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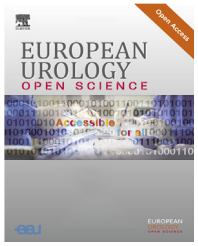

European Association of Urology

Open to Debate: For

Cytoreductive Nephrectomy: Still Necessary in 2021

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Cytoreductive nephrectomy (CN) is by no means obsolete in 2021 and depends on the clinical presentation of the patient. First, major renal cancer guidelines are unanimous that upfront CN should be offered to patients in whom single or oligometastatic disease sites can be either completely treated with focal therapy (metastasectomy, radiotherapy, ablation) or observed until systemic therapy is required [1,2]. In the latter setting, the median time to systemic therapy can be as long as 1.5 yr [3], during which adverse events associated with systemic therapy are avoided.

However, for patients requiring systemic therapy with sunitinib, the CARMENA and SURTIME trials have shown that upfront CN is no longer the standard of care [4,5].

A post hoc analysis of CARMENA evaluating patients with one versus two intermediate risk factors according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) classification showed that upfront CN could be proposed for patients with low-volume metastatic renal cell carcinoma (mRCC) and a single IMDC intermediate risk factor [6], whereas the presence of a second risk factor should lead to preference of systemic treatment with the option to perform deferred CN in cases with a response at metastatic sites. Guidelines recommend this option [1,2] because deferred CN was part of the intention-to-treat analysis of the sunitinib-only arm in CARMENA, in which 40 patients underwent deferred CN because of near-complete responses at metastatic sites [4]. In addition, although SURTIME was underpowered, the trial revealed that patients in the deferred CN arm had better overall survival (OS). While the longer survival did not reach statistical significance, it is interesting to note the large difference in median OS between 32.4 mo (95% confidence interval [CI] 14.5–65.3) in the deferred CN arm and 15.0 mo (95% CI 9.3–29.5) in the upfront CN arm [5].

The open question is whether these results can be extrapolated to immune checkpoint inhibitor (ICI) combination therapies, which are now the standard of care for patients with intermediate- and poor-risk disease [7]. Several randomised trials are under way to test this. Nevertheless, the efficacy of these new treatments and their good tolerance do not seem to preclude a similar approach as with sunitinib, and patient selection remains fundamental.

Primary tumour shrinkage in the metastatic setting has been observed with ICI combination therapies [8,9]. Nivolumab plus ipilimumab, as well as avelumab plus axitinib combination therapies have resulted in partial responses by primary tumours in more than 30% of cases [8,10]. All pivotal ICI trials included patients with their primary tumours in place and observed downsizing (Table 1). This suggests a continuation of the paradigm established by CARMENA and SURTIME of treating patients who require systemic therapy with their primary tumour in place, with the option to perform deferred CN in cases with a response at metastatic sites or local symptoms.

With complete response rates at metastatic sites of up to 16% with some of these combinations [11], patients are

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Table 1 – Pivotal trials of ICIs for patients with metastatic renal cell carcinoma treated with the primary tumour in place

Trial	Patients treated, n/N (%)			Hazard ratio (95% CI)	
	Overall	ICI combination	Sunitinib	PFS	OS
CheckMate 214	187/847 (22)	84	103	NA	0.63 (0.42–0.94)
CheckMate 9ER	196/651 (30.1)	101	95	0.63 (0.43–0.92)	0.79 (0.48–1.29)
Javelin 101	75/660 (11.4)	37	38	0.63 (0.31–1.29)	NA
Keynote 426	146/861 (16.9)	NA	NA	NA	NA
Clear	175/712 (24.6)	93	82	0.44 (0.28–0.68)	0.52 (0.31–0.86)

CI = confidence interval; ICI = immune checkpoint inhibitor; NA = not applicable; OS = overall survival; PFS = progression-free survival.

being offered secondary CN to achieve surgical complete remissions. In a retrospective analysis of the National Cancer Data Base involving 20 patients who underwent deferred CN following ICI therapy, 10% experienced a complete pathological response in the primary tumour [12]. Two phase 3 RCTs are currently investigating the role of deferred CN versus no CN after pretreatment in this population. Interestingly, both trials no longer include an upfront CN arm and randomise patients after a clinical benefit has been achieved following at least 3 mo of pretreatment [13]. PROBE (NCT04510597) is evaluating whether deferred CN after an objective response or stable disease at metastatic sites following systemic therapy adds a survival benefit to systemic therapy alone. The investigators anticipated multiple first-line options and have included nivolumab, pembrolizumab with axitinib, and avelumab in combination with axitinib in their systemic therapy regimens.

NORDICSUN (NCT03977571) is investigating if deferred CN after ipilimumab and nivolumab combination therapy in patients with up to three IMDC risk features improves OS. This trial uses only the ipilimumab and nivolumab combination as systemic therapy.

In the interim, patients with primary mRCC who require systemic therapy should be treated with their primary tumour in place, with the option to undergo deferred CN.

Finally, there remains the problem of non–clear cell mRCC, for which we have no data. As it stands and in the total absence of data, CN should be proposed in this setting when it is feasible.

Conflicts of interest: Arnaud Méjean is a consultant for Pfizer, Novartis, GSK, BMS, MSD, Roche, Ipsen, Pierre Fabre, Astellas, Janssen, Ferring, and AstraZeneca. Axel Bex has received company speaker honoraria from Pfizer; has participated in trials for Pfizer Europe; has participated in advisory boards for BMS, GlaxoSmithKline, and Novartis; is a company consultant for Pfizer and Novartis; has received grants/research support from Pfizer; is the principal investigator of a neoadjuvant trial supported with a restricted educational grant from Pfizer.

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