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Case Report

Deferred Nephrectomy after a Surprising Response to Immunotherapy in Poor Risk Patients: A Case Report

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Abstract

On the basis of the results of CARMENA and SURTIME trials, the role of cytoreductive nephrectomy (CN) has been redefined and CN has been reserved to selected cases. These trials were designed in the Tyrosine Kinase Inhibitors (TKIs) era, when sunitinib was the standard of care for the treatment of advanced renal cancer. However, new drug combinations (lenvatinib plus pembrolizumab, nivolumab plus cabozantinib, nivolumab plus ipilimumab, pembrolizumab plus axitinib) have shown to be superior to TKIs in terms of progression free survival (PFS) and/or overall survival (OS). All of these combinations are currently recommended as a first line therapy for metastatic renal cell carcinoma (mRCC). While ipilimumab plus nivolumab is recommended only for intermediate and poor risk groups, the other regimens can be used regardless of the International Metastatic RCC Database Consortium (IMDC) prognostic score. The role of CN in this new modern era, where randomized clinical trials (RCTs) have led to the approval of several new drug combinations for the treatment of advanced renal cancer, has not been investigated yet. We described two cases where a deferred CN was offered to poor risk IMDC pts after a major response to the combination of pembrolizumab and axitinib.

Keywords: Cytoreductive surgery; Immunotherapy; Papillary renal cell carcinoma; Case report

Introduction

New treatment strategies with Immune Checkpoint Inhibitors (ICIs) have radically changed the medical history of cancer pts [1]. In recent years combination of Vascular Epithelial Growth Factors Tyrosine Kinase Inhibitors (VEGF-TKIs) [2] and ICIs or ICI-ICIs have improved mRCC clinical outcomes and these combinations are now the recommended first line treatment for mRCC pts [1-4]. In the next future it is likely that a triplet therapy (dual checkpoint inhibition plus a TKI) will be available as well, based on the encouraging results of COSMIC-313 [5]. As these regimes have not been directly compared with each other, the choice of the best first line treatment is complex and mainly relies on disease features (e.g. the combination of ipilimumab and nivolumab has provided a clinical benefit only in intermediate/poor risk pts according to the IMDC score and sarcomatoid histology has shown to respond particularly well to the ICI-ICIs combinations), tumor burden (ICIs/TKIs combination is preferred in case of high tumor burden where a rapid tumor shrinkage is needed) and comorbidities (e.g. TKIs-based regimens should be avoided in pts at high cardiovascular risk). Published data from two prospective randomized studies, CARMENA [6] and SURTIME [7], have redefined the role of CN in mRCC treatment strategy. In fact, while CN was very popular in the cytokine era (mainly based on the results of the SWOG 8949 and EORTC 30947 [8,9]) CARMENA and SURTIME questioned its role. Although they started in 2010 and hence considered only VEGF-TKIs therapies, the European Association of Urology (EAU) renal cell carcinoma guideline panel updated their recommendations based on the results of these trials. Therefore, the role of CN in the ICIs era is still debated and not well defined. We report two cases where CN has been performed upon multidisciplinary discussion, after a major response to a first line therapy based on pembrolizumab and axitinib, which at the time was the only reimbursed combination treatment in Italy for mRCC.

Case reports

Patient	Age	Histology	IMDC	Treatment	Treatment duration (days)	Surgical Pathology CN	TFI (days)
1	56 yo	Papillary	4	Pembrolizumab+axitinib	112	100% necrosis	386
2	78 yo	Clear Cell	4	Pembrolizumab+axitinib	184	100% ccRCC, 11cm, grade 3, 2-3% necrosis, ypT3a	155

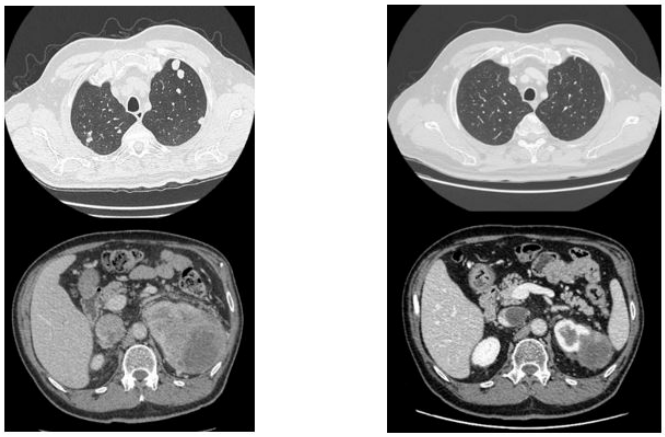
Table 1: Clinical and pathological features of the two reported cases.

Case 1

In February 2021 a 55-years old male patient with a history of myocardial infarction and type 2 diabetes presented with left lumbar pain and an episode of macrohematuria. An abdominal ultrasound and a CT scan showed a 10 × 12 cm mass in the left kidney with bilateral metastases to lungs and mediastinal lymph nodes. The CT scan also showed a large thrombus involving the inferior vena cava from the left renal vein up to the cavoatrial junction. A renal biopsy was performed and a papillary renal carcinoma, G3 was diagnosed. PD-L1 Combined Positive Score (CPS) was < 1.

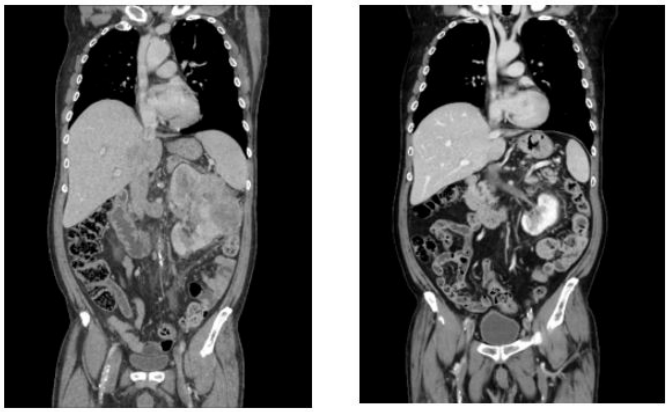
Laboratory testing demonstrated: Hemoglobin (Hgb) 8.2g/dL, Absolute Neutrophil Count (ANC) 5.47 k/mcL, Platelet (Plt) counts 5.37 k/mcL, Calcium (Ca) 2.25mMol/L.

After multidisciplinary discussion, surgery was excluded in consideration of the extent of disease. Given the Karnofsky Performance Status (KPS 90%), age and IMDC score, we proposed a first-line combination treatment with pembrolizumab (200mg) intravenously once every 3 weeks plus axitinib (5mg) orally twice daily. The combination therapy was well tolerated for the first three months and the best treatment response, achieved after 98 days of treatment, was partial response (PR) based on RECIST 1:1. The CT scan performed in August 2021 showed a meaningful shrinkage of the renal mass and caval thrombosis and a reduction in the size of secondary lesions was also evident (Figures1-2).



(a) (b)

Figure 1: Case 1 Axial CT scan of lung metastases, mediastinal nodes and primitive renal mass before; (a) and after (b) ICIs/TKI combination treatment.



(a) (b)

Figure 2: Case 1 Coronal CT scan before; (a) and after (b) ICIs/TKI combination treatment.

In August 2021 the patient reported a grade 3 diarrhea unresponsive to loperamide and axitinib was stopped. As diarrhea did not resolve despite axitinib withdrawal, immune-related colitis was suspected and pembrolizumab was discontinued as well. The patient required hospitalization and received systemic corticosteroids (methylprednisolone 1mg/kg) which led to the resolution of symptoms. During steroid therapy an elevation of AST and ALT levels was also evident. While initially an ICI-associated immune mediated hepatitis was suspected, the elevation of liver enzymes was then attributed to exotoxic factors (previous abuse of alcohol) and corticosteroid-induced liver injury. Due to the experienced toxicity, the patient remained off treatment since August 2021.

The shrinkage of the primary lesion and of venous neoplastic thrombosis, confirmed by a subsequent CT scan, made it possible to perform a CN with vena cava thrombectomy in November 2021. At the macroscopic examination of the surgical specimen, a yellow-gray crumbly tumor of 7 cm was observed, which microscopically corresponded to a large area of tumor necrosis in the absence of living cells (complete pathological response) (Figure 3).

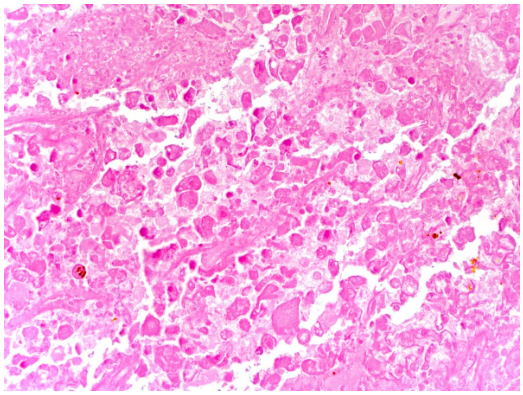


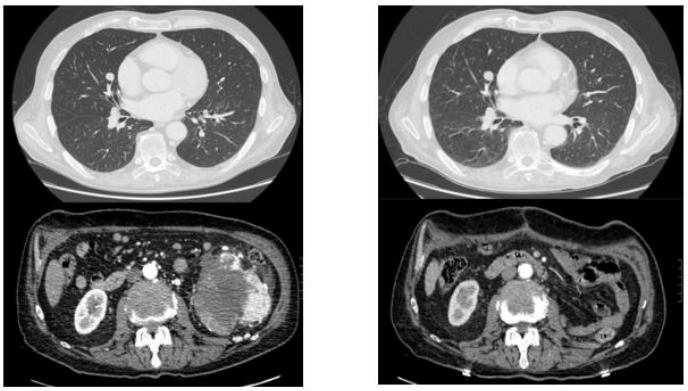
Figure 3: Tumor microenvironment in the surgical specimen.

The postoperative course was complicated by prerenal acute renal failure which required dialysis treatment. In January 2022 a bilateral thrombosis of femoral and tibial veins, involving the inferior vena cava up to the confluence of the right renal vein was diagnosed and required therapy with parenteral anticoagulants first and then with warfarin. The partial response with minimal residual pulmonary disease persisted at a CT scan of May 2022 and the patient is currently off treatment for approximately a year.

Case 2

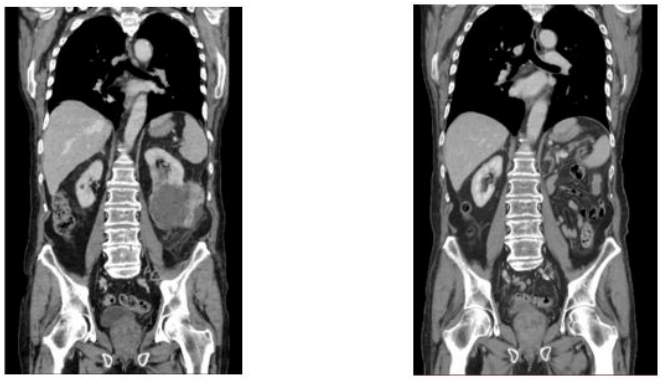
A 77-year-old male without comorbidities was diagnosed with a 13 cm left renal tumor with metastases to the lungs and lymph nodes. The brain CT scan was negative. A renal biopsy was performed and confirmed a clear cell carcinoma with wide necrosis. PD-L1 CPS was negative. The patient was classified in the poor-risk subgroup according to the IMDC score: 4 of 6 factors were present, namely a KPS of 70%, piastrinosis, anemia and concomitant onset of metastatic disease. After multidisciplinary discussion, in May 2021 a first-line treatment with a TKI-ICI combination was proposed (pembrolizumab 200mg intravenously once every 3 weeks plus axitinib 3mg orally twice daily). After the second course of treatment KPS worsened to 50%, G3 hypertension was observed, and the patient was hospitalized for the onset of mild heart failure, G1 hypokalemia, G1 hyponatremia, and prerenal azotemia. He was treated with ACE inhibitors and diuretics and supplemented with intravenous potassium. During hospitalization, a total body CT scan was performed, showing PR to treatment. Given the clinical condition of the patient and the scarce tolerance

to TKI, only pembrolizumab was restarted after discharge. The CT scan performed after 6 months of treatment revealed stable disease on the primary tumor and complete radiological response on lung metastases. After discussion, the multidisciplinary team decided for CN which was performed in December 2021 (Figure 4-5).



(a) (b)

Figure 4: Case 2 Axial CT scan of lung metastases, mediastinal nodes and primitive renal mass before; (a) and after; (b) ICIs/TKI combination treatment and surgery.



(a) (b)

Figure 5: Case 2 Coronal CT scan before; (a) and after; (b) ICIs/TKI combination treatment and surgery.

The histological examination confirmed the diagnosis of clear cell carcinoma and showed a partial pathological response to treatment (Figure 6).

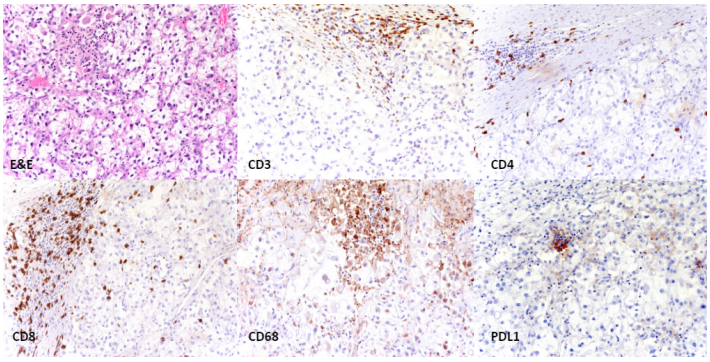


Figure 6: Tumor microenvironment in the surgical specimen.

About one month after surgery the CT scan detected a unique new solitary cerebellar metastasis of 5 mm and a new solitary lung lesion, in the absence of any other localization. Radiosurgery (21 Gy in a single fraction) was performed on the cerebellar lesion and on the lung lesion (50 Gy in five fractions), while pembrolizumab as a single agent was re-started with good tolerance.

The CT scan of July 2022 showed multiple bilateral pulmonary lesions and new metastases on the brain. Both in the brain and in the lungs the irradiated nodules were no longer detected. Treatment with pembrolizumab was stopped and the patient underwent whole brain radiotherapy. A second line treatment with cabozantinib was then started.

Discussion

Biologic Rationale For Cn

We presented 2 cases of delayed CN in poor-risk mRCC pts with partial response to a first-line treatment with a TKI-ICI combination and a different outcome. Focusing on a possible rationale of CN in advanced renal cancer, the resection of the primary tumor may be a tool to eliminate a source of immunosuppressive cytokines and other bio-humoral mediators that otherwise may hinder an effective anti-tumor immune response [10]. It is well known that RCC develops an immunosuppressive tumor microenvironment. In the era of cytokine, rare cases of spontaneous regression of metastases after removal of the primary tumor have been described (most frequently in the elderly with pulmonary metastases) [11]. Several cytokines, such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and transforming growth factor-beta (TGF-β1) contribute to generate an immune suppressive tumor microenvironment in

RCC. [12]. Of note, VEGF inhibits the innate immune system by hampering the differentiation of monocytes into mature dendritic cells and upregulating PD-L1 expression on dendritic cells: this is the rationale for combining ICIs and antiangiogenic drugs for the treatment of clear cell carcinoma [13]. Distinct immune cell subsets which are known to promote tumor immune evasion, such as myeloid-derived suppressor cells (MDSCs), are significantly higher in pts with RCC, which positively correlates with the metastatic tumor burden [14]. Their presence, together with the expression of specific molecules such as CTLA-4, PD-L1, B7-H3, B7-H4 and PD-1 on the surface of tumor cells and T cells, leads to a downregulated anti-tumor immune response [15,16]. The disruption of these immunosuppressive signals originating from the primary tumor may constitute a biological rationale for proposing CN.

Since CN has shown to enhance immune response against metastatic lesions, we could think that performing it before ICIs would enhance the efficacy of immunotherapy. However, removal of the primary tumor may reduce the tumor mutational burden which is an emerging biomarker for response to ICIs [17]. Moreover, in renal cancer it was demonstrated that surgical resection decreases PD-L1 expression on the tumor [18,19]. In addition to that, a deferred surgical removal of the neoplasm would help to eradicate immune resistant clones. For all these reasons, performing CN after initial systemic therapy would seem to be the most beneficial approach.

Therefore, the rationale of ongoing clinical trials on CN (Table 2) [17,20-23] is to evaluate if renal surgery improves overall survival (OS) in metastatic RCC when it is performed after starting systemic immune checkpoint-based combination therapy. These ongoing studies should also add precious details about tumor microenvironment.

Trial	Histology	Interventional arm	Control arm	Primary end point
CYTOSHRINK	ANY RCC	IPI+NIVO+SBRT to the primary	IPI+NIVO	PFS
PROBE	ANY RCC except collecting duct	ICI-based regimen+deferred CN	ICI-based regimen	OS
NORDIC-SUN	ANY RCC	IPI+NIVO+deferred CN	IPI+NIVO	OS

Table 2: Ongoing randomized clinical trials (RCTs) on CN in mRCC.

Cn In The Tkis Era

To date, CARMENA and SURTIME phase III trials [4,5] have contributed to redefine international guidelines for the role of CN in pts with mRCC, exploring its advantages and trying to define the correct sequence in the context of systemic treatment with TKIs. In the CARMENA trial, authors have studied upfront CN in mRCC pts in the TKI era. Pts were randomized 1:1 to receive CN followed by sunitinib or sunitinib alone and stratified according to Memorial Sloan-Kettering Cancer Center (MSKCC) risk factors. A total of 450 pts were enrolled, and OS for the sunitinib alone group was non inferior to the sunitinib+CN group. Median OS (mOS) was 18.4 *vs* 13.9 months, respectively. In this trial, several factors could have affected the final outcome: slow accrual rate and lack of full accrual, high rate of poor-risk pts, high-volume distant metastases, high percentage of pts receiving deferred nephrectomy in the sunitinib-alone group and substantial number of pts who did not receive sunitinib after CN.

It is to be pointed out that the CARMENA trial was enriched by a clinically relevant population of poor-risk pts that typically do not benefit from CN. In particular, 58.6% pts were IMDC intermediate and 41.4% were IMDC poor risk. When looking at the intermediate-risk group only, 48.1% had one risk factor and 51.9% had two risk factors.

Overall, CARMENA clearly demonstrates that poor risk pts do not obtain an advantage from CN, which confirms previous retrospective data. Regarding CN in the intermediate-risk group, the update on CARMENA trial presented at ASCO 2019 with focus on intermediate IMDC-risk population reported the beneficial effect on OS of upfront CN in pts with only one IMDC risk factor while pts with 2 risk factors did worse with upfront CN than with sunitinib alone (median OS was 31.2 months with only sunitinib *vs* 16.6 months with CN+sunitinib) [24].

However it must be recalled that 40 pts that were initially assigned to the sunitinib-only arm underwent secondary nephrectomy (mainly for a complete or near-complete response) and the median mOS of these pts was 48.4 months versus 15.7 months of pts who did not have surgery: thus the long mOS of 31.2 months in the sunitinib only arm in the IMDC intermediate-risk group with two factors must be interpreted in the light of the high percentage of deferred CN [25]. Results from the SURTIME confirmed the benefit of deferred CN in intermediate risk pts.

In this randomized phase 2 study including 99 pts (largely with intermediate IMDC score), the authors aimed to assess the timing of CN during TKI first-line treatment. Pts were randomized into two treatment groups: immediate CN followed by sunitinib versus a deferred approach in which CN was performed after three cycles

of sunitinib and then followed by sunitinib therapy resumption. The results showed no difference in 28-week progression-free rates between the groups, suggesting that a deferred approach to CN (after sunitinib and only if the disease did not progress) might be comparable to upfront CN followed by sunitinib. Notably, the intention-to-treat OS hazard ratio of deferred *vs* immediate CN was 0.57 (95% CI, 0.34 - 0.95; p = 0.03), possibly due to a higher compliance to sunitinib in the deferred CN arm. Due to poor accrual, the trial closed prematurely with only a 99-patient cohort completing the study over the 458 initially planned. Moreover, the primary endpoint was remodulated from progression free survival (PFS) to a 28-week progression-free rate [7]. Thus, according to literature and current guidelines [26,27], CN should be proposed to pts with favorable risk scores, while preferring upfront systemic treatment in poor-risk mRCC.

In a recent Open To Debate discussion published on European Urology Open Science, expert opinions were still discordant about the ideal candidate for CN [28,29]. While Meza and colleagues believe that CN should only be considered as a symptomatic treatment in selected cases (gross hematuria, local pain), Méjean and Bex claim that upfront CN can also be proposed to oligometastatic pts whose disease may be surgically radicalised and to pts with a single IMDC risk factor, whereas the presence of a second risk factor should lead to choose an upront systemic treatment with the option of performing a deferred CN if a response at metastatic sites is achieved [28,30].

CN In The Icis Era

While results from CARMENA and SURTIME [7] phase III trials suggest the use of nephrectomy in metastatic setting for a selected population, in the new era of immunotherapy neither clear nor validated data support the use of nephrectomy in first-line setting.

Mazzaschi et al recently performed a comprehensive review of the literature [31]. They focused on two important issues concerning CN: its role, and which subsets of pts could represent the ideal candidates. Their analysis of data from the most recent pivotal trials leading to the approval of ICI-based regimens has showed that 85% of the partecipants underwent CN. On Expanded Access Programs (EAPs), better depicting the attitude in clinical practice, CN was performed in 89% of cases. A large retrospective analysis was conducted on 391 pts including 221 (56.5%) who received CN+ICIs and 170 (43.5%) who received ICIs only. Of the 221 pts who received CN+ICIs, 97 underwent upfront CN, while 24 received immunotherapy before CN. In this study, pts who underwent CN+ICIs had superior OS [32].

As already mentioned, in the new studies testing ICIs-based regimens in mRCC, the proportion of pts who did not have prior nephrectomy is quite low.

CHECKMATE 9ER [33] enrolled the highest proportion of pts without nephrectomy (around 30%) while about 22% of pts enrolled in the CHECKMATE-214 [1] and 20% of pts enrolled in the CLEAR [4] did not undergo nephrectomy.

All these data suggest that CN may play an important role in mRCC pts suitable for ICIs-based regimens, considering the positive results obtained with these therapies in nephrectomized pts. However new treatments are apparently effective in pts with the primary tumor in site as well.

A post-hoc analysis of CHECKMATE-214 conducted in a subgroup of 108 pts with mRCC without prior nephrectomy and with an evaluable primary tumor showed OS, PFS and ORR benefit for pts treated with first-line nivolumab/ipilimumab *vs* sunitinib alone and a >30% of primary tumor shrinkage in 35% of pts in nivolumab/ipilimumab group *vs* 20% in sunitinib one [34].

A post-hoc exploratory analysis of the CHECKMATE 9ER showed that nivolumab plus cabozantinib improved PFS, ORR, complete response and response durability outcomes *vs* sunitinib regardless of nephrectomy status. Longer follow up is needed to characterize OS outcomes between the two arms in pts without prior nephrectomy. In pts without prior nephrectomy, median reduction in target kidney lesions was 30% in the nivolumab+cabozantinib group *vs* 16% in the sunitinib group [35].

At the 2022 GU ASCO Annual meeting Dr. Panian et al. presented the pathologic outcomes at CN of 52 mRCC pts that had received an ICIs-based regimen. 4% of pts were IMDC favorable-risk, 55% intermediate-risk, 26% poor risk with 15% unknown. Before CN, 49% of pts had received a combination of nivolumab and ipilimumab, 30% a single agent immunotherapy, and 21% an ICI/TKI combination. After the systemic treatment, 44% of pts downstaged from the baseline clinical T stage to the CN pathological T stage. Interestingly, 13% of pts had no residual disease in the surgical specimen while necrosis was present in 75% of cases [36].

Several works suggest that in mRCC pts treated with a systemic therapy and their primary tumor in situ, a response in the primary tumor correlates with an improved OS. In a retrospective analysis studying the primary tumor response to sunitinib in intermediate and poor-risk mRCC pts, an early minor primary tumor response (10% decrease within 60 days of treatment initiation) was associated with an improved OS [37]. A recent analysis also showed that IMDC intermediate-poor risk pts treated with ipilimumab+nivolumab with a partial response in the primary had a 1-yr OS rate of 89% versus 67% in those without [38].

A work by Pieretti et al has shown that tumor diameter response in mRCC pts at intermediate or poor prognosis correlates with OS, irrespective of the systemic treatment that was

administered (ICI/ICI, ICI/TKI, TKI single agent) [39]. Finally, a recent analysis by Iacovelli et al has concluded that in poor and intermediate pts with advanced renal carcinoma treated with cabozantinib or nivolumab+ipilimumab, extension of the primary tumor did not affect patient survival, while primary tumor response was significantly related to the response on metastatic disease and survival [40].

In addition to that, CN is not without risk: it is associated with higher morbidity (intraoperative complications rate 6-30%, major complications rate 3-29%, perioperative mortality 1-13%) relative to radical nephrectomy in pts with non metastatic RCC.

Immune-related toxicities and the potential need for corticosteroids may further complicate the surgical procedure. In fact, it was found that nephrectomy following ICIs may be a technically tricky procedure [30].

A retrospective study evaluating the feasibility of delayed nephrectomy in 11 pts with mRCC and complete response on metastatic sites following ICI therapy showed that surgeons experienced technical difficulties due to inflammatory infiltration in 81.8% of cases. The median duration of surgery was 243 min and the 30-day postoperative complication rate was 54.6%, including 1 surgery-related death. Pathological complete response was reported in 18.2% of cases [41].

In another similar work conducted on 21 pts, median duration of surgery was 147 min and 30-day overall complication was 14%, while pCR was observed in 14% of cases [42].

Of note, pts with non-clear cell histology have been mostly excluded from recent phase III trials with frontline immunotherapy-containing regimens. However, promising responses to immunotherapy in advanced papillary RCC have been observed with pembrolizumab single agent, ipilimumab+nivolumab, cabozantinib+nivolumab, atezolizumab+bevacizumab and atezolizumab+erlotinib. Several trials are ongoing which aim to further assess the efficacy of ICIs in non clear cell histologies.

A proposed flowchart for the treatment of mRCC in the ICIs era and incorporating CN is depicted in Figure 7 [28].

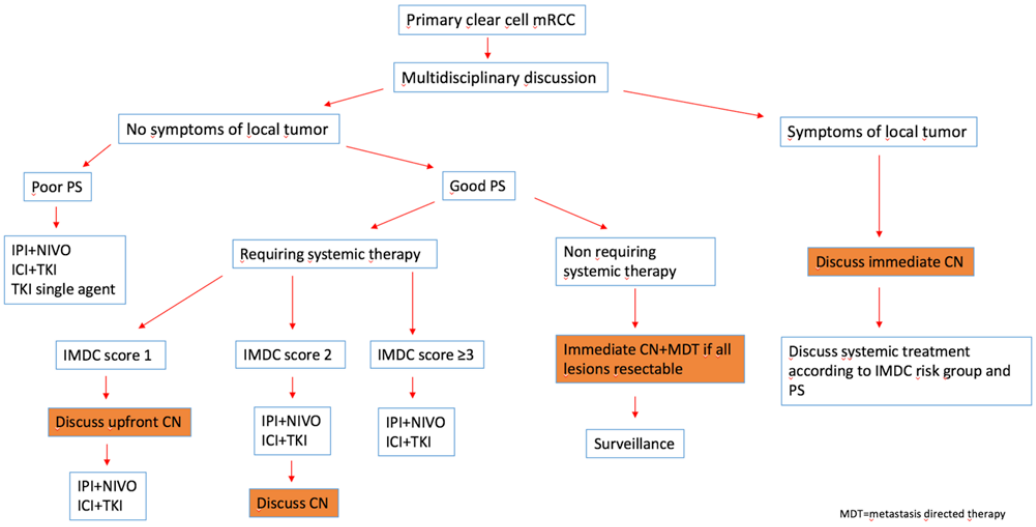


Figure 7: A proposed flowchart (incorporating CN) for the treatment of clear-cell mRCC.

Cn In The Icis Era: Future Perspectives

To date, we have four significant open questions about CN role in mRCC pts: if CN may still have a role in the ICIs era, why proposing nephrectomy, when and above all to whom. Ongoing phase II and III trials investigating the role of deferred CN in the ICI-combination era will be hopefully able to answer these questions. The PROBE trial aims to evaluate if deferred CN performed in mRCC pts which are responding to an ICI-based regimen may improve OS. Pts may have clear cell or non-clear cell renal carcinoma. They are treated with an upfront ICI-based systemic therapy and disease status is evaluated at 9-12 weeks of therapy. Pts with stable disease or partial response are randomized 1:1 to CN (followed by systemic therapy) *vs* systemic therapy alone. Pts who have rapid disease progression are not considered for randomization and will receive a second line therapy [17,21].

The NORDIC-SUN phase III trial is designed to assess the advantage of deferred CN in intermediate and poor risk mRCC pts treated with ipilimumab and nivolumab in the first-line setting. All histologies of mRCC can be enrolled. After 4 courses of ipilimumab and nivolumab or 3 months of treatment, pts with 3 or less IMDC risk factors which are deemed suitable for CN by a multidisciplinary team will be randomized to either maintenance with nivolumab or to CN followed by maintenance nivolumab.

In the phase II Cyto-KIK study, mRCC pts with clear cell histology treated with first-line combination of nivolumab and cabozantinib undergo CN after 12 weeks of treatment followed by either 14 or 21 days of break from therapies. Primary endpoint is complete response rate according to RECIST version 1.1. A 3+3 design will be used to define which is the safest interval between cabozantinib discontinuation and surgery (14 *vs* 21 days). After surgery, treatment with cabozantinib and nivolumab will be resumed until disease progression. Secondary endpoints are the extent of tumor size reduction, response rate, PFS, OS and surgical outcomes. Importantly, tumor microenvironment will be studied on the diagnostic biopsy and surgical specimen [43].

A randomized phase II trial (CYTOSHRINK) is also ongoing, evaluating the effect of SBRT on the primary tumor in advanced renal cancer pts (poor and intermediate IMDC risk) treated with ipilimumab+nivolumab. In this study, untreated mRCC pts (any histology) are randomized to ipilimumab+nivolumab and SBRT to the primary tumor between cycles 1 and 2 (30-40 Gy in 5 fractions) versus ipilimumab+nivolumab alone. Primary endpoint is PFS [20].

Patient's Choice

Last but not least, it stands the question of the patient's choice. Old analyses highlighted how the presence of an expert panel of surgeons facilitates the acceptance of a randomized trial where pts should undergo surgery [44]. In addition, sharing clear and direct information encourages pts to participate in clinical trials [45]. The poor accrual on CARMENA and SURTIME studies suggests the need to support pts' decision and to promote enrollment in trials where surgery could be an opportunity for increasing OS and quality of life.

Conclusion

Before the advent of ICIs, based on the results of CARMENA and SURTIME, CN was recommended for the treatment of mRCC in selected cases. In particular, an upfront CN was generally performed for symptoms control (e.g. in case of gross hematuria), for an oligometastatic disease not requiring systemic therapy if all lesions were resectable, and in pts with one IMDC risk factor in whom metastatic disease could be just observed until systemic therapy would be required. Deferred CN was instead usually performed in pts with 2 IMDC risk factors only in case of a good response to systemic therapy. CN was historically not recommended for poor-risk pts. However, the role of CN in the immunotherapy era is still a matter of debate. We described two cases where CN has been performed after a good initial response to the combination of pembrolizumab and axitinib in poor risk pts with mRCC. Tumor microenvironment was similar in the two surgical specimens and PD-L1 CPS score was <1 in both of them. Of note, a complete pathological response on the renal tumor was achieved in case 1, even if only a few cycles of therapy were administered and albeit the papillary histology, whose response to ICIs-based regimen has been less extensively investigated. In case 1 systemic therapy was stopped after CN and the patient is still maintaining a partial response after one year off treatment. Therefore, althought CN is not classically recommended for poor risk pts, it is conceivable that factors which may predict the benefit derived from renal surgery exist. Interestingly, based on retrospective data, primary tumor response could be of help in predicting response to systemic therapy in the metastatic sites and OS. In case 2 therapy was resumed with only pembrolizumab (in order to spare axitinib toxicity) after CN but disease progression was seen in lungs and brain about 7 months after surgery and a second line treatment was started.

Overall, the role of CN has to be further explored in the ICIs era and the results of at least 3 ongoing RCTs will probably help to clarify the issue. Finally, given the availability of many therapeutic approaches for the management of advanced RCC (different medical treatment options, SBRT on the primary and/or on metastatic sites, upfront CN, delayed CN), multidisciplinary case-by-case discussion is essential.

Conflict of Interests

Authors have no conflict of interest to declare Informed consent statement: informed verbal consent was obtained from the patient for publication of this report and any accompanying images.

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