Bone Metastases of Renal Cell Carcinoma: The Role of Surgery

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Due to its visceral anatomic location and the existence of a second functional kidney, renal cell carcinoma is characterized by a lack of early warning signs, resulting in a high proportion of patients with either locally advanced disease or metastases already present at the time of diagnosis [1,2]. RCC metastasizes via the lymphatic or venous routes, and the lung parenchyma, bone, liver and brain are the most common sites of metastases [1,2]. Imaging studies allow the detection of asymptomatic RCC more frequently and at an earlier stage of disease or in the early stages of metastatic dissemination [1–4].

Patients with metastatic RCC of bone were long considered to have a poor oncologic outcome. The traditional treatment reflected this hypothesis and was based on non-surgical means, such as radiation therapy, protected weight-bearing when the pelvic girdle and lower extremities were involved, and liberal use of narcotics. Over the last two decades, numerous reports have consistently shown a median survival of a few years in this unique subgroup of patients, primarily as the result of the biologic nature of the disease, the response of the host immune system to its presence, and advances in adjunctive therapies [5–16]. Those observations motivated medical oncologists as well as cancer surgeons to employ more aggressive treatment modalities to allow a durable palliation. Kollender et al. [17] reported 45 patients with metastatic RCC of bone who underwent surgical intervention; 22 (49%) survived for more than 2 years and 17 (38%) for more than 3 years after surgery.

Skeletal complications and their subsequent treatment are mainly responsible for the decline in the quality of life of metastatic RCC patients [7]. The vast majority of skeletal metastases do not require surgical intervention; however, intractable pain, present or impending pathologic fracture, and the presence of a solitary bone metastasis are common indications for conducting such operations [6,17]. Surgical intervention is aimed at achieving local tumor control and good functional outcome. Less than an excellent surgical outcome may result in local tumor recurrence, mechanical implant failure, unnecessary functional impairment, pain, and the need for additional surgery, all of which are devastating complications with a major impact on an already impaired quality of life. Yazawa and colleagues [18] reported a 33% implant failure rate during 60 months in their series of 166 patients with long bone metastases. This rate was even higher (44%) in the femur, probably the result of the mechanical load on this bone [Figure 1]. We focus here on the rationale and indications for surgical intervention in the management of metastatic RCC of bone, and describe the principles of the surgical technique.

Figure 1. Metastatic renal cell carcinoma of the proximal femur. This lesion was initially treated with internal fixation using a side-plate and sliding screw. Tumor resection prior to fixation and reinforcement of the hardware with bone cement were not performed. As the tumor and the associated bone destruction progressed, the fixation device was the only weight-bearing element; it broke 5 months from the day of surgery.

**Indications for surgical intervention**

Indications for surgery are intractable pain, present or impending pathologic fracture, and, occasionally, a solitary bone metastasis.

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RCC = renal cell carcinoma
As compared to patients with metastatic RCC, patients with a solitary bone metastasis comprise a unique subgroup in which a relatively prolonged survival has been reported [17]. This phenomenon was also shown by Lavenkov et al. in the current issue of *IMA* [19]. It is difficult to determine if this better outcome is simply the result of the very early detection of metastatic disease or whether the presence of a solitary metastasis reflects an inherent favorable biologic behavior of the disease in a particular patient [6,17]. Nevertheless, even if these lesions are not painful or do not pose a mechanical threat to the axial skeleton, surgical treatment aimed at providing the most optimal local tumor control is preferred.

Appropriate surgical intervention is associated with good local tumor control and functional outcome. Tumor-associated pain is relieved almost immediately, and ambulation is achieved within a few weeks from the day of surgery. Kollender et al. [17] reported their surgical results on 56 lesions in 45 patients with metastatic RCC of bone: 91% of these patients experienced significant pain relief, 89% achieved good-to-excellent functional outcome, and 94% of patients with metastatic lesions of the pelvic girdle and lower extremities became ambulatory [17]. Local recurrence occurred in only 4 of the 56 lesions (7.1%). Similar results were reported by others [6,20,21].

**Principles of surgery**

The aim of surgery is to achieve the best local tumor control with minimal injury to the surrounding healthy bone and soft tissues. Preservation of function is of high priority. Detailed preoperative evaluation is mandatory, as physical examination and imaging studies allow accurate determination of both local tumor extent and the most appropriate surgical technique. Embolization of the tumor-feeding blood vessels is strongly recommended prior to surgery since these tumors are highly vascular and extensive bleeding may occur during the course of surgery as the tumoral tissue is exposed [22,23].

Surgical intervention for metastatic RCC of bone consists of two steps: tumor resection and mechanical reconstruction. Marginal excision (i.e., curettage of the tumoral tissue with hand curettes and a mechanical burr) is performed for lesions in which the circumferential rim of cortex, remaining after tumor removal, is sufficient for ensuring a mechanically stable reconstruction (Figure 2). In these cases, cryosurgery using liquid nitrogen or argon gas is also practiced to further extend the margins of resection after curettage. Following excision, the tumor cavity is reconstructed with a combination of metal hardware and bone cement, an approach that achieves the greatest mechanical stability (Figure 2). Wide excision (i.e., en bloc removal of the tumor with a cuff of normal bone and soft tissues) is performed when bone destruction is extensive or the patient has a solitary bone metastasis (Figure 3). Amputations are performed for lesions in which there is a massive tumor extension to the soft tissues with invasion of the major neurovascular bundle of the extremity.

The common indications for surgical interventions in patients who have metastatic RCC are intractable pain, present or impending pathologic fracture, and the presence of a solitary bone metastasis. Local tumor control, pain relief, and good functional outcome can be achieved in the majority of these patients.

**References**

CD39 is the dominant Langerhans cell-associated ecto-NTPDase

CD39, the endothelial ecto-nucleoside triphosphate diphosphohydrolase (NTPDase), regulates vascular inflammation and thrombosis by hydrolyzing ATP and ADP. Although ecto-NTPDase activities have been used as a marker of epidermal dendritic cells (DCs) known as Langerhans cells, the identity and function of these activities remain unknown. Mizumoto et al. report that Langerhans cells in CD39-/ mice express no detectable ecto-NTPDase activity. Irritant chemicals triggered rapid ATP and ADP release from keratinocytes and caused exacerbated skin inflammation in CD39-/ mice. Paradoxically, T cell-mediated allergic contact hypersensitivity was severely attenuated in CD39-/ mice.

As to mechanisms, T cells increased pericellular ATP concentrations upon activation, and CD39-/ DCs showed ATP unresponsiveness (secondary to P2-receptor desensitization) and impaired antigen-presenting capacity. The results show opposing outcomes of CD39 deficiency in irritant versus allergic contact dermatitis, reflecting its diverse roles in regulating extracellular nucleotide-mediated signaling in inflammatory responses to environmental insults and DC-T cell communication in antigen presentation.

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