schaberg and Gainor found that 36% of patients with spinal metastases did not complain of bone pain<sup>4</sup>. Patients with bone metastases may present with a pathologic fracture upfront therefore, checking the state of underlying

bone for disease is important if such a fracture is suspected. The commonest neoplasm's affecting bones are breast (35%), prostate (30%), bronchus (10%), kidney (5%), thyroid (2%) and others (18%). Patient may present with various symptoms but commonest presentation in oncology clinics are pain, bony lump, pathological fracture, hypercalcemia and rarely spinal cord compression. Various differential diagnosis quoted in literature are calcified enchondroma, hyperparathyroidism, chronic osteomyelitis, rarely bone infarct and myeloma deposit<sup>5</sup>

### **INVESTIGATIONS**

Investigations most commonly include 99mTc radionuclide bone scan. It is regarded as the most cost-effective and available whole-body screening test for the assessment of bone metastases. Conventional radiography is the best modality for characterizing lesions that are depicted on bone scans. Combined analysis and reporting of findings on radiographs and 99mTc bone scans improve the diagnostic accuracy in detecting bone metastases and help in assessing the response to cancer therapy. CT and MRI are useful in evaluating suspicious bone scan findings that appear equivocal on radiographs. MRI can help in detecting metastatic lesions before changes in bone metabolism make the lesions detectable on bone scan<sup>6</sup>. CT scan is usually helpful in guiding needle biopsy, particularly in vertebral lesions.

### **TREATMENT**

Bone metastases can present to different specialties and the success of treatment depends on the coordination between multiple disciplines. The team approach should be always considered. Treatment options primarily depend on where is the primary malignancy? Other important clinical and prognostic factors helpful in decision making are whether affected bones are severely weakened or associated with impending pathological fracture, overall performance status of the patient, how symptomatic is the patient, response to primary therapy. Patients who are responsive to hormonal or systemic chemotherapy can live longer so it is worth to palliating these patients in order to preserve functions and maintain quality of life. Various treatment modalities often used are orthopedic or neurosurgical intervention, radiation external or nuclides, systemic hormonal therapy, chemotherapy, opioid and localized nerve blocks.

If pathological fracture is suspected then urgent consult to orthopedic surgeon should be generated. In oncology we often come across what is called a compression fracture.

This usually affects front portion of a vertebrae in spine and it collapses due to tumor or underlying osteoporosis. Fractures should be treated as an emergency if found at weight bearing areas such as femoral neck. Immediate ORIF (open reduction and internal fixation) in majority of fractures can have good results. Autogenously bone grafting can be carried out in some fractures<sup>7</sup>. Vertebroplasty and Kyphoplasty are relatively new procedures that are being increasingly used in the treatment of patients with vertebral compression fractures. Advocates of both procedures claim to offer advantages over the conservative therapy in immediate pain relief and mechanical stabilization of the vertebral body. Vertebroplasty is performed by percutaneous injecting bone cement into the vertebral bodies under fluoroscopic and/or computed tomography guidance. Kyphoplasty includes an attempt to expand the vertebra with an inflatable balloon prior to the injection of bone cement<sup>8</sup>. Currently, only certain polymethylmethacrylate (PMMA) bone cements are licensed for use in these procedures. Serious complications associated with the use of the bone cements in these procedures have been reported. They include death due to sudden blood pressure drop that may be related to the release of the PMMA monomer into the vascular system. Bone cements extravasation into the spinal canal leading to neurological deficit, with compression of the spinal cord and/or nerve roots. These adverse events can result in neurological complications ranging from minor motor and sensory loss to paraplegia. Though the available data does not allow for a direct comparison of the rates of new fracture after vertebroplasty, kyphoplasty and conservative treatment, there is evidence to suggest that the occurrence of new vertebral fractures after vertebroplasty and kyphoplasty may be nonlinear, with the majority of cases diagnosed within the first few months after augmentation. Augmentation of the vertebral body with PMMA cement increases the strength and stiffness of the vertebrae and may dispose the adjacent vertebral bodies to new fractures<sup>9</sup>.

Radiotherapy is a well-recognized and effective palliative treatment of painful bone metastases. Radiation therapy treatment uses high energy gamma x-rays to kill malignant cells or at least decrease further progression of destruction. Radiation may prevent fractures once the bone has healed. If there is an impending risk of a bone fracture, radiation will not prevent it. Instead the bone must be stabilized surgery first followed by radiation. The most common way to deliver radiation to a bone metastasis is to carefully focus a beam of radiation from a machine outside the body. This is known as

external beam radiation. To reduce the risk of side effects radiation oncologists carefully delineates the target as per information provided by imaging and relevant clinical examination<sup>10</sup>. If there are many metastases scattered throughout the body, treatment with radiation is technically very challenging and increases normal tissue toxicity. Rarely patients can benefit from radiation therapy to either the entire upper or lower half of the body. The optimal dose-fractionation schedule for the treatment of bone metastases is unclear. Two surveys of Canadian patterns of practice found that various fractionation schedules are employed by radiation oncologists, ranging from a single large-dose fraction (e.g., 8 Gy) to a more prolonged course of 30 Gy/10 fractions over 2 weeks. It has been suggested that the choice of fractionation is influenced not only by patient-related factors but also by physician level of comfort, toxicity, resources and individual institutional policies. The optimal treatment is which will provide pain relief without undue toxicity to the patient<sup>11</sup>.

During the past decade, significant clinical trial efforts have been devoted to comparing single large-dose radiation (8 Gy to 10 Gy) with multifraction regimens (five to ten fractions). In RTOG 97-14, phase III randomized Trial of 8 Gy in 1 Fraction vs. 30 Gy in 10 Fractions for Palliation of Painful Bone Metastases 949 pts; pts with breast or prostate cancer were evaluated. Preliminary results presented at ASTRO 2003 confirmed that palliative external beam radiation therapy is very effective in providing pain relief, with complete or partial improvement in pain seen in 66% of patients. Pain and narcotic relief was equivalent for both 30 Gy in 10 fractions and 8 Gy in a single fraction. At 3 months follow-up, there was no difference between the two treatment arms, regardless of stratification. Treatment was well tolerated with few adverse effects. Complete pain response in 17%, partial response in 49%; for 8 Gy: 15 % (complete response) 50% (partial response) and for 30 Gy: 18%/48%. There was no difference in pain or narcotic relief between arms.<sup>12</sup>

Based on intention-to-treat principle, meta-analysis of published data from eight randomized trials of single fraction versus multifraction radiotherapy for the treatment of uncomplicated painful bone metastases was done. This study did not detect a significant difference in response rate (pain reduction or control) between a single fraction of 8 Gy prescribed to the appropriate target depth and fractionated radiotherapy. Pooled complete response rates were 33% with single fraction and 32% with multifraction (relative risk,

1.03; 95% confidence interval, 0.94 to 1.13,  $p=0.5$ ) and overall response rates were 62% and 59% respectively (relative risk, 1.05; 95% confidence interval, 1.00 to 1.11,  $p=0.04$ ). The majority of patients enrolled in the studies were breast, prostate, and lung cancer patients. Other less common epithelial and non-epithelial tumors were often included, but relative efficacy of dose-fractionation schedules cannot be determined in such subgroups. Median duration of response was 12 to 24 weeks, with no significant difference between fractionation schedules within individual trials. No significant difference in quality of life after radiotherapy (in the few studies assessed), analgesic consumption, or acute adverse effects (vomiting and tiredness) was detected between single- and multiple-fractionation schedules. One study showed greater remineralization following fractionated radiotherapy (30 Gy/10 fractions) than single fraction (8 Gy). The implication of this finding on prevention of pathologic fracture is unclear. There is no evidence to suggest that fractionated regimens result in fewer cases of acute nausea and vomiting compared with single fraction treatment. Nausea and vomiting are better controlled by prophylactic anti-emetics, as demonstrated in the Canadian study. Complete emesis control was superior with single fraction radiotherapy using prophylactic ondansetron, 8 mg twice a day x 3 days, compared with 2000 cGy/5 fractions without prophylactic anti-emetic (53% emesis-free after single fraction + prophylactic ondansetron versus 35% emesis-free for multiple fractionation without prophylaxis). Vomiting was equally common (30%) in either treatment arm in a subgroup of patients evaluated ( $n=124$ ) for nausea/vomiting in the Bone Pain Trial study. Observed re-irradiation rates were higher with single fraction treatment (11-25%) than with multiple-fraction treatment (3-12%).<sup>13</sup>

Another systematic and meta-analysis was performed by the supportive care guidelines group of Ontario which essentially is a multidisciplinary guideline development panel

Based on their interpretation and evidence from the existing literature it is evident that there is no difference in complete or overall pain relief between single treatment and multifraction palliative radiotherapy for bone metastases. Where the treatment objective is pain relief, a single 8 Gy treatment, prescribed to the appropriate target volume, is recommended as the standard dose-fractionation schedule for the treatment of symptomatic and uncomplicated bone metastases<sup>14</sup>

The use of stereotactic body radiation therapy (SBRT) can enable oncologists to give much higher dose of treatment to a smaller volume of tissue. There are good reports that have provided an excellent review of the current status of SBRT for the treatment of painful bone metastases. They have addressed many questions regarding SBRT, including the feasibility, safety, and efficacy of the technique. The promise of SBRT compared to conventional treatment is that it provides the precise delivery of an ablative dose of radiation to a tumor. The hypothesis is SBRT will give better local control and relief of pain. This rationale assumes that tumor control is the primary reason for pain relief. However, the causes of pain may be structural (weakening of the bone) or may be related to the tumor microenvironment. Treatments that re-establish the normal osteoblasts-osteoclast cycle may provide relief of pain even with minimal tumor cell kill. This is one reason that bisphosphonates such as zoledronic acid are effective in treating painful bone metastases, but with an added benefit of preventing the appearance of new bone metastases.<sup>15</sup>

If bone metastasis is widespread and not amenable to safe radiation portals then fractionated hemibody irradiation can be employed. In RTOG 88-22 the effect of fractionated hemibody irradiation in the treatment of osseous metastases was evaluated. One hundred and forty two patients with painful bone mets (single or multiple) confined to one hemibody upper or mid or lower from breast or prostate cancer were evaluated. Treatment of local painful site by local radiation followed by hemibody RT dose, 2.5 gray per fraction to 4-8 fractions (total of 10- 20 gray). Hemibody began within 3 days of local radiation and the local radiation portal was shielded during hemibody radiation. Time to new disease in the hemibody field was 19% at 1 yr, no survival difference between the two arms was found no difference in retreatment rates<sup>16</sup>.

Occasionally systemic radiopharmaceuticals can be used for palliation of bony metastasis. They are radioactive isotope given by intravenous approach .They interacts with osteoblasts present in the neoplastic islands in affected bone. They emit radiation and kill the cancer cells and relieves some pain caused by bone metastases. Some of the radiopharmaceuticals that are most often used are strontium-89 and samarium-153 .Other radiopharmaceuticals, such as rhenium-186, rhenium-188, and tin- 17, are also being studied. These drugs work best when the metastases are osteoblastic. Osteoblastic means the cancer has stimulated the bone cells (osteoblasts) to form

new areas of bone. The major side effect of this treatment is myelosuppression, nausea, vomiting, and bladder irritation and flare phenomenon<sup>17</sup>.

In addition to these approaches often some surgical techniques are available to control pain when other conventional treatments don't work. Cordotomy essentially involves treatment of pain on one side of the body. Cordotomy may be performed as an open operation, or as a percutaneous procedure. The percutaneous procedure is more commonly used nowadays, and is performed in the cervical region at C1-2. The highest level of analgesia obtainable is about C4 which corresponds to the shoulder. Neck pain does not normally respond. Special care is needed in patients with impaired lung function, as percutaneous cervical cordotomy may cause some reduction in the expansion of the lung on the side of the procedure. This is obviously important in patients with lung tumors, who will commonly have pain and reduced lung function on the side of the tumor<sup>18</sup>. Other surgical procedures are loco-regional anesthetic procedures such as central neural blocks (e.g. spinal or epidural anesthesia), plexus blocks (e.g. brachial plexus block) or peripheral nerve blocks (e.g. femoral nerve block). These can be performed as single shot techniques, or a catheter inserted which allows prolonged use. Rarely central neural blocks are used for pathological fractures or procedures such as painful dressing changes in the perineum or lower limbs. If complete anesthesia is required, then the attendance of fully trained staff with all the relevant monitoring and resuscitation equipment is mandatory. In lung malignancies the brachial plexus blocks are done. This is achieved by anaesthetizing the nerves of the brachial plexus at the neck, the shoulder or the axillary area. This can provide anesthesia of the upper limb and is routinely used for hand and arm surgery in many hospitals. It can be used for incident pain, such as painful dressings, or for longer term pain relief if a catheter is inserted into the sheath of the brachial plexus. Block of the femoral nerve can provide useful short-term analgesia for femoral fractures. Intercostals' nerve block with local anesthetic can provide good short term relief for pain from ribs or other chest wall problems. Some other blocks are trigger point injection, facet joint injection and satellite ganglion blocks.<sup>19</sup>

Recently there is emerging data regarding the use of bisphosphonates. Bisphosphonates are a class of drugs that inhibit osteoclast action and the resorption of bone .Its uses include the prevention and treatment of osteoporosis, metastasis related complications and hypercalcemia and

other conditions that affect bone fragility<sup>20</sup>. There is evidence to support the effectiveness of bisphosphonates in providing some pain relief for bone metastases. There is insufficient evidence to recommend bisphosphonates for immediate effect; as first line therapy; to define the most effective bisphosphonates or their relative effectiveness for different primary neoplasms. Bisphosphonates should be considered where analgesics and/or radiotherapy are inadequate for the management of painful bone metastases. Thirty randomized controlled studies (21 blinded, four open and five active controls) with a total of 3682 subjects were included. For each outcome, there were few studies with available data. For the proportion of patients with pain relief (eight studies) pooled data showed benefits for the treatment group, with an NNT at 4 weeks of 11 [95% CI 6-36] and at 12 weeks of 7 [95% CI 5-12]. In terms of adverse drug reactions, the NNH was 16 [95% CI 12-27] for discontinuation of therapy. Nausea and vomiting were reported in 24 studies with a non-significant trend for greater risk in the treatment group. One study showed a small improvement in quality of life for the treatment group at 4 weeks. The small number of studies in each subgroup with relevant data limited our ability to explore the most effective bisphosphonates and their relative effectiveness for different primary neoplasm's .Bisphosphonates clearly improve the quality-of-life of patients with metastatic bone disease. Questions remain concerning mechanisms of action and their potential role in preventing metastases in high-risk patients.<sup>21</sup>

Immunotherapy is another form of systemic therapy that helps a patient's immune system recognize and destroy cancer cells more effectively. Several types of immunotherapy are used to treat patients with metastatic cancer, including cytokines, monoclonal antibodies, and tumor vaccines. Most of these are still experimental. Cytokines, IL-2 and IFN-alfa, are treatment options for people with advanced kidney cancer. Interferon-alfa is often used to treat people with hairy cell leukemia, chronic myelogenous leukemia, follicular lymphoma, multiple myeloma, and cutaneous T cell lymphoma. In some cases, interferon is used along with chemotherapy. Rituximab, a monoclonal antibody, is used to treat some kinds of B cell non-Hodgkin lymphoma. Ibritumomab tiuxetan (Zevalin<sup>®</sup>) and tositumomab (Bexxar<sup>®</sup>) are radio labeled monoclonal antibodies used to treat non-Hodgkin lymphoma, usually in people who aren't helped by other treatments such as chemotherapy or rituximab. Whether immune response elicited by these vaccines helps directly with pathophysiology of bone metastases is largely unknown<sup>22</sup>.

Several other monoclonal antibodies are being studied in clinical trials for people with leukemia, lymphoma, and multiple myeloma. but are not approved. GVAX is an autologous whole cell vaccine which is injected into the patient to cause an immune response. Early studies of patients with advanced prostate cancer with bone metastasis that no longer responded to hormone therapy have shown some promising results in terms of survival time. However all these are still investigational .With more clinical trials in future we will have more information regarding the clinical use of these agents.<sup>23</sup>

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