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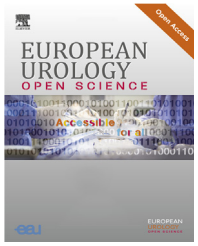

European Association of Urology

Open to Debate – Referee

Cytoreductive Nephrectomy in 2021: Obsolete but Necessary

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Two prospective randomized clinical trials (RCTs) recently changed the treatment paradigm for patients with metastatic renal cell carcinoma (mRCC) and the current role of cytoreductive nephrectomy (CN) [1,2]. CN is associated with higher morbidity (intraoperative complications rate 6–30%, major complications rate 3–29%, perioperative mortality 1–13%) relative to radical nephrectomy in patients with non-metastatic RCC [3–5]. Therefore, significant downsizing of the contemporary role of CN has recently been observed.

At present, immuno-oncology (IO) agents—alone or in combination—represent the standard of care in mRCC, and single VEGF therapy, which was the standard treatment at the time of the above-mentioned RCTs, no longer has a role in the first-line setting. As a consequence of these and many other factors, the contemporary role of CN in this setting poses a considerable dilemma.

The Open To Debate discussion in this issue of *European Urology Open Science* addresses this topic from two opposite perspectives by Meza and colleagues [6] and Méjean and Bex [7]. Meza and colleagues [6] argue that CN should only be considered in very select cases (gross hematuria, local pain, and palliation) owing to the available data and the lack of prospective RCTs evaluating the role of CN in the IO era. By contrast, Méjean and Bex [7] argue for the use of CN (1) in patients with oligometastatic RCC who may undergo complete removal of the primary tumor and all metastatic lesions, (2) in patients with a single intermediate risk factor in whom metastatic disease might be just observed until systemic therapy would be required, and (3) after initial systemic treatment in responding patients.

Until current ongoing IO trials (NCT03977571, NCT04510597, NCT04090710, and NCT03142334) better clarify which patients might benefit from CN (and when), the current indication for CN can be only indirectly derived from a critical analysis of the available evidence and taking into consideration patient- and disease-specific characteristics. Available translational findings somewhat support the use of CN in the IO setting. For instance, CN can play a synergistic role in immunotherapy [8] by limiting the onset of new biological clones and the secretion of protumoral cytokines. Moreover, CN can also eliminate the immunological sink to which the primary tumor diverts circulating immune cells away from distant metastases [8].

If we consider recently published RCTs in the IO setting (Table 1), up to 21% of patients treated with IO combination therapy were classified as having poor risk. Nonetheless, the proportion of patients who had previously undergone surgery ranged from 69% to 84%. A direct post hoc comparison of patients enrolled in those trials between the groups with and without nephrectomy is extremely difficult for countless reasons. All the trials were designed to compare sunitinib to an experimental arm involving an IO combination and not to evaluate the effect of CN in a post hoc setting. In addition, some nephrectomies were performed before clinical evidence of metastases and progression, and median OS was not reached for the majority of the arms, thus

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Table 1 – Randomized clinical trials published in the past 2 yr comparing immunotherapy combinations to sunitinib and including patients with metastatic renal cell carcinoma treated with or without CN before enrollment

	CheckMate 214	Javelin Renal 101	IMmotion151	KEYNOTE 426	CheckMate 9ER	CLEAR
Experimental group	Nivolumab Ipilimumab	Avelumab Axinitinib	Atezolizumab Bevacizumab	Pembrolizumab Axinitinib	Nivolumab Cabozantinib	Pembrolizumab Levantinib
Control	Sunitinib	Sunitinib	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Poor risk (%)	21	10–12	11	12–13	19–21	9–10
CN (%)	76–80	80	83–84	83	69–71	74–77

CN = cytoreductive nephrectomy.

limiting the possibility to accurately compare patients with and without CN over medium-term follow-up.

Besides PFS and OS endpoints, many clinical and surgical features should also be considered when evaluating the need for CN: upfront nephrectomy, for instance, can lead to iatrogenic inflammatory and metabolic events induced by surgical trauma. Significant fibrosis and desmoplastic reactions have been described [8,9]. The net effect is immunosuppression immediately after surgery that can last for several weeks via expansion of regulatory myeloid cells with increased PD-1/CTLA-4 expression and of T cells, as well as impairment of natural killer cell activity [9,10]. However, postponing nephrectomy only in IO responders might be challenging from a technical point of view. Pignot et al [11] recently reported results for a multicentre cohort of patients (n = 11) surgically treated after IO. The rate of 30-d postoperative complications was 55% (18% for major complications), there was one surgery-related (9%), and 81.8% of the cases were considered difficult by the surgeons.

Another point of discussion is related to the long-term effects of IO: the rate of immune-related adverse events is approximately 80% and up to 35% of patients require high-dose corticosteroids [9,10]. These toxicities and the potential need for corticosteroids must be considered in the perioperative setting, especially when surgery is planned after a long period of immune checkpoint inhibition. For instance, adrenal insufficiency and hypoxemia may be related not only to surgical stress or pulmonary embolism (surgical complications) but also to the IO regimen (immunotherapy iatrogenic effects) previously administered. Furthermore, immune-related adverse events usually require high-dose glucocorticoids, which may impair surgical outcomes and can cause hyperglycemia, fluid retention, and adrenal insufficiency [9,10]. It is noteworthy that the risk of opportunistic infections is also not negligible.

Lastly, the presence of local and systemic symptoms may affect the indication for surgery with palliative intent. We previously investigated the impact of CN on symptomatic improvement and perioperative morbidity and elucidated the trade-off between such benefits and associated harm. We found that 43% of patients experienced resolution of and 71% experienced an improvement in any signs or symptoms after CN. For local signs or symptoms, 91% experienced resolution and 95% experienced an improvement after CN. The complication risk was 37% for any complication and 10% for a major complication. Two out of three patients suffer from any sign or symptom, and one out of three suffers from local signs or symptoms. According to these data, CN has a positive impact on symptomatic status [12].

Although the role and timing for CN in the IO era remain to be further elucidated, patient selection remains critical for treatment planning. In summary, upfront CN should probably not be considered as the standard of care for patients with intermediate- or poor-risk mRCC. In these cases, upfront systemic therapy is the preferred option and CN is beneficial only in selected patients. Indeed, the rationale for such an approach stems from the ability of systemic therapy to select nonresponders who might not benefit from surgery. Conversely, CN is still the preferred choice for low-risk cases and/or patients with oligometastatic disease who could be managed with either active surveillance or local treatment (stereotactic radiation therapy or metastasectomy) for survival free from systemic treatment without compromising OS. Finally, an imperative need for CN is sometimes mandated by the presence of local symptoms.

All the above-mentioned factors should be considered for the best clinical decision. Specifically, oncological and internal medicine considerations should be interrelated with technical and surgical aspects. As a consequence, now more than ever a multidisciplinary team approach appears to be not only important but also mandatory to maximize patient outcomes.

Conflicts of interest: Andrea Necchi has received honoraria from Roche, MSD, AstraZeneca, Janssen, and Foundation Medicine; has a consulting or advisory role for MSD, Roche, Bayer, AstraZeneca, Clovis Oncology, Janssen, Incyte, Seattle Genetics/Astellas, Bristol-Myers Squibb, and Rainer Therapeutics; has received institutional research funding from MSD and AstraZeneca; has received travel and accommodation expenses from Roche, MSD, AstraZeneca, and Janssen; and reports employment and stock ownership (spouse) with Bayer. The remaining authors have nothing to disclose.

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