



Editorial – referring to the article published on pp. 302–310 of this issue

Renal Cell Carcinoma with Inferior Vena Cava Invasion: An Orphan Disease?

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Sometimes, medical fields experience rapid changes that modify everything that we knew over previous decades. Therefore, all concepts suddenly have to be revisited, resulting in exciting times for both physicians and patients. Unfortunately, that does not seem to be the case for renal cell carcinoma (RCC) with inferior vena cava (IVC) invasion where progress, although existing, appears to be slow. In many aspects we are, indeed, having the same discussions that we had 10 or 20 yr ago on surgical techniques, morbidity and mortality of complex surgical procedures, and the prognostic value of the level IVC invasion. It is obvious that RCC with IVC invasion is rare (4–10% of all RCC cases), thus clinical and biologic research is not stimulated. The paper from Rigaud et al. published in this issue of *European Urology* provides a realistic and somewhat pessimistic picture of where we are today in this field [1]. In their well-documented series including 40 patients operated in the last decade, that is, in the modern era of surgical and imaging techniques, the authors reported as many as 37.5% of patients who had metastases at the time of diagnosis and among those without metastases at the time of surgery, 40% and 72%, respectively, later experienced local recurrence and distant metastases. Morbidity and mortality rates were 47.7% and 7.5%, respectively, during the postoperative period. Although having distant metastases and being subjected to risky surgery, only 47% of the patients were amenable to

systemic treatment with immunotherapy. At the end of follow-up only 2.5% of the patients were considered free of disease. This is an honest view and a terrible acknowledgement of our failure to change the natural history of this disease. Therefore, based on this report it is not the time to compliment ourselves on the exploits of multi-disciplinary surgery but rather than to ask what we could do to improve these poor results.

1. Biologic aspects

It is obvious that the biology of RCC with IVC invasion is poorly understood. For example, it is now well known that RCC histology is composed of three major subtypes: clear cell, papillary, and chromophobe carcinomas, respectively, accounting for 80–85%, 12–15%, and 4–5% of the cases [2]. However, it is noteworthy that RCC histology leading to the development of an IVC thrombus is almost always of clear a cell subtype with a frequently significant sarcomatoid component. In the paper of Rigaud et al., clear cell, collecting duct, and sarcomatoid carcinomas accounted for 90%, 5%, and 5% of the cases, respectively. No papillary or no chromophobe carcinomas was found in this series. Goetzl et al., in a series of 56 patients, reported the respective rates of 97% clear cell, 28% sarcomatoid, and no papillary RCC [3]. Similarly, Parekh et al. in a series including

49 patients reported clear cell histology, sarcomatoid features, and papillary histologies in 42, 4 and 1 cases [4]. It is intriguing that a particular histologic subtype is more likely to invade a vein wall and to proliferate in a large vessel lumen when we know that histology is driven at the molecular level [5]. What molecular event is responsible for such a natural tissue barrier invasion and crossing is unknown. To enhance our understanding of the molecular mechanisms leading to vein invasion and progression, we compared the level of vascular endothelial growth factor (VEGF) tumour expression according to the extent of vein invasion in a pT3 RCC series. It appeared that VEGF tumour expression was equally high in all stages of vein invasion [6], and thus, is probably not specifically associated with vein progression at the molecular level. Rey et al. have very nicely compared, by using Ki67 immunostaining, proliferation between primary tumour and respective thrombus as well as between different types of tumour thrombus. It appeared that proliferation was constantly higher in tumour thrombus compared to the primary tumour and in vena cava thrombus compared to isolated renal vein thrombus [7]. Further studies using gene expression profiling comparison techniques should be more informative for analysing early molecular mechanisms driving such a rare and biologically intriguing event. From this research, definition of new molecular targets specific for great vessels vascular invasion in RCC could result.

2. Prognostic aspects

Some controversies continue even in the recent literature about the intrinsic prognostic value of the IVC invasion. One could summarise these debates by saying that renal tumours with IVC invasion are more likely to be larger, have higher Fuhrman grades, and contain sarcomatoid features. It probably explains their aggressive behaviour. It is not a contradiction with the fact that in localised tumours the presence or the extent of IVC invasion is often identified as a prognostic factor in univariate analysis. However, in metastatic disease it is clear that IVC invasion is no longer a prognostic parameter [8].

3. Therapeutic considerations

Two distinct groups of patients should be considered: those with and without distant metastases. Although patients with localised or locally advanced

renal tumours with IVC invasion cancer should be considered at high risk of dying from cancer, there is no doubt that radical surgery is the preferred option in this setting. However, as stressed by the paper from Rigaud et al., morbidity and perioperative mortality risks are not negligible and have to be taken into account when considering this type of surgery in aged people or in patients with important comorbidities. After completion of surgery, 5-yr probability of survival in patients with NOM0 tumours is between 35% and 56% [8]. Such a poor outcome is undoubtedly a strong argument for adding medical treatments after surgery. No adjuvant treatment has proven effective so far, but there is a great hope that in these type of tumours associated with a particular vascular phenotype, antiangiogenic drugs could be effective for improving survival [9]. Finally, in locally advanced tumors including T4 or N1N2 tumors with extensive local or nodal invasion rendering primary surgery difficult or impossible a neoadjuvant approach should also be tested.

Although advocated by many authors [3,8,10], surgery in patients with metastatic RCC invading the vena cava is much more debatable due to the absence of controlled studies proving the benefit of surgery in this setting. So far, the benefit of radical nephrectomy in the setting of metastases has only been proven in selected patients and it is not clear that such a strategy is applicable to all or some patients with IVC invasion. Particularly, it is not obvious that immunotherapy alone or palliative care would have done worse than a 10.7 mo median survival time, which is obtained in some recent series combining surgery and immunotherapy in patients having metastatic RCC and IVC invasion [3]. Additionally, patients with IVC invasion are more likely to have poor performance status [8] and to be subjected to surgical complications that could alter their chance to benefit from a systemic treatment. As noted in the paper of Rigaud et al., a significant number of patients will not be amenable to systemic therapy although they have experienced a potential life-threatening surgery without any proven long-term survival benefit. On the other hand, some arguments plead for combining aggressive surgery and systemic treatment when possible. First, it is clear that the presence of IVC invasion is not a prognostic factor when metastases are present. Second, surgery seems to have the same complication rate when IVC is present regardless of the presence of metastases [10]. Third, some authors have reported that patients with distant metastases and IVC invasion had a significantly better response to immunotherapy than those treated nonopera-

tively [8]. The truth is probably between two extreme unreasonable attitudes and the good way to proceed is to try to select those patients who could benefit from such an aggressive strategy. However, we will probably never know whether patients with RCC with IVC thrombus could benefit from combined surgery and immunotherapy because it is likely that randomised studies answering these questions will never be performed.

As mentioned, a new era is now open with targeted therapies based on the results that were obtained in metastatic disease. Therefore, many concepts have to be revisited. Specifically in case of metastatic RCC with IVC invasion, the role of first-line nephrectomy should be addressed as well as the potential risks of antiangiogenic treatments when tumour and thrombus are left in place. Similarly the potential haemorrhagic risk of surgery after antiangiogenic therapy should be addressed and consequently guidelines for appropriated timing between treatment and surgery should be determined. It can be expected that thanks to these new therapeutic approaches patients with RCC and IVC invasion will be proposed for specially designed clinical trials, including smart translational research.

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