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## Open to Debate: Con

# Partial Nephrectomy for Metastatic Renal Cell Carcinoma: Con

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Currently, up to half of patients presenting with treatment-naïve synchronous metastatic renal cell carcinoma (mRCC) are being treated with systemic therapy when the primary tumour is in place [1]. This paradigm change followed evidence from two randomised controlled trials investigating the role (CARMENA [2]) and sequence of cytoreductive nephrectomy (CN; SURTIME [3]) in the era of VEGF targeted therapy. However, as evidence matures from the pivotal immune checkpoint inhibitor (ICI) combination trials demonstrating complete response rates at metastatic sites of up to 16% and median overall survival (OS) of 4 yr, an increasing number of patients with primary mRCC on ICI therapy are being offered deferred CN following a disease response [4]. Whether partial nephrectomy (PN) is of benefit in this patient population is debatable and we argue against this approach for several reasons.

First, it needs to be acknowledged that only few undisputed indications remain for CN. Indications for upfront CN traditionally include patients with good performance status and low-volume metastatic disease that can either be focally treated or observed with the aim of delaying systemic therapy and related adverse events. These represent only 25% of patients with primary mRCC [1]. A recent

unplanned post hoc analysis of CARMENA data suggests that indications for upfront CN may be extended to patients with International Metastatic RCC Database Consortium (IMDC) intermediate prognosis on the basis of only one risk factor [5]. An even smaller percentage require upfront CN because of symptoms.

On the basis of the CARMENA data, guidelines currently recommend treating the majority of patients with intermediate IMDC risk with systemic therapy and to consider deferred CN, including the poor risk group if response to therapy is good [5,6]. Despite the assumption that the overall indication for deferred CN may therefore increase, overall response rates to systemic therapy range from 46% to 60%, with complete responses occurring in only one in every ten patients [6]. Real-world data for patients treated with nivolumab and ipilimumab with the primary tumour in place revealed that only 13% were offered deferred CN [7]. Thus, cytoreductive surgery for the primary tumour as a procedure, whether upfront or deferred, has become a rare intervention for which to select candidates for PN.

An additional argument against PN in the metastatic setting is the complexity of primary tumours. In metastatic disease, primary tumours are 9 cm in diameter on average [2,3] and although downsizing can be expected on ICI combination therapy [7,8], a reduction in primary tumour diameter of  $\geq 30\%$  occurs in only one-third of patients [8]. According to real-world data for patients in the intermediate IMDC group treated with dual ICI and the primary tumour in place, the baseline median primary tumour size was 14 cm, which decreased by a median of only 12.9% [7]. Therefore, the majority of tumours remain too complex for PN (Table 1). For the upfront CN setting, it has been reported that the prevalence of primary tumours of  $\leq 4$  cm is only 6.9%. Although these patients tended to have fewer metastatic sites, these were mainly located in bones and

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**Table 1 – Response of the primary tumour**

Author	Systemic therapy	Primary tumour in place		Median tumour size (cm)	Median primary tumour reduction	
		Patients	Response rate (%)		(cm)	(%)
Meerveld-Eggink [7]	Nivolumab/ipilimumab	69	PR: 33 dCN: 18	10.14	3.4	33.3
Albiges [8]	Nivolumab/ipilimumab	49	PR: 35 dCN: 15	7.9	2.4	≥30
Courcier [12] (NIVOREN)	Second- or third-line nivolumab	67	PR: 6	8	2.4	30
Albiges [13]	Avelumab/axitinib	55	PR: 34.5	NA	NA	≥30

PR = partial response; dCN = deferred cytoreductive nephrectomy; NA = not applicable.

the central nervous system, which are associated with unfavourable prognosis [9]. According to these data, OS for patients with smaller tumours suitable for PN was poor, with 2-yr and 5-yr survival rates of 65% and 28%, respectively.

This leads to the potentially most significant argument against PN in the metastatic setting. The generally accepted benefit of PN in the nonmetastatic setting is long-term preservation of renal function, which is associated with better OS [6]. However, despite impressive improvements in median OS and some individuals potentially being cured with ICI therapies, life expectancy remains limited for the majority of patients with mRCC. This in turn would not justify PN for kidney function preservation in these very few patients who would be eligible for nephron-sparing surgery, unless imperative.

In the retrospective series of patients treated with the primary tumour in place, some dramatic responses have been described following ICI combination therapy, with primary tumour downsizing of >70% to <4 cm in diameter [7,8]. We acknowledge that it is tempting to consider PN in these individual cases, but it should be noted that the evidence for this approach is poor. The role of cytoreductive treatment of the primary tumour following response to ICI combination therapy is a dynamic and evolving field. Two randomised controlled trials (PROBE [NCT04510597] and NORDICSUN [NCT03977571]) are accruing patients to improve the evidence level and investigate if deferred CN improves OS. In the meantime, deferred CN is being offered on the basis of paradigms established in the era of VEGF-targeted therapy. Nevertheless, until evidence of OS improvement becomes available, it may be more prudent to consider less invasive management options such as ablation or stereotactic radiotherapy for tumours after dramatic shrinkage. Although equally unproven options in the metastatic setting, these avoid the morbidity of surgery and may be promising because of their abscopal effect. The CYTOSHRINK trial (NCT04090710) is investigating stereotactic radiotherapy of the primary tumour following ICI combination therapy and results are eagerly awaited [10].

Finally, systemic therapy for mRCC is not nephrotoxic and therefore nephron-sparing surgery is rarely needed. A recent retrospective study demonstrated that reduced kidney function is not a predisposing risk for cancer-specific mortality in patients with nonmetastatic T1–T3a RCC [11]. This suggests that reduced renal function does not impact on management of recurrences from kidney cancer.

In summary, we argue that imperative situations aside, PN is not indicated for patients with synchronous mRCC.

The decreasing indication for cytoreductive removal of the primary tumour, the complexity of the kidney mass at baseline, and limited life expectancy caution against performing nephron-sparing surgery in the metastatic setting. In a situation in which even deferred CN has a low evidence base, PN should not be performed just because it is technically feasible. However, the concept of PN may be revisited if ongoing trials demonstrate long-term OS following deferred CN in patients responding to ICI combination therapy.

**Conflicts of interest:** The authors have nothing to disclose.

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