# **Multidisciplinary management of vertebral metastases in patients not amenable to surgery**

Antonio Manca<sup>1,2</sup>, Lorenzo D'Ambrosio<sup>3,4</sup>, Gabriele Chiara<sup>1,2</sup>, Marco Gatti<sup>5</sup>, Stefano Marone<sup>6</sup>, Antonia Salatino<sup>5</sup>, Giovanni C. Anselmetti<sup>7</sup>, Giuseppe Rossi<sup>8</sup>, Cinzia Ortega<sup>3</sup>, Giovanni Grignani<sup>3</sup>, Daniele Regge<sup>2,9</sup>

#### **Abstract**

Bone metastases occur in up to 70% of cancer patients, and frequently involve the spine. Spine metastases are often associated with pain, disability and progressive deformity, and may also have neurological complications, all of which can dramatically impair quality of life. There are a number of different approaches to managing vertebral metastases, including surgery, vertebroplasty and radiotherapy. The variety of treatment modalities involved, the presence of underlying cancer and frequent severe pain means that patients with vertebral metastases need to be managed by a multidisciplinary team, ideally including a medical oncologist, radiation oncologist, interventional radiologist, pain therapist and spine surgeon. Although a number of different multidisciplinary therapeutic algorithms have been proposed, there is no clear consensus on the best way to manage vertebral metastases. After reviewing current literature, this article proposes a new visual algorithm created by merging some existing guidelines and introducing additional interventional radiology techniques.

**Key words:** interventional radiology, multidisciplinary team, radiotherapy, vertebral augmentation, vertebral metastases

## **Introduction**

After liver and lung, bone is the third most common location of metastases, occurring in up to 70% of cancer patients, and the spine is the most frequently involved site [1-3]. The skeletal system is the only or main metastatic site for many tumors; in particular, breast and prostate cancer account for up to 80% of primary tumors with bone spread [1]. Overall, vertebral fractures are found in up to 30% of patients with solid tumors [4, 5].

Spine metastases, and in particular those leading to spinal instability, can have a significant impact on quality of life due to the occurrence of refractory pain, disability, progressive deformity, and potential neurological complications [6-16]. The management of these metastatic patients needs to be discussed in multidisciplinary teams (MDT) involving a medical oncologist, radiation oncologist, interventional radiologist, pain therapist and spine surgeon because spine stability, pain and tumor growth often need to be treated at the same time.

A number of different multidisciplinary therapeutic algorithms have been proposed, which take various approaches depending on tumor involvement, patient symptoms and performance status [13, 17-20]. In general, surgery has a well-established role in the management of spinal cord

1 Interventional Radiology, Candiolo Cancer Institute - FPO, IRCCS Candiolo, Torino, Italy.

2 Radiology Unit, Candiolo Cancer Institute - FPO, IRCCS Candiolo, Torino, Italy.

3 Division of Medical Oncology, Candiolo Cancer Institute - FPO, IRCCS Candiolo, Torino, Italy.

4 University of Torino, Department of Oncology, Italy.

5 Radiotherapy Unit, Candiolo Cancer Institute - FPO, IRCCS Candiolo, Torino, Italy.

6 Department of Orthopaedic Oncology and Reconstructive Surgery, Azienda Ospedaliero Universitaria Città della Salute e della Scienza, CTO Hospital, Torino, Italy.

7 Interventional Radiology, Istituto Europeo di Oncologia, Milan, Italy.

8 Department of Interventional Angiographic Radiology, Istituto Ortopedico Rizzoli, Bologna, Italy.

9 University of Torino, Department of Radiology, Italy.

**Correspondence to:**  Antonio Manca, MD, PhD

Interventional Radiology, Radiology Unit, Candiolo Cancer Institute – FPO, IRCCS,

Strada Provinciale 142, Km 3,95, 10060 Candiolo (TO), Italy. Phone: +39 011 9933 041 – Fax: +39 011 9933 301

E-mail: antonio.manca@ircc.it

Lorenzo D'Ambrosio, MD

Division of Medical Oncology, Candiolo Cancer Institute – FPO, IRCCS,

Strada Provinciale 142, Km 3,95, 10060 Candiolo (TO), Italy. Phone: +39 011 9933 623 – Fax: +39 011 9933 290

E-mail: lorenzo.dambrosio@ircc.it

CANCER BREAKING NEWS 2016;4(2):23-33

DOI: 10.19156/cbn.2016.0015

compression and/or instability [6, 19], while vertebroplasty is primarily advised for symptomatic patients not suitable for surgery and not responding to pain medications. Radiotherapy remains an important therapeutic option and is synergistic with interventional radiology procedures. However, the optimal timing of these two approaches is still not clearly defined.

This article suggests MDT ways of managing patients with spinal metastases deemed unsuitable for surgery or refusing surgical intervention. A visual algorithm was created by merging some existing guidelines and introducing further possible interventional radiology techniques on the basis of the available literature.

## **Spine metastases evaluation**

#### **Imaging**

Magnetic resonance imaging (MRI) has the highest sensitivity for bone metastases [21, 22], but computed tomography (CT) is usually required to assess bone lesion quality (lytic, blastic, or mixed), potential spine instability and risk of pathologic fracture [23, 24]. CT scan performed during follow-up in oncology patients should be integrated with multiplanar reconstructions (MPR) of the spine for metastases detection. Sagittal MPR of the spine should be routinely performed in patients with multiple myeloma, lung, breast and prostate cancer given the high incidence of vertebral lesions associated with these tumors. Irrespective of the specific examination, the key point is to identify high-risk metastatic patients that need to be discussed in MDT. Nuclear medicine plays an important role in oncologic staging. In case of tumor metabolic uptake at baseline, positron emission tomography (PET)-CT is fundamental for evaluation of the response to systemic therapy, but also after local treatments like radiotherapy and thermal ablation.

#### **Assessment of spinal instability**

Any spinal cord compression with actual or potential neural deficit demands an urgent surgical consultation [6], but patients with spine instability due to bone neoplastic lesions should also have a consultation with a spinal surgeon, possibly within a MDT. The Spine Oncology Study Group (SOSG) defined spine instability as the "loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or progressive deformity and/or neural compromise under physiological loads" [25].

To stratify the risk of spine lesions, SOSG developed the Spinal Instability Neoplastic Score (SINS) system [25] that is the sum of the scores taking into account location (from 0 points [sacrum] to 3 points [junctional tracts]), pain (3 points if present, 1 if occasional, 0 if absent), bone lesion (2 points for lytic, 1 for mixed and 0 for blastic), alignment (4 points for subluxation/translation, 2 for scoliosis or kyphosis), vertebral body collapse/involvement (3 points for  $>50\%$  collapse, 2 for  $\leq 50\%$  collapse, 1 for  $>50\%$  body involvement), and posterolateral involvement of spinal elements (3 points for bilateral, 1 for unilateral) [19]. According to SOSG, patients with SINS from 0 to 6 have stable lesions, from 7 to 12 points have potentially unstable lesions, and from 13 to 18 points have unstable lesions. Patients with higher SINS (7 points or more) should be visited by a spine surgeon as soon as possible to avoid neurological complications [25].

However, patients with lower SINS score can also be treated for metastases, even if the lesions are small and/or asymptomatic, and these cases are also worthy of discussion with the MDT. In such situations, oncologists need to recognize which patients are suitable candidates for local treatments. Apart from the SINS score, several other important disease and patient features have to be carefully taken into account when selecting the best treatment option for spine lesions (i.e. tumor histology, life expectancy, bone quality, tumor size, location of vertebral defects, involved level, response to non-operative treatment, prognosis, patient medical fitness, and informed patient preference) [8, 15, 26-34].

## **Treatment for spine metastases**

#### **Surgery**

Surgery is generally mandatory in the presence of spinal cord compression (about 8% of tumors) with neurological symptoms and when spinal instability is present. The combination of spinal surgery and radiotherapy (RT) has been shown to be superior to RT alone [6, 35]. Several scores have been proposed to assist with determining how aggressive surgery needs to be taking into account functional status, extravertebral osseous metastases, vertebral metastases, visceral metastases, neurological dysfunction and histology of the primary tumor [36-38]. According to Tomita et al., the treatment goal depends on life expectancy and tumor extension [38]. Thus, for patients with rapidly growing tumors and widespread systemic metastases, the best approach was suggested to be limited palliative decompression surgery or supportive care only. Conversely, patients with slow-growing tumors and/or solitary spinal metastasis can be considered for wide or marginal excision of the tumor, with the goal of achieving long-term disease control [38, 39].

#### **Radiation treatment**

Radiation therapy is often the only therapeutic option for radiosensitive tumors, which may vary according to tumor





**Fig. 1.** 63-year-old man with lung cancer and multiple painful vertebral lytic metastases. The disease rapidly progressed with numeric and dimensional increase of metastases. The lesion on T9 showed cortical disruption and bulging of posterior wall (see MRI in bottom box) with reduction of vertebral height; new wide lytic lesions appeared on T6, T8 and T10. Surgery was not considered because of rapidly progressing disease, absence of neurological symptoms, poor general condition and many wide lytic lesions involving multiple contiguous levels. Vertebroplasty was not performed "upfront" also because of posterior vertebral wall disruption and bulging with spinal cord initial compression. The MDT decided on RT and medical treatment, achieving partial control of symptoms. Interestingly, the levels treated with RT (T8, T9, T10) still appeared lytic while other metastases became sclerotic (third CT image from left) after zoledronic acid therapy. After RT a severe pathologic fracture of T9 appeared. Vertebroplasty of T6, T8, T9 and T10 was then performed, achieving complete pain relief. Blastic lesions had no indication to vertebroplasty.

type and prognosis [40]. For example, in the setting of painful bone metastases, treatment with single fraction 8 Gy radiation was non-inferior to classic treatment (30 Gy in 10 fractions or 20 Gy in 5 fractions) in more than one prospective randomized clinical trial, even if retreatment was required in the longer term [40, 41]. Stereo body radiotherapy (SBRT) can be considered in patients with good life expectancy who are not suitable candidates for surgery [42]. Moreover, it needs to be taken into account that tumors defined as radioresistant according to classic radiobiologic ranking may respond to high-dose single-fraction SBRT [43, 44].

Radiation therapy represents an important tool in the treatment of vertebral metastases, but post-radiation therapy vertebral body fracture can occur in almost half the patients and may complicate the clinical scenario [17, 42, 45]. The risk of spine-related events is higher after administration of 8 Gy single fraction, which is usually reserved for patients with life expectancy  $\leq 6$  months [46]. In order to avoid postradiation fractures, some authors recommend prophylactic vertebral stabilization or percutaneous vertebral augmentation (VA) that, based on data from existing studies, can be undertaken prior to RT in older patients with painful lytic lesions involving >40% of vertebral body, especially if the affected level is below T10. In contrast, RT is indicated "upfront" in cases of epidural tumor bulging with no surgical indication but with contraindication to vertebroplasty in order to reduce spinal canal stenosis and allow a safe VA (Figure 1). When cortical disruption is detected, RT can reduce tumor bulk and promote cortical regrowth, reducing the risk of bone cement leakage.

When RT is not feasible at higher doses because of the proximity of critical structures (i.e. spinal cord) or previous treatments, interventional radiology procedures such as thermal ablation and/or embolization can be used to provide tumoral debulking or local control.

## **Interventional radiology**

Interventional radiology (IR) utilizes many therapeutic tools to manage pain, vertebral stability and local tumor control at once. The main procedures are VA techniques, all consisting of bone cement injection, and thermal ablation that can be applied both with palliative or curative intent. These techniques can be used alone or in combination, even by other spine specialists, but IR can also choose a vascular approach using embolization, or introduce high-precision brachytherapy probes with intra-operative radiotherapy (IORT) or treat lesions noninvasively using MRI-guided focused ultrasound (MRgFUS). All these procedures require an in-depth knowledge of radiologic anatomy and different diagnostic techniques, which are all fundamental to correct patient selection, interventional guidance and appropriate follow-up designed to correctly recognize and treat relapses as soon as possible.

## **Thermal ablation**

Thermal ablation refers to any procedure that exploits temperature to provoke tumor cell death; this can be induced by either heating (radiofrequency, microwaves and laser) or freezing (cryoablation) [47]. Although thermal ablation has an accepted role in visceral tumors and metastases [48-52], there is still a lack of strong evidence regarding the local control of vertebral metastases. Worldwide experience with treating the spine is limited due to concern about potential neurological complications, although different techniques have been proposed to monitor and prevent these relevant events (i.e. thermal sensors along the ablation needle or placed in nerve foramina/epidural space, carbon dioxide or warmed fluid injection, motor-evoked potential monitoring) [47, 53, 54]. Nevertheless, some authors reported good pain relief and local control, mainly in lytic lesions [54, 55]. Ablation can be combined with VA to provide good pain relief and improve quality of life [56], but when ablation is followed by vertebroplasty is not possible to know whether consolidation alone could provide the same analgesic effect. On the other hand, the presence of acrylic cement artifacts could hide tumor recurrence at follow-up imaging (with the exception of PET-CT). Tomasian et al. reported significant pain relief and very good local control with cryoablation performed mainly without VA, suggesting that tumor ablation itself has an analgesic effect [57]. Nonetheless, thermal ablation is generally followed by VA because peritumoral bone marrow necrosis may weaken the vertebral body [58, 59]. Most papers on thermal ablation have typically focused on pain relief in a palliative setting rather than on antitumor activity, although some recent studies have also reported good activity in terms of local control [57, 59-62]. Furthermore, a recently published paper by Greenwood et al. suggests the possible synergic effect of radiotherapy, bone cement injection and ablation [55].

On the basis of existing literature thermal ablation is mostly likely best applied in the treatment of oligometastatic disease or in selected cases of widely metastatic disease with few critical lesions not amenable to RT.

### **Focused ultrasound surgery (FUS)**

FUS is a thermal ablation technique based on a focused ultrasound beam, often performed under MRI guidance (MRgFUS), that is able to destroy tumor tissue by heating without the requirement to insert a needle. In the latest consensus conference by an international panel of experts, FUS was considered applicable on the spine only for posterior elements below the level of the conus medullaris [63]. MRgFUS allows the administration of precise "point by point" ablation with the possibility of real-time ablation and temperature monitoring. One of the main advantages is the ability to treat radioresistant or previously irradiated lesions. Nonetheless, FUS is a technique with the potential to cause thermal harm to vital structures, nerve roots or skin, and therefore must be carefully applied by expert operators and in very selected cases. The procedure can be also painful, necessitating pain control and sedation. The effects of FUS on bone lesions have been shown to be good, both in terms of pain relief and local control [64].

# **Vertebral augmentation: percutaneous vertebroplasty, kyphoplasty, and endoprosthesis placement**

All percutaneous vertebral consolidations are generally labeled as VA and are performed under radiological monitoring using fluoroscopy and/or CT. In vertebroplasty (VP) the acrylic bone cement is injected into the vertebral body through a needle inserted percutaneously via the safer anatomical pathway (usually anterior wall, costo-vertebral joint or pedicle at the cervical, thoracic and lumbar levels, respectively). In kyphoplasty (KP), a balloon is inserted through a similar needle and inflated within the vertebral body creating a cavity before cement injection. In vertebral percutaneous endoprosthesis placement, a mesh stent or a different device (coil or cage) is introduced through a largebore vertebroplasty needle, then expanded and left in place in the vertebral body before cement injection. Both KP and vertebral percutaneous endoprosthesis placement are intended to lift the endplates to restore vertebral height and/or



limit bone cement leakage. However, in KP the height gain can be lost because of elastic recoil after balloon deflation while the expanded prosthesis or stent should maintain the restored height.

Several lines of evidences strongly support the use of VA for pain control in cancer patients, with level I evidence for pain relief in metastatic fractures [65, 66]. No differences between VP and KP were observed in two recently published trials in osteoporotic fractures [67, 68]. Considering that there is level I evidence that KP and VP have comparable analgesic effects on osteoporotic fractures and also level I evidence that KP is superior to non-surgical management in metastatic fractures, we can assume that all VA procedures are similarly effective for metastatic disease with a high level of evidence. The use of KP is often preferred by some operators, with a lower likelihood of leakages; some studies comparing VP and KP in osteoporotic patients reported that venous leakages were less frequent with KP [67, 68]. Nonetheless, in metastases leakages can occur also through interruptions. Balloon inflation cannot prevent leakages through cortical gaps and the inflation of a balloon inside tumor tissue seems, in our opinion, more aggressive than simple bone cement perfusion because this could theoretically lead to tumor displacement and bleeding. Moreover, KP usually requires a bilateral (rather than unilateral) approach, larger needle size and use of contrast medium to inflate the balloons. The greater invasiveness of this procedure can also require deeper sedation that is not always easy to obtain in prone patients who may be in poor health. Given that the cost of KP is also higher than that of VP, it is likely that VP is more cost-effective than KP.

VA using polymethylmethacrylate (PMMA) cement combined with radionuclides was investigated in a phase I trial and intraoperative radiotherapy (IORT) was performed in association with KP (Kypho-IORT) in a pilot study [69, 70]. Both procedures were deemed safe and feasible but to date there is still no strong evidence about the cost-effectiveness of this approach compared with standard VP/KP and external beam radiation therapy. Other experimental studies investigating bone cements containing drugs, radioactive seeds and metal particles have been published or are currently ongoing [71].

The exothermal effect and direct chemical cytotoxicity of PMMA have often been advocated as a possible curative effect of VA. However, local control in vertebrae treated with VA alone is incidental given the different sensitivity of each metastasis to heat depending on size, histology aggressiveness, cortical erosions, and sensitivity to concomitant systemic therapies. Thus, VA procedures should be used alone mainly with palliative intent in widely metastatic disease.

Whenever a curative intent is pursued, radiotherapy or ablation should be added to the procedure.

## **Embolization**

In some patients, vertebral lesions are not treatable with RT or with ablation procedures because of their proximity to critical structures or size exceeding the ablation capabilities of the devices. In these cases embolization or chemoembolization could be considered an option, especially for hypervascular lesions less sensitive to RT such as metastases from renal cell cancer and hepatocarcinoma. These techniques were found to be able to provide good pain relief in a high percentage of patients (97% with embolization, 83% with chemoembolization). However, these procedures were associated with post-embolization syndrome, mainly manifesting as moderate to severe pain, in nearly 50% of patients [72, 73].

#### **Medical treatment**

In addition to all the above mentioned techniques for local control, all cancer patients with bone metastases should be evaluated for systemic treatment with bisphosphonates or denosumab to reduce or delay the risk of skeletal-related events (SRE) [74, 75]. According to reviews and metaanalyses, bisphosphonates can reduce the incidence of SRE in 17% of breast cancer patients, 5% of prostate cancer patients (non-responders to hormonal therapy) and up to 19% of those with non-small cell lung cancer (NSCLC) [76-78]. Denosumab showed even better results compared with bisphosphonates, with a delay of the onset of SRE in 18% of breast cancer patients and an increase in the median time to first SRE from 17.1 to 20.7 months in prostate cancer patients, and from 16.3 to 20.6 months in those with solid tumors, including NSCLC [79-81].

## **Multidisciplinary management**

There are several lines of evidence suggesting that managing cancer patients within a MDT is associated with increased survival and better treatment in different types of cancer [82-86]. Bone MDT has the unique feature that it is focused on the management of bone metastases as a "medical problem" to solve independently of the primary cancer. Patients with bone metastases, often disabled and sympthomatic, should not have to take the time to get different and conflicting information from several specialists. Many patients evaluated by MDT have no indication for surgery (for a variety of different reasons) and for a significant proportion, brace support and analgesics are not sufficient to control pain or are poorly tolerated. In these cases, interventional radiologists, radiation oncologists and medical oncologists need to collaborate to provide the best combination of their skills. In cases of chord compression,

there is little alternative to urgent surgery and radiotherapy, although RT alone can be used in selected cases.

Indications for surgery not only include chord or epidural compression but, in selected cases, may also be instability due to posterior element involvement or spinal alignment alterations. However, when spinal instability is only due to single or multiple vertebral body collapse or lesions, VP should be preferred over surgery due to the lower morbidity and invasiveness of the procedure.

Patient input and preferences must be taken into account in therapeutic decision making because even if single metastasis or oligometastatic disease can be considered an indication for radical surgery, this may be refused by the patient, especially if symptoms are lacking or not problematic; a less invasive option should be suggested for these patients. In selected cases, interventional radiology, with thermal ablation and/or vertebroplasty in association with RT, can provide pain relief and local disease control, preventing pathologic fractures.

For some patients, surgical intervention can be avoided or delayed by the use of local treatment with interventional radiology techniques or RT, which is still feasible if a local relapse is visible at time of disease revaluation. Follow-up imaging after local treatment can be also a good "test of time" to select appropriate candidates for radical surgery. Figure 2 shows a single vertebral body metastasis



**Fig. 2.** 51-year-old female patient with a lytic metastasis (A, E) on T12 from breast cancer found at follow-up 30 months after mastectomy; the metastasis was the only FDG (fluorodeoxyglucose) uptake site at PET-CT (row H). The lesion was deemed stable and the patient had mild back discomfort but not significant pain. There was no indication for surgery. The MDT decision was to perform prophylactic vertebroplasty (C, D, B, F, G) to avoid any risk of post-irradiation vertebral collapse, and radiotherapy (30 Gy in 10 fractions). After two years of follow-up, zoledronic acid, ormonotherapy and different chemotherapeutic lines, FDG-PET still shows complete metabolic response on T12 (row I) despite the occurrence of lymph nodes, single sacral and single liver metastases.



in a young women treated with VP and RT that achieved complete metabolic response despite the occurrence of new metastases. The indication for radical surgery would have been incorrect because both stabilization and local control were achieved with a non-surgical approach and because of progressive disease in other sites.

In radioresistant tumors or heavily pretreated patients, thermal ablation can be considered to achieve local disease control and pain relief. Given that smaller lesion size is associated with better local control, asymptomatic but growing lesions can also be successfully treated in order to prevent pathologic and/or painful fractures.

To date, different algorithms have been created by leading authors in the field taking into account different features of the bone lesion itself along with patient and disease characteristics, such as tumor histotype, symptoms, and life expectancy, with the goal of suggesting the best palliative or curative treatment strategy for spine metastases [18, 20, 71]. In particular, the 2010 Cardiovascular and Interventional Radiologic Society of Europe (CIRSE) guidelines represented a step forward in the management of bone metastases with interventional radiology [18]. This important document separated interventional radiology procedures involved in bone tumor management into curative and palliative categories. Thermal ablation techniques were recommended when the intent is curative but also within a palliative approach when there is no need for consolidation, and pain relief can be obtained by means of tumor debulking alone. Bone cement injection alone was advised when consolidation is needed and the therapeutic intent is palliation. These guidelines were created for bone and musculoskeletal lesions in general, without a specific spine focus. More recently, the Metastatic Spine Disease Multidisciplinary working group published five different therapeutic algorithms for the management of spine metastases according to five different scenarios: asymptomatic spinal metastases (A); uncomplicated painful spinal metastases (B); spinal metastases complicated by stable (C) or unstable (D) fractures; and metastatic epidural spinal cord compression (E) [20].

# **New visual algorithm for multidisciplinary management of non-surgical spine metastases**

We propose a "visual algorithm" that merges some of the existing therapeutic recommendations and current clinical evidence but also takes into account some alternative interventional radiology techniques that have not yet been included in previously published algorithms. We chose a "mind map" or "visual map" because this provides a graphic representation of problem solving in different disciplines that has been more recently applied in medical and scientific algorithms.

To summarize currently available treatment options for non-surgically amenable vertebral metastases we created the visual algorithm described below that focuses mainly on lesion features, feasibility of RT and life expectancy in the management of non surgical metastases (Figure 3). We considered 4 main scenarios according to vertebral body involvement (above or below 50%) and posterior bulging (absent or present). Moreover, we included 2 specific scenarios: involvement of critical structures (i.e. spinal canal, peduncles, foramina) and involvement of posterior elements below conus medullaris. For the present visual map we considered RT as not feasible if RT had been done already or was contraindicated, or there was no indication for RT according to an expert radiotherapist evaluation.

This new algorithm has not yet been validated in large studies, but appears safe and has shown interesting proof of effectiveness in our clinical practice experience. Indeed, one aim of this visual algorithm is also to advise the best indication for these techniques in order to promote further research and stimulate discussion among physicians involved in spine metastases management.

## **Main scenarios of the new algorithm**

- 1. *Less than 50% vertebral body involvement without posterior bulging (blue route)*
	- In the presence of pain and short life expectancy  $( $6$$ months), perform RT if feasible, with or without VA; if RT is not feasible consider VA alone with the goal of relieving pain.
	- In the presence of pain and good life expectancy  $($  >6 months), perform RT if feasible with or without VA; if RT is not feasible consider ablation techniques (radiofrequency ablation [RFA], cryoablation), with or without VA.
	- In the absence of pain in patients with short life expectancy (<6 months), consider observation or prophylactic VA in selected cases.
	- In the absence of pain in patients with good life expectancy (>6 months), consider observation, RT if feasible, with or without VA, ablation techniques (RFA, cryoablation) with or without VA, or prophylactic VA in selected cases with or without RT especially in growing lesions or lesions that become symptomatic.
- 2. *Less than 50% vertebral body involvement with posterior bulging (green route)*
	- Perform RT if feasible, then repeat imagining to evaluate VA if safe and indicated for pain or stability
	- If RT is not feasible, take life expectancy into account:



**Fig. 3.** Visual algorithm for the treatment of vertebral metastases. BSC: best supportive care; HIFU: high-intensity focused ultrasound; IORT: intra-operative radiotherapy; RFA: radiofrequency ablation; RT: radiotherapy; VA: vertebral augmentation.

- short life expectancy  $( $6$  months): consider best$ supportive care (BSC) or embolization in selected cases (i.e. untreatable pain, hypervascular lesions),
- good life expectancy  $($  >6 months): consider embolization in selected cases (i.e. painful, fastgrowing and hypervascular lesions) or bipolar RFA with or without VA in presence of limited posterior bulging.
- 3. *More than 50% vertebral body involvement without posterior bulging (red route)*
	- If RT is feasible consider RT or, in selected cases, ablation techniques (RFA, cryoablation) followed by VA.
	- If RT is not feasible take life expectancy into account:
- short life expectancy  $( $6$  months): consider best$ supportive care (BSC) or VA alone,
- good life expectancy  $($  >6 months): consider VA alone or in combination with ablation techniques (RFA, cryoablation) or with IORT in carefully selected cases (waiting for further evidence; VA+IORT can be evaluated in all cases when ablation and RT are contraindicated or not feasible).
- 4. *More than 50% vertebral body involvement with posterior bulging (orange route)*
	- If RT is feasible, perform RT then repeat imagining to evaluate VA if safe. In selected cases (i.e. high risk of vertebral body collapse), consider percutaneous placement of vertebral prosthesis followed by RT.
	- If RT is not feasible take life expectancy into account:



- short life expectancy  $( $6$  months): best supportive$ care (BSC) such as steroids and analgesics,
- $\blacksquare$  good life expectancy ( $\geq 6$  months): consider embolization in selected cases (i.e. painful, fastgrowing and hypervascular lesions) or bipolar RFA with or without VA in presence of limited posterior bulging.

## **Specific scenarios**

**Involvement of critical structure (purple route)**

- If RT is feasible, perform RT.
- If RT is not feasible take life expectancy into account:
	- short life expectancy  $( $6$  months): consider best$ supportive care (BSC) or embolization in selected cases (i.e. untreatable pain, hypervascular lesions),
	- good life expectancy (>6 months): consider embolization in selected cases (i.e. painful, fast-growing and hypervascular lesions).

**Involvement of posterior elements below conus medullaris (light green route)**

– Consider high-intensity focused ultrasound (HIFU) if RT is not feasible.

# **References**

- 1. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001;27(3):165-76.
- 2. Gilbert RW, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. Ann Neurol 1978;3(1):40-51.
- 3. Aaron AD. The management of cancer metastatic to bone. JAMA 1994;272(15):1206-9.
- 4. Paterson AH, Ernst DS, Powles TJ et al. Treatment of skeletal disease in breast cancer with clodronate. Bone 1991;12 Suppl 1:S25-30.
- 5. Bartels RH, van der Linden YM, van der Graaf WT. Spinal extradural metastasis: review of current treatment options. CA Cancer J Clin 2008;58(4):245-59.
- 6. Patchell RA, Tibbs PA, Regine WF et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 2005;366(9486):643-8.
- 7. Fourney DR, Abi-Said D, Lang FF et al. Use of pedicle screw fixation in the management of malignant spinal disease: experience in 100 consecutive procedures. J Neurosurg 2001; 94(1 Suppl):25-37.
- 8. Fourney DR, Gokaslan ZL. Spinal instability and deformity due to neoplastic conditions. Neurosurg Focus 2003;14(1):e8.
- 9. Gokaslan ZL, York JE, Walsh GL et al. Transthoracic vertebrectomy for metastatic spinal tumors. J Neurosurg 1998; 89(4):599-609.

# **Conclusions**

It is our opinion that interventional radiology for spine metastases can be thought of not only as a treatment to palliate pain, but also as a preemptive approach to avoid dangerous evolution of bone lesions. Most newly available techniques for curative treatments need further large studies to provide better evidence before these can become part of standard care. Nonetheless, some of these interventional radiology tools have proven safe and effective under appropriate conditions. Indeed, when surgery is not indicated, interventional radiology and radiotherapy can have a synergic effect, thus providing an alternative treatment. In cases where radiotherapy is not an option, interventional radiology offers different solutions that warrant investigation to try and improve quality of life to patients with bone metastases.

# **Acknowledgments**

The authors thank Nicola Ryan, an independent medical writer, who provided native English editing and journal styling on behalf of HPS. This editorial assistance was funded by PharmaMar, Spain.

# **Conflicts of Interest**

The Authors declare there are no conflicts of interest in relation to this article.

- 10. DeWald RL, Bridwell KH, Prodromas C, Rodts MF. Reconstructive spinal surgery as palliation for metastatic malignancies of the spine. Spine (Phila Pa 1976) 1985; 10(1):21-6.
- 11. Falicov A, Fisher CG, Sparkes J et al. Impact of surgical intervention on quality of life in patients with spinal metastases. Spine (Phila Pa 1976) 2006;31(24):2849-56.
- 12. Thomas KC, Nosyk B, Fisher CG et al. Cost-effectiveness of surgery plus radiotherapy versus radiotherapy alone for metastatic epidural spinal cord compression. Int J Radiat Oncol Biol Phys 2006;66(4):1212-8.
- 13. Fourney DR, Schomer DF, Nader R et al. Percutaneous vertebroplasty and kyphoplasty for painful vertebral body fractures in cancer patients. J Neurosurg 2003;98(1 Suppl):21-30.
- 14. Bilsky M, Smith M. Surgical approach to epidural spinal cord compression. Hematol Oncol Clin North Am 2006; 20(6):1307-17.
- 15. Taneichi H, Kaneda K, Takeda N et al. Risk factors and probability of vertebral body collapse in metastases of the thoracic and lumbar spine. Spine (Phila Pa 1976) 1997;22(3):239-45.
- 16. Asdourian PL, Mardjetko S, Rauschning W et al. An evaluation of spinal deformity in metastatic breast cancer. J Spinal Disord 1990;3(2):119-34.
- 17. Georgy BA. Metastatic spinal lesions: state-of-the-art treatment options and future trends. AJNR Am J Neuroradiol 2008;29(9):1605-11.
- 18. Gangi A, Tsoumakidou G, Buy X et al. Quality improvement

guidelines for bone tumour management. Cardiovasc Intervent Radiol 2010;33(4):706-13.

- 19. Fourney DR, Frangou EM, Ryken TC et al. Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. J Clin Oncol 2011;29(22):3072-7.
- 20. Wallace AN, Robinson CG, Meyer J et al. The Metastatic Spine Disease Multidisciplinary Working Group Algorithms. Oncologist 2015;20(10):1205-15.
- 21. Flickinger FW, Sanal SM. Bone marrow MRI: techniques and accuracy for detecting breast cancer metastases. Magn Reson Imaging 1994;12(6):829-35.
- 22. Eustace S, Tello R, DeCarvalho V et al. A comparison of whole-body turboSTIR MR imaging and planar 99mTcmethylene diphosphonate scintigraphy in the examination of patients with suspected skeletal metastases. AJR Am J Roentgenol 1997;169(6):1655-61.
- 23. Muindi J, Coombes RC, Golding S et al. The role of computed tomography in the detection of bone metastases in breast cancer patients. Br J Radiol 1983;56(664):233-6.
- 24. Durning P, Best JJ, Sellwood RA. Recognition of metastatic bone disease in cancer of the breast by computed tomography. Clin Oncol 1983;9(4):343-6.
- 25. Fisher CG, DiPaola CP, Ryken TC et al. A novel classification system for spinal instability in neoplastic disease: an evidencebased approach and expert consensus from the Spine Oncology Study Group. Spine (Phila Pa 1976) 2010;35(22):E1221-9.
- 26. Windhagen H, Hipp JA, Hayes WC. Postfracture instability of vertebrae with simulated defects can be predicted from computed tomography data. Spine (Phila Pa 1976) 2000; 25(14):1775-81.
- 27. Tschirhart CE, Finkelstein JA, Whyne CM. Biomechanics of vertebral level, geometry, and transcortical tumors in the metastatic spine. J Biomech 2007;40(1):46-54.
- 28. Whyne CM, Hu SS, Klisch S et al. Effect of the pedicle and posterior arch on vertebral body strength predictions in finite element modeling. Spine (Phila Pa 1976) 1998;23(8):899-907.
- 29. Krishnaney AA, Steinmetz MP, Benzel EC. Biomechanics of metastatic spine cancer. Neurosurg Clin N Am 2004; 15(4):375-80.
- 30. Dimar JR, Voor MJ, Zhang YM et al. A human cadaver model for determination of pathologic fracture threshold resulting from tumorous destruction of the vertebral body. Spine (Phila Pa 1976) 1998;23(11):1209-14.
- 31. Windhagen HJ, Hipp JA, Silva MJ et al. Predicting failure of thoracic vertebrae with simulated and actual metastatic defects. Clin Orthop Relat Res 1997(344):313-9.
- 32. Weber MH, Burch S, Buckley J et al. Instability and impending instability of the thoracolumbar spine in patients with spinal metastases: a systematic review. Int J Oncol 2011; 38(1):5-12.
- 33. Melton LJ, Kyle RA, Achenbach SJ et al. Fracture risk with multiple myeloma: a population-based study. J Bone Miner Res 2005;20(3):487-93.
- 34. Song IC, Kim JN, Choi YS et al. Diagnostic and prognostic implications of spine magnetic resonance imaging at diagnosis in patients with multiple myeloma. Cancer Res Treat 2015;47(3):465-72.
- 35. Weinstein JN. Surgical approach to spine tumors. Orthopedics 1989;12(6):897-905.
- 36. Tokuhashi Y, Matsuzaki H, Toriyama S et al. Scoring system for the preoperative evaluation of metastatic spine tumor prognosis. Spine (Phila Pa 1976) 1990;15(11):1110-3.
- 37. Tokuhashi Y, Matsuzaki H, Oda H et al. A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis. Spine (Phila Pa 1976) 2005;30(19):2186-91.
- 38. Tomita K, Kawahara N, Kobayashi T et al. Surgical strategy for spinal metastases. Spine (Phila Pa 1976) 2001; 26(3):298-306.
- 39. Laufer I, Sciubba DM, Madera M et al. Surgical management of metastatic spinal tumors. Cancer Control 2012;19(2):122-8.
- 40. Chow E, van der Linden YM, Roos D et al. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. Lancet Oncol 2014;15(2):164-71.
- 41. Steenland E, Leer JW, van Houwelingen H et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. Radiother Oncol 1999;52(2):101-9.
- 42. Boehling NS, Grosshans DR, Allen PK et al. Vertebral compression fracture risk after stereotactic body radiotherapy for spinal metastases. J Neurosurg Spine 2012; 16(4):379-86.
- 43. Greco C, Zelefsky MJ, Lovelock M et al. Predictors of local control after single-dose stereotactic image-guided intensitymodulated radiotherapy for extracranial metastases. Int J Radiat Oncol Biol Phys 2011;79(4):1151-7.
- 44. Garcia-Barros M, Paris F, Cordon-Cardo C et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science 2003;300(5622):1155-9.
- 45. Janjan NA. Radiation for bone metastases: conventional techniques and the role of systemic radiopharmaceuticals. Cancer 1997;80(8 Suppl):1628-45.
- 46. Rose PS, Laufer I, Boland PJ et al. Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. J Clin Oncol 2009;27(30):5075-9.
- 47. Munk PL, Murphy KJ, Gangi A et al. Fire and ice: percutaneous ablative therapies and cement injection in management of metastatic disease of the spine. Semin Musculoskelet Radiol 2011;15(2):125-34.
- 48. Lencioni R. Loco-regional treatment of hepatocellular carcinoma. Hepatology 2010;52(2):762-73.
- 59. Mayo SC, Pawlik TM. Thermal ablative therapies for secondary hepatic malignancies. Cancer J 2010;16(2):111-7.
- 50. Veltri A, Gazzera C, Busso M et al. T1a as the sole selection criterion for RFA of renal masses: randomized controlled trials versus surgery should not be postponed. Cardiovasc Intervent Radiol 2014;37(5):1292-8.
- 51. de Baère T. Lung tumor radiofrequency ablation: where do we stand? Cardiovasc Intervent Radiol 2011;34(2):241-51.
- 52. Dupuy DE. Image-guided thermal ablation of lung malignancies. Radiology 2011;260(3):633-55.
- 53. Kurup AN, Morris JM, Boon AJ et al. Motor evoked potential monitoring during cryoablation of musculoskeletal tumors. J Vasc Interv Radiol 2014;25(11):1657-64.
- 54. de Freitas RM, de Menezes MR, Cerri GG et al. Sclerotic vertebral metastases: pain palliation using percutaneous imageguided cryoablation. Cardiovasc Intervent Radiol 2011;34 Suppl 2:S294-9.



- 55. Greenwood TJ, Wallace A, Friedman MV et al. Combined ablation and radiation therapy of spinal metastases: a novel multimodality treatment approach. Pain Physician 2015;18(6):573-81.
- 56. Zheng L, Chen Z, Sun M et al. A preliminary study of the safety and efficacy of radiofrequency ablation with percutaneous kyphoplasty for thoracolumbar vertebral metastatic tumor treatment. Med Sci Monit 2014;20:556-63.
- 57. Tomasian A, Wallace A, Northrup B et al. Spine cryoablation: pain palliation and local tumor control for vertebral metastases. AJNR Am J Neuroradiol 2016;37(1):189-95.
- 58. Pezeshki PS, Davidson S, Murphy K et al. Comparison of the effect of two different bone-targeted radiofrequency ablation (RFA) systems alone and in combination with percutaneous vertebroplasty (PVP) on the biomechanical stability of the metastatic spine. Eur Spine J 2015 Jul 24. [Epub ahead of print].
- 59. Anchala PR, Irving WD, Hillen TJ et al. Treatment of metastatic spinal lesions with a navigational bipolar radiofrequency ablation device: a multicenter retrospective study. Pain Physician 2014;17(4):317-27.
- 60. Deschamps F, Farouil G, Ternes N et al. Thermal ablation techniques: a curative treatment of bone metastases in selected patients? Eur Radiol 2014;24(8):1971-80.
- 61. Kashima M, Yamakado K, Takaki H et al. Radiofrequency ablation for the treatment of bone metastases from hepatocellular carcinoma. AJR Am J Roentgenol 2010;194(2): 536-41.
- 62. McMenomy BP, Kurup AN, Johnson GB et al. Percutaneous cryoablation of musculoskeletal oligometastatic disease for complete remission. J Vasc Interv Radiol 2013;24(2):207-13.
- 63. Huisman M, ter Haar G, Napoli A et al. International consensus on use of focused ultrasound for painful bone metastases: Current status and future directions. Int J Hyperthermia 2015;31(3):251-9.
- 64. Rodrigues DB, Stauffer PR, Vrba D et al. Focused ultrasound for treatment of bone tumours. Int J Hyperthermia 2015;31(3):260-71.
- 65. Berenson J, Pflugmacher R, Jarzem P et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol 2011;12(3):225-35.
- 66. Anselmetti GC, Marcia S, Saba L et al. Percutaneous vertebroplasty: multi-centric results from EVEREST experience in large cohort of patients. Eur J Radiol 2012;81(12):4083-6.
- 67. Dohm M, Black CM, Dacre A et al. A randomized trial comparing balloon kyphoplasty and vertebroplasty for vertebral compression fractures due to osteoporosis. AJNR Am J Neuroradiol 2014;35(12):2227-36.
- 68. Evans AJ, Kip KE, Brinjikji W et al. Randomized controlled trial of vertebroplasty versus kyphoplasty in the treatment of vertebral compression fractures. J Neurointerv Surg 2015 Jun 24. [Epub ahead of print].
- 69. Schmidt R, Wenz F, Reis T et al. Kyphoplasty and intra-operative radiotheray, combination of kyphoplasty and intra-operative radiation for spinal metastases: technical feasibility of a novel approach. Int Orthop 2012;36(6):1255-60.
- 70. Hirsch AE, Medich DC, Rosenstein BS et al. Radioisotopes and vertebral augmentation: dosimetric analysis of a novel ap-

proach for the treatment of malignant compression fractures. Radiother Oncol 2008;87(1):119-26.

- 71. Cazzato RL, Buy X, Grasso RF et al. Interventional Radiologist's perspective on the management of bone metastatic disease. Eur J Surg Oncol 2015;41(8):967-74.
- 72. Facchini G, Di Tullio P, Battaglia M et al. Palliative embolization for metastases of the spine. Eur J Orthop Surg Traumatol 2016;26(3):247-52.
- 73. Chiras J, Adem C, Vallée JN et al. Selective intra-arterial chemoembolization of pelvic and spine bone metastases. Eur Radiol 2004;14(10):1774-80.
- 74. Gartrell BA, Saad F. Managing bone metastases and reducing skeletal related events in prostate cancer. Nat Rev Clin Oncol 2014;11(6):335-45.
- 75. Wang Z, Qiao D, Lu Y et al. Systematic literature review and network meta-analysis comparing bone-targeted agents for the prevention of skeletal-related events in cancer patients with bone metastasis. Oncologist 2015;20(4):440-9.
- 76. Wong MH, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev 2012;2:CD003474.
- 77. Yuen KK, Shelley M, Sze WM et al. Bisphosphonates for advanced prostate cancer. Cochrane Database Syst Rev 2006(4):CD006250.
- 78. Lopez-Olivo MA, Shah NA, Pratt G et al. Bisphosphonates in the treatment of patients with lung cancer and metastatic bone disease: a systematic review and meta-analysis. Support Care Cancer 2012;20(11):2985-98.
- 79. Stopeck AT, Lipton A, Body JJ et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, doubleblind study. J Clin Oncol 2010;28(35):5132-9.
- 80. Fizazi K, Carducci M, Smith M et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011;377(9768):813-22.
- 81. Henry DH, Costa L, Goldwasser F et al. Randomized, doubleblind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 2011;29(9):1125-32.
- 82. Levine RA, Chawla B, Bergeron S et al. Multidisciplinary management of colorectal cancer enhances access to multimodal therapy and compliance with National Comprehensive Cancer Network (NCCN) guidelines. Int J Colorectal Dis 2012;27(11):1531-8.
- 83. Wood JJ, Metcalfe C, Paes A et al. An evaluation of treatment decisions at a colorectal cancer multi-disciplinary team. Colorectal Dis 2008;10(8):769-72.
- 84. Croke JM, El-Sayed S. Multidisciplinary management of cancer patients: chasing a shadow or real value? An overview of the literature. Curr Oncol 2012;19(4):e232-8.
- 85. Pan CC, Kung PT, Wang YH et al. Effects of multidisciplinary team care on the survival of patients with different stages of non-small cell lung cancer: a national cohort study. PLoS One 2015;10(5):e0126547.
- 86. Friedland PL, Bozic B, Dewar J et al. Impact of multidisciplinary team management in head and neck cancer patients. Br J Cancer 2011;104(8):1246-8.