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Treatment of spinal metastases in renal cell carcinoma: A critical review

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ABSTRACT

Kidney cancer is the 9th most common cancer in men and the 14th most common in women worldwide. Renal cell carcinoma (RCC) constitutes 90% of all malignancies of the kidney. RCC, is known to be highly vascular and relatively radioresistant. Bone metastases are one of the most common metastatic sites and occur in around 30% of RCCs. They significantly impact the quality of life of patients causing pain and pathological fractures. Spinal metastases represent a particular case with regard to symptoms and treatment. Indeed, neurological pain is often added to the nociceptive pain caused by metastases. More importantly, neurological impairment can be seen, caused by spinal cord or nerve root compression (MSCC). Due to close contact with the spinal cord, the treatment of spinal bone metastases is challenging and requires a multidisciplinary approach.

Specific treatment is currently focused on 4 main avenues which are surgery, radiotherapy, interventional radiology and systemic treatment.

In June 2017 we carried out an extensive search on PubMed, Web of Science, and Cochrane Library to review the various treatment options and to establish a treatment strategy.

This article presents the result of our critical review of the literature, given our expertise in the field.

1. Introduction

In 2012, there were around 338 000 new cases of kidney cancer worldwide (Ferlay et al., 2014). It represents the 9th most common cancer in men (214 000 cases) and the 14th most common in women (124 000 cases). Renal cell carcinoma (RCC) constitutes 90% of all malignancies of the kidney and is divided into 3 main histological subtypes: clear cell (70%), papillary (10–15%) and chromophobe (5%) carcinoma (Eble, 2004).

Incidence of RCC has increased over the past several years, but mortality trends are stable in most countries, and have been decreasing since the mid-1990s in North America, and Northern, Western, and Eastern Europe (Znaor et al., 2015). This can be explained, among other things, by the increasing use of imaging techniques, which can result in accidental findings of small renal masses, and by the advent of targeted therapies. In favourable-risk groups of primary tumour, survival can span several years and metastatic renal cell carcinoma is moving toward becoming a chronic disease (Jonasch et al., 2014).

Bone metastases are one of the most common metastatic sites and occur in around 30% of RCCs (Bianchi et al., 2012; Woodward et al., 2011). Undoubtedly, even with no available data, as patients in the metastatic setting are living far longer due to efficacy of targeted agents and immune checkpoint inhibitors, they are more exposed to osseous metastatic events. Pain and fracture are usually the first symptoms in 90–95% of patients. They can be the only complaint for several days or months but they have a significant impact on quality of life (Botterell and Fitzgerald, 1959; Beuselinck et al., 2011).

Spinal metastases must be highlighted because they represent a particular type of bone metastases with regard to their symptoms and their treatment. Pain is more complicated to treat, neuropathic pain often being associated with nociceptive pain. Neurological impairment also worsens quality of life. Other symptoms can also appear such as loss of sensation, weakness, bladder and bowel disorders generally evaluated by the Frankel scale (Frankel et al., 1969) or the ASIA score (Kirshblum et al., 2011), indicating spinal cord or nerve root compression (MSCC). Lastly, malignant hypercalcemia can add to the

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compression (Mavrogenis et al., 2016).

Bone metastases, and thus skeletal metastases, in RCC are particular among metastases. Indeed, they are relatively frequent and multiple. A retrospective study reported that skeletal related events (SRE) could happen in 85% of RCC patients with bone metastases. Out of these 28% will experience a MSCC (Woodward et al., 2011). Metastases from RCC are also highly vascular, requiring cautious surgery, they are less sensitive to radiotherapy, and they can progress rapidly without systemic treatment. So the therapeutic strategy is often challenging, combining different types of treatment and requiring synchronisation of the medical staff.

Currently, treatment of spinal metastases is based on surgery, radiotherapy, interventional radiology and systemic therapy.

The aim of this article is to present a critical review of the literature regarding treatment techniques for spinal metastases, advantages, disadvantages and indications in renal cell carcinoma.

2. Materials and methods

We carried out an extensive search on PubMed, Web of Science, and Cochrane Library. In June 2017, we selected a combination of Medical Subject Headings (MeSH) and free text words, including kidney neoplasms, spinal neoplasms, vertebroplasty, kyphoplasty, catheter ablation, radiofrequency, cryotherapy, cryosurgery, cryoablation, interventional radiography, radiosurgery, radiotherapy, drug therapy and related terms. The electronic search was complemented by a manual search of reference lists for relevant publications. In addition, we collected information from national and international oncological guidelines for further data. We chose only clinical trials or reviews with more than 15 patients. The search was limited to articles written in English. All articles fulfilling the criteria were incorporated to make a narrative review on the subject.

3. Surgery

3.1. Techniques

Historically, spinal cord compressions were treated by decompressive laminectomy followed by radiotherapy. However, results were poor and some studies suggested that laminectomy followed by radiotherapy was no better than radiotherapy alone (Young et al., 1980). Indeed, spinal metastases arise mostly in vertebral bodies (Siegal et al., 1982) and laminectomy does not provide enough exposure to resect lateral and anterior epidural or vertebral body tumours. Moreover, it can lead to kyphosis and thus increase neurological impairments (Dunning et al., 2012).

In surgery, the antero-lateral approach was developed and several studies showed a benefit of this procedure followed by stabilization and radiotherapy over gait, ASIA score, Frankel Grade and OS (Patchell et al., 2005; Witham et al., 2006). Then, the surgical approach was determined by tumour location. Anterior or lateral approaches were used to access the vertebral body when indicated (Bhatt et al., 2013). Stabilization is usually obtained using bone graft, cages, plates, or cement (polymethylmethacrylate (PMMA)) implants.

Spinal metastases from RCC are known to be highly vascular. There are many examples of patients requiring additional surgery for excessive blood loss, or haematomas, after a procedure for metastatic spinal lesion (Gottfried et al., 2004).

Transcatheteral arterial embolization enables blood loss and also the duration of surgery to be significantly reduced. It consists in the injection of coils, liquid, or particle agents directly into the feeding artery of the tumour. The most commonly used agent is Polyvinyl alcohol particle (PVA). A recent meta-analysis showed that complete or near-complete devascularization (80% reduction in tumour blush) was reached in 72.4% of cases, and there was only around 3% of complications linked to embolization (Griessenauer et al., 2016).

A diagnostic spinal angiography should be carried out before embolization with 2 objectives: Firstly, to assess vascularization of the lesion, looking for segmental vessels that supply the spinal cord and the radiculomedullary branch of the anterior spinal artery. Secondly, to determine whether an anterior spinal artery shares the same pedicle as the feeding artery of the tumour. Embolization procedures should be avoided if a lesion is hypovascular, which is confirmed by the absence of tumour stain on spinal angiography, or if the tumour blood supply is in proximity to the anterior spinal artery, artery of Adamkiewicz, or other major vessels feeding the spinal cord (Gottfried et al., 2004).

Regarding timing, surgery should be performed within 24–48 h after embolization to avoid revascularization of the tumour by collateral vessels (Gottfried et al., 2004; Kato et al., 2013).

There are only a few studies specifically looking at the surgical management of spinal metastases from RCC (Jackson et al., 2001; Olerud et al., 1993; Chaichana et al., 2009; Quraishi et al., 2013; Manke et al., 2001; Han et al., 2015; King et al., 1991; Sundaresan et al., 1990, 1986). All are retrospective, with 20–79 patients. Regarding the impact of surgery on neurological impairment, these studies show an amelioration of at least one letter in Frankel Grade in 20–93% of cases, and stabilization of the neurological symptoms in 52–94% of cases. Pain relief was not always described, and occurred in 78–89% of cases (Jackson et al., 2001; King et al., 1991; Sundaresan et al., 1986). Severe complications, when related, occurred in 8–15% of cases and 30-day mortality was around 6% (Jackson et al., 2001; Quraishi et al., 2013; Sundaresan et al., 1990, 1986). Lastly, median overall survival after surgery was between 12.3 and 20 months. Several factors influencing overall survival after surgery have been identified. These factors, associated with a good prognosis, are related to the severity of the spinal disease (none preoperative neurological deficit), the aggressiveness of RCC (Fuhrman grade less than 3, absence of extraspinal metastatic sites, controlled disease) and the patients' status (young patients, absence of severe comorbidities) (Petteys et al., 2016; Claudio et al., 2014).

All these results must be taken with caution, the studies being retrospective, with small populations and several biases, and a low level of evidence. If the impact on symptoms can easily be assessed, the overall impact on local disease-free progression and/or overall survival is more challenging as major improvements have been made in general treatment and knowledge has evolved on radiotherapy in RCC.

3.2. Advantages and disadvantages (Table 1)

Surgical procedures guided by tumour location act rapidly and are effective on pain, maintaining ambulation, continence, muscle strength and functional ability (Patchell et al., 2005). It should be considered as standard care to proceed rapidly when spinal cord compression occurs, knowing that after 48 h of medullary compression, the chances of regaining neurological functions are very low. Another advantage is that metastases from contiguous levels can be treated at the same time. Lastly, surgery can also provide a histological diagnosis in the case of unknown primary .

Some studies have also shown that resection of solitary metastases in RCC could improve overall survival (Kavolius et al., 1998; Kwak et al., 2007; Sciubba et al., 2010; Eggener et al., 2008), even more in spinal cord compression, OS being decreased by paraplegia (Moon et al., 2011) although other studies did not show this benefit (van der Poel et al., 1999; Lee et al., 2006).

On the other hand, surgery cannot be performed on everyone. It depends on the patient's co-morbidities. In addition, patients in a metastatic setting, are likely to have decreased performance status and to be fragile. Perioperative mortality is low (around 6%) but is still present. Anterior approaches show better results but are associated with an increase in surgery-related morbidity/mortality. The upper thoracic spine (T1-T4) is difficult to access anteriorly and requires a combination of anterolateral cervical approach and sternotomy or thoracotomy (Cohen et al., 2004).