

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: <http://Elsevier.com/locate/radcr>

## Interventional Radiology

# Successful selective arterial embolizations for bone metastases in renal cell carcinoma integrated with systemic therapies: A case report

L. Gatto MD<sup>a,\*</sup>, G. Facchini MD<sup>b</sup>, M. Saponara MD<sup>a</sup>, M. Nannini MD<sup>a</sup>, G. Rossi MD<sup>b</sup>, V. Di Scioscio MD<sup>c</sup>, G. Biasco PROF<sup>a</sup>, M.A. Pantaleo PROF<sup>a</sup>

<sup>a</sup> Department of Specialized, Experimental and Diagnostic Medicine, Sant'Orsola-Malpighi Hospital, University of Bologna, via Massarenti n. 9, 40138 Bologna, Italy

<sup>b</sup> Department of Interventional Angiographic Radiology, Istituto Ortopedico Rizzoli, Bologna, Italy

<sup>c</sup> Radiology Unit, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

## ARTICLE INFO

## Article history:

Received 4 May 2017

Received in revised form 16 June 2017

Accepted 3 July 2017

Available online

## Keywords:

Renal cell carcinoma

Arterial embolization

Bone metastases

Locoregional therapy

Integration strategy

## ABSTRACT

Herein is described the case of a 64-year-old patient affected by metastatic clear-cell carcinoma, with exclusive bone disease, subjected after the initial cytoreductive nephrectomy to 3 successive lines of medical treatment (sunitinib, everolimus, and sorafenib) and multiple locoregional treatments (spinal surgery, radiation therapy, and selective arterial embolization), resulting in a surprisingly long survival of over 75 months. In the era of target therapy, integration strategies, including additional locoregional treatment to medical therapy, are essential to optimize the clinical benefit, to maximize treatment duration overcoming focal progressive disease, and to improve the quality of life. In this context, we would highlight that selective transcatheter embolization of bone metastases from renal cell carcinoma should be considered as an effective and safe option in the palliative setting for patients with bone metastasis, especially for pain relief.

© 2017 the Authors. Published by Elsevier Inc. under copyright license from the University of Washington. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Renal cell carcinoma (RCC) represents 3% of all cancers, with the highest incidence occurring in western countries and representing the seventh most common cancer in men and the ninth most common cancer in women [1]. Approximately 30% of all patients with RCC have metastatic disease at presentation,

and distant metastases occur most often in the lungs, the lymph nodes, the liver, the bones, and the brain. In particular, lung metastases affect 45%–50% of patients with advanced disease, followed by bone (30%) and liver (20%) metastases [2]. The estimated average 5-year survival in metastatic renal cancer is approximately 20% [3].

Bone metastases represent a crucial point in patient management because of the significant morbidity related to skeletal

Competing Interests: The authors have declared that no competing interests exist.

\* Corresponding author.

E-mail address: [lidia.gatto83@gmail.com](mailto:lidia.gatto83@gmail.com) (L. Gatto).

<https://doi.org/10.1016/j.radcr.2017.07.008>

1930-0433/© 2017 the Authors. Published by Elsevier Inc. under copyright license from the University of Washington. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

complications, such as pathologic fracture, spinal cord compression, and hypercalcemia, and correlate with a poor prognosis and a reduced overall survival [3,4].

The recent advances in our understanding of the pathogenesis and the molecular landscape of renal cancer, and in particular of clear-cell carcinoma, have led to the development of molecular therapies targeting the vascular endothelial growth factor and the mammalian target of rapamycin (mTOR) pathways, and of immunotherapy resulting in a significant improvement of treatment options, rates of survival, and quality of life [5]. The introduction of these new drugs revolutionized the clinical management of patients affected by RCC with more attention to the early clinical and imaging predictive factors of treatment efficacy, with a more accurate management of the side effects, and with a systematic and critical attitude on the treatment sequence [5–8].

In addition to these varied scenarios of systemic approach, the locoregional treatments should be placed, with the aim of controlling disease symptoms and optimizing systemic therapies, expanding the duration of each therapeutic line and improving the quality of life.

Preoperative and palliative transarterial selective embolization is a safe and effective minimally invasive, interventional treatment for pain relief and devascularization of primary and metastatic bone tumors by various primary cancers [9–15]. This treatment can also be repeated during the course of disease and can be combined with other treatment modalities such as radiotherapy and chemotherapy.

Here we present the case of a patient affected by metastatic RCC managed with a multimodality approach, consecutively treated, for over 6 years, with 3 tyrosine kinase inhibitors and several local treatments, including surgery, radiotherapy, and, in particular, with two superselective arterial embolizations of bone metastases, one in the right femur bone and one in the right pubic region.

---

## Case presentation

In April 2008, a 63-year-old man with a smoking habit and hypertension, and overweight in personal medical history presented with cruralgia and an intermittent pain in the left lumbar region. The subject underwent a contrast-enhanced computed tomography (CT) scan study, which demonstrated a large infiltrative mass in the lower pole of the left kidney measuring  $5.7 \times 5.6 \times 6.0$  cm, with vertebral metastasis (D9–L3) and with D12 and L1 cord compression and a right iliac crest metastasis. Admission laboratory tests revealed a normocytic anemia, a mildly elevated white cell count, and an elevated platelet count (Hb of 8.9 g/dL, MCV 87 fL, white blood cell count 12,000/ $\mu$ L, platelet count 573,000/ $\mu$ L). Chemistry laboratories revealed an elevated lactate dehydrogenase (584 U/L) with normal kidney and liver functions. A bone biopsy was performed, and the pathologic examination revealed a metastasis by clear-cell RCC.

The patient underwent, in the first instance, a left cytoreductive nephrectomy, followed by a surgical spinal decompression (D12 and L1) and stabilization (D9–L3) to avoid bone complications and a radiation treatment of the back-lumbar spine (D9–L3) with 20 Gy in 5 fractions for pain control.

After surgery, a first-line treatment with sunitinib as the first-line therapy at a dose of 50 mg/day in a 4/2 schedule and zoledronic acid was started. Under sunitinib treatment, which was well tolerated, the patient had a progression-free survival of approximately 41 months, higher than the median progression-free survival observed in clinical trials [16–18]. A CT scan performed after the sixth cycle of sunitinib documented an increase in the diameter of the metastatic lesion localized in the right iliac crest associated with osteolytic aspects and the new appearance of a right femoral osteolytic metastasis.

Radiotherapy of the right iliac crest (30 Gy in 10 fractions) was performed for pain control, and an mTOR inhibitor was started as a second-line therapy. Between April 2012 and November 2013, the patient was administered everolimus at a dose of 10 mg/day, obtaining a surprisingly stable disease for about 19 months. After 6 months of everolimus treatment, the patient experienced an interstitial pneumonitis, which required drug discontinuation for 20 days, therapy with supplemental oxygen,  $\beta$ -agonists, and prednisone 0.5 mg/kg.

In July 2013, during everolimus treatment, there was a significant clinical progression of the disease with worsening of the painful symptomatology in the right femur, with poor response to opioid analgesics. A fluorine-18 fluorodeoxyglucose-positron emission tomography scan showed hypermetabolic lesions in the right femoral neck (SUVmax = 4.5) and the omolateral pubic bone (SUVmax = 9) (Fig. 1).

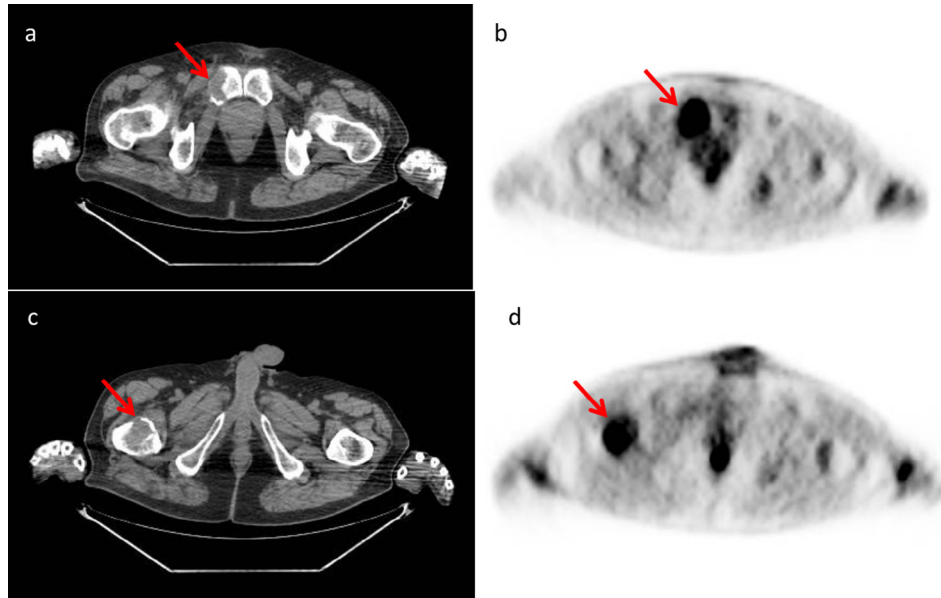
With the aim of improving pain control and delaying the occurrence of local complications, such as pathologic fractures, an arterial embolization treatment was proposed. The angiography, realized by microcatheter insertion into the common femoral artery, showed the presence of 2 hypervascular metastases in these 2 regions. The femoral and pubic lesions, characterized by a rich and pathologic neovascularization (Fig. 2), were embolized using N-butyl-cyanoacrylate with palliative intent, obtaining a complete devascularization, with the postembolization angiography showing a complete occlusion of the pathologic feeding vessels (Fig. 3). Moreover, a significant reduction in the pain score and the need for analgesics were observed.

In June 2014, because of a further skeletal disease progression, a third-line therapy with sorafenib was started, at a standard dose of 800 mg/day. After a 2-cycle occurrence of G2 anemia, G2 thrombocytopenia, fatigue, and G2 hand-foot syndrome required a dose reduction to 400 mg/day. In December 2014, because of a severe deterioration of the performance status and disease progression, the cancer treatment was suspended, directing the patient only to supportive care.

---

## Discussion

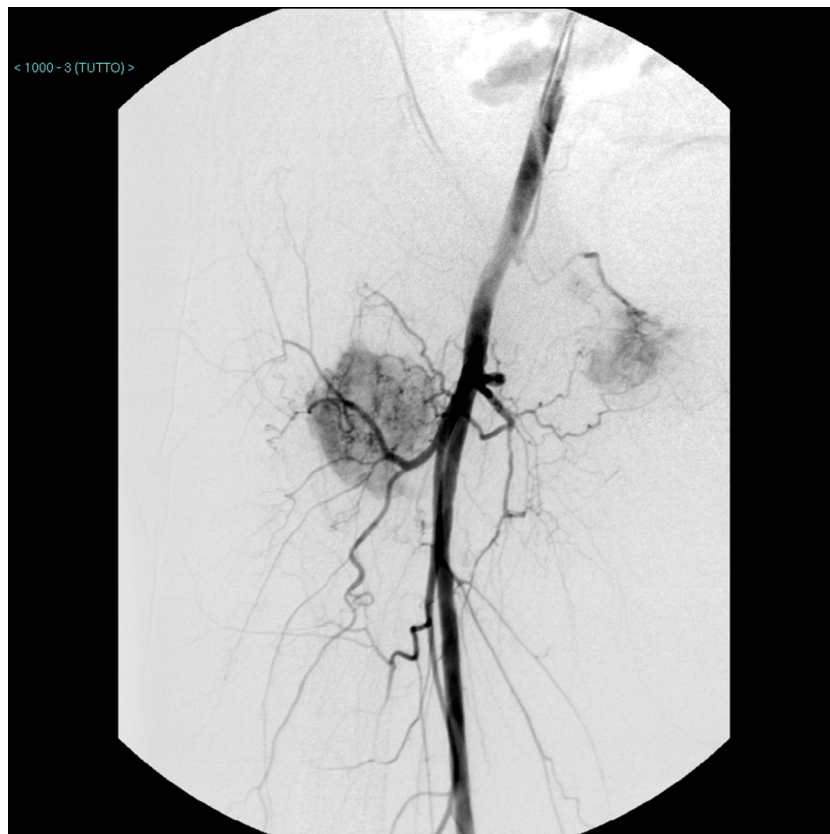
Before 2005, kidney cancer was considered a malignancy orphan of effective therapies, but in the past 10 years, the treatment options have been greatly expanded. The discovery of the crucial role of angiogenesis and the approval of sorafenib and sunitinib, respectively, in 2005 and 2006 dramatically changed the clinical outcome in these patients. In the following years, several other therapeutic options, characterized by a high rate of disease control, were approved, including vascular endothelial growth



**Fig. 1** – Pre-embolization axial computed tomography (A, C) and positron emission tomography (B, D) images showing metastatic lesions and a pathologic fluorine-18 fluorodeoxyglucose uptake in the right pubic bone (SUVmax = 9) (A, B) and in the right femoral neck (SUVmax = 4.5) (C, D). The red arrows in A and B indicate the pubic metastatic lesion, whereas the red arrows in C and D indicate the right femoral neck metastatic lesion. SUV, stands for standardized uptake value.

factor and vascular endothelial growth factor receptor multikinase inhibitors (bevacizumab, pazopanib, axitinib, cabozantinib, and lenvatinib), 2 mTOR inhibitors (everolimus and temsirolimus), and, more recently, the immune checkpoint

inhibitor nivolumab [5]. Together with systemic therapies, a multimodality approach integrating locoregional treatments (surgery, radiotherapy, and arterial embolization) also repeated over the patient's history, is currently increasing.



**Fig. 2** – Pre-embolization angiography. Two hypervascularized lesions: one in the proximal femur and one in the pubic bone.



**Fig. 3 – Postembolization angiography. Disappearance of the vasculature of the lesions.**

We report a case of a patient with bone metastases from renal cancer locally treated with superselective arterial embolizations of 2 hypervascular bone lesions for pain management. The patient experienced a clinical benefit with pain control for 6 months and continued the same systemic therapy, thus avoiding to replace a treatment still potentially effective against the highest portion of disease.

All literature data regarding the use of the arterial embolization for the treatment of bone metastasis are retrospective; further prospective studies are needed to better define the real effectiveness of this treatment and the ideal setting to use. The current main indications for arterial embolization are (1) a first-line treatment of aneurysmal bone cyst as an alternative to traditional surgery [19]; (2) a definitive treatment of benign lesions such as hemangiomas or arteriovenous malformations; (3) a primary or an adjuvant treatment such as surgery, radiation therapy, or chemotherapy of both benign and malignant lesions to reduce bleeding before surgery and to facilitate other therapies; and (4) a palliative treatment of skeletal metastases [11–15].

The procedure, performed under local anesthesia, consists of a hyperselective catheterization through femoral artery and embolization of the pathologic vessels feeding the lesion, and is preceded by a diagnostic angiography to determine the vascular mapping of the tumor [13].

Multiple embolic agents are currently available (polyvinyl alcohol particles, gelatin sponge, N-butyl-cyanoacrylate, etc.). Many factors determine the best choice of embolic material, such as the duration of occlusive effect and the preservation of normal tissue, but the most important is operator experience [14,20].

The main effects of the procedure are devascularization and pain palliation. Vessel occlusion decreases the blood flow, the edema, and the volume of the tumor, with a consequent reduction of periosteum distention and of pressure effects on adjacent structures and nerves, resulting in pain relief, which may last between 1 and 9 months; at this time, re-embolization is safe and may be necessary. Complications of embolization include dissection of the femoral artery, accidental embolization of adjacent nontargeted vessels, subcutaneous or muscle necrosis, infection caused by tissue ischemia, and postembolization syndrome, characterized by fever and pain caused by tumor necrosis [21].

The effectiveness of the procedure also depends on the specific histologic type, with a higher rate of successful treatment in hypervascular metastases, such as in renal or thyroid lesions [11,12,15].

In RCC, bone metastases are present in 30%-40% of the patients and are a major cause of morbidity, resulting in pain, decreased mobility, and pathologic fracture. Palliative treatment options for patients with bone metastases are limited, such as standard radiation therapy, if possible, and analgesic medical treatments for pain control starting (nonsteroidal anti-inflammatory drugs or opioids); the lead role is played by radiation therapy, which, however, has limitations related to the cumulative regional dose delivered and the consequent inability to reradiate the same area. In one of the first published experiences on arterial embolization of bone metastasis from RCC, a retrospective review of 21 patients was performed [22]. Thirty separate embolizations to treat 39



metastatic lesions obtained a clinical response (pain relief) in 36 treated sites; the mean duration of the response was 5.5 months.

More recently, a larger retrospective analysis was conducted on 107 patients with bone metastases from RCC [15]. One hundred sixty-three embolizations using N-2-butyl cyanoacrylate were performed from December 2002 to January 2011. The mean tumor diameter before embolization was 8.8 cm. After a mean follow-up of 4 years, a clinical response was achieved in 157 (96%) embolizations of sacroiliac metastases, and the mean maximal tumor diameter after embolization was 4.0 cm. The mean duration of the clinical response was 10 months (range 1–12). Moreover, hypoattenuating areas on the CT scan, resembling tumor necrosis, were observed in all patients (mean 75%). The most common complications (25% of the cases) were transient paresthesias in the lower extremities after embolizations of the pelvis and sacrum metastatic lesions; all patients completely recovered within a week. These data suggest that embolization may represent a rational therapeutic approach for pain relief as an important and efficacious adjunct in managing patients with hypervascular RCC bone metastases.

The case herein described surprisingly achieved a long survival (75 months after diagnosis, despite a bone metastasis generally correlated with a poor prognosis), thanks to the long disease control obtained by systemic therapies (41 months with sunitinib and 19 months with everolimus, respectively; practically a “super-responder” to everolimus) and the multiplicity of locoregional approaches carried out, including arterial embolization, which is a nonconventional procedure not currently indicated in the international guidelines of RCC. Therefore, this procedure should be considered in selected cases for the significant clinical benefit that it can bring to patients.

The progressively better survival of patients with metastatic RCC requires clinicians to use an increasing number of therapeutic tools aimed at symptom control and improvement of quality of life also in patients with a generalized metastatic disease with multiple metastases in several sites. Selective transcatheter embolization of bone metastases from renal cancer represents a reasonable tool for symptom palliation.

In conclusion, transcatheter arterial embolization does not represent a standard treatment in bone metastasis management but, in our case, brought significant clinical benefits, especially in terms of a long-lasting pain relief in both treated lesions and in the absence of embolization-related complications.

#### REFERENCES

- [1] Ljungberg B, Campbell SC, Choi HY, Jacqmin D, Lee JE, Weikert S, et al. The epidemiology of renal cell carcinoma. *Eur Urol* 2011;60:615–21.
- [2] Bianchi M, Sun M, Jeldres C, Shariat SF, Trinh QD, Briganti A, et al. Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. *Ann Oncol* 2012;23:973–80.
- [3] McKay RR, Kroeger N, Xie W, Lee JL, Knox JJ, Bjarnason GA, et al. Impact of bone and liver metastases on patients with renal cell carcinoma treated with targeted therapy. *Eur Urol* 2014;65:577–84.
- [4] Woodward E, Jagdev S, McParland L, Clark K, Gregory W, Newsham A, et al. Skeletal complications and survival in renal cancer patients with bone metastases. *Bone* 2011;48:160–6.
- [5] Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. *N Engl J Med* 2017;376:354–66.
- [6] Donskov F, Michaelson MD, Puzanov I, Davis MP, Bjarnason GA, Motzer RJ, et al. Sunitinib-associated hypertension and neutropenia as efficacy biomarkers in metastatic renal cell carcinoma patients. *Br J Cancer* 2015;113:1571–80.
- [7] Maleddu A, Pantaleo MA, Castellucci P, Astorino M, Nanni C, Nannini M, et al. 11C-acetate PET for early prediction of sunitinib response in metastatic renal cell carcinoma. *Tumori* 2009;95:382–4.
- [8] Arakawa-Todo M, Yoshizawa T, Zennami K, Nishikawa G, Kato Y, Kobayashi I, et al. Management of adverse events in patients with metastatic renal cell carcinoma treated with sunitinib and clinical outcomes. *Anticancer Res* 2013;33:5043–50.
- [9] Rossi G, Mavrogenis AF, Rimondi E, Ciccicarese F, Tranfaglia C, Angelelli B, et al. Selective arterial embolization for bone tumours: experience of 454 cases. *Radiol Med* 2011;116:793–808.
- [10] Mavrogenis AF, Rossi G, Rimondi E, Calabrò T, Papagelopoulos PJ, Ruggieri P. Palliative embolization for osteosarcoma. *Eur J Orthop Surg Traumatol* 2014;24:1351–6.
- [11] Rossi G, Mavrogenis AF, Rimondi E, Bracciaioli L, Calabrò T, Ruggieri P. Selective embolization with N-butyl cyanoacrylate for metastatic bone disease. *J Vascol Interv Radiol* 2011;22:462–70.
- [12] Barton PP, Waneck RE, Karnel FJ, Ritschl P, Kramer J, Lechner GL. Embolization of bone metastases. *J Vasc Interv Radiol* 1996;7:81–8.
- [13] Mavrogenis AF, Rossi G, Rimondi E, Papagelopoulos PJ, Ruggieri P. Embolization of bone tumors. *Orthopedics* 2011;34:303–10.
- [14] Munk PL, Legiehn GM. Musculoskeletal interventional radiology: applications to oncology. *Semin Roentgenol* 2007;42:164–74.
- [15] Rossi G, Mavrogenis AF, Casadei R, Bianchi G, Romagnoli C, Rimondi E, et al. Embolisation of bone metastases from renal cancer. *Radiol Med* 2013;118:291–302.
- [16] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356:115–24.
- [17] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:3584–90.
- [18] Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. *Lancet Oncol* 2009;10:757–63.
- [19] Mavrogenis AF, Angelini A, Rossi G, Rimondi E, Guerra G, Ruggieri P. Successful NBCA embolization of a T2 aneurysmal bone cyst. *Acta Orthop Belg* 2014;80:126–31.
- [20] Basile A, Rand T, Lomoschitz F, Toma C, Lupattelli T, Kettenbach J, et al. Trisacryl gelatin microspheres versus polyvinyl alcohol particles in the preoperative embolization of bone neoplasms. *Cardiovasc Intervent Radiol* 2004;27:495–502.
- [21] Wirbel RJ, Roth R, Schulte M, Kramann B, Mutschler W. Preoperative embolization in spinal and pelvic metastases. *J Orthop Sci* 2005;10:253–7.
- [22] Forauer AR, Kent E, Cwikiel W, Esper P, Redman B. Selective palliative transcatheter embolization of bony metastases from renal cell carcinoma. *Acta Oncol* 2007;46:1012–8.