Rebuttal from Authors re: Vincenzo Ficarra, Antonio Galfano and Stefano Cavalleri. Is Simple Enucleation a Minimal Partial Nephrectomy Responding to the EAU Guidelines' Recommendations? Eur Urol 2009;55:1315–8

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In recent years current opinion in urology has changed from widespread skepticism against tumor enucleation (TE) for the treatment of renal cell carcinoma (RCC) to widespread acceptance based on published studies of larger surgical series with longer follow-up periods [1–4]. Indeed, we ourselves and others recently showed that TE provides oncologic results similar to those of standard nephron-sparing surgery (NSS) [1–6].

We adopted the TE technique in the early 1980s because, along with its favorable oncologic results, it has the advantages of preserving more kidney parenchyma and of avoiding major bleeding and opening of the collecting system [7]. Between 1986 and April 2007, 803 patients had kidney surgery for pathologically confirmed, single, sporadic renal tumors. Of these, 502 patients (62.5%) had TEs and 301 patients (37.5%) had radical nephrectomies. Moreover, the number of TEs in our department has increased over time due to increasing surgical experience and better understanding of the technique.

Nevertheless, the retrospective nature of published series on TE, along with the reported risk of pseudocapsule invasion on the parenchymal side (based on data obtained by studies after an ex vivo TE or tumor sections of radical nephrectomy specimens) led many urologists to consider TE to be an unsafe technique with a high risk of incomplete tumor excision [8,9]. The excellent clinical results reported using the TE technique were considered to be related to the theoretically very slow local progression of RCC remaining in the surgical bed, which was not detectable in short-term and medium-term follow-ups. The host immune response was proposed as a possible explanation for the persistent good results, similar to those of partial nephrectomy reported in long-term studies; others hypothesized that the key role of laser or diathermy ablation of the tumor bed was to theoretically free the kidney parenchyma from any tumor cells that extended beyond the pseudocapsule [1,4].

The wide acceptance and approval of a surgical technique that aims to cure patients with RCC depends on its technical feasibility and oncologic safety as reported in retrospective series, along with prospective confirmation, on pathological examination, that the technique is able to obtain negative surgical margins (SMs).

Our study confirmed that the tumor pseudocapsule can be penetrated regardless of tumor size, with a reported infiltration rate of 26.6% on the parenchymal side and 6.6% on the perinephric adipose tissue side. The presence of a thin layer of parenchymal tissue, however, invariably allows for negative SMs, which also occur if no efforts are made to leave a rim of healthy kidney tissue around the neoplasm.

All of these data explain the excellent results of TE for treating not only intracapsular small masses <4 cm in diameter (pT1a) but also larger lesions [10]. All pT1b–pT2 RCCs enucleated in our series (18.9%) published in this issue had negative SMs on pathological examination [10]. Indeed, all RCCs were surrounded by a continuous (not fenestrated) fibrous pseudocapsule, regardless of tumor size, with a mean pseudocapsule thickness of 0.39 mm (range: 0.048–0.798 mm) that does not correlate with tumor dimension. Moreover, although the risk of an infiltrated pseudocapsule correlates with pathological tumor size, the risk is already significant within the pT1a group, which explains why the 4-cm threshold cannot define two groups of tumors with a statistically significant difference in pseudocapsule infiltration rate (see Table 2 and 3 in Minervini et al [10]).

One possible conclusion to be drawn from our study is that if the surgeon follows the natural cleavage plane between the tumor pseudocapsule and the kidney parenchyma by blunt dissection, there is no risk of positive SMs, even with larger masses [10]. This surgical maneuver perfectly reflects the strategy, ''Keep your friends close but your enemy closer.'' Always ''keeping an eye'' on the tumor margin surrounded by its pseudocapsule allows the surgeon to avoid entry into the tumor, and if the pseudocapsule is microscopically penetrated, a minimal layer of kidney tissue with a mean thickness of 1.05 mm (range: 0.38–1.60 mm) invariably ensures negative SMs. We noted that this thin rim of normal

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parenchymal tissue with signs of lymphoplasmocytic inflammation is present as ''leopard spots'' on the intact pseudocapsule and that it is always present in the case of neoplastic penetration of the pseudocapsule into the kidney tissue.

We concur with Ficarra et al [11], who in their editorial published in this issue of European Urology concluded, in agreement with the European Association of Urology (EAU) guidelines, that TE should be considered to be a minimal partial nephrectomy in which a very small rim of peritumoral tissue is removed. But we also think that, for the future, the EAU guidelines should focus attention on the SM status without considering the width of the resection margins. Either a ''minimal'' or a ''maximal'' tumor-free SM is irrelevant and does not correlate with the risk of either local or distant disease progression.

How can we explain the presence of a microscopic margin of normal parenchyma scattered around the pseudocapsule and invariably present in case of pseudocapsule penetration with tumor cells beyond it? Taking into consideration the hypotheses and suggestions for future studies by Ficarra et al [11], we can add that the presence of a pseudocapsule with signs of infiltration within its layers or that is completely penetrated (as in a third of patients undergoing NSS) could represent the first pathologic evidence of the capacity of tumor cells to infiltrate and invade surrounding normal tissue. Cancer cell invasion into surrounding tissue is an early and crucial step in carcinogenesis, and several recent studies identified the genes and the expressions of their corresponding products that are thought to be involved in local and metastatic progression. These factors include matrix metalloproteinases and adhesion molecules of the integrin family, and their overexpression or downregulation could allow cancer cells to infiltrate surrounding tissues. When started, however, cell–cell adhesion could be more effective between cancer cells and parenchymal cells than within the normal parenchyma, thus explaining negative SMs if the enucleation is carried out bluntly [12–13]. To further investigate this aspect, it could be useful to explore the correlations between these protein levels and both pseudocapsule status and the extension of the pseudocapsular infiltration.

In conclusion, ''keeping the enemy closer'' by staying close to the tumor would minimize the risk of positive SMs. Our study clearly represents a rationale for adopting the TE technique as the standard procedure for the excision of pT1a and pT1b RCC tumors, in conformity with the EAU guidelines [10]. For the future, we think that the EAU guidelines should focus attention on the SM status without consideration of the width of the resection margins.

Conflicts of interest: The authors have nothing to disclose.

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