Annals of Case Reports
Ammoni LC, et al. Ann Case Rep: 9: 102042
www.doi.org/10.29011/2574-7754.102042
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Case Report

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What is the Role and Timing of Cytoreductive Surgery in the Management of Patients with Renal Carcinoma in the Immunotherapy Era? A Case Report and Literature Discussion

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Citation: Ammoni LC, Dalla Volta A, Valcamonico F, Lagana M, Berruti A, et al (2024) What is the Role and Timing of Cytoreductive Surgery in the Management of Patients with Renal Carcinoma in the Immunotherapy Era? A Case Report and Literature Discussion. Ann Case Report. 9: 2042. DOI:10.29011/2574-7754.102042

Received: 26 October 2024, **Accepted:** 30 October 2024, **Published:** 04 November 2024

Abstract

In recent years, the survival of patients (pts) with metastatic renal cell carcinoma (mRCC) has increased significantly with the advent of antiangiogenic drugs (TKIs) and immunotherapy-based regimens.

As a result, the role of cytoreductive nephrectomy (CN) and loco-regional treatments has changed over time, being reconsidered in the era of immunotherapy in pts with oligometastatic disease; therefore, sharing cases in a multidisciplinary board should be recommended to offer the pts the best therapeutic approach.

We report the case of a young patient diagnosed with oligometastatic RCC treated with a multimodal approach, discussing the historical role of CN and focusing on emerging evidence from recent studies.

Keywords: Renal Cancer; Oligometastatic Disease; Multidisciplinary Team; Cytoreductive Nephrectomy; Immunotherapy; Stereotactic Radiotherapy.

Introduction

Renal carcinoma is diagnosed in 25% of cases in advanced stage due to the presence of synchronous metastases [1,2]; however, the survival of patients (pts) with metastatic renal cell carcinoma (mRCC) has increased significantly with the advent of TKIs and immunotherapy-based combinations, as demonstrated by different studies [3-6]. Several regimens are available for mRCC, providing clinicians the possibility to select the best regimen for the individual patient according both on patient's and disease characteristics. In this regard, the Memorial Sloan Kettering Cancer Center (MSKCC) score and the International Metastatic RCC Database Consortium (IMDC) score (or Heng's prognostic system) are currently used to stratify mRCC pts in three different risk classes associated to different survivals [7,8]. Cytoreductive surgery (CN) in pts with metastatic renal carcinoma has always been considered as an additional strategy to systemic therapy. However, as shown in Table 1, the changes in standard therapies that have occurred over time have affected the clinical benefit of

this therapeutic strategy. Studies by Flanigan et al and Mickisch et al showed that nephrectomy followed by interferon therapy led to a longer survival among pts with mRCC compared to interferon alone, suggesting the role of upfront CN in improving these pts' outcome during the interferon-era [9,10].

This approach was completely reassessed with the introduction of TKIs, based on the results of CARMENA trial in which median overall survival (OS) of pts receiving upfront CN followed by sunitinib was even worse compared to sunitinib alone [11]. Furthermore, in SURTIME trial deferred nephrectomy did not guarantee a benefit in progression-free survival (PFS), although OS was higher with the deferred CN approach [12].

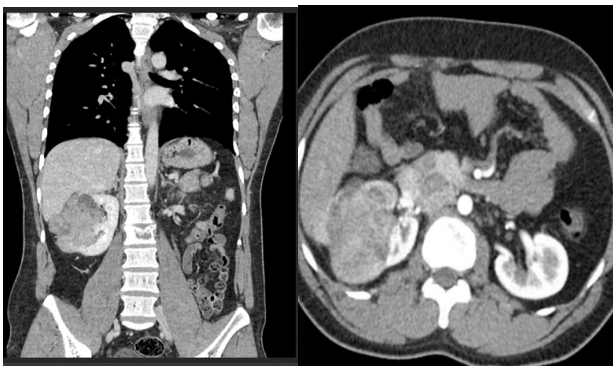
The role and timing of CN has then been strongly reconsidered in the era of immunotherapy both for clinical and biological reasons and further studies are ongoing to define the optimal sequence of multimodal approaches. Here we report the case of a young patient diagnosed with oligometastatic RCC undergoing multimodal treatment, and we discuss the role and timing of CN based on literature data with a look on emerging evidence from recent studies.

Trials	Systemic Treatment (ST)	ARMS	OS
Flanigan, et al [9]	interferon alfa-2b	upfront CN + ST vs ST alone	11,1 vs 8,1 months
Mickisch, et al [10]	interferon-alfa	upfront CN + ST vs ST alone	17 vs 7 months
CARMENA	sunitinib	upfront CN + ST vs ST alone	13,9 vs 18,4 months
SURTIME	sunitinib	upfront vs deferred CN	15 vs 32,4 months

Table 1: Summary of trials investigating the role of CN in mRCC in pre-immunotherapy era.

Case Report

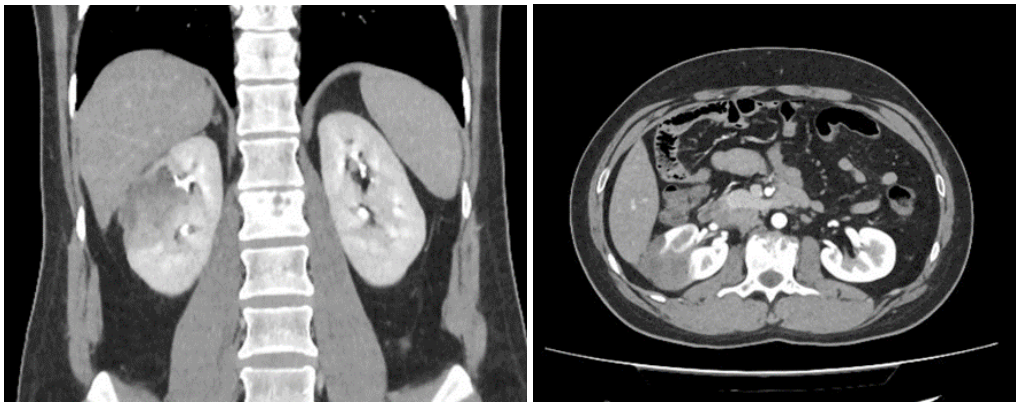
In March 2023, a 24-year-old Bangladeshi man in good clinical condition and without significant comorbidities came to the emergency room due to the onset of right lumbar and testicular pain and hematuria. He underwent a thoracic and abdominal CT (computed tomography) scan that revealed the presence of a right renal lesion of 8 centimeters in the largest diameter, infiltrating the fourth hepatic segment, the intercostal posterior muscles, and the ascending colon. In addition, a single metastatic lesion of the second lumbar vertebra was found, which was also confirmed on bone scintigraphy.



The patient was admitted to the urology unit where staging was completed with a brain CT scan, which was negative, and on 03/27/2023 he underwent a needle biopsy of the right renal lesion that diagnosed high-grade renal carcinoma with diffuse positivity for PAX8, racemase and high molecular weight cytokeratins on immunohistochemistry.

The case was discussed at a multidisciplinary meeting where, considering the oligometastatic disease and the patient's age, we chose a multimodal approach, which would have included systemic therapy, CN and stereotactic radiotherapy on the single bone lesion.

On 04/18/2023, we started a first-line systemic treatment based on the combination of an antiangiogenic agent, cabozantinib 40 mg/day, and an immune-checkpoint inhibitor, nivolumab 240 mg every 14 days. Treatment was initially well tolerated with the onset of mild diarrhea and nausea that were managed with adequate support therapy, hypertension that required the introduction of antihypertensive therapy with amlodipine, and hypothyroidism that required thyroid replacement therapy with levothyroxine. However, two months later, a high-grade hand-foot syndrome (HFS) occurred: cabozantinib was then temporarily discontinued and subsequently reintroduced with a dose reduction (20 mg/day). The CT scan performed on 07/24/2023 showed a partial response of the right renal lesion with less infiltration of adjacent organs, while the lesion of the second lumbar vertebra was stable.



Considering the radiological response, the multidisciplinary team confirmed the initial program. On 09/06/2023 the patient underwent a right nephrectomy without complications. Histological examination diagnosed unclassifiable high-grade renal carcinoma characterized by post- iatrogenic alterations and large necrotic areas, with invasion of the renal pelvis and without involvement of surgical margins. On 10/04/2023, a stereotactic radiotherapy was performed on the second lumbar vertebra (a total dose of 24 Grays in three daily fractions with the Cyberknife technique). The patient returned to the oncology unit to resume systemic treatment with cabozantinib 20 mg/day plus nivolumab 240 mg every 14 days, which is still ongoing and well tolerated. The patient was free from progression at the last CT scan performed in September 2024.

Discussion

The use of CN in treating metastatic renal carcinoma, which was a common practice during the interferon era [9,10] and was later questioned with the advent of anti-angiogenic therapies [11,12], deserves to be reconsidered during the era of immunotherapy (Table 2).

The clinical case presented here shows the efficacy of a multimodal approach based on an excellent response to the combination treatment with TKI and immunotherapy followed by effective surgery. The results of the sequential approach taken in this case are consistent with the data from the National Cancer Database (NCD). In this study, pts who responded to immunotherapy and then underwent deferred nephrectomy achieved a better survival advantage than those who received upfront nephrectomy [13]. Moreover, the CheckMate214 post hoc analysis conducted by Shirotake et al, who retrospectively investigated the clinical outcomes of Japanese pts treated with deferred CN after nivolumab plus ipilimumab for mRCC, showed higher objective response rate (ORR) and an OS gain adopting this strategy [14]. Similarly, the retrospective study conducted by Yoshino et al showed that pts receiving deferred CN after responding to immunotherapy achieved tumor shrinkage in both primary and metastatic lesions with a meaningful OS gain compared to pts who underwent upfront CN [15]. Results from the multicenter study by Gross et al also demonstrated that, when added to immunotherapy, CN is independently associated with longer OS and a 67% reduction in terms of mortality for all causes [16].

TRIALS	**Systemic Treatment (ST)**	**ARMS**	**OS**
NCD New Jersey	immunotherapy (ICI)	CN + ICI vs ICI alone	NR vs 11,6 months
CM214	nivolumab + ipilimumab	ICI + deferred CN	24,3 months
Yoshino et al [15]	nivolumab + ipilimumab	ICI + deferred CN vs upfrontCN vs ICI alone	1 year-OS: 100 vs 72,4 vs 58,2%
Gross et al [16]	immunotherapy (ICI)	ICI + CN vs ICI alone	56,3 vs 19,1 months

Table 2: Summary of trials investigating the role of CN in mRCC in the immunotherapy era.

Based on literature data regarding the evolution of CN role (as summarized in Table 1 & 2), a possible paradigm shift is emerging. In this perspective, our case supports the use of deferred CN after response to immunotherapy rather than upfront. Indeed, as demonstrated by several studies across different cancers, immune checkpoint inhibitors such as anti-programmed cell death-1 (PD1) and anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) can enhance antitumor immunity by activating antigen-specific T cells found in the primary tumor. These T cells continue to exert antitumor effects on remaining neoplastic cells after the resection of the primary tumor, potentially preventing relapses [17]. In other words, the introduction of immunotherapy has revived the old paradigm, where CN stimulated the immune system in mRCC pts to improve survival, which was doubted in the anti-angiogenic era.

Among the available regimens, we choose the combination of nivolumab plus cabozantinib based on the results of the Checkmate9ER trial which showed a meaningful benefit from such combination in terms of PFS (primary endpoint), ORR and median duration of response (DoR) compared with sunitinib [5]. The need to achieve rapid tumor shrinkage and the efficacy of cabozantinib on the bone metastases were crucial for our decision.

Considering the short follow-up after surgery, we cannot draw any definitive conclusions about the efficacy of this sequential approach in our patient. Data on the role of CN for pts undergoing immunotherapy seem to be quite encouraging, however there is still no evidence from prospective randomized trials, which were instead conducted in the era of anti- angiogenetic therapy. Further uncertainty is the best strategy after CN. The results of the study conducted by Song et al, albeit with the limits of a small number of cases; show that resumption of immunotherapy appears to be associated with a benefit in terms of disease-free survival and cancer- specific survival [18]. Contrary to this, the retrospective analysis of Pignot et al on oncological outcomes of pts who responded to immunotherapy- based regimens and subsequently underwent nephrectomy, opens up the possibility of discontinuing systemic therapy, especially in pts that achieve a complete or a major pathological response [19]. The opportunity to interrupt systemic therapy after CN also emerges from the study conducted by Shapiro et al, in which half of the pts did not resume such treatment [20]. Overall, these data suggest that immunotherapy discontinuation after CN is a possible option; however, additional data are needed to identify which patients are candidates for continuing systemic treatment and which ones to keep in follow-up. Moreover, no data are available on how long a complete response will last after discontinuing systemic treatment, and further studies are needed. In this perspective, several ongoing trials (NORDIC-SUN, PROBE and CYTO-KIK), whose completion is expected in the next few years, will provide further answers to this question.

The role of stereotactic radiotherapy in pts with vertebral metastases from solid tumors has been widely demonstrated. As revealed by Wang et al, the benefit of this treatment was significant in terms of both pain palliation (resulting in reduced opioid need) and PFS [21]. An assessment of stereotactic radiotherapy in oligometastatic RCC was conducted in the study by Marvaso et al, in which radiant treatment (average dose 25 Grays) was also carried out in pts undergoing systemic therapy and was found to be well tolerated, ensuring excellent local control [22]. The rationale to integrate radiotherapy (RT) with immunotherapy is based on the abscopal effect, which, induced by local RT, is considered an anti-tumor systemic immune response and reflects the regression of non-irradiated metastatic lesions at a distance from the primary site of irradiation [23]. Since the administration of immunotherapy can enhance the systemic anti-tumor response of RT, the combination of both strategies has got increasingly attention by medical and radiation oncologists.

Conclusions

In conclusion, the advent of immunotherapy-based combinations has revolutionized prognosis of pts diagnosed with mRCC. Therefore, the role and timing of CN and loco-regional treatments has changed from the era of interferon and TKIs. Available data and the case presented here are in favour of CN performed after immunotherapy administered upfront in a neoadjuvant setting. The decision to perform nephrectomy should be made based on individual factors, including the patient's response to systemic immunotherapy, performance status, and disease characteristics. In this respect, a multidisciplinary discussion is mandatory. Ongoing research is refining the optimal use of surgery in combination with immune checkpoint inhibitors.

Acknowledgments: None

Conflicts of Interest: The authors have no conflicts of interest to declare.

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