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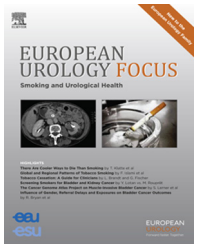

Renal Disease

Nephron Sparing for Renal Cell Carcinoma: Whenever Possible?

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1. Introduction

Nephron-sparing surgery (NSS) has been used for decades for imperative indications, that is, in patients with a solitary kidney or with bilateral tumours, and in those with more or less advanced renal failure.

With the increasing incidence of small renal masses [1], most often renal cell carcinomas (RCCs), the indications for NSS have moved from imperative to elective indications in the presence of a normal contralateral kidney. Over the years, an increasing number of partial nephrectomies have been performed, not only for small renal masses but also for larger tumours, to preserve as many nephrons as possible [2]. We started elective NSS in 1981 and reported in and reported in 1991 on 38 patients undergoing conservative surgery for malignant renal tumours varying in diameter between 1.3 and 12 cm [3]. Since then, many single-centre studies and multicentre analyses on NSS have been published without any proof of functional or oncological equivalence with radical nephrectomy in any randomised clinical trial (RCT) [4].

2. Actual guidelines and recommendations

The European Association of Urology (EAU) recommends that patients with low-stage RCC (T1) should undergo NSS rather than radical nephrectomy whenever possible. The level of evidence (LE) is 3 and the grade of recommendation is B. Thus, for a solitary renal tumour up to a diameter of 7 cm, NSS is the standard procedure whenever technically possible (LE 3, grade C) [5].

Obviously, NSS is recommended because a lower glomerular filtration rate (GFR) can lead to chronic kidney disease (CKD), and this is more likely to occur after radical than after partial nephrectomy [6]. It has been reported that CKD increases cardiovascular disease that might eventually lead to cardiovascular death [7]. Many open studies suggested at least oncological equivalence or superiority and therefore favoured the use of NSS [8–12].

The concept of sparing nephrons has changed over the years. While partial nephrectomy, heminephrectomy, and wedge resection—resecting the tumour within a given margin of healthy parenchyma—were initially advocated, urologists now try to remove as little healthy parenchyma as possible. Thus, the classical wedge resection has moved from enucleo-resection/excavation (in which just a few millimetres of healthy parenchyma are resected with the tumour) to pure enucleation relying on the tumour pseudocapsule. Enucleation has been performed for years in a number of Italian centres [13], and a recent multicentre study showed that enucleation is technically and oncologically safe [14]. Moreover, the importance of positive surgical margins was questioned, and at least two collaborative reviews revealed that cases with positive surgical margins are best followed up with regular computed tomography imaging rather than a second surgical intervention (broader excision or radical nephrectomy) [15,16]. It remains obvious that positive surgical margins increase the risk of disease recurrence, especially in patients with adverse pathological features [17].

A second change in the mind of urological surgeons is related to reducing the warm ischaemia time as much as possible. While it was once claimed that every minute counts when the renal hilum is clamped during partial nephrectomy, it has become clear that the limit for the warm ischaemia time is approximately 25 min without increasing the risk of developing end-stage renal disease

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[18]. Obviously, more complex tumours will need a longer warm ischaemia time; conversely, partial resection in these cases will result in a lesser amount of remaining parenchyma, and the latter is the most important factor for postoperative renal function [19,20].

Finally, besides resected parenchyma, we need to take into account nephron loss due to renorraphy resulting from closure of the kidney parenchyma and renal cortex, which is mostly achieved with a couple of stitches. In the case of pure enucleation of smaller tumours, closure of the renal cortex is therefore not attempted and haemostatic agents are used to stop the bleeding [21].

3. Phase 3 RCT

In 1990, at a time when many surgeons still believed that every solid kidney tumour should be treated using radical nephrectomy, we decided to launch an RCT to compare the safety and oncological efficacy of radical versus partial nephrectomy in patients with renal tumours of up to 5 cm in diameter. While initial trial recruitment was very good, more and more centres became reluctant to perform radical nephrectomies for increasingly frequent small renal masses, and there was a steep increase in the application of NSS outside clinical trials. The aim in our noninferiority trial by the European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group was to randomise 1300 patients, but the trial was closed by the EORTC Central Office because of slow accrual after randomisation of 541 patients. A first report on this trial showed that partial nephrectomy had more complications than radical nephrectomy, mostly haemorrhagic [22]. In a second publication [23] the overall survival among RCC patients was unexpectedly better for radical than for partial nephrectomy.

In the meantime, in the absence of any scientific evidence, more and more partial nephrectomies were performed, not only for small renal masses but also for increasingly advanced cases [24,25]. An open study showed that partial nephrectomy is as good as radical nephrectomy for tumours between 4 and 7 cm in terms of cancer-specific and overall survival [26]. A single centre reported on NSS for T2–T3 RCC and showed an equal outcome compared to radical nephrectomy [27]. Besides these two American studies, two German centres published their experience with NSS for RCC masses >7 cm and the cancer-specific survival was equal [28]. Even for T3b RCC confined to the renal vein, successful NSS was reported by a couple of centres [29,30].

Since so many open studies from single or multiple centres favoured NSS, we needed to look again at our randomised trial database, and analysed the data according to the estimated GFR (eGFR). Finally, 259 patients with radical nephrectomy were compared to 255 who underwent NSS, all with reliable eGFR follow-up. The analysis showed that the radical nephrectomy group did not do worse over time as expected in terms of mean eGFR up to 15 yr after surgery. It seemed that the beneficial effect of NSS on eGFR did not result in improved survival over median follow-up of 9.3 yr for all-cause mortality [31]. We concluded, in accordance with other groups [32], that the moderate renal dysfunction arising from surgery does not have the same negative implications for overall health as when it arises from medical causes such as diabetes and hypertension.

4. Systematic reviews and meta-analysis

A meta-analysis of more than 20 studies (of which one was our RCT) revealed that for all-cause mortality and cancer-specific mortality, partial nephrectomy confers a survival benefit and a lower risk of CKD [33]. The authors, however, clearly acknowledge that for all studies (except the RCT) the existing evidence was of low quality.

A multi-institutional study of 1331 T1a–b renal masses in patients with initially normal renal function analysed the occurrence of cardiovascular events related to radical or partial nephrectomy. Cardiovascular events were defined as the onset of coronary artery disease, cardiomyopathy, hypertension, hearth failure, or dysrhythmia. The authors concluded that there was a significant advantage for NSS, with a lower incidence of cardiovascular events ($p = 0.001$) [34]. However, the two Kaplan-Meier curves separate very early after surgery and tend to come together again after 15 yr. If NSS does indeed lead to fewer cardiovascular events, this benefit should be a delayed event, with benefits accumulating over time. The apparent and obvious immediate benefit is likely to be unrelated to the type of surgery, but rather to different risks in the two groups before the tumour surgery [35]. This means that patients who were selected for partial nephrectomy had a higher likelihood of long-term survival at baseline, and this constitutes the major selection bias in almost all nonrandomised studies. It is possible that the higher incidence of de novo arterial hypertension after radical nephrectomy is responsible for the early split of the two curves. The authors are reanalysing the data, realising that arterial hypertension after radical nephrectomy tends to regress after longer follow-up, which is the reason why the curves come together after more than 10 yr.

For the time being, urologists have to abandon the idea that partial nephrectomy is always better because it avoids CKD and thus leads to better overall survival. In a matched cohort study of the Surveillance, Epidemiology, and End Results–Medicare data set, data set, 1471 partial nephrectomies and 4299 radical nephrectomies were matched to controls. Analysis revealed that the number of cardiovascular events was higher in both the partial and the radical nephrectomy arms, confirming that the seemingly obvious advantage of partial nephrectomy suggested in many open studies is due to a selection bias [36].

Thus, while it seems that elective NSS for T1 renal cell carcinoma in presence of a normal contralateral kidney is probably not warranted to improve overall, cancer specific and cardiac specific survival, it is obvious that patients with CKB should obviously benefit from NSS. In an analysis of 1306 patients, the 5-yr probability of survival in the overall cohort was significantly better after NSS than after radical

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nephrectomy ($p < 0.001$). However, when analysing the 364 with CKD stage 1 (eGFR >90 ml/min/1.73 m^2) there was no difference; similarly, in 188 patients with CKD stage 3A (eGFR 30–59 ml/min/1.73 m^2) there was no difference. The probability of developing renal function impairment was only significantly different in the group of 680 patients with CKD stage 2 (eGFR 60–89 ml/min/1.73 m^2; $p = 0.002$) [37]. Thus, this group of patients deserves imperative NSS and will do worse when undergoing radical nephrectomy. Another recent collaborative database analysis showed that patients who are more ill with relevant comorbidities are those who benefit the most from NSS in terms of other-cause mortality [38].

5. Concluding remarks

Open studies have definitely and repeatedly favoured NSS in improving overall, cancer-specific, and cardiac disease–specific survival in cases with a normal contralateral kidney. However, the only RCT could not confirm this superiority of NSS over radical nephrectomy. Surgery-induced CKD seems to be much less relevant than CKD induced by medical conditions such as hypertension and diabetes. Both partial and radical nephrectomy harm the patient to some extent, and urologists should not be blamed for performing a safe radical (minimally invasive) nephrectomy for a complex T1b or T2 renal cancer for which the technical and oncological safety of an elective partial nephrectomy is not guaranteed.

In conclusion, urologists should not resect kidneys or remove nephrons if it is safe to do otherwise. Many small renal masses will be amenable to an oncologically and technically safe NSS procedure, whether via open surgery or laparoscopic (eventually robot-assisted) techniques. Larger and more complex RCCs can be treated using NSS if this is oncologically and technically safe. In the presence of a normal contralateral kidney, radical nephrectomy will only induce CKD and impact on overall survival in exceptional cases, and is not inferior to partial nephrectomy in the long run. Obviously, the experience gained in large-volume centres from so many partial nephrectomies is useful in treating those patients for whom NSS is imperative. The only advantage of performing more complex NSS in elective cases could be the increase in experience and expertise of the surgeon that will ultimately benefit patients who really need NSS.

Conflicts of interest: The authors have nothing to disclose.

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