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Diagnosis and Treatment Options of Spinal Metastases

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ABSTRACT

Cancer patients with spinal metastases are a diagnostic and treatment challenge for the clinician. This challenge must be addressed through a multidisciplinary, multimodal, and individualized management. The presence of tumor cells in bone metastases results in homeostatic disruption between bone formation and remodeling. Bone destruction is a late event in the formation of lytic bone metastasis, starting when tumor cells proliferate; this in turn activates osteoclasts, seen as trabecular destruction in imaging studies. There may be excessive bone destruction and increased bone formation, which produce blastic lesions. Bone scintigraphy is currently the most widely used diagnostic method and is considered as the reference test for the diagnosis of spinal bone metastasis. However, we believe that in the near future positron emission tomography associated to computed tomography with ^{18}F-NaF, or magnetic resonance using diffusion-weighted whole-body imaging with background body signal suppression, will replace bone scintigraphy due to their improved diagnostic accuracy. These new diagnostic tools will help prevent bone metastasis complications such as: intractable pain; spinal cord or cauda equina compression; hypercalcemia; pathological fractures; and spinal instability. With regards to the treatment, it can be uni- or multimodal, depending on the type and number of bone metastases. Among the types of treatment available for bone metastasis are chemotherapy, radiotherapy, and invasive procedures. The prognosis of patient survival depends on the histopathology of the primary tumor, the presence of bone metastasis, and the presence of neurological deficits. (REV INVES CLIN. 2015;67:140-57)
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INTRODUCTION

Currently, cancer is a public health problem; it is the third leading cause of death worldwide, the second in developed countries, and is responsible for approximately 13% of all deaths worldwide[1]. In 2008, 7.6 million deaths due to cancer were reported in the USA[1]. The World Health Organization estimates 15 million new cancer cases by 2020[2,3]. Metastasis is defined as the process by which cancer cells leave the primary tumor, migrate, and implant into a distant organ where they proliferate and form new tumor foci[4]. Metastatic spread is a key event in the evolution of cancerous disease by transforming a curable, localized illness into a more difficult to control systemic disease.

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Figure 1. Anatomic distribution of bone metastases in the spine. **A:** paravertebral metastases with spinal nerve involvement; **B:** asterisk: intramedullary metastasis, arrow: extramedullar-intradural metastasis; **C:** metastases with posterior arch involvement; **D:** vertebral metastases with epidural involvement.

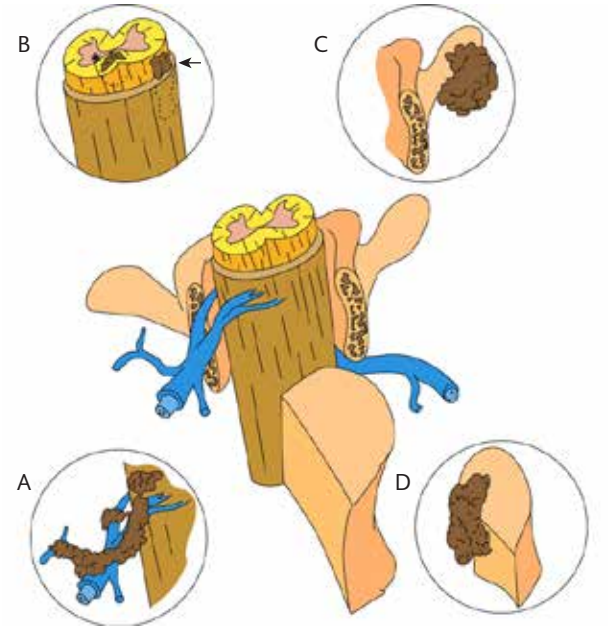
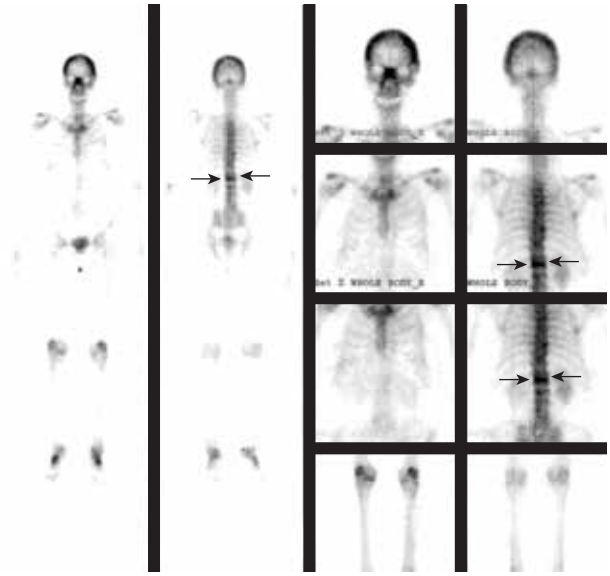


Figure 2. Bone scintigraphy.
The case shown corresponds to a 65 years old female patient with breast cancer. Bone scintigraphy with ^{99}Tc, with increased uptake at T12 and L1 compatible with bone metastases.



The most common sites of metastases are the liver, lungs, and bone tissue[5]. Post mortem studies report that about 70% of patients diagnosed with primary cancer had evidence of bone metastasis (BM)[6]. Over 70% of BM corresponds to adenocarcinomas; the five cancers that produce over 80% of BM are breast, lung, prostatic, thyroid, and renal carcinomas[6]. In up to 20% of cases of BM, the primary tumor may be unknown[7]. In adults, the most frequent sites of BM are: vertebra (69%), pelvis (41%), femoral proximal metaphysis (25%), and the skull base (14%)[8]. Krishnamurthy, et al., in a study in cancer patients with suspected BM, found that 60% of the lesions were located in the axial skeleton and 40% in the appendicular region[9]. Bone sarcomas are rare diseases seen especially in adolescents and young adults, having a marked bone tropism[10].

Bone metastases are implanted in the spine through several mechanisms, including: hematogenous dissemination; direct invasion; and seeding through the cerebrospinal fluid (CSF)[11]. Hematogenous spread, via the arterial route and/or venous pathways, is the most common course for primary tumors to generate BM to the spine[11,12]. The adult axial skeleton contains abundant red bone marrow cells, major blood flow, as well as an extracellular matrix and growth factors that favor the formation of BM[6]. The vertebral venous flow, provided by the venous plexus of Batson, consists of a system of venous vessels that connect to other venous beds such as the venous system of the vena cava, the venous system of the portal vein, the venous system of the azygos vein, the renal venous system, the pulmonary venous system, the intercostal veins system, and the epidural venous plexus, all of which contribute to the spread of the BM in the spine[11,13].

Lesions with an aggressive behavior in the chest, abdomen, or pelvis may disseminate by direct extension and invade the spine while the patient remains asymptomatic. Additionally, bladder, prostate, and colorectal carcinomas can invade the spine. Bone metastasis may be disseminated through the CSF spontaneously or during surgical manipulation of a primary brain neoplasm or cerebral and cerebellar metastases[11]. According to the anatomical distribution, BM in the spine is classified into four categories (Fig. 1): a) intramedullar and extramedullar-intradural; b) vertebral metastases with epidural involvement; c) metastases with posterior arch involvement; and d) paravertebral metastases with spinal nerve involvement[14]. The extradural compartment is most frequently affected (90% of cases),

Figure 3. Positron emission tomography-computed tomography. The study corresponds to a female patient patient, 19 years old with Hodgkin's lymphoma mixed cellularity type. PET-CT with ^{18}F-FDG, showing increased uptake at T11 and T12 with 6.1 of SUVmax in the sagittal and coronal views, where bone metastases are identified.

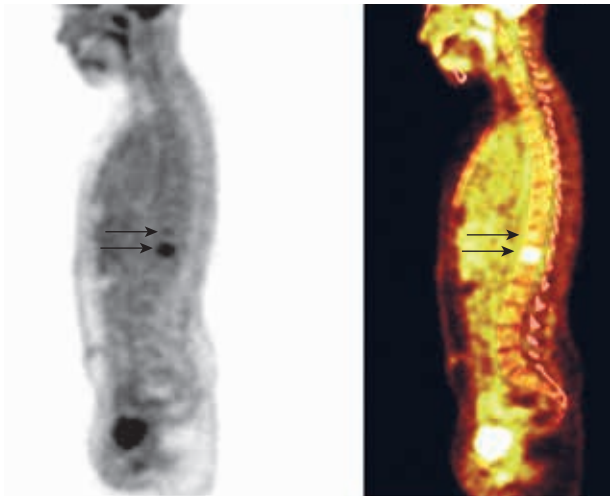


Figure 4. Diffusion-weighted whole-body imaging with background body signal suppression.
The study is from a 19-year-old female women with Hodgkin's lymphoma mixed cellularity type. Diffusion-weighted whole-body imaging with background body signal suppression in coronal view, with positive and negative images with restriction regions at T11 and T12, compatible with bone metastases.

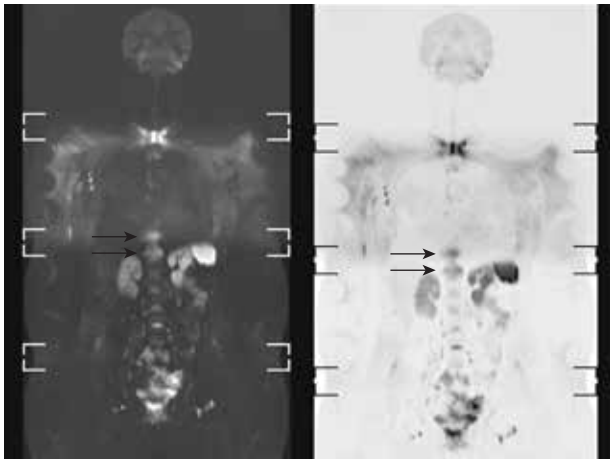


Figure 5. Structural magnetic resonance imaging from a 19-year-old female women with Hodgkin's lymphoma mixed cellularity type. Magnetic resonance in sagittal view, structural sequences T1, T2 and T1 with contrast medium, displaying lesions at T11 and T12, which behave with low intensity in T1-weighted, high intensity in T2-weighted, and marked enhancement in T1 FASAT with contrast medium.

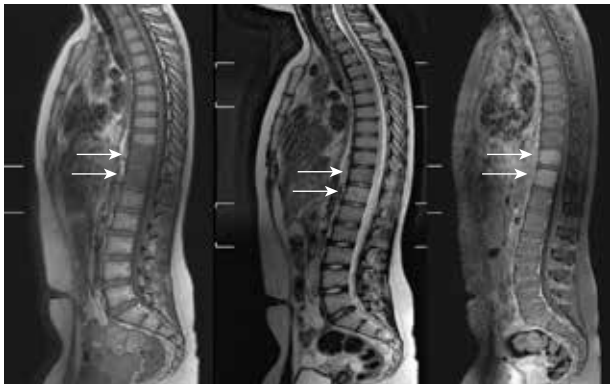
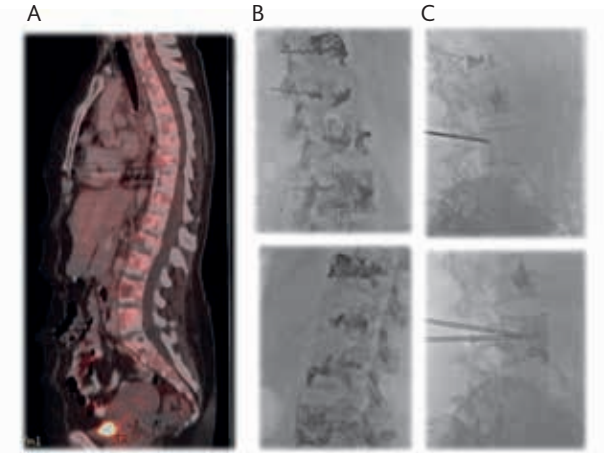


Figure 6. Percutaneous vertebroplasty with biopsy.
This case corresponds to a 53-year-old female patient with breast cancer, treated with radical mastectomy, and chemotherapy (6 cycles with 5-fluorouracil, Adriamycin, and cyclophosphamide) and radiotherapy (33 fractions). **A:** PET/CT with lytic lesions in spine. **B:** percutaneous vertebroplasty in four vertebrae, with 80% pain reduction. **C:** vertebral body biopsy reporting metastatic carcinoma compatible with breast cancer. Immunohistochemical results: HER-2/neu +++; estrogen Rc +++; progesterone Rc negative.



composed of vertebral and paravertebral tissue[14]. The extradural compartment is connected to the venous system. Intradural or intramedullar metastases are rare and are associated with CSF seeding[11,14]. The segmental distribution of BM in the spine is as follows: thoracic region (70%), lumbar region (20%), cervical region (9%), and sacral region (1%)[11,15].

PATHOGENESIS

Bone remodeling

Bone is a specialized connective tissue, consisting of non-mineralized tissue (osteoid), primarily composed of type I collagen, and a mineralized component

characterized by hydroxyapatite crystals. The bone marrow contains a variety of cells (osteoblasts, osteoclasts, stromal cells, immunological cellsG, endothelial stem cells, adipocytes, fibroblasts, and megakaryocytes) and interstitial fluid. Bone tissue is remodeled during childhood and adolescence, peaking in adulthood, with this turnover continuing throughout life. The bone remodeling cycle in a young adult lasts approximately 200 days. The presence of tumor cells in BM leads to a disruption in bone formation and absorption balance. There may be excessive bone destruction or increased bone formation, producing blastic lesions[16]. Lytic BM begins when there is proliferation of tumor cells, which activate osteoclasts and produces trabecular destruction in imaging studies[17,18]. In some cases the lesions may be mixed, a combination of lytic and blastic processes[6,19].

This bone resorption is mediated by osteoclastic cells, multinucleated giant cells derived from precursor cells of the granulocyte-macrophage series. Several factors may stimulate osteoclasts, with the most important mediators being interleukins (IL-1 and 6), insulin-like growth factor, prostate-specific antigen, transforming growth factor-β, and parathyroid hormone-related protein (PTHrP)[19]. The RANK/RANKL (receptor activator of nuclear factor kappa-B/receptor activator of nuclear factor kappa-B ligand) signaling pathway is the first mediator to initiate osteoclast bone remodeling[20]. RANK is a transmembrane receptor for the tumor necrosis factor (TNF) signaling cascade, belonging to the receptor superfamily expressed in the surface of osteoclast precursors[20]. Its coupled ligand, RANKL, is expressed on stromal cells contained in bone marrow and is regulated by the factors previously mentioned[20]. The interaction between RANK and RANKL is necessary for the formation, function, survival, and bone resorption of osteoclasts. Osteoprotegerin is a receptor for TNF, which is secreted by osteoblastic cells, binding to RANK and hence modifying the RANK/RANKL complex, therefore affecting the osteogenesis process[20].

Bone formation is generated by osteoblasts derived from mesenchymal cells associated with fibroblasts, adipocytes, myocytes, and chondroblasts[21]. Endothelin-1, a vasoconstrictor peptide produced by prostate and breast cancer cells, stimulates the proliferation of osteoblasts[5]. In animal models, it has been found that endothelin-1 inhibits osteoclast activity[5]. Prostate cancer BM is typically osteoblastic, occurring with increased bone calcium due to calcium retention[19]. This calcium accumulation can produce hypocalcemia and hence induce hyperparathyroidism, consequently originating generalized bone loss[19]. Prostate cancer patients may show distant foci of bone resorption to the osteoblastic metastatic site, while in the minority of cases a pure osteolytic pattern may be seen[19]. Myeloma patients have lytic bone lesions, in some cases they produce mixed lesions and, rarely, pure osteoblastic lesions[19].

CLINICAL PRESENTATION OF SPINAL BONE METASTASIS

Bone metastasis in the spine may be clinically manifested as: intractable pain; spinal cord compression or cauda equina syndrome; hypercalcemia; pathological fractures; and spinal instability[5,7,11,14,22]. These symptoms worsen the quality of life and reduce survival, which are significantly different compared with patients without these complications[5,7,23]. Bone metastasis rarely has a silent clinical expression[19].

Intractable pain

The most frequent symptom in patients with BM is intractable pain, and it occurs in 80-95% of cancer patients[11,23]. In 10% of cases, pain may be the initial manifestation of BM[11]. Known mechanisms that cause pain include: structural damage, periosteal irritation, nerve root compression, muscle spasm, and secretion of chemical mediators during osteolysis (TNF-α and IL-1), or type E prostaglandins that activate osteoclasts and stimulate nociceptive receptors[14,24]. The characteristics of intractable pain are progressive onset, persistent or increasing intensity (often at night, preventing sleep), exacerbated by torsional movements or even by the Valsalva maneuver, is resistant to nonsteroidal anti-inflammatory drugs (NSAID) commonly leading to the use of morphine, and in some cases the pain can lead to prostration[13,24].

Malignant spinal cord compression

Malignant spinal cord compression (MSCC) is defined as a compressive protrusion, displacement, or encasement of the thecal sac around the spinal cord or cauda equina by spinal metastases and is present in advanced cancers. The compression may occur due to: tumor extension in the spine, resulting from a spinal

cord anterior compression (epidural involvement); anterior extension of a mass derived from posterior arch elements; vertebral foraminal mass growth; and fractures with posterior wall displacement[14].

Malignant spinal cord compression occurs in the thoracic region in 60-80% of cases, in the lumbosacral region in 15-30%, and in the cervical region in 10%[5]. Approximately 50% of patients have more than one region of the spine affected. It is common in patients that have breast cancer (20-30% of cases) and lung cancer (10% of cases); other cancers associated with MSCC include prostatic, renal, and lymphoma[5]. Malignant spinal cord compression is a neuro-oncological emergency and, if it is suspected, immediate treatment is required. The pain occurs in areas adjacent to the tumor, exacerbated by activities that increase intradural pressure such as coughing, sneezing, and physical exertion. This pain is usually distal at the beginning, unilateral or bilateral in lower extremities, usually asymmetric, and manifests as radiculopathy especially if the MSCC includes the lumbosacral spinal column. Patients with spinal cord compression have weakness or paralysis in 70% of cases[14,25]. Lhermitte's sign, manifested by an electric discharge sensation in the back and/or upper or lower extremities following neck flexion, occurs in cervical or thoracic MSCC, although it could also be present in non-compressive myelopathy associated with chemotherapy or radiation[14]. In later stages, MSCC manifests as numbness, distal anesthesia, or motor deficit (60-80%) at the level of the compromised segment[14]. Autonomic dysfunction, manifested as neurogenic bladder, is the main complication associated with MSCC[6,14].

Malignant hypercalcemia

Malignant hypercalcemia (MH) is an important complication found in one-third of patients with advanced cancer (10-30%) and is associated with a poor prognosis[19,21,26,27]. The MH is classified as mild (serum calcium, 10.5-11.9 mg/dl), moderate (12.0-13.9 mg/dl), and severe (≥ 14 mg/dl)[28]. Breast, lung, and renal cancer, along with hematologic neoplasms (mainly myeloma, lymphoma and T-cell leukemia) are the main MH-producing cancers[6,26]. The MH is the result of bone destruction, present in 80% of lytic BM[6].

Disorders of calcium regulation in patients with MH are classified into three categories:

– paracrine or endocrine secreted humoral factors, such as diverse cytokines and PTHrP, produced by multiple myeloma, lymphoma, and breast cancer;

– patients with BM, in whom the tumor's local direct effects can lead to bone dissolution and calcium mobilization, manifested by local osteolysis present in certain cancers (head and neck squamous cell carcinoma, esophageal, cervical, renal cell carcinoma, lung, ovary, and endometrial);

– in the minority of the cases, hypercalcemia is a paraneoplastic sign that results from excess vitamin D activated by neoplastic cells[6,28].

An association between MH and hepatic metastases has been described[6], which affects the metabolism of bone effector humoral factors, such as PTHrP[19]. The association between elevated serum PTHrP and cancer has been found in two-thirds of patients[6]. The kidney plays an important role in MH, resulting in volume depletion and a decrease in PTHrP activity; consequently, calcium renal absorption is increased, thereby raising calcium serum levels[6]. Additionally, vitamin D analog-producing tumors can elevate calcitriol levels, causing a secondary MH[26]. The clinical presentation is nonspecific and its early recognition is essential. When calcium serum levels are > 12 mg/dl, the typical symptoms include nausea, emesis, constipation, abdominal pain, anorexia, weight loss, polyuria, fatigue, and decreased strength. Patients with a calcium serum levels > 14 mg/dl have neurological symptoms such as confusion, coma, and even death due to renal failure, or cardiac arrest secondary to arrhythmias[6,21,26].

Pathological fractures

Pathological fractures (PF) occur in 8-30% of cancer patients[19,29]. Bone destruction secondary to BM decreases its carrying capacity; consequently, micro fractures form and pain occurs. When the critical threshold engages over 50% of the vertebral cross-sectional area and there is mineral loss, the vertebral body becomes prone to a PF[6]. Pathological fractures are more frequent in the costal arches and the vertebral body, causing kyphoscoliosis or height reduction of the vertebral body, which may induce a restrictive lung pattern. The PF depends on the tumor type, size, location, bone mineral loss, and degree of destruction[6,10,19]. They are more common due to lytic BM; these erode trabecular

and cortical bone tissue structures, as in breast cancer or in most cases of multiple myeloma[6,10,19].

Spinal instability

Spinal instability occurs in 10% of advanced cancer cases and is a determining factor for surgical treatment[6]. In 2010, the Spine Oncology Study Group (SOSG) defined spinal instability as: the loss of integrity of the spine as a result of neoplastic processes, associated with pain during movement; and a progressive symptomatic deformity with neural compromise under diverse physiological loads[30]. Along with the definition of spinal instability, the SOSG proposes a score for the presence of instability (Table 1)[30].

Table 1. Scoring system for spinal instability secondary to neoplasm[30]

Location within the spine	
– Rigid sacrum	0 points
– Semi-rigid segment (T3-T10)	1 point
– Mobile spine (C3-C6) or (L2-L4)	2 points
– Junctional segment (C1-C2, C7-T12, T11-L1 or L5- S1)	3 points
Pain relief with recumbence and or pain with movement/loading of the spine	
– Pain-free lesion	0 points
– No (occasional pain but not mechanical)	1 points
– Yes	3 points
Type of lesion	
– Blastic	0 points
– Mixed	1 point
– Lytic	2 points
Radiographic spinal alignment	
– Normal alignment	0 points
– *De novo* deformity (kyphosis/scoliosis)	2 points
– Subluxation/translation present	4 points
Vertebral body collapse	
– No vertebral body collapse	0 points
– Without collapse with < 50% body involved	1 point
– Vertebral collapse < 50%	2 points
– Vertebral collapse > 50 %	3 points
Posterolateral involvement of spinal elements	
– No posterolateral involvement	0 points
– Unilateral involvement	1 point
– Bilateral involvement	3 points

Total score: 0-6 indicates stable spine, 7-12 indicates undetermined spinal instability, and 13-18 indicates spinal instability.

DIAGNOSIS

All cancer patients with a prolonged course and significant pain triggered by motion and at rest should be evaluated, searching for BM[31]. A complete physical examination is essential to explore spinal process pain and neurological deficit. Examination of neurological deficit, both sensory and motor, should look for signs of spasticity, hyperreflexia, paraparesis, plantar responses, and the presence of Brown-Séquard syndrome. Early recognition of these deficits improves the patients' prognosis after palliative intervention[31]. There is no biochemical analysis to confirm BM[4]. Several biomarkers of bone metabolism may rise 50-150% above normal values, serving as a parameter to predict BM[6,32]. A rise in bone metabolism biomarkers occurs in patients with a history of malignancy[32]. Bone scintigraphy (BS) currently is the most frequently used diagnostic procedure and is considered a reference exam for the diagnosis of spinal BM. However, in the near future, positron emission tomography-computed tomography (PET/CT) with 18F-sodium fluoride (^{18}FNaF) or magnetic resonance imaging (MRI) using diffusion-weighted whole-body imaging with background body signal suppression Diffusion-weighted whole-body imaging with background body signal suppression (DWIBS) will replace BS due to their improved diagnostic accuracy[33,34].

Bone remodeling biomarkers

Serum alkaline phosphatase is a biomarker of bone metabolism elevated in patients with BM[32]. It is secreted by osteoclasts, hence elevating its total serum levels, especially in blastic BM[35]. Alkaline phosphatase has limited bone specificity since various physiological processes such as normal growth and pregnancy, and malignant (liver and bone) and non-malignant (cirrhosis, hepatitis and diabetes mellitus) diseases are also associated with increased serum levels[6,35]. Recent studies report that Fab isoenzyme is more specific as a marker of bone remodeling in patients with lung cancer than alkaline phosphatase; however, no close relationship has been found between a tumor-specific pattern and high osteoblastic activity, product of excessive bone resorption[35]. There are other biomarkers such as osteocalcin, pyridinoline, deoxypyridinoline and tartrate-resistant acid phosphatase isoform 5b (TRAcP b5)[35]. The TRAcP is formed during type I collagen extracellular maturation process, where it is released into the

systemic circulation and excreted in urine[35]. The use of TRAcP is limited due to its variable bone specificity, mainly diverse factors including diurnal variation, sex, and menopause, among others[32].

Diagnostic imaging

Imaging studies are the next step to establish the diagnosis in patients with suspected BM. Patient follow-up is performed by using conventional radiography (Rx), computed tomography (CT), BS, PET/CT, as well as structural and diffusion MRI[8,31,36,37]. Such studies allow staging the patient, determining treatment and establishing a prognosis[8,36].

Conventional radiography

Radiography is the first study in the evaluation of patients with significant bone pain and suspected BM because it is inexpensive, fast, and easily accessible[19]. Radiography allows evaluation of spinal instability and disc space, as well as the location, extent, and classification of BM (Table 2)[4,7,10,11,38,39]. Although Rx has a high specificity, the sensitivity is low (44-50%)[18]. The radiographic appearance depends on the type of injury and the predominance of osteolytic and osteoblastic activity[40]. Lesions in the trabecular bone are more difficult to detect by Rx than lesions affecting the cortical bone, due to limited resolution of the former[40]. Lesions smaller than 1 cm may go unnoticed since there must be more than 50% of affected mineral density in the trabecular bone to be detected by Rx[8,11,19]. Through Rx, lesions suggestive of BM can be observed in the spine. These lesions are characterized as: vertebral body osteolysis; inability to visualize the pedicle; spinous process erosion; and pathological vertebral collapse[31].

Computed tomography

Computed tomography study is useful in the evaluation of BM due to its excellent assessment of trabecular and cortical bone, as well as the vertebral body, the spinal canal, the presence of local bone fragments, and of data relating to vertebral collapse. Myelography is an alternative study performed in the search for BM with epidural involvement in patients where an MRI is contraindicated. The sensitivity for CT myelography ranges between 71 and 100%[8,18,31]. This method facilitates the timely diagnosis of MSCC and paraspinal tumors; however, the soft tissue is best assessed by MRI. A CT is crucial for planning surgical management on the spine, mainly for surgical instrumentation[14].

Table 2. Radiographic classification of bone metastasis by tumor type[4,10]

Vertebral bone metastasis		
Lytic	**Blastic**	**Mixed**
Breast	Prostate	Lung
Melanoma	Breast	Gastrointestinal
Thyroid	Lung	Breast
Kidney	Pancreas	Cervical
Adrenal	Cervical	Bladder
Bladder	Small intestine	Testicular
		Ovary

Bone scintigraphy

Imaging studies with radionuclides are quick, relatively cheap, and with high sensitivity for diagnosis of many bone diseases[41]. For several decades, BS has been established as the reference exam to assess BM due to its ability to scan the entire body[34]. The procedure is performed with technetium labeled with bisphosphonate (^{99}Tc MDP) isotope, which rapidly accumulates in the bone tissue, while only 50% of the radiolabel remains in the skeletal system after 2-6 hours[41]. The uptake mechanism of bisphosphonates depends on two factors: most importantly, bone formation rate; and blood flow[41,42]. Although protocols vary among institutions, the image is typically obtained with ^{99}Tc MDP at a dose of 740-925 MBq (20-35 mCi). A low-power camera equipped with a high-resolution collimator is used to obtain anterior and posterior whole-body images used to find bone disorders (e.g., BM, Paget's disease, osteoarthropathy, avascular necrosis, trauma, osteomyelitis, etc.)[41,43]. The activity distribution of the radiolabel is symmetrical in healthy adults. The urinary bladder, the urinary tract, and minimally, soft tissues, uptake the ^{99}Tc MDP radiolabel[41]. Bone scintigraphy has played an important role in the staging and management of patients with cancer since 1980. This method is very sensitive for the detection of skeletal abnormalities and numerous studies consider it more sensitive than Rx for detection of BM[43]. About 75% of patients with a history of cancer and bone pain have an abnormal BS[41,43]. Metastatic disease may occasionally manifest as a solitary increased uptake

site in the spine[43]. Nevertheless, degenerative changes may also manifest as an isolated increased uptake site on the BS. Hormonal therapy and chemotherapy affect BS interpretation, as an increase in intensity with the appearance of new uptake foci does not necessarily indicate disease progression. This phenomenon is usually observed three months after the start of treatment and is associated with sclerotic changes that indicate its response[41]. If, after six months, the areas of tracer uptake increase in size or in saturation, this is indicative of disease progression[41,44]. One of the diagnostic limitations of BS is the visualization of the blastic BM[18]. False negatives can occur in pure lytic BM, as in avascular sites, where they appear as regions of low tracer uptake[18,41]. In contrast, false positives have been linked to various pathological processes such as inflammation, degenerative changes, and trauma[18,41]. Bone scintigraphy has a sensitivity of 87.5%, specificity of 92.9%, positive predictive value (PPV) of 91.3%, negative predictive value (NPV) of 89.7%, and accuracy of 90.4% for detection of BM[34].

Single photon emission computed tomography (SPECT) is used to differentiate between BM, degenerative changes, and infectious processes. It has the advantage of being able to select a region of interest, providing a better assessment of the injury. SPECT is the most frequently used diagnostic test in the evaluation of the spine as it can be interpreted using axial, coronal, sagittal, and three-dimensional images, thus facilitating localization and characterization of such lesions[41]. Metastatic disease can manifest in SPECT as increased radiolabel uptake; however, occasionally there are regions of low uptake. In acute-phase tumors treated with radiotherapy, osteitis occurs due to the increasing tracer uptake, represented by a peak at 2-3 months after treatment; this peak occurs in 80-90% of cases, called activation phenomenon[41]. SPECT has a sensitivity of 94%, specificity of 71%, NPV of 97%, and PPV of 53% for detection of BM[45].

Positron emission tomography-computed tomography

PET/CT is a modern imaging study in nuclear medicine, which couples high-resolution tomographic images with the use of radiolabels to detect the presence of tumors by identifying zones of increased cellular metabolic activity. Using this physiological principle, PET/CT detects BM in early stages, as well as evaluating the response to anticancer treatment[36,38]. PET/CT has the benefit of using different radiolabels to detect lesions in both bone and soft tissue. It can also detect bone marrow infiltrative lesions in early stages, as well as assessing lytic lesions[46].

Currently, 2-deoxy-2-[18F]-fluoro-D-glucose (^{18}F-FDG) is the most-used radiolabel in PET/CT. The ^{18}F-FDG is transported to the interior of the cell through the glucose transport proteins (GLUT-1 and GLUT-5), where it is phosphorylated by a hexokinase into glucose 6-phosphate. Increased glycolysis by tumor cells is associated with accumulation of the radiolabel in PET/CT images[43,46,47]. Fogelman, et al. performed a comparative study between PET/CT with ^{18}F-FDG and BS with ^{99}Tc for detection of BM in patients with lung cancer. The group reported the following results: sensitivity of 91%, specificity of 96%, and diagnostic accuracy of 94% for PET/CT; whereas BS had a sensitivity of 75%, specificity of 95%, and diagnostic accuracy of 85%[48]. With this data, the authors suggest that PET/CT with ^{18}F-FDG can replace BS with ^{99}Tc. In another study, Ohta, et al. compared these same diagnostic tools and radiolabels for the detection of BM in 51 patients with breast cancer. These authors report a sensitivity of 77.7%, specificity of 97.6%, and diagnostic accuracy of 94.1% for PET/CT; whereas, BS had a sensitivity of 77.7%, specificity of 80.9%, and diagnostic accuracy of 80.3%[49]. The discrepancies between the results reported for PET/CT compared with BS in the detection of BM is due to the fact that ^{18}F-FDG has a higher glycolytic rate in blastic BM than in lytic BM[49]. A retrospective study of 119 patients with recent diagnosis of locally advanced breast cancer, where BM was detected comparing PET/CT with ^{18}F-FDG, conventional imaging (Rx, BS, and abdominal ultrasound) and CT reported sensitivity of 87% and specificity of 83% for PET/CT, sensitivity of 43% and specificity of 98% for conventional imaging, and sensitivity of 83% and specificity of 85% for CT[50]. Compared with BS, PET/CT with ^{18}F-FDG is considered a diagnostic test with higher potential in the exploration of early stage BM[46].

There are other useful radiolabels in PET/CT that have pharmacokinetic properties similar to ^{18}F-FDG that are used in the exploration of BM[51]. Among these radiolabels, 18F-sodium fluoride (^{18}F-NaF) is worth noting. The ^{18}F-NaF is seized by osseous tissue through a process of chemisorption, where ^{18}F-NaF is irreversibly fixed to the surface of hydroxyapatite[42]. This

interaction occurs in two phases: hydroxide ion (OH^-) exchange with hydroxyapatite crystals, and through ^{18}F migration across the osseous crystal matrix, where it is held, becoming fluorapatite[52]. Accumulation of ^{18}F-NaF depends on blood flow to the bone as well as the remodeling bone surface, thus proving its usefulness in the study of primary bone cancer, BM, as well as for the differentiation between benign and malignant lesions[39]. Iagaru, et al. performed a prospective study in 52 patients (aged 19-84 years) with cancer diagnosis and suspected BM. A BS with ^{99}Tc, a PET/CT with ^{18}F-NaF and a PET/CT with ^{18}F-FDG were completed with less than one month between procedures. They found evidence of BM in 22 of the 52 patients when using BS; in 24 when PET/CT with ^{18}F-NaF was used; and in 16 when PET/CT with ^{18}F-FDG was used[34]. They conclude that PET/CT with ^{18}F-NaF has a sensitivity of 95.8%, specificity of 92.9%, PPV of 92%, NPV of 96.3%, and diagnostic accuracy of 94.2% for the recognition of BM; PET/CT with ^{18}F-FDG had a sensitivity of 66.75%, specificity of 96.4%, PPV of 94.1%, NPV of 77.1%, and diagnostic accuracy of 82.7%; and BS with ^{99}Tc had a sensitivity of 87.5%, specificity of 92.9%, PPV of 91.3%, NPV of 89.7%, and diagnostic accuracy of 90.4%. Due to the limited accessibility and elevated price of PET/CT with ^{18}F-NaF, this diagnostic modality is not routinely used in clinical practice, being reserved for those patients with high clinical suspicion of BM and negative BS results[38].

Magnetic resonance imaging

Magnetic resonance imaging studies are performed as a second-line diagnostic tool, after Rx and BS, when searching for BM. This diagnostic modality can establish the presence of BM as well as the number, extent, and type of injury. With this information, appropriate treatment may be selected for each patient with BM[8,53]. An MRI is the gold standard procedure for evaluating the spine due to its exceptional ability to visualize and differentiate between soft tissue and bone tissue, as well as to assess vertebral compressions, cortical or cancellous bone destruction, epidural involvement, neural damage, and paravertebral invasion[11,31]. An MRI has been used for the assessment of the various clinical presentations of BM. In patients with MSCC, MRI has a sensitivity of 93%, specificity of 97%, and diagnostic accuracy of 95% for spinal BM detection[14]. MSCC is often present at different levels, hence a complete spinal MRI is recommended, although in the clinical setting this is not done due to time constraints. An MRI also can differentiate between malignant and benign causes of vertebral collapse, with a sensitivity of 97.6%, specificity of 100%, and diagnostic accuracy of 98.2%[14]. To our knowledge, there are no bio-statistical data reported on MRI for the assessment of BM in patients with intractable pain, MH, and spinal instability.

The adult bone marrow contains mostly fat and water. Yellow bone marrow contains 80% fat, 15% water, and 5% cellular components, while red bone marrow contains 40% water, 40% fat, and 20% cellular components[54]. In infiltrative diseases, whether diffuse, disseminated, or solitary, fatty tissue usually disappears[8]. To assess spinal bone marrow, the following sequences are used: T1-weighted images; T2 fat saturation (FatSat); as well as short Tau inversion recovery (STIR) and T1-weighted images with gadolinium[8,54].

Spinal BM assessed in T1-weighted sequences have a longer relaxation time and show decreased signal intensity compared to that of fatty tissue, due to increased water content and replacement of adipose tissue with tumoral tissue. Changes in T2-weighted images are variable because they tend to show an increased signal at the site of injury as a result of increased cellularity[55]. Added to this, the T2-weighted images show the presence of a peritumoral halo. This halo is related to edema and is described as a hyperintense area surrounding the hypointense metastatic lesion[55]. The presence of peritumoral halo for the diagnosis of BM has a sensitivity of 75% and specificity of 99.5%[56]. These changes mentioned earlier occur primarily in malignant tissues with high mucinous content, suggesting malignancy, and have been correlated with the presence of blastic BM[43,55]. Bone metastasis with sclerotic component behaves as a lytic lesion in MRI and only when the sclerosis is marked, it manifests as a low-intensity signal in all MRI sequences[54]. The etiology of PF is difficult to differentiate by MRI[55]; however, findings suggestive of BM secondary to PF compression are:

– presence of posterior convex edge of the vertebral body;

– signal strength abnormality of the pedicle or posterior arch elements;

– epidural involvement;

– spinal cord encroachment due to epidural tumor;

– focal paraspinal tumor; and

– multiple lesions in one or more vertebral bodies[43,55,57].

– In contrast, findings suggestive of osteoporotic vertebral compression fracture in acute phase are:

– low signal intensity band on T1-weighted and T2-weighted images;

– normal bone marrow;

– high signal intensity in STIR;

– absence of signal abnormality of the pedicle or posterior arch elements; and

– multiple fracture lines due to compression[55,57].

T1-weighted images with gadolinium help evaluate bone marrow metastases due to the fact that normal bone marrow does not present enhancement after contrast medium administration, while in zones compatible with BM, contrast media enhancement is detected[8].

Diffusion-weighted imaging

Diffusion-weighted imaging (DWI) is a new MRI technique, which assesses cellular tissue and can be used for noninvasive detection of abnormal tissues. Therefore, DWI has great potential to increase the specificity in the detection of abnormalities in osseous tissue and bone marrow in cancer patients; however, DWI should be interpreted in association with structural MRI sequences for the lesion's characterization[58-61]. A DWI allows visualization and measurement of the Brownian motion (intra-, trans-, and extracellular) of water molecules, which generates a signal intensity by MRI[8]. Biological tissue barriers, cell membranes, and macromolecules restrict and interfere with the free movement of water molecules, known as water diffusion. Signal strength depends on diffusion through semi-permeable barriers to water, resulting in DWI signal restriction[62].

Physiopathological processes, such as tumors, infections, inflammation, and ischemia, can change the ratios between intra- and extracellular volume, hence altering the physical nature of cell membranes and thereby affecting the diffusion of water molecules. As mentioned earlier, DWI can measure water's Brownian motion through the apparent diffusion coefficient (ADC)[58]. The first clinical application of DWI was to diagnose ischemic stroke; having Na^+/K^+-ATPase pump function failure produces water movement translocation from the extracellular to the intracellular space[62]. As a result, the water diffusion gradient through the cell membrane increases, which corresponds to an increase of signal restriction in DWI[58,62]. Beginning in 1990, DWI was performed outside the brain, including abdomen and pelvis. A DWI may be used to detect tumors and metastases, as long as it is correlated to structural MRI sequences[62]. Takahara, et al. introduced DWIBS, a high spatial resolution three-dimensional MRI sequence providing better image quality[63,64]. Using DWIBS to differentiate between benign and malignant spinal lesions is controversial because it must be assessed along with T1-weighted, T2-weighted, and STIR sequences[64]. Tumors with a high cell density have high diffusion gradient, and therefore greater restriction on DWIBS signal[65]. Intratumoral edema and the tumoral cystic component are also capable of generating restriction signals in DWIBS[58,65]. In areas with high cellular density compatible with malignancy, DWIBS presents regional signal restriction compared with benign tissue[61,62]. Due to movement artifacts affecting signal restriction, malignant lesions might not be identified in areas surrounding the heart such as mediastinum, lung hila, and left hepatic lobe. Causes that increase false positives in DWIBS are: bone marrow edema caused by fracture; degenerative disease; bone necrosis; infection; and hemangioma[61]. Causes that increase false negatives are: poor bone marrow infiltration; and zones of signal interference adjacent to the base of the skull, where the signal intensity emitted from the brain is typically not well delimited[61]. The ADC values in malignant processes are significantly lower compared with benign processes[59]. The ADC range reported for PF compression of vertebral bodies secondary to malignant processes is 0.69-0.92 x 10^{-3} mm^2/s, while the ADC range reported for vertebral fractures with post-traumatic edema is 1.21-1.94 x 10^{-3} mm^2/s[59]. With this parameter, suspicious BM lesions could be differentiated into benign and malignant with DWIBS.

Biopsy

Histopathological examination is the gold standard exam for neoplasms, being required: if the diagnosis

is uncertain; to confirm results obtained from an imaging study before treatment initiation (since immunohistochemical examination allows identification of multiple receptors that can orient a more specific therapeutic strategy); and to differentiate between BM and osteonecrosis prior to bone radiation[31,37,66]. The most common indication to perform a biopsy in soft and bone tissue is to differentiate infectious processes from tumors[67]. Tissue may be obtained by: open biopsy; and percutaneous biopsy, which is guided by fluoroscopy, CT, and in some centers by MRI[67,68]. The advantage of an open biopsy is to obtain sufficient sample tissue for cytometric, cytogenetic, and immunohistochemical studies[67]. Disadvantages of the open biopsy are inherent to the procedure, such as infections, hematomas, neuronal injuries, anesthetic complications, and longer hospital stay[67]. Using guided percutaneous biopsy has several advantages such as: low cost compared with open biopsy; multiple sample procurement; and the immediate start of neoadjuvant chemotherapy and radiation to the injury[68]. Among its disadvantages are a wide range of diagnostic accuracy (74-97%) and insufficient sampling[67].

TREATMENT

Generally, the recommended treatment for spinal BM is conservative, provided there is no spinal instability, neurological deficit, and pain refractory to adequate treatment (including opioids)[10,31]. Among the noninvasive palliative treatments, the options are bisphosphonates, chemotherapy, radiotherapy, and radioisotope therapy (RIT)[10,31]. Invasive treatments include surgery, percutaneous vertebroplasty, and radiofrequency ablation[10,31].

Bisphosphonates

Bisphosphonates are a group of drugs that inhibit osteoclast activity and bone resorption. The structure of these agents is based on a pyrophosphate that contains a phosphorus-carbon-phosphorous (P-C-P) in its core. These agents bind to the bone matrix through a variable R' DNA chain, which participates in the mechanism of action, determines its relative potency, and causes secondary effects of bisphosphonates[19]. Following administration, bisphosphonates bind to hydroxyapatite crystals of bone matrix, reaching high local concentrations in bone resorption lacunae, where they are internalized by osteoclasts and cause their apoptosis[19,69]. A representative example of this mechanism of action is zoledronic acid, which induces apoptosis in metastases of breast and prostate cancer in humans[19,69]. Recently, it has been reported that bisphosphonates have the ability to suppress enzymes in the mevalonate pathway, which are responsible for the last events that lead to union protein post-translational modifications, such as Ras protein[69].

Bisphosphonates provide, secondarily, an analgesic effect in BM with moderate-to-severe pain. Their main property is to prevent PF as well as MH[3]. New bisphosphonates contain nitrogen, such as pamidronate disodium, zoledronic acid, and ibandronate sodium, and hence have greater potency[19], while first-generation de-nitrogenized bisphosphonates, such as clodronate disodium and etidronate, have lower potency[19]. Common side effects are anemia, diarrhea, and peripheral edema, as well as symptoms similar to the common cold such as fever, arthralgia, myalgia, osseous pain, and overall weakness[19,70]. Although rare, major side effects, such as mandibular osteonecrosis, have been reported; this has occurred in patients with breast cancer and multiple myeloma who used intravenous bisphosphonates[19,70].

Renal function must be monitored in patients with aggressive neoplasms, such as multiple myeloma, or undergoing chemotherapy treatment having a glomerular filtration rate lower than 60 ml/min before bisphosphonate therapy initiation because they are prone to develop nephrotoxicity[19,70]. It is worth noting that a poor state of hydration, NSAIDs, oral antidiabetic drugs, and hypolipidemic agents decrease glomerular filtration rate[19,70].

Chemotherapy

Due to its systemic action, chemotherapy is a treatment option for BM in metastatic tumors such as breast cancer, lymphoma and renal carcinoma[25]. Efficacy of chemotherapy depends on the histology, chemosensitivity, as well as the presence of hormonal receptors[3]. Antitumor therapy has a limited effect on BM in the spine; however, it plays an important role in the treatment of chemosensitive tumors such as Ewing's sarcoma, osteogenic sarcoma, and lymphoma[25]. There are no data suggesting that BM is more or less sensitive to chemotherapy or hormone therapy than other metastatic sites[71]. Among the novel therapeutic modalities for BM treatment, monoclonal antibodies are worth noting.

Denosumab is a monoclonal antibody that inhibits the RANKL complex, and hence it decreases osteoclastic-mediated bone resorption[72,73]. Fizazi, et al. performed a phase III study with patients with prostate cancer and BM resistant to castration without previous use of bisphosphonates. From 2006 to 2008, 1,901 male patients were included; 950 received denosumab, while 951 received zoledronic acid[72]. Among the reported results, the subcutaneous administration of 120 mg denosumab every four weeks had a better outcome than the administration of 4 mg zoledronic acid every four weeks in the prevention of complications related to BM[72]. Compared to zoledronic acid, denosumab had an 18% decrease in complications[72].

Denosumab does not affect glomerular filtration rate, and hence it does not require renal function monitoring and it was not associated with acute reactions[72]. Due to solid evidence of decreasing complications associated with BM[73], in November 2011, denosumab was approved by the U.S. Food and Drug Administration as a molecular therapy to inhibit osteoblastic activity.

Among the complications associated with chemotherapy are pain, fatigue, hematological abnormalities, alopecia, infertility, immunity, and gastrointestinal alterations[25]. Complications related to denosumab are mandibular osteonecrosis and hypercalcemia, which are similar to the use of bisphosphonates[74,75].

Radiotherapy

Radiotherapy is the most frequent initial treatment used in patients with spinal BM[76]. The indications for palliative radiotherapy in patients with BM are: bone pain refractory to adequate treatment (patients had significant pain reduction of 90% with radiotherapy[77]); PF prevention; and MSCC prevention, without evidence of instability[19,22,24,74,75].

The radiation dosage depends on the type and size of the primary tumor[71]. Conventional external beam radiotherapy typically uses 25-40 Gy of total dosage, which is divided in 8-20 fractions[76]. Radiotherapy may be applied in single or multiple fractions, as well as hemibody radiotherapy. In non-complicated BM, radiotherapy with a single fraction of 8 Gy is considered the gold standard for analgesic purposes[78]. For lytic BM at risk of PF, a 10-fraction scheme of 3 Gy should be used with the objective of achieving re-calcification. In patients with MSCC, the use of 10 fractions of 3 Gy is recommended as it has proved to be more effective than a scheme consisting of a single fraction of 8 Gy and five fractions of 4 Gy.[77] Several studies report a greater risk of re-irradiation after using a single fraction scheme of radiotherapy rather than multiple fractions (24 Gy in six fractions or 30 Gy in 10 fractions)[22,79].

The medical indications for single fraction radiotherapy are: treatment for unmanageable bone pain with NSAIDs, opioids, and medical orthopedic corset; treatment of BM in non-weight-bearing bones, such as ribs, clavicles, and sternum; and treatment of patients with terminal stage BM. The medical indications for multiple fractioned radiotherapy are: treatment of lytic lesions in weight-bearing long bones; treatment of BM in the spine with MSCC; and postoperative therapy for PF.

The medical indication for hemibody radiotherapy is palliative treatment for multiple symptomatic BM[80]. Hemibody radiotherapy as adjuvant to local irradiation reduces the late emergence of occult metastases and decreases retreatment frequency[80].

The most frequent side effects are nausea, emesis, and gastrointestinal malaise, which occur in BM that are irradiated next to the stomach or the gastrointestinal tract. There are less reported cases of acute toxicity with the use of multi-fractioned radiotherapy; there is a 26% acute toxicity with a 4.5 Gy in 5-fraction scheme, compared with a 22% toxicity using 10-Gy single-fraction radiotherapy. Post-radiation pain is present in 14-44% of the radiotherapy schemes and may be ameliorated with prophylactic administrations of dexamethasone[77].

Radioisotope therapy

Radioisotope therapy (RIT) is a systemic treatment for advanced cancer patients, performed through the emission of α or β radiation, which can be used to treat BM. The most commonly used isotopes are strontium 89 (^{89}Sr) and samarium 153 (^{153}Sm)[23]. Medical uses of RIT include unmanageable bone pain and BS with more than one region with high uptake associated with bone pain[81].

Strontium 89

Strontium is a group II metallic element that behaves biologically similarly to calcium[81,82]. Bone regions with

blastic activity uptake ^{89}Sr and β particle emission is delivered with a maximum energy of 1.46 MeV, with approximately 7-10 mm tissue radius[80,81]. Strontium is administered intravenously as strontium chloride, acting on bone regions with high calcium turnover like osteosclerotic foci, having renal and gastrointestinal elimination[23]. An increase in pain occurs during the second or third day after ^{89}Sr administration, which can be limited with the administration of NSAIDs. Although the biological half-life of ^{89}Sr is 4-5 days, about 20% can still be traced in the body after 20 days[81,82].

Samarium 153

Samarium 153 has a biological half-life of 46.3 hours, emits β particles with a maximum energy of 0.81 MeV, with approximately 0.6-0.7 mm tissue radius[80]. Samarium is linked to ethylenediamine-tetramethylene phosphonic acid (EDTMP); this phosphonate complex is accumulated in osseous tissue in a direct proportion to the osteoblastic activity generated by tumor cells[82]. After the intravenous injection, less than 1% remains in the bloodstream, while after five hours about 65% of the dose remains in the bone[82]. Renal excretion lasts about six hours. The distribution of the ^{153}Sm-EDTMP is identical to ^{99}Tc-MDP used in BS, since it is coupled to hydroxyapatite[82]. Samarium is generally administered at a dose of 37 MBq/kg (1 mCi/kg)[82]. The absolute contraindications for RIT are: pregnancy; acute MSCC; chronic kidney disease with a glomerular filtration rate < 30 ml/min; neutropenia < 1,500/ml; thrombocytopenia < 60,000/mL; and leukopenia < 3,500/ml[81,82]. In general, RIT is a systemic therapeutic alternative that has a good cost-benefit ratio, lowering morbidity and increasing the quality of life in patients with BM[82].

Surgery

Bone metastasis decreases the bone's capacity to bear weight, which initially results in trabecular disruption and/or micro factures, leading to loss of total bone integrity[69]. Among the indications for surgery in BM are: neurological deficit due to progressive MSCC refractory to radiotherapy; spinal instability; unmanageable pain due to a radio- and chemoresistant tumor; and unstable fracture[24,31]. Prophylactic surgery has been proposed in patients with a high risk of PF through fixation with osteosynthesis material[19].

The main goal of surgery is to achieve nerve decompression as well as stabilization and reconstruction of the spine. The surgical approach may be anterior, transcavitary, posterolateral, or transpedicular[10,25]. The technique employed depends on the tumor localization and extension, as well as the presence of epidural involvement, evidence of paraspinal tumor, spinal instability, and MSCC[10,25]. Spinal decompression is done with a dorsal approach through a laminectomy, which eliminates spinal cord pressure and potentially resolves neurological deficits. However, BM in the spine commonly occurs in the ventral region, causing instability; therefore, posterior or anterior instrumentation is required[3]. Surgical complications include postoperative hematoma and fixation failure, requiring re-intervention. Wound dehiscence and infection are complications predominantly present in posterolateral approaches with 15% mortality[25].

Some tumors with a vascular component (e.g., BM from renal carcinoma, papillary thyroid cancer, and leiomyosarcoma) require a pre-surgical embolization, because this procedure reduces transoperatory blood loss[3,25]. Posterior spinal decompression and vertebral stabilization are considered standard surgical techniques for the treatment of BM in the thoracic and lumbar spine; glioblastoma multiforme in the cervical spine is treated preferably with anterior decompression and corpectomy with vertebral body replacement[25]. Lastly, minimally invasive techniques such as radiofrequency ablation (RFA) and percutaneous vertebroplasty with the injection of polymethylmethacrylate are used extensively in the treatment of vertebral collapse[3].

Percutaneous vertebroplasty

Percutaneous vertebroplasty (PV) was described in 1987 as a minimally invasive procedure guided through fluoroscopy, which entails an injection of polymethylmethacrylate at the site of painful vertebral metastases. This procedure was described as a treatment for aggressive pain secondary to vertebral hemangiomas[83]. Currently, the main indications for PV are pain treatment for fractures secondary to osteoporosis, BM and multiple myeloma[84]. The main indication for PV is refractory pain, defined as lack of pain relief 4-6 weeks after conventional treatment; another indication is spinal instability[85]. Contraindications for PV are: infections such as osteomyelitis, discitis, spinal abscess with fever, or sepsis; hemorrhagic diasthesis, defined as thrombocytopenia < 100,000/ml, prothrombin time

1.6 times greater than normal, and thromboplastin time 1.5 times greater than normal; metastases that involve posterior arch elements; and non-painful vertebral compression[83,85,86]. Percutaneous kyphoplasty is a variant of PV that includes the use of an inflatable balloon to create a cavity within the bone, reducing the pressure of the cement, whereby the risk of leakage of polymethylmethacrylate decreases[85]. There are reports of improvements within 24 hours with the use of PV and percutaneous kyphoplasty, with complete or partial pain improvement in 85.8 and 80%, respectively, maintaining pain improvement at 1, 3, 6, and 12 months[87,88].

Percutaneous vertebroplasty complications occur in 5-10% of neoplastic fractures, and in 1-2% of osteoporotic fractures[84,85]. These complications may be local, including: direct radicular injury, a rare complication where the nerve sheath ruptures; spinal cord cement compression, which can result in paraplegia; and CSF fistula secondary to thecal sac damage[86,89].

Systemic complications include: infections secondary to *Staphylococcus epidermidis*, among other pathogens; acute respiratory failure related to pleural injury with pneumothorax or hemodynamic instability due to injury to the aorta; and pulmonary cement embolism, an infrequent complication that induces acute respiratory failure and hemodynamic instability in a few cases[15,85].

Radiofrequency ablation

Radiofrequency ablation (RFA) involves the use of electrodes that penetrate the vertebral body, guided by fluoroscopy or CT, in order to destroy abnormal tissue by thermal injury, enough to cause local cell death[90]. Other forms of thermal ablation studied include microwave, laser, high-intensity ultrasound, and cryotherapy. The proposed mechanisms by which RFA decreases pain involve: inhibition of pain transmission by destruction of sensory nerve fibers in the periosteum; tumor volume reduction, with decreased stimulation of the sensory nerve fibers; destruction of tumor cells involved with nerve stimulating cytokine production, such as TNF-α and IL-6, among others; and inhibition of osteoclastic activity[91].

The selection criteria for the treatment of BM through RFA are[92]: refractory pain in the vertebral body with BM with diagnosis of PF with an osteolytic pattern by imaging studies; lesions that do not respond to chemotherapy and/or radiotherapy (these lesions should be reassessed at three weeks after treatment, before the RFA session); complications associated with chemotherapy that interrupt this treatment; and patients with more than two months of life expectancy that do not meet the criteria for surgical treatment.

One of the problems with RFA is the potential risk of nerve root and spinal cord damage[93]. The risk of neurological damage due to thermal injury is higher if the treated lesion is too close (< 10 mm) to a neural structure (spinal cord or nerve root)[93].

Absolute contraindications for RFA treatment in BM are[92]: asymptomatic vertebral compression fractures; refractory pain despite adequate treatment (e.g., NSAIDs, opioids, chemotherapy or radiotherapy); local or systemic infection; intractable coagulation disorders; and tumors causing spinal cord compression.

Pain relief occurs in a matter of minutes or days, with a median of 24 hours after the procedure, although transitory pain is a relatively rare complication[91]. It has been documented that RFA causes significant pain reduction in 80-95% of patients with painful BM, with complications occurring in 0-6.9%[94].

PROGNOSIS

In some patients with BM, this condition becomes chronic and requires multiple treatments, tending to disease progression. Tokuhashi, et al. developed a scoring system that helps to determine life expectancy in cancer patients with spinal lesions, focused on the histopathology of the primary tumor, presence of BM, and severity of the neurological deficit (Table 3). This scoring system includes six sections: (i) general condition; (ii) number of foci of extraspinal BM; (iii) number of metastases in the vertebral body; (iv) metastases to major internal organs; (v) primary site of the cancer; and (vi) neurological deficit[95]. Several prognoses for cancer with BM have been described. The five types of cancer that cause more than 80% of BM are: breast, prostatic, thyroid, lung and renal[7,96].

Table 4 describes the prognosis in cancer patients with and without BM, according to histopathological type of tumor with high bone affinity: frequency of BM in patients in remission, average survival with and without

Table 3. Tokuhashi's scoring system to determine life expectancy in cancer patients with spinal column lesions[95]

General condition	
– Poor	0 points
– Moderate	1 points
– Good	2 points
Number of extraspinal bone metastases foci	
– ≥ 3	0 points
– 1-2	1 point
– 0	2 points
Number of metastases in the vertebral body	
– ≥ 3	0 points
– 2	1 points
– 1	2 points
Metastases to major internal organs	
– Un-removable	0 points
– Removable	1 points
– No metastases	2 points
Primary site of the cancer	
– Lung, osteosarcoma, stomach, bladder, esophagus, pancreas	0 points
– Liver, gallbladder, unidentified	1 points
– Others	2 points
– Kidney, uterus	3 points
– Rectum	4 points
– Thyroid, breast, prostate, carcinoid tumor	5 points
Palsy	
– Complete (Frankel* A, B)	0 points
– Incomplete (Frankel C, D)	1 points
– None (Frankel E)	2 points

Total score: ≤ 8 indicates a life expectancy of 6 months, 9-11 indicates a life expectancy of 6-12 months, and ≥ 12 indicates a life expectancy of > 1 year.
*Frankel Grade Function. A: complete paralysis; B: sensory function only below the injury level; C: incomplete motor function below injury level; D: fair-to-good motor function below injury level; E: normal function.

BM, survival for at least one year in patients with and without BM, and survival for five years in patients with and without BM[24,96-121]. The presence of BM affects the patient's overall survival, hence the importance of detecting this complication promptly to intervene therapeutically and to adjust the patient's prognosis.

CONCLUSIONS

The patient with cancer and metastases in the spine presents a challenge for the clinician in the areas of diagnosis and treatment. This challenge must be addressed through a multidisciplinary, multimodal, and individualized management. The presence of tumor cells in BM results in a disruption of the homeostasis between bone formation and remodeling. There may be excessive bone destruction or formation, producing blastic lesions. Bone destruction is a late event in the formation of lytic BM, beginning with the proliferation of tumor cells, which activate osteoclasts, exhibiting trabecular destruction in imaging studies. Currently, bone scintigraphy is the most widely used diagnostic method and is considered a reference test for the diagnosis of spinal BM diagnosis. However, we believe that in the near future PET/CT with ^{18}F-NaF or MRI utilizing DWIBS, will replace bone scintigraphy due to their improved diagnostic accuracy. These new diagnostic tools will help to prevent BM complications, such as: intractable pain; MSCC; MH; PF; and spinal instability. As for the treatment, it can be uni- or multimodal, depending on the type and number of BMs. Prognosis of patient survival depends on the histopathology of the primary tumor, the presence of BM in the spine, and the presence of neurological complications.

Table 4. Patient survival prognosis with and without bone metastases

Tumor type	Frequency of BM in patients in remission (%)	Average survival without BM (months)	Average survival with BM (months)	Patients without BM that survive at least 1 year (%)	Patients with BM that survive at least 1 year (%)	Patients without BM that survive 5 years (%)	Patients with BM that survive 5 years (%)
Breast	80-85[96]	24-36[96,97]	24[98]	89[99]	40.2[99]	79-80[99,101]	20[24]
Prostatic	85[96]	36[101]	23-48[96,103]	87[104]	40-47[104]	56[101]	< 1-3[24,104,112]
Thyroid	50[96]	120[105] 2.5-3.0[106] (Anaplastic)	48[96]	90-100[107]	80[107] 9.7[106] (Anaplastic)	83.5[101]	29-53[24,108]
Lung	39.4-44.0[96,111]	7.9-15.0[109]	2.5-15.0[96,111,112]	17.2-40.8[110]	50-76[111]	14.0-15.7[112,113]	2-5[24,114]
Renal	20-35[96,115]	12.0-12.8[116]	10-24[96,117,118]	84[117]	42-88[118-120]	66[119]	10-45[24,115,117]

BM: bone metastases.

DECLARATION OF INTEREST

The authors declare no conflicts of interest.

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