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Management of bone metastases

M. CAPPUCCIO, S. BANDIERA, L. BABBI, L. BORIANI, A. CORGHI, L. AMENDOLA, S. COLANGELI, S. TERZI, A. GASBARRINI

Department of Oncologic and Degenerative Spine Surgery, Rizzoli Institute, Bologna (Italy)

Abstract. – Bone metastases are only apparently similar lesions, considering the large varieties of istotypes and the spread of the primary tumour. Although these metastases develop early and are not terminal events, they have to be considered as severe complications. When possible, surgical treatment can improve the history of the patient in terms of life expectancy and quality of life. The approach to these lesions should be multidisciplinary in collaboration with oncologists and radiotherapists. In fact the average of survival of these patients has increased in recent years. The evolution of anesthesiological techniques permits surgical treatments that once were considered prohibitive. The application of new adjuvant therapies increases the effectiveness for surgical treatment. Controversy exists over the most appropriate treatment for patients with bone metastatic disease. The purpose was to determine the best sequential process to arrive at the most appropriate treatment considering the individual general conditions and the parameters of the metastases. As the number of treatment options for metastatic bone disease has grown, it has become clear that effective implementation of these treatments can only be achieved by a multidisciplinary approach.

Key Words:

Bone metastases, Cancer, Spine metastases, Vertebroplasty.

Introduction

The incidence of bone metastases from carcinoma is second only to pulmonary and hepatic metastases[1]. The most frequently affected segment of the skeleton is the vertebral column. It is estimated that more that 10% of tumour patients develop symptomatic spinal metastases[2,3]. The vertebral bodies are reached largely via the blood stream. Neoplastic substitution of the bone tissue causes progressive structural destruction leading to loss of stability and/or compression of the intracanal nerve structures.

Refinement of the protocols for treating tumour patients has led to a progressive improvement in the prognosis for many tumour histotypes in terms of increase of life expectancy. As a consequence, symptomatic bone metastases in patients without other evidence of disease are increasing and severely affecting the patient's quality of life[4].

The choice of the most appropriate treatment is of crucial importance for the patient who may be severely disabled by the presence of untreated bone metastases, not only a cause of severe deterioration in the quality of life, but also a direct or indirect cause of death. The correct treatment of bone metastases therefore affects life expectancy. Although there is widespread agreement in the literature regarding the need to treat symptomatic metastases, the best treatment protocol to adopt is still a matter of discussion[5].

Bone metastases are an expression of a systemic disease; they therefore require a multi-disciplinary treatment, integrating radiotherapy, chemotherapy and surgery[6,7]. The indications for surgical treatment are intractable pain, the onset of neurological deficit (caused by compression of the myeloradicular structures by the tumour mass or by the pathological fractures of the vertebra), and the instability of the segment affected, causing ingravescent mechanical pain and/or neurological deficit[2,8]. The first and most serious symptom affecting patients with bone tumour is pain, which is extremely frequent, non-specific and sometimes non-sensitive even to major analgesic drugs. Bone metastases have different patterns and types of behaviour related to the large varieties of histotypes and the spread modality of the primary tumor. Early developed metastases must be considered as severe complications, requiring a multidisciplinary approach with the collaboration of oncologists, radiotherapists and

Corresponding Author: Alessandro Gasbarrini, MD; e-mail: alessandro.gasbarrini@ior.it

surgeons. The evolution of anesthesiological techniques allows surgical treatments which a few years ago were considered prohibitive. The application of new adjuvant therapies increases the effectiveness of the surgical treatment. Controversy exists over the most appropriate treatment for patients with metastatic disease[9,10], considering the individual general conditions and the parameters of the metastases[11-13].

As the number of treatment options for metastatic bone disease has grown, it has become clear that effective implementation of these treatments can only be achieved by a multidisciplinary approach.

The aim of surgery is to relieve the pain, improve functions and stabilise the bone. Another important target is the reduction of the tumour mass (debulking) to achieve local control of the disease and mostly in combination with the other treatments[14]. In bone metastases the primary objective is local control. The longer the follow-up period, the greater the possibility that the disease will relapse with a compression of the spinal cord and/or pathological fractures which could worsen the clinical neurological conditions.

Decision Making Process in Bone Metastases

The first element to be considered in the treatment of bone metastases is the diagnosis[15-17]. Excluding a number of lesions that are easily diagnosed with instrumental and technical-laboratory examinations, the majority of tumours require pathological evaluation. In the bone, a CT-guided trocar biopsy, performed without invading the extracompartmental space, seems to be the best way to reduce the spread of the tumour cells.

While a systematic approach has been accepted for the treatment of primary tumours[18], there are no accepted guidelines in the treatment of spinal metastases. Protocols of chemotherapy, hormone therapy, immunotherapy and radiotherapy have progressively increased survival for the majority of patients with solid and hematological tumours. However, bone fractures and tumour mass are responsible for pain and severe functional limitations, particularly if nerve roots or cord compression are affected, which cannot be controlled by drugs.

Despite these elements, the incorrect conviction of many physicians that a patient with secondary skeletal localizations should be considered terminal, and therefore not of orthopedic interest, often makes a surgical approach indispensable and urgent, creating problems for the patient, the relatives and the surgeon. The development of aggressive surgical techniques, made possible by progress in anesthesiology, enables complete fracture fixation in limbs, allowing decompression and adequate stabilisation at all levels of the vertebral column. In addition, "curettage" ("debulking") or en bloc resection can be performed with significant results on the local control of the tumour.

Many factors must be taken into account when choosing the most appropriate surgical technique: the patient's general conditions, the histotype of the primary tumour and its sensitivity to adjuvant treatments, the spread of the disease and the current neurological conditions[1,19]. Briefly, a patient with diffuse neoplastic disease, generally impaired conditions and incipient neurological deficit should be treated with palliative decompression and stabilisation followed by radiotherapy that may noticeably improve the quality of life. In a patient in good general conditions suffering from a primary tumour with a relatively positive prognosis and a symptomatic isolated bone metastases, more aggressive treatment similar to that for a primary tumour is justified[9].

Sioutos et al.[14] statistically analysed the factors influencing the incidence of complications and the length of survival after surgical treatment of spinal metastases and showed that this is influenced by the preoperative neurological conditions, the histotype of the primary tumour and the number of vertebrae involved, but not by the degree of diffusion of the disease or the age of the patient. On the basis of these observations, the Authors recommend careful patient selection. The literature proposes many preoperative scoring systems to classify patients by creating repeatable treatment protocols[2,10,19,20]. These systems attribute a score to each parameter and the sum of these scores suggests the appropriate treatment. Therefore, the same importance is attached to the various parameters considered in individual cases. For example, the histotype of the primary tumour and general conditions of the patient have the same influence on the final score and on the decisive choice of the type of treatment.

We have built up two algorithms: one for treating spinal metastases and one for limb metastases in which the importance of the parameters taken into account varies according to when they

are considered (Figures 1 and 2). Each patient follows his or her "personal" sequential process which does not necessarily consider all the parameters every time, as some may be irrelevant for the purposes of choosing the type of treatment. For example, a patient in poor general conditions with a high "ASA" score[21] is not usually a candidate for surgery, irrespective of the histotype of the primary tumour or the number of secondary localizations. Therefore, for this patient, the most important parameter will be the sensitivity of the tumour histotype to an adjuvant treatment. In the same way, a patient with acute and ingravescent spinal cord damage will undergo emergency palliative decompression and stabilization surgery without considering a more demanding operation. Finally, we consider the patient not just in terms of the disease, reducing the choice of treatment to an overly simplistic mathematical score. Instead, we analyse the case holistically, firstly considering the individual and his or her general conditions and only subsequently the parameters of the metastases.

The Role of Vertebroplasty in Vertebral Metastases

Vertebroplasty (VP) is a minimally invasive technique that consists in the injection of polymethylmethacrylate cement (PMMA) inside the vertebral body by percutaneous approach under radioscopic control or under CT-guide[22]. Performed for the first time in 1984 by Deramond et al.[23] in France for the treatment of an aggressive angioma of C2, in these last years it has undergone considerable development, extending the indications to the treatment of vertebral metastases. Tumours inside the vertebra are mostly solid, and if cement or any other material is injected inside the vertebra, without having first destroyed or eliminated the tumour, this is able to enter the vertebral channel or spread around the vertebra, provoking further dissemination of the illness.

An interesting study was performed by Reidy et al.[24] in which the pressure was measured inside vertebral bodies of cadavers with and without the presence of adenocarcinoma metastases after VP. This experimental study showed that the presence of a tumour determines an increase of pressure of about 8 times inside the vertebral body and that this notable increase can determine the exit of tumour material out of the vertebral body, which is therefore able to enter the epidural space. The increase in pressure is justified in terms of a difference of hydraulic permeability of the neoplastic tissue. The smaller "porosity" of the tumoral mass prevents and hinders fluid diffusion of the PMMA inside the vertebral body. This also leads to non-homogeneous distribution of cement inside the vertebral body. It is also important to know that if the tumour does not respond to adjuvant therapies and continues to grow, PMMA can represent an additional problem if it is necessary to resort to surgery.

An analysis of the literature reveals very few homogeneous data from the pathogenetic point of view. Follow-up was very brief in all cases. In addition, almost all the studies analyzed do not indicate the percentage of local recurrence, even if it would be more correct to speak of progression of disease. It is intuitive that VP does not determine local control, even if an anti-neoplastic role of PMMA has been hypothesized[25]. We believe that the low incidence of local recurrence is not due to the tumoral cytolysis from PMMA, but from the brief survival of these patients.

In an attempt to achieve local control and to reduce the migration of the cement inside the perivertebral vessels, some authors have proposed the use of combined tumoral thermo-ablation through radio frequency with VP[26]. This allows not only the thermal destruction of the tumour, which is also not completely shown histologically, but also the thrombosis of the perivertebral venous plexus. There may be some changes of the physical properties of the tumoral mass and the hydraulic permeability, with consequent reduction of the pressure following VP and therefore a smaller risk of spillage of PMMA. Already for example used widely in the oncological field for the treatment of non-resectable liver tumours, and in muscle-skeletal diseases for the treatment of osteoid osteomas, this method could, in the future, be used to treat skeletal metastases. There are no studies in the literature on the histological modifications following radiofrequency but the validity of this methodology, considering bony metastases, consists in the reduction of pain[27,28]. The most dangerous complication of this method is thermal cytolysis of the nervous structures. However, it seems that a safety border level against neural structures exists if the back cortical wall is entire[29]; the presence of cortical bone, in fact, leads to a considerable decrease in temperature. In reality, the Authors believe that the presence of cerebrospinal fluid is sufficient between the tumoral mass and

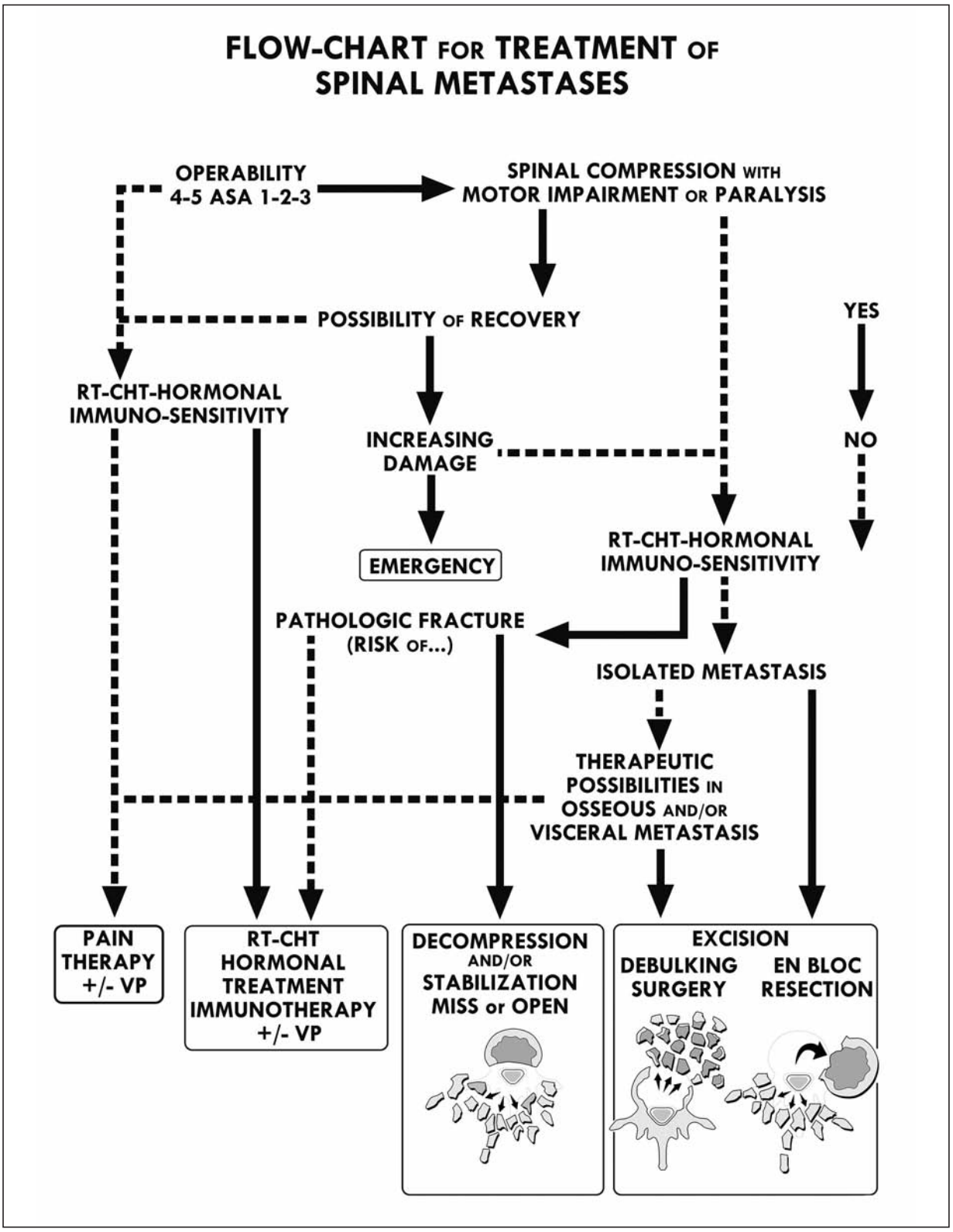
FLOW-CHART FOR TREATMENT OF SPINAL METASTASES
OPERABILITY 4-5 ASA 1-2-3
SPINAL COMPRESSION WITH MOTOR IMPAIRMENT OR PARALYSIS
POSSIBILITY OF RECOVERY
YES
NO
RT-CHT-HORMONAL IMMUNO-SENSITIVITY
INCREASING DAMAGE
EMERGENCY
RT-CHT-HORMONAL IMMUNO-SENSITIVITY
PATHOLOGIC FRACTURE (RISK OF...)
ISOLATED METASTASIS
THERAPEUTIC POSSIBILITIES IN OSSEOUS AND/OR VISCERAL METASTASIS
PAIN THERAPY +/- VP
RT-CHT HORMONAL TREATMENT IMMUNOTHERAPY +/- VP
DECOMPRESSION AND/OR STABILIZATION MISS or OPEN
EXCISION
DEBULKING SURGERY
EN BLOC RESECTION

Figure 1.

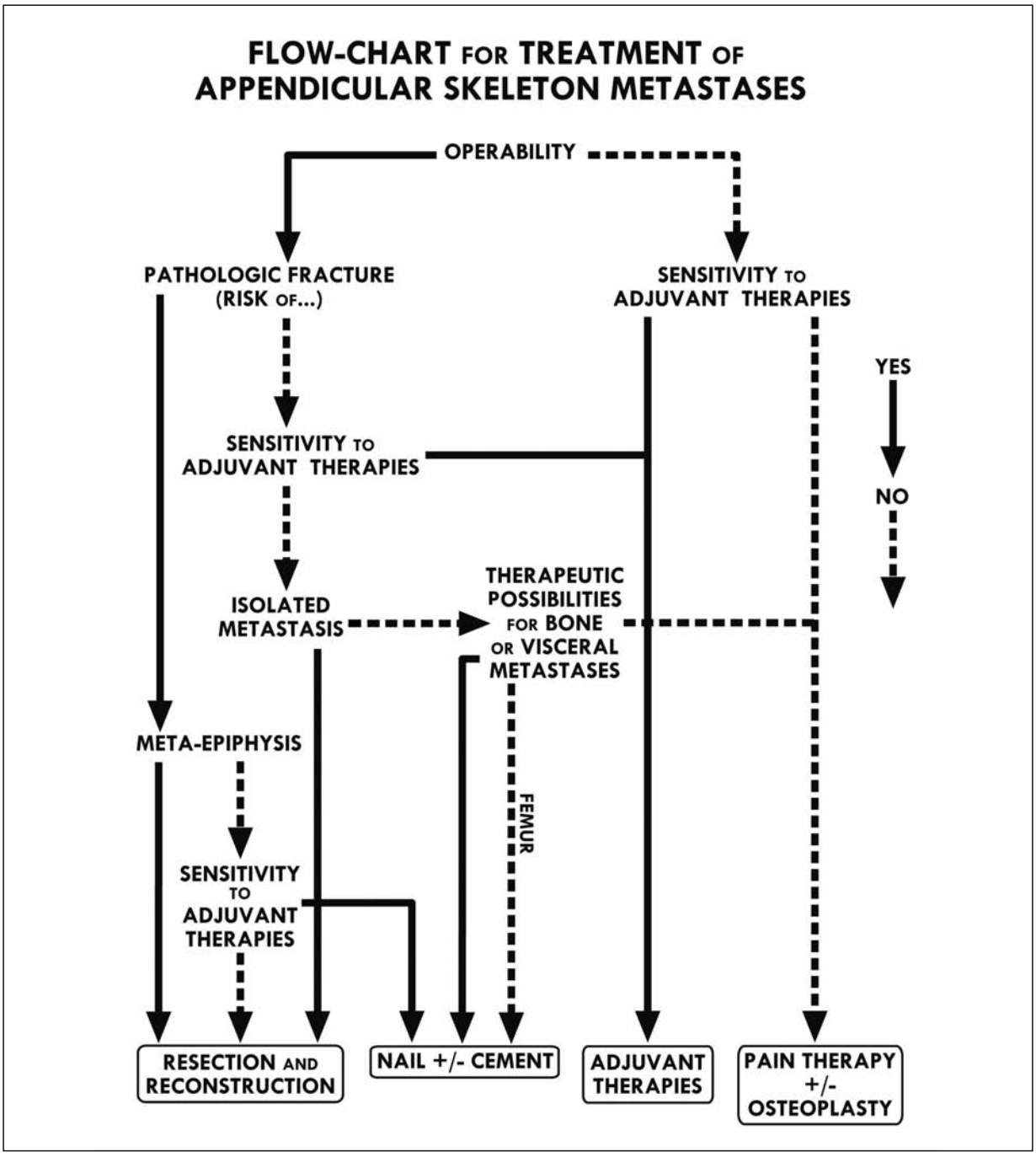

Figure 2.

the spinal cord to prevent any thermal damage, even if they advise against the use of thermo-ablation in cases of wide vertebral osteolysis with invasion of the back vertebral wall.

An algorithm has been proposed also for the treatment of vertebral fractures in oncological patients[30] where, besides VP and the kyphoplasty, radiotherapy, decompression and surgical stabilization are also proposed as treatment alternatives. Kyphoplasty is preferred to VP if integrity of the back cortical wall of the vertebral body is lacking or when this involves kyphosis greater than 20°. It should be noted that a histological diagnosis of the lesion is not possible in every patient , and that there was no distinction between plasmacytoma and vertebral metastases fractures.

We agree that there is a high incidence of greater complications in patients with vertebral metastases, in comparison with patients affected by vertebral osteoporotic collapse[31]. The most frequent type of complication is surely an asymptomatic leakage of cement to the outside of the vertebra, varying from 2% to 73%[26]. The leakage of cement inside the vertebral channel or to foraminal level is frequent, in the metastatic vertebrae, if there are some defects of the back wall or a trabecular pedicle. An absolute contraindication exists in the presence of coagulation problems, local or general infectious state, symptomatic cord compression or serious cardio-respiratory problems[26].

We believe that when treating metastatic skeletal lesions and vertebral lesions in particular, a multidisciplinary treatment is needed, in which radiotherapy, chemotherapy and surgery must combine in order to achieve local control of the lesion[5-7,32]. Surgical treatment of vertebral metastases must consider: life expectancy, the need to guarantee good function while limiting the pain and the possibility of associating adjuvant therapies and the demand for appropriate local control. VP for the treatment of the vertebral metastases is a method that, despite a low morbidity and good post-operative control of pain, does not allow local control; moreover, it can determine, even in the absence of valid scientific tests, a dissemination of the illness to pulmonary level. Association with radio frequency seems to be able to obviate these problems, at least in part, even if there are no scientific tests of its full validity. VP can thus be very useful if there is a good response from the tumour to the adjuvant therapies with complete tumour "sterilization", determining nevertheless the permanence of an osteolysis. We believe that in such cases VB can be of value. In addition, when faced with a plurimetastatic patient in terminal phase VP can be used for analgesic purposes.

In the future, the indications for VP could increase if it is associated with methods that can sublimate or in any case to first destroy the tumour.

Flow-Chart for Multidisciplinary Management of Bone Metastases

Without considering all the clinical and instrumental examinations which the patient undergoes on admission and forming part of preoperative staging, our treatment algorithm begins with diagnosis of bone metastases.

The first assessment must be performed by the anaesthetist who must decide whether the patient is operable or not.

If the patient is not operable due to a high ASA score, non-surgical options are considered. Next, the sensitivity of the tumour histotype to adjuvant therapies (CHT, RXT, hormonal, …) is considered. If the tumour does not respond to any form of treatment, the only option for the patient is pain relief.

Vertebral Metastases (Figure 1)

If the patient is operable, the severity of spinal cord compression and neurological damage is evaluated by means of the Frankel score. If there is neurological deficit or paralysis, the possibility of recovery is evaluated on the basis of time from symptom onset.

Finally, if the neurological recovery of the patient is not possible, sensitivity to adjuvant treatments is re-evaluated. However, if the patient has acute and ingravescent spinal cord damage, emergency surgery is performed.

If there is no deficit or the damage is recoverable and stable, sensitivity to adjuvant treatments is evaluated. If the tumour histotype is not sensitive and there is only a single metastasis, resection of the lesion is chosen.

However, if there are multiple metastases and they are treatable, the choice is decompression and stabilization. If they are not treatable, only pain relief is administered.

When there is no deficit or the damage is recoverable and not ingravescent and the tumour is sensitive to some form of adjuvant treatment, pathological fracture (actual or impending) is evaluated. This parameter is, in fact, decisive in orienting the choice towards either surgical treatment with compression and stabilization or adjuvant treatment only.

Resection of the tumour may be performed en bloc with a wide margin or through debulking. Generally speaking, en bloc removal is suggested for hypervascularized tumours, metastases from renal cell carcinoma and from sarcoma and the cases in which this type of operation is easy to perform.

Appendicular Skeleton Metastases (Figure 2)

If the patient is operable, it is necessary to evaluate the presence (or risk) of a pathological fracture, whether the metastases is isolated, and

the location of the metastases in the skeletal segment. Depending on these factors, various therapeutical options will be considered, from resection and reconstruction, to pinning with or without cement.

Conclusions

Appropriate surgical treatment of bone metastases and tumours in general has now become an integral part of the correct approach to the tumour patient.

The evolution of *anesthetic techniques* now allows correct treatment of spinal metastases, both dramatically improving the quality of life and also prolonging the patient's life expectancy, protecting him or her from the complications of these lesions, often either directly or indirectly fatal.

In the majority of cases, it is therefore possible to restore or maintain movement, sensitivity, dignity and hope, as well as controlling pain, reducing the use of adjuvant and analgesic treatments.

The *surgical indication* for spinal metastases must consider:

– the life expectancy of the patient;
– the need to improve function and to limit pain;
– the need for complete local control;
– the possibility of associating adjuvant treatments to improve the efficacy of the treatment, reducing morbidity.

References

1) Hosono N, Yonenobu K, Fuji T, Ebara S, Yamashita K, Ono K. Orthopedic management of spinal metastases. Clin Orthop 1995, 312: 148-159.
2) Harrington KD. Orthopedic surgical management of skeletal complications of malignancy. Cancer Suppl 1997; 80: 1614-1627.
3) Sundaresan N, Digiacinto GV, Hughes JE, Cafferty M, Vallejo A. Treatment of neoplastic spinal cord compression: results of a prospective study. Neurosurgery 1991; 29: 645-650.
4) Schoeggl A, Reddy M, Matula C. Neurological outcome following laminectomy in spinal metastases. Spinal Cord 2002; 40: 363-366.
5) Ryken TC, Eichholz KM, Gerszten PC, Welch WC, Gokaslan ZL, Resnick DK. Evidence-based review of the surgical management of vertebral column metastatic disease. Neurosurg Focus 2003; 15: E11.
6) Damron TA, Sim FH. Surgical treatment for metastatic disease of the pelvis and the proximal end of the femur. Instr Course Lect 2000; 49: 461-470.
7) Schuster JM and Grady MS. Medical management and adjuvant therapies in spinal metastatic disease. Neurosurg Focus 2001; 11: e3.
8) Wise JJ, Fischgrund JS, Herkowitz HN, Montgomery D, Kurtz LT. Complication, survival rates and risk factors of surgery for metastatic disease of the spine. Spine 1999; 24: 1943-1951.
9) Sundaresan N, Rothman A, Manhart K, Kelliher K. Surgery for solitary metastases of the spine. Rationale and results of the treatment. Spine 2002; 27: 1802-1806.
10) Tokuhashi Y, Matsuzaki Y, Toriyama S, Kawano H, Ohsaka S. Scoring system for the preoperative evaluation of metastatic spine tumor prognosis. Spine 1990; 15: 1110-1113.
11) Boriani S, Gasbarrini A. Point of view. Spine 2005; 30: 2227-2229.
12) Gasbarrini A, Cappuccio M, Mirabile L, Bandiera S, Terzi S, Barbanti Bròdano G, Boriani S. Spinal metastases: treatment evaluation algorithm. Eur Rev Med Pharmacol Sci 2004; 8: 265-274.
13) Gasbarrini A, Cappuccio M, Bandiera S, Mirabile L, Paderni S, Boriani S. Il trattamento delle metastasi vertebrali. Lo Scalpello 2008; 21: 136-145.
14) Sioutos PJ, Arbit E, Meshulam CF, Galicich JH. Spinal metastases from solid tumors. Analysis of factors afecting survival. Cancer 1995; 76: 1453-1459.
15) Cappuccio M, Gasbarrini A, Van Urk P, Bandiera S, Boriani S. Spinal metastases: a retrospective study validating the treatment algorithm. Eur Rev Med Pharmacol Sci 2008; 12: 155-160.
16) Li H, Gasbarrini A, Cappuccio M, Terzi S, Paderni S, Mirabile L, Boriani S. Outcome of excisional surgeries for the patients with spinal metastases. Eur Spine J 2009; 18: 1423-1430.
17) Tokuhashi Y, Ajiro Y, Oshima M. Algorithms and planning in metastatic spine tumors. Orthop Clin North Am 2009; 40: 37-46, v-vi.
18) Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop Relat Res 1980; 153: 106-120.
19) Tomita K, Kawahara N, Kobayashi T, Yoshida A, Murakami H, Akamuru T. Surgical strategy for spinal metastases. Spine 2001; 26: 298-306.
20) Capanna R, Campanacci DA. The treatment of metastases in the appendicular skeleton. J Bone Joint Surg Br 2001; 83: 471-481.
21) Anonimous. New classification on physical status. Anesthesiology 1963; 24: 111.

22) Barbanti Bròdano G, Cappuccio M, Gasbarrini A, Bandiera S, De Salvo F, Cosco F, Boriani S. Vertebroplasty in the treatment of vertebral metastases: clinical cases and review of the literature. Eur Rev Med Pharmacol Sci 2007; 11: 91-100.

23) Galibert P, Deramond H, Rosat P, Le Gars D. Preliminary note on the treatment of vertebral angioma by percutaneous acrylic vertebroplasty. Neurochirurgie 1987; 33: 166-168.

24) Reidy D, Ahn H, Mousavi P, Finkelstein J, Whine CM. A biomechanical analysis of intravertebral pressures during vertebroplasty of cadaveric spines with and without simulated metastases. Spine 2003; 28: 1534-1539.

25) Weill A, Chiras J, Simon JM, Rose M, Sola-Martinez T, Enkaoua E. Spinal metastases: indications for and results of percutaneous injection of acrylic surgical cement. Radiology 1996; 199: 241-247.

26) Halpin RJ, Bendok BR, Liu JC. Minimally invasive treatments for spinal metastases: vertebroplasty, kyphoplasty and radiofrequency ablation. J Support Oncol 2004; 2: 339-355.

27) Groenemeyer D, Schirp S, Gevargez A. Image-guided radiofrequency ablation of spinal tumors: preliminary experience with expandable array electrode. Cancer J 2002; 8: 33-39.

28) Goetz MP, Callstrom MR, Charboneau JW, Farrel MA, Maus TP, Welch TJ, Wong GY, Sloan JA, Novotny PJ, Petersen IA, Beres RA, Regge D, Capanna R, Saker MB, Groenenmeyer D, Gevargez A, Ahrar K, Choti MA, de Baere TJ, Rubin J. Percutaneous image-guided radiofrequency ablation of painful metastases involging bone: a multicenter study. J Clin Oncol 2004; 22: 300-306.

29) Dupuy DE, Hong R, Oliver B, Nahum Goldberg S. Radiofrequency ablation of spinal tumors: temperature distribution in the spinal canal. AJR 2000; 175: 1263-1266.

30) Fourney DR, Schomer DF, Nader R, Chlan J, Suki D, Ahrar K, Rhines LD, Gokaslan ZL. Percutaneous vertebroplasty and kyphoplasty for painful vertebral body fractures in cancer patients. J Neurosurg Spine 2003; 98: 21-30.

31) Pilitsis JG, Rengachary SS. The role of vertebroplasty in metastatic spinal disease. Neurosurg Focus 2001; 11: E9.

32) Klimo P, Schmidt MH. Surgical management of spinal metastases. Oncologist 2004; 9: 188-196.

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