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Management of Renal Cell Carcinoma Metastasis of the Spine

Alessandro Gasbarrini[1], Christiano Esteves Simões[2], Michele Cappuccio[3] and Stefano Boriani[1]
[1]*Department of Oncologic and Degenerative Spine Surgery, Rizzoli Institute*
[2]*Department of Orthopedics and Traumatology – Spine Unit, Felício Rocho Hospital*
[3]*Department of Orthopedics and Traumatology – Spine Surgery, Maggiore Hospital*
[1,3]*Italy*
[2]*Brazil*

1. Introduction

Renal cell carcinoma (RCC) is the most frequent malignant neoplasm of the kidneys, accounting for 85% of all renal cancers, and 2% of all adult malignancies. Forty-five percent of these tumors have been diagnosed as locally advanced or metastatic disease (Stage IV, according to the American Joint Committee on Cancer staging system), and the five-year survival rate varies between 0 to 8% according to the United States National Cancer Data Base (American Cancer Society, 2011). Bones metastases from renal cell carcinoma occur in up to 50% of patients (Swanson et al., 1981), and from this group approximately one half is located in the spine. RCC is the fourth most common metastatic tumor of the spine and the most common cancer to present as a neurologic deficit secondary to an undetected primary malignancy. According to Les et al, the prognosis is generally worse when metastases occur in the axial skeleton rather than in the extremities. In general, the average survival of all patients diagnosed with metastatic RCC is about four months and only 10% of these survive for one year (Thyavihally et al., 2005).

The RCC has a well know angiotropism associated to the anatomical and hemodynamic characteristics of the blood supply of the spine, and to the persistence of hematopoietic tissue inside the vertebral body, making this region the most susceptible localization for the metastases in the spine.

Vertebral lesions determine a severe compromise of the quality of life, with pain that can become intractable and a high risk of vertebral fracture and/or paralysis. The substitution of the healthy bone with the metastatic tissue cause a weakening of the vertebra, and sometimes an acute fracture with spinal canal invasion, that can be the most dramatic result from the clinical point of view.

Kidneys cancer cells are not usually susceptible to chemotherapy agents and traditional radiation therapy. Only a small number of patients have been shown good responses to these drugs vinblastine, floxuridine, 5-fluorouracil (5-FU), capecitabine, and gemcitabine, and therefore it should be reserved for cases in which target drugs and/or immunotherapy

are not effective. Radiation therapy can be used for patients that the general health is too poor to have surgery, however it is not routinely recommended because there is no evidence that it can improve survival.

The management of bone metastasis from RCC is often a difficult task. The progressive improvement in the survival rate of the patients due to new forms of treatment, and the radiation therapy, and chemotherapy resistance associated to this tumor, imposes a great challenge to its proper treatment. The role of the spine surgeon in these cases, is to choose the best treatment considering not only the factors associated with the primary tumor, but specially the individual characteristics of every patient.

New therapies, known as "target therapies", directed to specific molecular targets implicated in angiogenesis and tumor proliferation have presented encouraging results. Even though these results coupled with a fuller understanding of molecular pathways in RCC have paved the way for new targets in the treatment of kidney cancer. These drugs are often used as the first line of treatment against advanced kidney cancers. While they may shrink or slow the growth of the cancer, it does not seem that any of these drugs can actually cure RCC (American Cancer Society, 2011). Immunotherapy associated to surgery should also be considered the first treatment of choice in selected cases or in cases of failure of previous treatment with target therapies. In the authors' experience, this treatment has been the one to show the best results so far. The surgical treatment of the spine metastasis varies from local decompression to en bloc resection of the lesion. Although the en bloc resection does not have the objective to cure the patient from the disease, it should be considered to minimize the risk of local disease progression (Les et al., 2001). However, many patients treated with en bloc resection can still develop local recurrence.

2. Metastatic pathways to the spine

The tumor dissemination to the bone can come from three pathways: direct extension, the lymphatic vessels and, the most frequent, the hematogenous pathway. The most frequent site in the vertebrae is the vertebral body, because of its abundant vascularization and the presence of bone marrow inside.

In 1928, Ewing suggested that the metastatic diffusion was influenced only by mechanical factors. The abundant tortuous vessels inside the vertebral body contribute to the metastatic embolus deposit locally and the localization of the blood vessels near the vertebral end plate can explain the normal localization of the metastases in the spine. Batson showed in 1940 the role of the paravertebral venous plexus in the metastatic dissemination of pelvic and abdominal tumors to the spine. This valveless plexus allows a retrograde blood flow from the inferior vena cava to the paravertebral venous plexus any time that the intra-abdominal or intra-thoracic pressure rises, even if temporally. This retrograde flow can deliver metastatic embolus direct to the spine, escaping from the natural filters of the organism, as the liver and lungs.

Renal cell carcinoma presents a peculiar venotropism, which is the capacity of its cells to reach the venous circulation. The diffusion can occur through an anterograde flow in the renal vein to the inferior cave vein reaching the right atrium, or through a retrograde diffusion. Moreover, the anatomical connections between the renal venous circulation and

the paravertebral venous plexus through the azygos and hemiazygous systems can also favor a metastatic implantation at the spine.

The associations of the well-known angiotropism of the renal cell tumors, the anatomical and the hemodynamic characteristics of the spinal circulation, and the persistence of the hematopoietic tissue inside the vertebral spongeous bone matter are the responsible for the high frequency of metastasis of RCC.

3. Diagnosis

3.1 Clinical diagnosis

The early diagnosis of metastatic spinal disease is important because functional outcomes depend on neurologic condition at the time of presentation. The presentation of spinal metastases can vary widely from back pain to different degrees of neurologic deficit including complete paralysis at the lesion level. Pathologic fracture and a complete spinal cord lesion are the worse conditions associated to the spinal disease and, in most of the cases, can and should be avoided. Clinically, the symptoms associated to RCC spinal metastases do not differ from most of the other metastatic primary tumors. The past history of renal cell carcinoma is usually the most important clue to localize the primary site. Often, spinal metastases can occur in patients submitted in the past to nephrectomy to treat RCC, and that have been considered as "no evidence of disease" for several years.

Back pain is the most common symptom caused by spinal metastases, and often precedes the neurologic symptoms by weeks, sometimes even months. In some cases, back pain can be the first symptom related to the original cancer disease, and the primary site diagnosis is reached through a biopsy of the spinal lesion. There are mainly three different sources of back pain: mechanical, radicular and local pain. The mechanical pain is caused by the spinal instability secondary to the structural abnormality of the spine, and is also known as axial back pain (Gokaslan and York, 1998). The instability can be diagnosed because of its clinical symptoms or with obvious alterations such as pathologic fractures. This pain is movement-related and exacerbate by sitting or standing which increases the axial load on the spine. Patients presenting with pathological fractures of the spine may also present pain in recumbence and often give a history of sleeping upright in a chair for several weeks. The presumed mechanism is extension of the unstable kyphosis. At the beginning, mechanical pain maybe relieved with narcotics or an external orthosis, however it does not respond to steroids. The source of local pain can also be increased by the muscle, tendon, ligament and/or joint capsule strain that secondarily occurs from the vertebral body damage. Radicular pain may occur when spinal metastases compress or irritate an exiting nerve root, yielding pain in the dermatomal distribution of the involved nerve root. This type of pain is often described as "sharp," "shooting," or "stabbing" (Perrin et al., 1982). The periosteal stretching and/or a local inflammatory process stimulate the pain fibers within the periosteum causing local pain. It is predominantly nocturnal or early morning pain and generally improves with activity during the day, and it is usually described as a persistent "gnawing" or "aching" pain originated from the affected spinal segment. Inflammatory pain usually responds to administration of low dose steroids.

The second most common presenting complaint is motor dysfunction. Myelopathic abnormalities begins with hyperreflexia, clonus, Babisnki reflex and can progress to

weakness, proprioceptive sensory loss, and loss of pain and temperature below the level of spinal cord compression. Autonomic dysfunction can occur secondarily to spinal cord compression or cauda equina compression. Bladder dysfunction is the most common autonomic finding and often correlates with the degree of motor dysfunction (Schiff 2004). The proper identification of neurologic deficit is of paramount importance, considering the motor function at the time of diagnosis correlates with the prognosis (Arguello et al., 1990). Unfortunately, the presence of back pain is extremely common in the general population, and it is likely that delay diagnoses of vertebral metastases occur in the presence of only back or neck pain. For these reasons, in every patient with a past history of RCC, the hypothesis of vertebral metastasis must be considered until proven otherwise.

Generally, the motor dysfunction is associated with sensory dysfunctions, such as anesthesia, hyperesthesia, hypoesthesia and/or paraesthesia. Complains of sensory abnormalities can occur in the dermatomal distribution of the radicular pain or weakness, while the patients with myelopathy may elicit a sensory level across the chest or abdomen.

The clinical evaluation of spinal patients should include general performance status, a pain assessment and a quantitative neurologic score. The most common method of pain assessment is the visual analog scale. The performance status reflects ambulation, medical comorbidities and extent of the disease. A patient may have normal motor strength, but be unable to walk from loss of proprioception, fracture of lower limbs or from a variety of other reasons.

The neurologic status is assessed using the modified Frankel grading system (McGuire et al., 1998) and/or the American Spinal Injury Association (ASIA) score (Table 1). Both systems assess the motor function with a score of "E" being normal and "A" being a complete paralysis.

Grade	Description
A	Complete: No motor or sensory function is preserved in the sacral segments S4-S5.
B	Incomplete: Sensory but not motor function is preserved below the neurological level and extends through the sacral segments S4-S5.
C	Incomplete: Motor function is preserved below the neurological level, and the majority of the key muscles below the neurological level have a muscle grade less than 3.
D	Incomplete: Motor function is preserved below the neurological level, and the majority of the key muscles below the neurological level have a muscle grade greater than 3.
E	Normal: Motor and sensory function is normal.

Table 1. ASIA impairment scale.

The modified Frankel score system divides the clinical-neurologic status in seven stages:

- A: Complete loss of the motor and sensitive functions.
- B: Presence of sensory but absence of voluntary motor functions.
- C: Motor deficit that allows the deambulation, but only with antibrachial support and lower limbs bracing.

- D1: High degree of motor deficit that allows deambulation using only an antibrachial support, and/or bladder or bowel paralysis.
- D2: Moderate degree of motor deficit that allows the deambulation without support or bracing, and/or bladder or bowel neurologic dysfunction.
- D3: Mild motor deficit with a normal bladder and bowel functions.
- E: Complete motor and sensitive function (osteotendinous reflexes can be abnormal)

3.2 Diagnostic imaging

Plain radiography (with or without myologram), myelography, computed tomography (CT) (with or without myelogram), magnetic resonace imaging (MRI), and positron emission tomography (PET) all play important roles in the imaging assessment of spinal cancer and metastatic lesions from RCC.

3.2.1 Plain films

Plain radiographs are readily available, easy to perform, relatively low cost, and provides a detailed assessment of osseous structures. Lytic or sclerotic areas of bone, pathologic compression fractures, deformity, and paraspinal masses can be seen, however, according to Gabriel et al., up to 50% of the bone must be eroded before there is a noticeable change on plain radiographs.

3.2.2 Computed tomography (CT)

CT provides a detailed assessment of osseous structures and the extent of tumor involvement within the bone. It is indispensible for pre-operative staging according to the Weinstein-Boriani-Biagini and surgical planning (Boriani et al., 1997). When associated to myelography, it demonstrates any suspected compression of the neural elements caused by tumor extension to the canal or osseous fragments from a pathologic fracture.

The CT is very important also to evaluate the risk of pathologic fracture based on the tumor's extension in the vertebrae.

3.2.3 Nuclear scintigraphy

Nuclear scintigraphy or bone scan demonstrates areas of active bone metabolism. A major advantage of bone scans is its cost-effective ability to scan the entire axial and appendicular skeleton at the same time and its capacity of revealing lesions at an earlier stage when compared to plain films. Its disadvantage is the low specificity, as increased metabolic activity in the presence of inflammation or infection. The image correlation with CT and MRI is necessary due to its low imaging resolution. The PET scanning with ^{18}F-fluorodeoxygucose is more sensitive and specific for whole body metastatic evaluations, but as with bone scans, it also necessitates concomitant use of CT or MRI. Koga et al, assessed the diagnostic value of bone scan in 205 patients with confirmed renal cell carcinoma, and concluded that bone scan may be omitted in patients with stages T1-3aN0M0 tumors and no bone pain because of the low proportion of missed cases with bone metastasis (Koga et al., 2001).

3.2.4 Magnetic Resonance Imaging (MRI)

MRI is currently the gold standard imaging technique for assessing the spinal metastasis. It combines excellent spatial and contrast resolution. MRI is also more sensitive than CT, and bone scans, and does not exposes patients to ionizing radiation. It provides superior resolution of soft-tissue structures such as paraspinal muscles, intervertebral disc, spinal cord and nerve roots. Standard MRI protocols include T1-weighted images (T1 WIs) without and with intravenous contrast, T2-weighted images (T2WIs) in axial, coronal and sagittal reconstructions. Fat suppression techniques are useful in evaluating osseous lesions that enhance with contrast. Disadvantages include relatively long acquisition times, insurmountable safety contra-indications in some patients, and lower sensitivity to osseous structural abnormalities.

3.2.5 Angiography

Metastasis from hypervascular tumors as RCC may have diagnostic and therapeutic benefits from angiography. Pre operative angiography can provides the knowledge about the tumors vascular supply and allows preoperative embolization, decreasing the blood loss during the intralesional excision.

3.3 Anatomopathologic diagnosis

Percutaneous biopsy to confirm the diagnosis is paramount. Although imaging modalities can provide a great definition of the anatomical aspects of the lesions the correct diagnosis is mandatory prior to the treatment planning. Patients with well-known primary cancer can present with a spinal lesion from another hidden metastatic tumor or a primary bone tumor associated. CT guided percutaneous trocar biopsies provide relatively easy access to most lesions with success rates approaching 90%. Traspedicular biopsy is the most adequate technique because of the smaller contamination of the adjacent tissues, facilitating its removal during the resection.

4. Management of spinal metastasis

When dealing with spinal metastasis factors need to be taken into consideration by the oncologist, spine surgeon, anesthesiologist and the entire multidisciplinary group involved in the caring of these patients. Considering that metastatic disease to the spine a systemic disease, at first, the curative excision of the entire secondary lesion does not seems necessary, particularly in the spine because of its anatomical characteristics and morbidity. The palliative treatment frequently applied has the primary objective to decrease the pain, stabilize the spine and, whenever is necessary, decompress the adjacent neural structures. The intralesional excision of the tumor (inadequate oncological margins) can be complete or incomplete, allowing a circumferential decompression of the spinal cord and a better local control of the disease.

RCC is well known as radiation therapy and chemotherapy resistant, and immunotherapies with cytokines based on interferon alpha and interleukin-2 (IL2) have shown poor results with significant toxicities. New therapies directed to molecular targets implicated in angiogenesis and tumor proliferation are being developed. Sunitinib is considered one of the new reference first-line treatment for RCC metastasis, however despite all the progress in recent years,

complete responses are still very rare, and many important issues regarding the use of these agents in the management of metastatic renal cell cancer still need to be properly addressed.

Surgical treatment has been the only recognized therapy to improve the quality of life in the patients with RCC metastatic disease in the spine. In most of the cases the surgery does not improve the survival prognosis of these patients but it can dramatically improve the their life quality. Moreover, in a small group of patients with solitary spinal RCC metastases the en bloc resection has shown to substantially improve the overall survival time. In their retrospective work, Thyavihally et al. demonstrated the complete resection of either synchronous or metachronous solitary metastases from RCC is justified and can contribute to a long-term survival in a selective group of patients. They also concluded that patients with long interval between diagnosis and development of metastasis and early stage of the primary tumor have a better prognosis after en bloc resection of the metastases.

The treatment goals of spinal metastasis is different than the primary bone tumors, the first one aims the patient's quality of life while the main target of primary bone tumor is to preserve life. The best treatment" should include local control of the disease and restoration of the spinal function.

4.1 Treatment planning

Surgical indications for spinal metastasis in general, have been subject of controversy because the ideal moment, patient and surgical technique are still trying to be defined in the literature. Many strategies have been proposed trying to appropriately direct the best surgical treatment. In 1987 Tokuhashi et al. published a point-addition-type scoring system for the preoperative prediction of the survival period to select treatment options. This score system was later on revised and magnified its the application to the group with conservative treatment. The general condition (Karnofsky performance status), the number of extraspinal bone metastases, the number of metastases in the vertebral column, the presence of metastases to major internal organs (lungs, liver, kidneys, and brain), the primary site of cancer, and the severity of spinal cord palsy were the items evaluated. Each parameter ranged from 0 to 5 points, and the total score was 15 points. RCC was considered as moderate prognosis receiving three points in the item "primary site of cancer". Tomita et al, also have described a scoring system based on the primary tumor, the presence of metastases to the vital organs and number of bone metastases. These systems have been used among the spine surgeons with reasonable results, unfortunately the scores systems are too simple, based in numbers that allocates extremely different types of patient in the same group, and also they do not consider the clinical status and other physicians opinions involved in the patient's care before deciding the best treatment option.

In 2008, the authors published their own treatment algorithm to guide the decision planning when dealing with spine metastasis, based on a retrospective study of 43 patients (Cappuccio et al., 2008). According to Cappucio et al., multidisciplinary treatment could be beneficial, and a failure to do so, is very like to end in a suboptimum prognosis and could even lead to sever impairment. The treatment planning, including the surgical planning should involve not only the spine surgeon, but also the nonsurgical physicians (anesthetist, oncologist, radiotherapist), and it should be chosen on each individual patient. Gasbarrini et al., conducted a semi-prospective clinical study in 2010 with 202 patients to evaluate the efficacy of this algorithm which furthermore evolved to a flow chart (Figure 1).

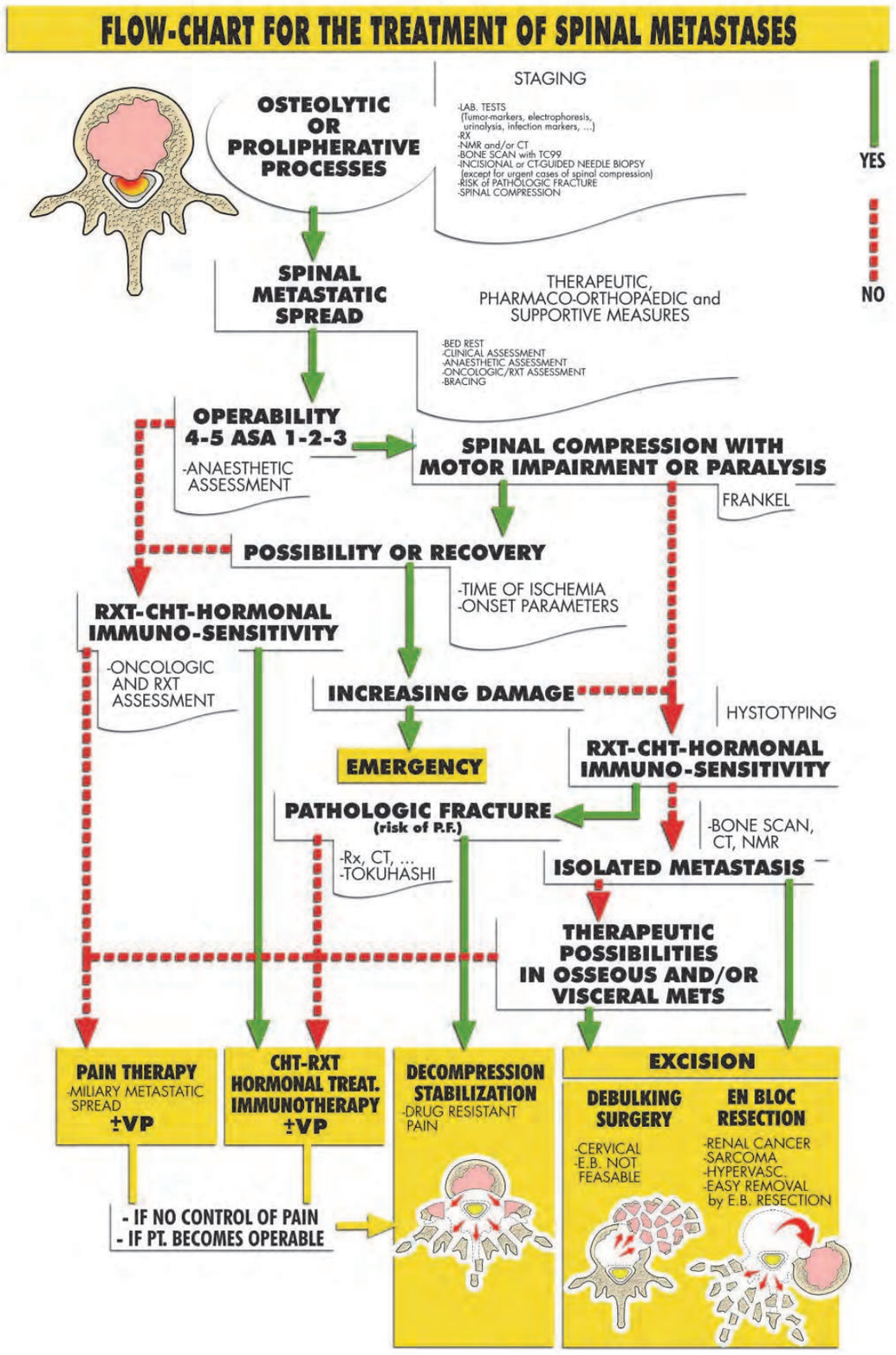

Fig. 1. Flow chart for the treatment of spinal metastasis.

According to this flow-chart, all spinal tumors must be staged, and the first question when planning the treatment is to discuss with the oncologist about the life expectancy of the patient and to reach a consensus with the anesthesiologist if the patient is operable or not (based on the ASA score). Other important items to consider is the neurological status and its capacity to deteriorate or to improve, the presence of pathologic fracture, the sensitivity of the primary tumor to non surgical therapies, and the number of spinal, bone or visceral metastasis. Following the flow chart the best therapeutic option can be achieved, ranging from only pain therapy to surgical procedures as en bloc resections.

Considering the RCC metastases, the surgical treatment is the only method that can improve the patient's quality of life, and in some well selected cases of single spinal metastases, a cure of these patients have been well documented after en bloc resections (Li et al., 2009). Patients with disseminated RCC metastasis, or clinically incapable to be submitted to surgical procedures, pain therapy is indicated.

4.2 Surgical planning

In order to apply the surgical indication determined by the oncological staging and the Gasbarrini's flow chart, it is necessary a complete work-up to evaluate the vertebral tumor that will be treated. The histological diagnosis, preferably obtained by CT-guided biopsy, is fundamental. Magnetic resonance imaging, CT-scan and in some selected cases, angiography, are the imaging techniques indicated to describe the tumor's extension on the transversal and longitudinal planes. The first attempt to determine a surgical staging system to guide the spine surgeons was made by Weistein in 1994. Boriani and Biagini modified this staging system in 1997 (Figure 2).

A. Extraosseous Soft Tissue
B. Intraosseous (Superficial)
C. Intraosseous (Deep)
D. Extraosseous (Extradural)
E. Extraosseous (Intradural)

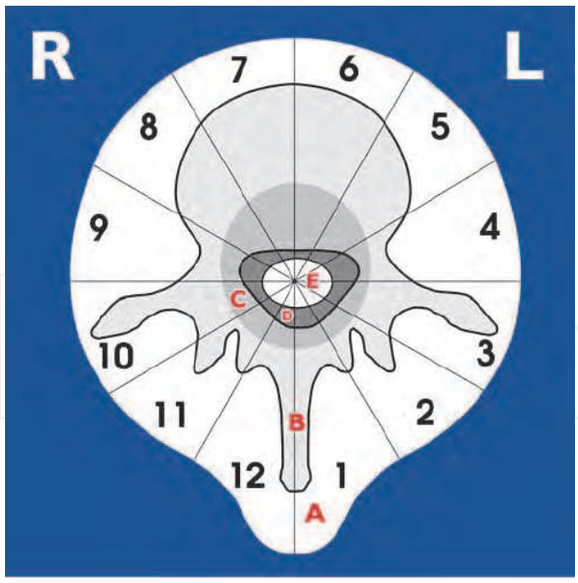

Fig. 2. WBB surgical staging system

4.2.1 Weinstein–Boriani–Biagini (WBB) surgical staging

The WBB surgical staging system is specific for spine tumors and was created to guide the planning of the surgical resection to achieve the appropriate histologic margins. It was first

described to treat primary spinal tumors, but its application was later on extended to the treatment of spinal metastasis as well. Pre-operative CT-scan and MRI are required to provide detail of the lesion and the normal tissues surrounding it.

The WBB divides the axial presentation of the vertebrae involved with the tumor into 12 zones similar to a clock face. Zone 1 is located at the left half of the spinous process followed by the others in a counter clockwise sense. Zones 4 and 9 are particularly important to know because they define respectively the left and right pedicles. Vertebrectomy with adequate surgical margins depends upon one of these zones to be free of tumor. The vertebra is further divided into 5 radial zones that define the depth of tumor invasion. These zones are also known as layers, starting from layer A that corresponds to the outside surrounding tissue of the vertebra to layer E that indicates intradural involvement of the tumor. In the cervical spine there is also layer F, which corresponds to the vertebral artery involvement. It is also important to describe the longitudinal extension of the tumor.

4.2.2 Pre-operative Selective Arterial Embolization (SAE)

Vertebral metastases of renal origin are highly vascular and often cause life-threatening intraoperative bleeding. This bleeding may influence the surgeon's ability to have an adequate view of the surgical field, and thus to achieve a complete resection. Preoperative embolization facilitates resection by decreasing intraoperative blood loss, improving visualization of the tumor during surgery, and decreasing tumor size.

Embolization can also be used as a palliative treatment in patients who are poor operative candidates or have recurrent, multiple, or unresectable tumors. It can also be used to treat painful metastatic disease or for patients with neurologic compromise from metastatic lesions by reducing the tumor size, tumor growth, and spinal canal compromise.

In cases of vascular metastatic spinal lesions, as in the RCC metastasis, a preoperative angiography should be performed to demonstrate the hypervascularity of the lesion, to identify the main arterial feeders, and, ultimately, to determine whether the lesion would benefit from the embolization. Angiography of a spinal RCC metastatic lesion typically demonstrates a hyper-dynamic pathologic circulation within the vertebral tumor, enlarged feeding intercostals or lumbar arteries, angiographic blush caused by venous congestion within the tumor nidus, and, possibly, a rapid arteriovenous transit with early filling of draining venous channels (Figure 3A). The enlarged venous pool may contribute to a tumor's mass effect; therefore, embolization may decrease spinal cord compression. Before embolization procedures, it is important to identify the segmental vessels that supply the spinal cord and the radiculomedullary branch of the anterior spinal artery and to determine whether an anterior spinal artery shares the same pedicle as the feeding artery of the tumor. The presence of an anterior spinal artery, also known as artery of Adamkiewicz (Figure 3B), at the same pedicle as the feeding artery at the tumor is considered by many authors a contraindication for embolization due to the risk of spinal cord ischemia, however some authors have demonstrated in animals models that in the presence of more than one artery of Adamkiewicz artery, the embolization of the tumor feeder would not cause damage to the spinal cord. Tomita et al., published in 2009 their techniques on total en bloc spondylectomy and showed that preoperative embolization of bilateral segmental arteries at

three levels (at the level of the tumor, and one segment above and another one bellow) should be tried within 48 hours before the operation.

There are many reports of surgeries on metastatic renal cell carcinoma that were aborted because of "uncontrollable bleeding" or excessive blood loss in control groups that did not have preoperative SAE, whereas no case was aborted were complete embolization was done.

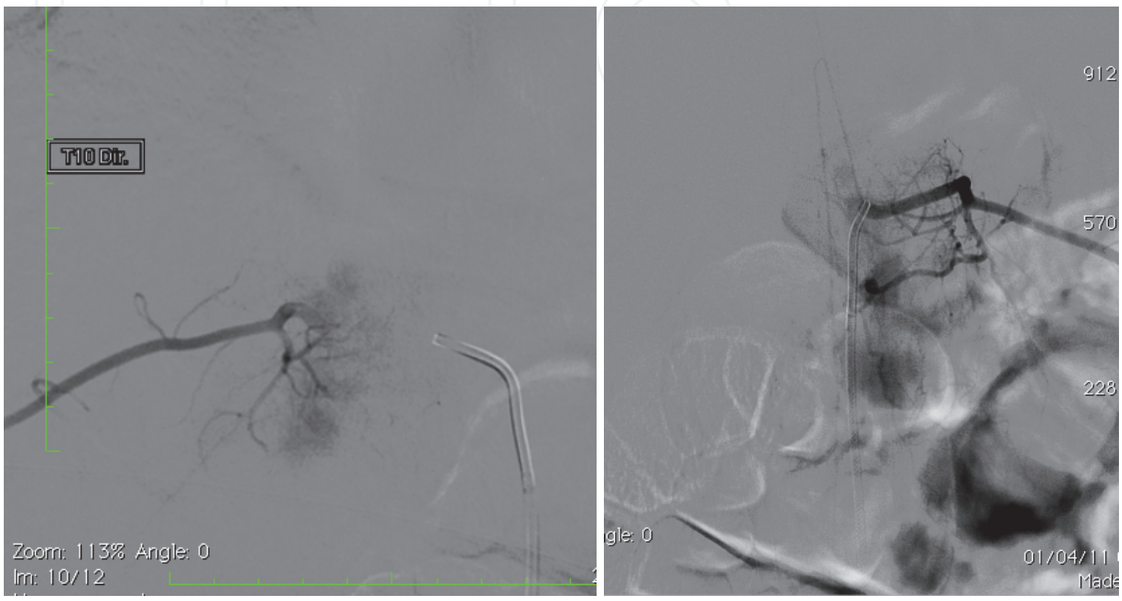

Fig. 3. A. Tumoral "blush" during angiography showing a metastatic RCC lesion in T10; 3B. Artery of Adamkiewicz.

In some cases of neurologic worsening before SAE was done the immediate surgery before the embolization can result into severe complications. Sundaresan et al., had 54% of complications in patients with RCC metastasis that were rushed into surgery without preoperative SAE. Because of this high rate of complications, some authors advocates for a delaying surgery for a few hours to perform preoperative embolization.

The choice of embolic material is based on the territory embolized, the vascular anatomy of the tumor, and the ability of selective delivery of an embolic agent via a catheter. The success of an embolization is judged by reduction in tumor vascularity and lack of tumor blush.

The timing of surgery after preoperative SAE is an important technical consideration. It is recommended that embolization be performed as close as possible to the time of surgery. Minimal blood loss occurs after embolization if surgery is performed within 24 to 48 hours after embolization. Earlier surgeries prevent the development of collateral circulation. The intraoperative blood loss can be reduced from one to two thirds in RCC metastatic lesions (Gottfried et al., 2004).

Complications rates are very low and have been reported to vary from 1% to 2%. Most complications are temporarily and are associated to a post-embolization syndrome that

includes malaise, nausea, emesis, low-grade fever, elevated white blood cell count, and local pain usually lasting three to seven days. Permanent paraplegia has been reported in the literature, but fortunately it is very rare.

4.3 Surgical treatment

In the past the patients with spinal metastasis were considered as terminal patients, therefore surgical treatment was reserved for patients with uncontrollable pain with medications, or patients with high risk of pathologic fracture. The surgical approach to the spine is basically anterior or posterior. Both approaches can be also combined in the same surgery or in separated surgical procedures.

The rational behind the adequate surgical option should include:

- The best decompression possible.
- The most efficacious spinal stabilization.
- Removal of the tumor with oncological adequacy.

The correct surgical treatment does not involve simple laminectomy of the spine of any extension. The outcomes of this procedure are comparable to isolated radiation therapy and can result in a severe instability with a high risk of neurological deterioration.

The surgical techniques to be considered are:

1. Spinal decompression and stabilization.
2. Intralesional excision (debulking) and spinal column reconstruction.
3. En bloc resection and spinal column reconstruction.

4.3.1 Decompression and stabilization

This is the fastest and less aggressive surgical procedure aiming to decompress the spinal cord and to stabilize the spine. This procedure does not necessarily include a direct approach to the tumor. It is considered a palliative treatment.

The indications for decompression and stabilization are:

1. Presence, or elevated risk, of pathological fracture in the thoracic and/or lumbar spine.
2. High sensitive tumors to hormonal, chemotherapy or radiotherapy, independently of the neurological status.
3. Patients with extremely poor prognosis aiming only the improvement of the patient's quality of life.

4.3.2 Intralesional excision

Intralesional excision includes a direct approach to the tumoral mass with a partial resection of the tumor in order to reach spinal decompression and tumor mass reduction. This procedure is considered more aggressive than simple decompression and stabilization, especially when dealing with systemic diseases, and it must include a multidisciplinary approach. Selective arterial embolization should be included in the treatment to decrease the hemorrhage, very often life threatening, and also a detailed surgical planning to achieve an

adequate excision and to reconstruct the spinal stability. Some times a double approach should be considered.

The indications for intralesional excision are:

1. Tumoral mass compression from radio-resistant metastasis.
2. Pathologic fractures in radio-resistant metastasis.
3. Necessity to reduce the tumoral mass ("debulking") in order to apply adjuvant therapies.

Surgical technique

The surgical technique for intralesional excision depends on the location of the metastases.

In the cervical spine the approach is always anterior, and for the thoracic and lumbar spine, a partial excision can be performed also using a posterior approach.

Cervical Spine: The anterior approach to the cervical spine (from C3 to T1) is well known among the spine surgeons. The approach to C1 and C2 can be transoral or extra-oral. An extension of this approach can be done through a very aggressive trans-mandible technique.

The vertebral arteries are a problem for the circumferential approach. The single anterior approach is indicated in the lower cervical spine for small metastasis (WBB: from sector 4 to 9). Every time that a tumor is located in the posterior elements, invading at least one articular process, a double approach not only is safer, but also indicated for the reconstruction in general.

Thoracic Spine: The metastasis in the thoracic spine can be completely excised through a thoracotomy using the classical anterolateral approach, technically challenging in the cervical-thoracic junction. Using only a posterior approach is also possible to perform a complete curettage of the lesion, legating one nerve root.

Thoracoscopy can also be used for intracapsular excision (McLain 2001).

Lumbar Spine: In the lumbar spine, the anterior approach with decompression, and reconstruction usually is the best option for an anterior lesion. A posterior approach at this level needs to scarify one or more nerve roots. The consequences of such action are persistent pain, loss of mobility and spinal cord ischemia.

4.3.3 En bloc resection

Stener in1989, and Roy-Camille in 1990, described the surgical techniques for en bloc resection in the thoracic and lumbar spine. Later in 1994, Tomita et al., described a similar technique for vertebrectomy using a posterior approach developed specially for spinal metastasis.

The preoperative planning is paramount to choose the best technique for en bloc resection. Each vertebral lesion needs to be evaluated carefully and the resection should be "customized". In order to plan the resection, all tumors should be surgically staged according to the WBB system, previously described.

The resection can be made throughout the external surface of the pseudocapsule (marginal resection), or outside of it, along with a margin of healthy tissue (wide resection).

The well accepted indications for en bloc resections are stage three benign tumors and in stage one, or stage two, primary malignant tumors. The indications for spinal metastasis are still controversial, however it should be considered in cases of a solitary metastases of primary tumors with longer life expectancy, as in the RCC.

Types of en bloc resections:

- Sagittal resection: The criteria to obtain oncologically adequate margins include: No extension to the layer D in the WBB system, or limited extension with dissection plane between the tumor's pseudocapsule and the dural sac.
- Posterior resection: According to the WBB system, the indications for posterior elements resection with oncological margins include sectors four and nine free of tumor e no extension to the layer D, or limited extension with dissection plane between the tumor's pseudocapsule and the dural sac.
- Vertebrectomy: The en bloc resection of the vertebral body is oncologically appropriate by a posterior approach only, in cases of tumors located inside the body (no invasion of layer A in the WBB system). If tumor mass is expanding anteriorly in layer A or when the tumor is located at the cervico-thoracic, thoraco-lumbar, lumbo-sacral junction, the surgical procedure should include an anterior release. In these cases, the posterior approach ends with the blunt dissection of the lateral aspect of the vertebral body not involved by the tumor, if exists. Cervical spine en bloc vertebrectomy is also feasible, however this technique is more difficult and associated to a higher morbidity and mortality because of its elevated risk of vertebral artery and spinal cord injuries.

Surgical technique

Sagittal resection: This technique aims at achieving en bloc resection of a tumor excentrically growing: it consists in the piecemeal removal of the uninvolved posterior elements in order to circumferentially release the dura and finalize the resection by a sagittal osteotomy. An anterior approach is required when the tumor is growing anteriorly and a margin of normal tissue must be left under visual control over the tumor, or vital structures must be protected. One or more neuroforamina are involved by tumor and the corresponding nerve root(s) needs to be sacrificed in order to obtain an appropriate margin. The uninvolved posterior elements are removed piecemeal. A complete release of the dural sac from the tumor should be done. Before the osteotomy, the contralateral pedicle is removed so that the dura is not retracted into its hard surface. First, the vertical cut is performed followed by the superior and inferior horizontal cut. The tumor is finally removed in one piece.

Posterior resection: The posterior resection requires both pedicles free of tumor in order to obtain an oncologically appropriate margin. The posterior arch is removed after both pedicles are transected. This technique is rarely used for RCC metastases because the great majority of spinal metastases are located anteriorly in vertebral body.

Vertebrectomy: Usually the surgical procedure is performed in two steps (first with the patient in prone decubitus position followed by a lateral oblique position at 45°), a posterior and anterior approach. For small lesions, inside the vertebral body the procedure can be done only by a posterior access with oncologically adequate margins, according to the technique described by Tomita et al. Although it is possible to perform an en bloc vertebrectomy using only the posterior approach in the lumbar spine, it should be avoided.

This technique involves a great risk of root damage and unlike the thoracic spine where one or more nerve roots can be sacrificed without causing major problems; in the lumbar spine a motor deficit can deteriorate dramatically the quality of life of these patients.

The advantages of the posterior only approach are less surgical time and blood loss, avoidance of the anterior approach and its morbidity, among others. The most important disadvantage is the high risk of spinal cord lesion and the difficult to obtain adequate cutting surfaces on the spinal column in order to reconstruct the anterior column. Nowadays several devices and techniques have been developed to overcome these problems. The use of a spinal cord protector is important in these cases, and should always be applied. In all en bloc vertebrectomies performed using only a posterior approach, the authors used a special device named PROMID®, to protect the spinal cord and guide the saw path through the vertebral body or intervertebral disc. (Figure 4) The device is positioned underneath the dural sac and secured to a rod. Once the Gigli saw passes through the spinal column, the protector restrains it. The little knots on both sides work as the saw guide, avoiding the use of chisels and scalpels that can cause a massive bone bleeding and also injure the spinal cord.

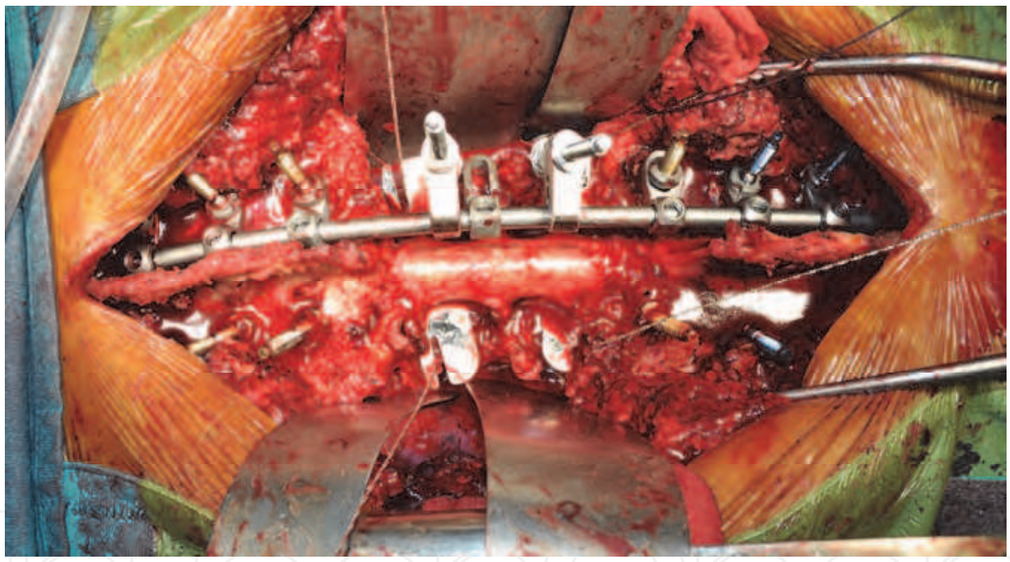

Fig. 4. The spinal cord protector and saw guide device (PROMID®) used during a posterior en bloc vertebrectomy.

The choice of the best surgical treatment is still a matter of debate, however vertebrectomy is becoming more popular among spine surgeons. This technique requires a more experienced surgical team and an adequate clinical support. It is very important to keep in mind that RCC metastases are hypervascular tumors, and intralesional excision can be associated to massive blood loss. On the other hand, en bloc resection is associated to specific techniques, sometimes a combined anterior and posterior approach, and therefore a longer surgical time. It usually requires a prolonged anesthesia, hemodynamic stability, important blood loss compensation and control of body heat loss. To overcome the necessity to complement the surgical procedure with an anterior approach and therefore to deal with its complications, the use of anterior release using thoracoscopy can be done in some selected

cases with less morbidity without affecting the oncological management (Cappuccio et al., 2010).

Cappuccio et al., reported a retrospective study comparing the variation of intra-operative hemodynamic parameters (arterial blood pressure, cardiac frequency and hemoglobin levels) between a group of patients submitted to en bloc resection and a group treated by intralesional excision. Surgical timing was significantly higher in the en bloc resection group, however the cardiac frequency, hemoglobin levels and arterial blood pressure were significantly more affected in the patients submitted to intralesional excision. They concluded that constant evolution of the anesthesia techniques allows the execution of surgical treatments that have been forbidden in the past. Hemorrhagic tumors as RCC metastases can be better managed with en bloc resection, even considering that this is a more complex procedure compared to intralesional resection.

Many authors reported the comparison between the different modalities of treatments for RCC spinal metastases. En bloc spondylectomy associated to adjuvant interferon and fractionated radiation presented good results with no recurrence in cases of solitary RCC metastases with epidural extension (Sakaura et al. 2004). In an unpublished series from Boriani, 90 cases of RCC were treated with a variety of techniques, including conventional external beam radiotherapy (4 patients), palliative decompression and instrumentation (19 patients), intralesional gross total resection (42 patients), and en bloc resection (25 patients) with recurrence rates of 100%, 84%, 24%, and 4%, respectively. In the en bloc cohort, 12 patients had no evidence of disease at a median follow-up of 30 months, 5 alive with disease at a median of 28 months, and 8 dead of disease at a median of 8 months. In the en bloc group, 1 patient showed local progression of disease (Bilsky et al., 2009).

4.4 Spinal column reconstruction

The surgical treatment of bone tumors usually results in a bone defect, secondary to curettage or resection that can be reconstructed using different types of implants associated to different methods of osteosynthesis. The complexity of the spinal anatomy requires a more specific and complex technique for resection and reconstruction.

The spinal instability and the criteria for reconstruction of each patient is different case by case, and each type of resection (posterior, corpectomy or vertebrectomy) requires a specific reconstruction technique.

Denis et al., have shown that the stability of the spine is secondary to the integrity of the middle column (posterior longitudinal ligament, posterior portion of the fibrous annulus e the posterior vertebral wall) e the anterior column (anterior longitudinal ligament, anterior portion of the fibrous annulus and the anterior vertebral wall). According to Gurwitz, and Lim et al., in cases where there is a lesion of the anterior column, a posterior stabilization is not sufficiently rigid to resist all weight bearing forces and therefore, needs to be associated to an anterior stabilization. In cases of en bloc vertebrectomy, a circumferential reconstruction is indispensable, in other words, it is necessary to associate a posterior stabilization to the anterior hardware.

The posterior elements resection requires stabilization associated to a lateral arthodesis while corpectomy needs also the substitution of the vertebral body, associated to an anterior stabilization.

4.4.1 Posterior reconstruction

In the majority of the cases an oncological surgical procedure in the spine produces a wide loss of substance associated to a major instability of the spine, thus becoming necessary a rigid stabilization of it. The most indicated system is the utilization of pedicle screws and longitudinal bars above and below the defect. In association for the patients that will not be submitted to radiotherapy, autogenous bone graft should also be used to obtain a permanent postero-lateral arthrodesis.

4.4.2 Anterior reconstruction

The anterior column is responsible for 80% of body weight support in the spine and its reconstruction is mandatory after en bloc vertebrectomies. The maintenance of the biomechanical principles is paramount.

The size of the defect can be measure, and appropriately sized cage can be inserted. The reconstruction can be made using different cages (titanium, carbon fiber, etc.) or a massive allograft bone (femoral shaft). The cages or the bone shafts are filled preferably with autogenous bone. When possible, a connection between the anterior device and the posterior construct should be performed in order to enhance stability of the whole construct.

The number of options for anterior column reconstruction devices is smaller than the posterior reconstruction. They are basically bars, plates and screws or cages that are anchored to the vertebral body. In spinal oncology these implants are frequently used to achieve an anterior stabilization especially at the long term, and also to provide an early rehabilitation.

Orthopedic cement: The use of cement as a spacer, easily adaptable and with a low cost has been abandoned in the past. It has been proven not to be a reliable system at medium and long term (Boriani et al., 1996), being indicated only in selected cases of patients with short life expectancy.

Bone Graft: Bone graft represents the oldest spacer used in the oncological surgery. The bone graft can be used to obtain an interbody fusion or to replace one or more vertebral bodies. The advantage of this kind of graft is its biological integrability. The disadvantages include the necessity of a bank bone (to collect, store, and distribute), risk of infection, the necessity of a long time to consolidate and therefore it needs to be protected (body casts, bed rest, etc.). All bone grafts are somehow damaged in the biological evolution in cases of post-operative radiotherapy (Boriani et al., 1996).

Vertebral prosthesis: There are many options of vertebral body replacement prosthesis. Nowadays the most common used are made of titanium, and recently, made of carbon fibers (Figure 5). The advantages are the immediate stability, they are not damaged by radiotherapy and there is no donor site morbidity. The disadvantages include the higher cost, the necessity to have different sizes available, to be responsible for images artifacts (image distortion in the MRI or CT-s can) and to interfere as an obstacle for post-operative radiotherapy if necessary.

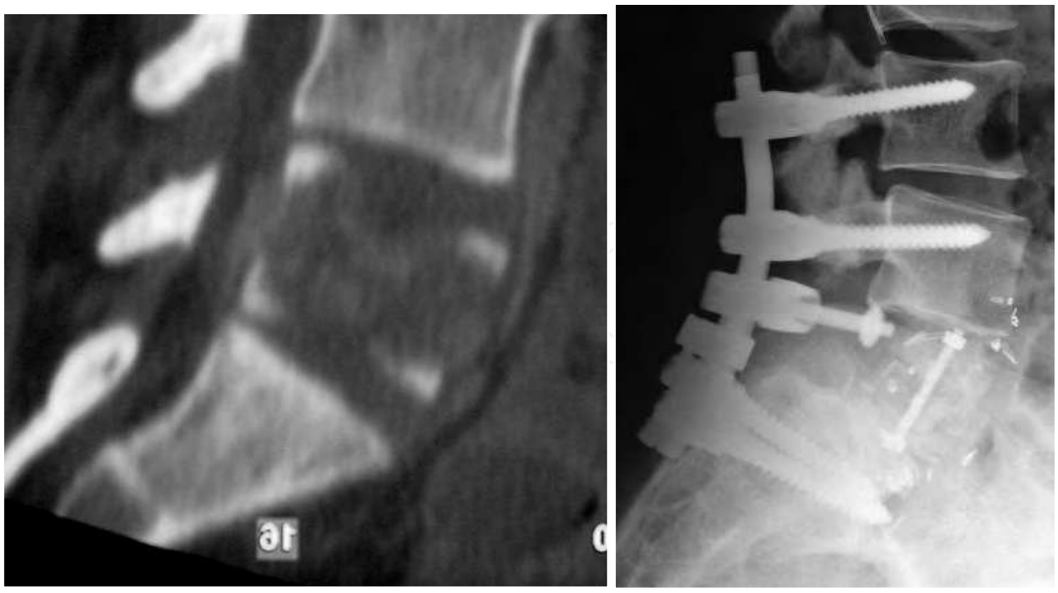

Fig. 5. A Solitary RCC metastasis of L5; 5B. 64 months of follow-up after posterior stabilization and anterior reconstruction with a carbon fiber cage filled with allograft. The bone fusion of the anterior column can be seen thorough the cage.

4.5 Stereotactic radiosurgery

Renal cell carcinoma metastases are well known to be resistant to conventional radiotherapy. In recent years, stereotactic body radiosurgery (SBRS) have allowed the safe delivery of high-dose radiation (image-guided intensity-modulated radiation therapy or spinal radio- surgery) to spinal metastases even in close proximity to the spinal cord and other paraspinal dose-sensitive organs. These treatments are often given in 1 to 5 fractions of high-dose radiation (to ensure safe doses) that are able to limit the dose to the spinal cord (Gerzsten et al., 2009). The aims of SBRS for spinal metastases are to improve on existing rates of clinical response and tumor control, and to reduce the retreatment rate by increasing the biologic equivalent dose (Sahgal et al., 2009).

According to Sahgal et al., the outcomes of spine radiosurgery can be grouped into four categories:

1. Unirradiated patients: spinal metastases in a previously unirradiated volume treated with SBRS.
2. Reirradiated patients: spinal metastases in a previously irradiated volume now containing new, recurrent, or progressive metastatic disease treated with SBRS.
3. Postoperative SBRS patients: spinal metastases treated with SBRS after open surgical intervention, with or without spinal stabilization.
4. Mixed patients: mixed populations involving patients in the previous 3 categories in which outcomes are not separately reported.

Gerzsten et al., reported a durable pain improvement in 94% of patients with RCC metastasis in the spine treated with radiosurgery. In his systematic review of the literature, radiographic control has been reported to be up to 87% in RCC (Gerzsten et al., 2009).

The use of stereotactic radiosurgery as primary option of treatment is indicated in cases of patients undergoing treatment to a symptomatic spine lesion with other significant but asymptomatic spine metastases. These asymptomatic metastases may be treated with radiosurgery to avoid further irradiation to the neural elements as well as to avoid further bone-marrow suppression and permit subsequent systemic therapy. The benefits for this approach include a single treatment that is radiobiologically larger than can be delivered with standard radiotherapy, with a minimal radiation dose to adjacent normal tissue. When used as a primary treatment modality, long- term radiographic tumor control was demonstrated in 90% of cases of isolated RCC metastases.

Stereotactic radiosurgery may be also indicated to treat patients presenting progressive neurologic deficit, where open surgery is contra-indicated, or in cases where the tumor is partially resected (intralesional resection) radiosurgery can be used to treat a residual tumor at a later date. In cases of severe compression of neural elements, the radiosurgery is not indicated and open procedure should be performed. Radiosurgery can also be used after vertebral body cement augmentation, with a local control rate as high as 92% (Gibbs et al., 2009).

Appropriate dose and fractionation schedules have not been determined and differ among institutions. There are institutions where the protocols include single-fraction radiosurgery from eight to 24 Gy or hypofractionated regimens consisting in different doses and number of fractions.

Complications associated to radiosurgery include esophagitis, mucositis, dysphagia, diarrhea, paresthesia, transient laryngitis, and transient radiculitis. Spinal cord injury has been reported, but is considered exceedingly rare.

Although the results so far reported using stereotactic radiosurgery have shown to be satisfying and promising, this technique does not treat spinal instability caused by the majority of the spinal tumors, and is contra-indicated in severe neural compression. Analysis of local tumor control rates after en bloc resection of solitary vertebral RCC metastases and after stereotactic radiosurgery appears to have comparable tumor control rates. The mean follow-up in Gerszten series of 60 patients treated with radiosurgery was 37 months and his final outcomes were comparable to the patients followed by Boriani, which showed 48% of patients with no evidence of disease after 30 months, while 52% presented systemic progression and were dead at eight to 28 months. Long-term prospective randomized studies are still to be done in order to establish to best indications and protocols for the use of stereotactic radiosurgery in RCC metastasis.

Recently, the Spine Oncology Study Group (SOSG) has conducted a systematic review trying to answer the following question "What is the optimal treatment for solitary renal cell metastases without significant epidural disease?". Their conclusion was that there is a very low quality of evidence, however stereotactic radiosurgery should be the first line therapy rather than en bloc resection (Bilsky et al., 2009).

4.6 Other treatment modalities

Radiotherapy is well known to be less effective in RCC metastases. Its use in higher doses to reach a satisfactory response increases the risk of spinal cord lesions, and also the side effects associated to it. The relationship between radiotherapy dose and duration of

response has not been well studied, and the results are conflicting in the literature. The palliation of bone pain has been reported to be satisfying by Wilson et.al when compared with the palliation of symptoms at other sites of metastases, but the duration of this effect is still controversial. Higher biological effective dose does not seem to be a predictor of response or of duration of response in the palliative treatment of RCC.

The development of new management techniques of vertebral metastatic lesions has increased. Vertebroplasty, kyphoplasty, and thermablation using radiofrequency techniques have been used. Radiofrequency is fairly used throughout the world, but results evaluating the tumor necrosis have been reported by Gasbarrini et al. in 2009. The purpose of this technique is to selectively destroy the metastatic lesion with local hyperthermia as well as resulting in thrombosis of the local paravertebral veins. In their report, the authors analyzed the tumor necrosis rate under light microscope and also under electronic microscope. They found that good results can be achieved in solid tumors as liver tumors, however the necrosis rate in RCC metastases were different, showing less necrosis rates. Their possible hypothesis for the treatment failure is that in highly vascular tumors is probably difficult to maintain the necessary temperature *in situ* for adequate necrosis. Selective arterial embolization should be considered prior to radiofrequency ablation in RCC metastases.

The use of vertebroplasty, and/or kyphoplasty in spinal metastases has no effect as far as inducing tumor necrosis. Considering the heat generated by the cement and its duration as heat source, these techniques should not be used for that purpose. The use of cement inside the vertebral body is indicated in spinal oncology to increase the vertebrae's resistance and to treat spinal instability secondary to pathologic fractures.

It is very important to always keep in mind that these treatment modalities (vertebroplasty, kyphoplasty, and thermoablation are absolutely palliative and aims only to alleviate the pain.

5. Conclusion

The different therapeutic options and their indications in the treatment of patients with RCC metastatic disease can be distributed as follow:

1. Only radiotherapy:
   - Multiple osseous metastases
   - Untreatable visceral metastases
   - Untreatable primary tumor
   - Patient's poor clinical conditions
2. Decompression, and stabilization associated to radiotherapy:
   - Intractable pain and/or neurological deficit in patients with disseminated disease
   - Untreatable or treatable visceral metastases
3. Intralesional excision and radiotherapy:
   - Solitary bone metastasis (in cases where en bloc resection is contra-indicated)
   - Treatable visceral metastasis
   - En bloc resection not feasible
4. En bloc resection:
   - Solitary bone metastasis
   - Treated primary tumor
   - Absence of visceral metastasis

- Technically feasible

5. Stereotactic radiosurgery:
   - Solitary bone metastasis
   - Absence or with minimal epidural disease
   - Absence of severe spinal instability

Considering all the treatment options, the management of RCC metastases is essentially a surgical treatment. The use of stereotactic radiosurgery has proven to be effective and comparable to en bloc resection for selected cases, however we need to consider that this treatment requires a very specific technology that, so far, is not widely available for the majority of treatment centers and patients throughout the world. This technique also does not provide any kind of mechanical reinforcement to the spinal instability.

The progressive increase of the life expectancy of these patients, associated to the low sensitivity to conventional radiotherapy and the absence of a valid protocol of chemotherapy, makes surgery, associated to immunotherapy, the treatment of election, especially in cases of targeted therapies fail. Furthermore, the vertebral location of the lesion, determines a severe compromise of the quality of life often caused by intractable pain and elevated risk of paralysis and/or pathological fracture. In this last case the surgical treatment is performed in an emergency basis and therefore associated to all the anesthesiology and surgical complication that an urgent procedure can have.

The final results, comparing the en bloc resection to intralesional excision associated to radiotherapy, seems to be similar considering the local control and long term survival. The comparison between the two options as far as morbidity and cost/efficacy favors the en bloc resection.

Isolated surgery is indicated in cases of isolated metastases, and when during the preoperative planning, the procedure is planned to be outside the tumor capsule (extralesional). Selected cases of small tumors in favorable locations, where en bloc spondilectomy is feasible, associated to good prognosis of the primary disease, en bloc resection should be the treatment of choice. This is particularly true in cases of RCC metastases, because of its high risk of local recurrence, after intralesional excision even if combined with radiotherapy. In reality, the worst result after curettage occurs in cases of incomplete excisions (posterior only approach) and the effect of additional radiotherapy is incapable to eradicate the lesion. This findings confirm that the intralesional excision needs to be complete (outside the tumor capsule) in tumors partially or totally radioresitant, like the renal cell carcinoma, becoming necessary a double surgical approach.

Both palliative surgery and intralesional excision may allow, in a good amount of patients, a certain degree of neurological improvement in the short term (improving quality of life), however the survival percentage at mid term is shorter for the patients treated with simple decompression and stabilization of the spine. Although we need to consider that, in general, patients treated with palliative surgery are in worse condition compared to those treated with intralesional excision. In cases of intralesional surgery, the use of adjuvant radiation therapy is indicated even considering the low sensitivity of tumor to this treatment.

Immunotherapy should always be associated to the post-operative radiotherapy, because it has been demonstrated that the association of the adjuvant therapy increases the survival, independently of the surgical technique applied.

The use of isolated radiation therapy is indicated only in the face of multiple RCC metastases in patients with a poor prognosis. Even in those cases, when radiation therapy fails to mitigate pain and/or in the presence of a pathologic fracture with progressive neurological deterioration, a surgical intervention with decompression and stabilization should be performed.

The early diagnosis of the primary tumor, the presence and location of the metastatic disease are paramount. The possibility of detecting the metastatic lesion in an early stage allows the spine surgeon to choose the best treatment for each patient and for each lesion. Unfortunately, the identification of these patients in an advanced stage makes the surgical intervention only a palliative measure used in cases of pathological fractures or severe neurological deficit. On the other hand, the early intervention permits a better local control of the disease, increasing the success possibility as far as improving the neurological status and treating the pain.

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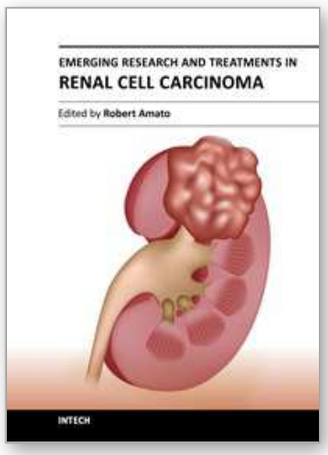

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The field of renal cell cancer has undergone a significant resurgence. This book summarizes up-to-date research and innovative ideas for the future in this rapidly changing field, which encompasses medicine, surgery, radiation oncology, basic science, pathology, radiology, and supportive care. This book is aimed at the clinician or scientist who has an interest in renal cell cancer, whether they are academic or nonacademic. The book covers tumor biology, molecular biology, surgery techniques, radiation therapy, personal testimonies, and present and future treatments of the disease that are on the horizon. The goal was to produce a textbook that would act as an authoritative source for scientists and clinicians and interpret the field for trainees in surgery, medicine, radiation oncology, and pathology.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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