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LONG-TERM SURVIVAL, WITH MULTIDISCIPLINARY APPROACHES, IN A PATIENT WITH METASTATIC RENAL CLEAR CELL CARCINOMA: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT – *Objective:* Kidney cancer represents 5% of all adult malignancies in men and 3% in women. The most common type is clear cell renal cancer, representing about 70-80% of the total. The medical approach to renal cancer has changed in the last few years, especially with the use of immunotherapy and tyrosine kinase inhibitors.

Case presentation: We present a case of a 48-year-old man, affected by clear cell renal cell carcinoma, detected in 2014. After nephrectomy surgery, clinical-instrumental follow-up was initiated. After only one year, a recurrence of bone disease was documented. Therefore, different types of treatments were undertaken, including systemic therapy with anti-VEGF and immunotherapy. The last treatment was Lenvatinib. Besides these, loco-regional treatments were used, which provided good disease control over time.

Results: We analyzed the case of a patient who survived for 10 years after being diagnosed with clear cell renal cell carcinoma. During these years, the patient underwent 5 lines of treatment and several loco-regional treatments. The use of drugs such as Sunitinib and Cabozantinib allowed good control of the disease while also maintaining a good quality of life. We finally offered our patient treatment with Lenvatinib, based on a study comparing the latter with Everolimus and the combination of the two. Lenvatinib treatment, which started in July 2023 and ended in February 2024, helped to further increase survival and maintain a good quality of life.

Conclusions: The case we presented is an example of how, with a good succession of systemic and loco-regional treatments and multidisciplinary and tailored approaches, long survival can be achieved while also maintaining a good quality of life.

KEYWORDS: Long-term survival, metastatic renal cell carcinoma, tailored approaches, target therapy, multidisciplinary approach.

INTRODUCTION

Kidney cancer accounts for 5% and 3% of all adult malignancies in men and women, respectively, thus representing the 7th most common cancer in men, and the 10th most common cancer in women[1]. In Italy, in 2023, approximately 12.700 new diagnoses have been estimated, mostly in men[2].

Renal cell cancer (RCC) is mostly incidentally detected. In this case, RCC tends to be lower stage and more likely to be localized than symptomatic lesions at diagnosis[3]. Only 30% of patients are diagnosed based on symptoms. Renal cell carcinoma might produce multiple hormone-like or cytokine-like products that lead to paraneoplastic syndrome[4].

The most common type of RCC is the clear cell RCC (ccRCC), representing about 70-80% of the total RCCs. Other common histotypes are papillary RCCs (10-15%) and chromophobe RCCs (5%)[5].

During the past 10 years, the medical approach to RCC has changed greatly. It started with the use of immunomodulates and continued with target therapy and immunotherapy overall today.

Looking toward precision medicine, recent advances in the biochemical, molecular, and histological features of RCC have shed light on many deregulated pathways involved in the pathogenesis of RCC. Emerging new tissue-based biomarkers and genetic abnormalities must be combined to take the best advantage of precision medicine[6]. The molecular and genomic profile of renal cell carcinoma (RCC) is characterized by mutations in key genes like *Von Hippel-Lindau (VHL), PIK3CA, TP53*, and *BAP1*, with *VHL* inactivation being central to clear cell RCC. This leads to the accumulation of HIF transcription factors, promoting angiogenesis and tumor growth *via* genes like *VEGF*. Other altered pathways include PI3K/AKT/mTOR, MAPK/ERK, and Wnt/β-catenin, contributing to cell survival and proliferation. Epigenetic changes, such as DNA methylation and altered histone modifications, further drive tumor progression. Therapeutically, VEGF inhibitors (e.g., sunitinib), mTOR inhibitors (e.g., everolimus), and immune checkpoint inhibitors (e.g., nivolumab) target these pathways, improving outcomes, especially in advanced RCC.

The use of certain tyrosine kinase inhibitors has greatly improved the survival of these patients[7]. There are four vascular endothelial growth factor (VEGF)-targeted agents that demonstrated efficacy: Bevacizumab, Sunitinib, Axinitib, and Pazopanib. They could be used in first-line therapy, regardless of the risk class. Nowadays, immunotherapy plays an important role, particularly with the combination therapies Nivolumab + Ipilimumab, Nivolumab + Cabozantinib, pembrolizumab + Axitinib, Pembrolizumab + Lenvatinib, used as first-line therapy according to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score. The IMDC risk model classifies patients with metastatic renal cell carcinoma (mRCC) into three risk groups based on six clinical factors. These groups are: favorable risk: Patients with 0 or 1 risk factors. These individuals typically have a better prognosis and may respond well to treatment; intermediate risk: Patients with 2 risk factors. Their prognosis is more moderate, and treatment responses can vary; poor risk: Patients with 3 or more risk factors. These individuals have a poorer prognosis and may experience limited benefit from certain therapies. It is also important to highlight the activity of Cabozantinib, an oral inhibitor of tyrosine kinases including MET, VEGFR, and AXL, used as a second-line therapy.

As we can see, the medical treatment of renal cancer has changed a lot over the years. All of this has led not only to increased survival of these patients but also to an improvement in quality of life and an increased adherence to treatment because most of these drugs are administered orally (TKIs), and they have milder side effects than classic chemotherapeutics.

Oligometastatic renal cell carcinoma refers to patients who have no more than 5 metastatic lesions. Depending on the rate of progression of metastatic sites, many patients may benefit from local therapy alone or a combination of local and systemic therapy. In any case, an individualized treatment approach should be pursued. Treatment strategies include local interventions such as radiotherapy, cryotherapy, surgery, and systemic therapy. There is no definitive treatment algorithm for these patients, and management often involves a multimodal strategy. Patient selection is crucial, and available data show that patients with the oligometastatic disease with favorable risk IMDC classification are more likely to benefit from loco-regional therapy to the primary tumor and metastatic sites.

CASE PRESENTATION

We describe a case of a 48-year-old man affected by clear cell renal cell carcinoma, incidentally detected in 2014. He was subsequently operated with a right nephrectomy, and then we started a clinical-instrumental follow-up according to the stage of disease (pT1a – I stage) and guidelines[5].

After a year (December 2015), tumor progression of bone disease was documented. Therefore, we started treatment with Sunitinib and bisphosphonates. The results were encouraging, giving a partial response (PR sec. Recist 1.1)[8].

In June 2016, our patient was submitted to a multidisciplinary board discussion to evaluate a surgical treatment of the bone disease (IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy).

Positron emission tomography (PET/CT scan) with fluorodeoxyglucose (18F) showed bone involvement consisting of lytic lesions in T10 and the posterior arch of the left 7th rib. Transpedicular CT-guided trocar biopsy confirmed the diagnosis of metastasis from RCC (Figure 1 A-E).

Local extension of the vertebral lesion was graded according to the Weinstein-Boriani-Biagini (WBB) surgical staging system[9], resulting in the involvement of sectors 8-5 and layers B-D.

Epidural disease (WBB layer D) was graded 1a (epidural disease without dural compression) according to the Epidural Spinal Cord Compression scale (ESCC)[10].

Considering the oligometastatic nature of bone disease and its local extension, the performance status (PS), and the patient's young age, surgical resection with tumor-fee margin was considered.

The day before the surgery, the patient was submitted to propaedeutic selective arterial embolization (SAE) of both lesions. The vertebral metastasis was fed from pathological vessels originating from T9 and T10 segmental arteries bilaterally, that have been closed with stable particles. No pathological vessels were detected from the T11 segmental arteries.

The left 7th rib metastasis was fed from the corresponding intercostal artery originating from the corresponding ipsilateral segmental bundle from which an afference to the anterior spinal artery arose.

Nevertheless, the lesion was amenable to embolization with stable particles since the pathological circle was distally from this.

Surgery was performed (June 15, 2016) with the patient in a prone position with double lumen pulmonary exclusion.

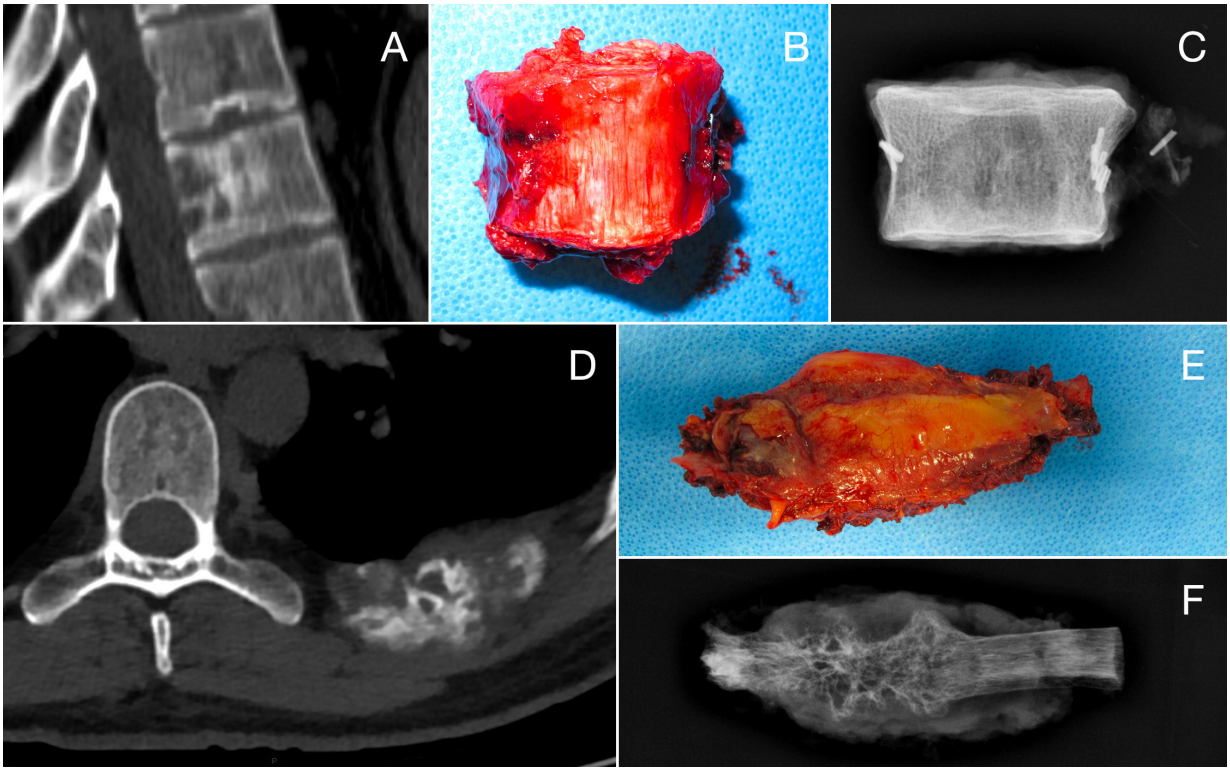

Figure 1. *A,* Preoperative axial CT-guided transpedicular trocar biopsy showing local extension of the tumor WBB 8-5/B-D; *B,* Intraoperative picture after tumor resection with temporary monolateral stabilization and malleable retractor protecting the visceral thoracic structures; *C,* Intraoperative final picture with custom made 3D-printed implant filling the gap in the anterior column and bilateral instrumentation; *D,* Postoperative axial CT-scan showing the anterior prosthesis; *E,* Postoperative x-rays: coronal view; *F,* Postoperative x-rays: sagittal view.

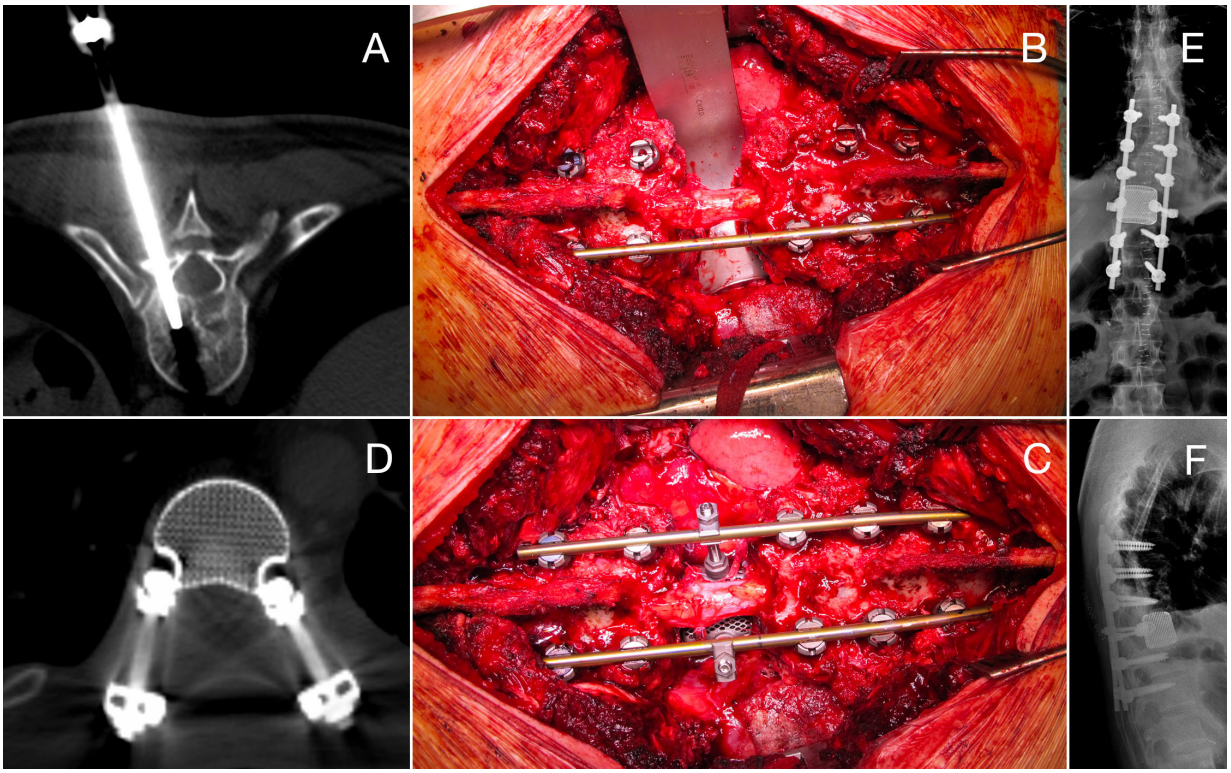

Figure 2. *A,* Preoperative sagittal CT-scan showing the T10 lytic lesion in the posterior half of the vertebral body breaching the posterior cortex; *B,* Surgical specimen of the T10 vertebral body including the tumor; *C,* X-ray of the vertebral surgical specimen. *D,* Preoperative sagittal CT-scan showing T7 and the left 7th rib lesion; *E,* Surgical specimen of the segmental rib resection; *F,* X-ray of the rib surgical specimen.

At first, the T10 metastasis was resected *en bloc* using a posterior-only technique (2B type[9,11]) with bilateral costotrasversectomy of the proximal 2-3 cm of the 9th, 10th and 11th ribs to access bilaterally the retropleural space and the posterior mediastinum. The gap in the anterior column was reconstructed with a custom-made 3D-printed titanium implant[12] and complemented with T7-T12 posterior instrumented fusion.

After completing the vertebral resection, thoracic surgeons joined the orthopaedic team to perform the segmental 7th rib resection.

Intraoperative localization of the costal lesion and confirmation of the extent of the planned rib resection was determined using video-assisted thoracic surgery (VATS), accessing the left thoracic cavity through the left costotransversectomy after deflation of the ipsilateral lung. The wall defect was reconstructed using a dual mesh, and a thoracic drain was left in place (Figure 2 A-F).

The postoperative course was uneventful, and the rehabilitation program allowed the patient to be discharged at home after 2 more weeks (July 4, 2016).

Pathologic examination on both surgical specimens (vertebrae and ribs) reported tumor-free margins (wide) of resection and confirmed the diagnosis of metastasis from RCC.

In August 2016, we started immunotherapy with IL-2 for 3 days a week and carried on treatment with bisphosphonates, up to December 2016.

In March 2017, the TC-scan revealed disease progression confirmed by right adrenal needle biopsy and then cryotherapy on these metastases. Considering the site and the oligoprogression, we chose cryotherapy over radiofrequency ablation for lower risk of necrosis and haemorrhage.

In April 2017, we started an immunotherapy treatment with Nivolumab, an anti-PD-L1 drug. The successive revaluation of disease showed progression disease (PD) (sec. Recist 1.1)[8], especially in bones and adrenal glands. Therefore, the patient underwent to laparoscopic bilateral adrenalectomy surgery.

In December 2017, we restarted the treatment with bisphosphonates and IL-2, but this time, we administered high doses of IL-2 intravenously. However, we had to interrupt after about 48 hours due to poor tolerance. After that, in January 2018, he underwent to cryotherapy on his left ribs.

In February 2018, we started a fifth line treatment with Cabozantinib 60 mg, which was newly approved, and in April 2018, he underwent cryotherapy on left ribs and right adrenal lesion.

During treatment with Cabozantinib, our patient underwent revaluation of disease with TC scan total body in March 2019 and in October 2019. They deposed for stable disease (SD).

In October 2020, the patient underwent removal of liver metastases surgery in S3 and S6 and cholecystectomy. After a month, for the appearance of two encephalic lesions, he performed brain radiotherapy treatment. He also underwent radiotherapy VMAT-IGRT technique in June 2021 on the cox-femoral joint.

We continued treatment with Cabozantinib 60 mg until June 2022, when due to poor clinical tolerance and after collective discussion, the dose was reduced to 40 mg/day.

Subsequent disease re-evaluations were performed with FDG PET because the patient had a single kidney and showed partial response (PR).

Between the end of 2022 and the beginning of 2023, our patient underwent radiotherapy on the left rear chest wall and on the right femur.

The instrumental re-evaluation with PET FDG and bone scan in January 2023 highlighted PD. So, after a multidisciplinary discussion and with the agreement of the Ethical Committee, the patients started a new line of treatment with Lenvatinib18 mg/die in July 2023.

After the beginning of this treatment, the patient underwent two total body CT scan, which showed disease stability. Among side effects, he presented only episodic G1 pressure spikes, which were managed with antihypertensive therapy. Most importantly, our patient had an improvement in quality of life and better control over bone pain.

The patient died in January 2024 when a rapid progression of disease was documented.

DISCUSSION

Renal cell carcinoma is a widespread pathological entity, and clear cell carcinoma is the most frequent histotype. Twenty-five to thirty percent of new diagnoses present an advanced stage, often already metastatic[13]. The most frequent sites of distant metastases are bone, liver, lung, and lymph nodes. Moreover, among patients treated surgically with a radical approach, 20-40% will develop distant metastases over time[14]. The prognosis of mRCC is based on several clinical, haematochemical and pathological risk factors that allow risk stratification into different classes. Based on this stratification, the most appropriate treatment is chosen[15]. The treatment landscape of mRCC has changed a lot over the last years, and consequently, so has the median survival. In patients with a good prognosis, the OS is 57 months, whereas in patients with a poor prognosis, the median Overall Survival (OS) is about 19 months[16].

We report the case of a 48-year-old patient with a diagnosis of ccRCC who lived 10 years after diagnosis. During this time, the patient underwent five lines of treatment with good tolerance and good quality of life. The systemic treatment was accompanied by several other locoregional treatments, including cryotherapy, resective surgery, and radiotherapy, which allowed local control of the disease. This met the goal of prolonging survival. Our case is a successful example of how the choice of sequential and tailored treatments due to multidisciplinary management is fundamental to clinical outcomes.

It was known since the 1980s that immunotherapy was an effective strategy in renal cancer when a viable therapeutic alternative was the administration of cytokines such as high-dose Interleukin 2 (IL2)[17], which was able to prolong the time to progression at the cost of significant toxicity. Various attempts to define which patients could benefit from IL 2 were unsuccessful[18].

In recent years, the discovery of new drugs and, in particular, of immune checkpoint inhibitors (ICIs) has radically changed the treatment of renal cancer as well as many other malignancies. This is due to the fact that renal carcinoma is infiltrated by TCD8+ lymphocytes that support the immune system against the tumor cell and allow excellent responses[19].

To better understand how this revolution in the treatment of RCC occurred, we reviewed the core discoveries behind the passage from old to new immunotherapies and targeted therapies reported by the major national and international guidelines[20].

According to the guidelines in place at the time of events, mRCC was treated with single agents targeting VEGF or mTOR[21]. The SUTENT clinical trial led to the first-line approval in the metastatic setting of sunitinib. In patients with International Metastatic RCC Database Consortium (IMDC) good risk scores, the median Progression Free Survival (PFS) was 14.1 months, and the treatment duration was 6 months. The

OS was 26.4 months. Sunitinib was also associated with a higher objective response rate than interferon alpha (31% *vs.* 6%, $p<0.001$)[22]. Similar results in terms of outcomes were obtained with Pazopanib, another VEGFR TKI that brought a new standard of care[23-24]. In the CABOSUN trial, Cabozantinib, a MET, AXL, and VEGFR2 inhibitor, was shown to improve median PFS compared to Sunitinib (8.6 months, 95% CI, 6.8 to 14.0 v 5.3 months, 95% CI, 3.0 to 8.2)[25]. More recently, Sunitinib has been used in randomized phase III trials as a control arm to evaluate the effectiveness of ICIs in patients with mRCC. Combination regimens are to date approved in the first line, and the choice of which one to use is based on side effects, comorbidities, and experience provider, considering that no predictive biomarkers of response is now available. Here are some examples of phase III studies that have changed the history of patients with metastatic clear cell renal carcinoma (mccRC). The **CheckMate 214** trial evaluated nivolumab (an anti-PD-1) plus ipilimumab (an anti-CTLA-4) for patients with untreated advanced kidney cancer. The combination improved survival outcomes compared to sunitinib, making it a key treatment option for intermediate and poor-risk patients. **KEYNOTE-426** tested pembrolizumab (another anti-PD-1) with axitinib (a tyrosine kinase inhibitor) in a similar patient group. This combination also showed better survival rates than sunitinib, establishing it as a strong first-line therapy. The **CheckMate 9ER** trial looked at nivolumab combined with cabozantinib (a TKI), which resulted in significantly better progression-free and overall survival than sunitinib, offering another robust first-line treatment. In the **CLEAR** study, lenvatinib (a TKI) was paired with everolimus (an mTOR inhibitor), showing improved progression-free survival compared to sunitinib, thus becoming a valuable alternative treatment. Ongoing studies are continuing to explore new combinations of immunotherapies and targeted treatments, aiming to refine and personalize therapy for kidney cancer, with many trials focusing on improving survival and reducing recurrence for patients.

Following disease progression from previous immunotherapy, patients should be offered a VEGF TKI, while patients progressing from VEGF and ICI could be offered another VEGF TKI single agent[26]. This is what is currently offered in this patient setting. At the time of treatment choice in our patient however, in third-line treatment, the patient previously treated with IL2 started immunotherapy with Nivolumab, which was reported in the CheckMate 025 trial to be superior to Everolimus in terms of median OS of 5.4 months (25 months in the Nivolumab arm *vs.* 19.6 months in the Everolimus arm) and improved PFS of 4.6 months[27].

In the fourth line, following the approval of Cabozantinib in patients with IMDC unfavorable risk group previously treated with one or more TKIs, our patient started this treatment with disease stability for about 65 months, with a dosage reduction due to clinical intolerance after 4 years of treatment. The METEOR trial[28] randomized 658 patients to Cabozantinib Everolimus, showing that Cabozantinib improved PFS, OS, and ORR in patients with advanced RCC after prior antiangiogenic therapy. Our patient, therefore, achieved a higher overall survival than what was observed in this clinical trial.

Anyway, prospective studies are still needed to study patients with mRCC who develop bone metastases to better define the role of locoregional therapies and medical treatment. A systematic review highlighted two phase III studies in mRCC patients with bone metastases. The METEOR study already mentioned above and the RADICAL study, which evaluates treatment with Cabozantinib and Radium 233 dichloride in patients with mRCC and bone metastases, is still ongoing[29]. Cabozantinib has demonstrated improved outcomes with the currently available data in this setting.

For patients treated with immunotherapy who undergo oligoprogression, it is certainly possible to offer locoregional therapy, such as radiotherapy, excisional surgery or thermoablation, while continuing immunotherapy. However, there are no randomized trials in the literature that evaluate these approaches. Recent data suggest that radiation therapy concomitant with ICI is safe, while caution should be exercised with TKIs[30].

The role of radiotherapy in the treatment of oligometastatic disease has few data in the literature. However, a recent meta-analysis suggests that radiotherapy treatment may improve long-term disease control and delay the use of next-line systemic therapies[31-32]. Concerning surgery, too, most of the data in the literature are retrospective[33] and its role is actually debated. It appears that, in patients selected for performance status, comorbidities, risk factors, and tumor border, metastasectomy could be associated with improved clinical outcomes[34]. Cryoablation is a technique that involves inserting a cryoprobe into the neoplastic mass, resulting in necrosis through low temperatures. In 2014, Welch et al treated 61 RCC patients with cryoablation or radiofrequency. The RFS rate at 1, 2, and 3 years was 94%, 94%, and 83%, respectively, while the OS rate was 87%, 83%, and 76%, respectively[35]. This highlights that cryotherapy may have a role in local control of metastases and may also be an alternative to surgery[36]. In our case, it is shown that we can have a good response in selected patients undergoing metastasectomy.

Finally in July 2023, following the further bone progression of the disease, and once the possibility of enrolling the patient in clinical trials had been ruled out, we proposed to the patient a new line of treatment with Lenvatinib 24 mg/day on the basis of a randomized, open-label, multicentre trial that

randomized pre-treated patients to receive Lenvatinib 24 mg/day *versus* Everolimus 10 mg/day or the combination of the two drugs[37]. Lenvatinib plus Everolimus and Lenvatinib alone resulted in a progression-free survival benefit for patients with metastatic renal cell carcinoma who have progressed after one previous VEGF-targeted therapy.

Although the study has a relatively short follow-up, the results obtained are promising. This combination fits well into the treatment landscape for subsequent lines of therapy in patients with metastatic renal cell carcinoma who have been heavily pretreated and are no longer responsive to immunotherapy. The choice of treatment based on the patient's specific condition is beneficial, as it highlights the effectiveness of a personalized approach, which could be crucial for treating patients with similar characteristics. This strategy ensures that therapy is tailored to the individual's needs, potentially leading to better outcomes for patients in challenging clinical situations.

The patient continued Lenvatinib with good tolerance and quality of life until his death in February 2024.

The case we reported clearly demonstrates how a multidisciplinary and integrated approach represents the optimal therapeutic strategy for patients with renal cell carcinoma. The combination of advanced technologies such as robotics[38], along with treatments like radiotherapy and integrated medicine, significantly contributes to improving oncological outcomes by offering more personalized and targeted treatment. This comprehensive approach not only allows for more precise and less invasive interventions but also optimizes the patient's well-being during and after treatment, maximizing the chances of therapeutic success[39].

The future of treatment for clear cell renal cell carcinoma (ccRCC) looks promising with several innovative therapies under investigation. The latest developments in adoptive cell immunotherapy for renal cell carcinoma (RCC) focus on various cellular strategies aimed at enhancing the immune system's ability to target and destroy tumor cells. Lymphokine-activated killer (LAK) cells and cytokine-induced killer (CIK) cells, which are modified to improve their cancer-fighting capabilities, have shown promise in preclinical and clinical trials. Tumor-infiltrating T cells (TILs), which are extracted from tumors and re-infused into patients, are also being explored for their potential to enhance the immune response.

T-cell receptor (TCR)-engineered T cells and chimeric antigen receptor (CAR) T cells are being investigated to improve the specificity and effectiveness of T cells in targeting RCC. CAR T cells, in particular, have made significant progress and are already being tested in clinical settings for their ability to recognize and eliminate RCC cells.

Additionally, dendritic cell vaccines are being studied to stimulate the immune system and promote a long-lasting immune response against RCC. Emerging cellular products, including CAR NK (natural killer) cells, CAR macrophages, and γδ T cells, are also being explored as potential treatments for RCC. These innovative therapies aim to further enhance immune responses, providing new hope for patients with RCC, especially those with advanced or metastatic disease.

CONCLUSIONS

Our clinical case is an example of long-term survival RCC patients who lived after the diagnosis of mRCC for 10 years, which is uncommon. The survival benefit is certainly due to the complex and multidisciplinary management of the patient and the sequence of treatments carried out. Moreover, the choice of an off-label drug such as Lenvatinib gave the patient an additional therapeutic chance. While it is important to note that this is a single-case study, it serves as a significant proof of concept. The results highlight how a multidisciplinary approach, coupled with new combinations of treatments, can potentially transform patient survival rates. This study underscores the potential for innovative strategies to drive meaningful change in patient outcomes. This initial finding paves the way for future research that could expand on these promising results, bringing us closer to more effective, holistic care models. The treatment strategies and the multidisciplinary approach for mRCC are constantly evolving, and combination approaches are increasingly advocated.

Several reports in the literature describe patients undergoing locoregional and systemic treatments with long-term outcomes. For example, Marshall et al[40] present data on 100 patients who achieved long survival after radiofrequency ablation. Fikatas et al[41], on the other hand, report the benefit of metastasectomy. De Raffaele et al[42] present a similar case of longevity in a patient treated with a multimodal approach, who benefited long-term from both an interventional and systemic approach simultaneously. Finally, Sawada et al[43] describe a case of metastasectomy on a thoracic vertebra, in addition to other systemic approaches, which differs from our case in terms of surgical reconstruction. Our patient, in fact, underwent metastasectomy followed by reconstruction with a custom-made 3D-printed titanium implant, which remains an innovative approach to date.

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