1. Introduction

Cancers of the renal parenchyma, also known as renal cell carcinomas (RCCs), account for just under 2% of all cancers worldwide. Although RCC is a relatively rare cancer, its incidence, as well as its associated mortality rates, have been increasing over the past 50 yr [1–4]. A significant part of this apparent increase is believed to result from the wider application of imaging techniques such as...
ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), leading to a rise in the number of incidentally diagnosed RCCs [4]. However, data from American studies showed that, besides an increase in presymptomatic localised tumours, there has also been an increase in locally advanced and distant metastatic RCCs, suggesting that advanced imaging techniques are not the sole contributors to the rapidly increasing incidence [5–7].

Prognosis for patients with RCC varies considerably depending on the stage of disease at diagnosis. According to the Surveillance Epidemiology and End Results (SEER) database, about 70–80% of the patients present with localised disease, which is associated with an 89.9% 5-yr survival rate. However, the 5-yr survival rate in patients with locally advanced disease drops to 61%, whereas patients with distant metastatic disease have only a 9% 5-yr survival rate [8].

These poor survival rates indicate that current therapies are insufficient, especially for patients with advanced disease characteristics. Over the past few years, however, increasing knowledge about the molecular and genetic basis of RCC has stimulated the development of novel and more targeted treatment strategies. Furthermore, advances in surgical techniques may favour a more conservative treatment for patients with localised disease.

This paper comprises the latest highlights on kidney cancer presented at the 2006 urologic and oncologic annual meetings of the European Association of Urology (EAU) in Paris, the American Urological Association (AUA) in Atlanta, and the American Society of Clinical Oncology (ASCO) also in Atlanta. A selection of abstracts from these congresses were discussed at a closed expert meeting “New Horizons in Urology” in Marbella. In addition, participants at this meeting were engaged in an interactive voting procedure to assess their opinions on a representative clinical case study and experts in RCC commented on the results.

2. Treatment of localised disease

Treatment approaches for RCC depend on disease stage at presentation. The standard treatment for patients who are diagnosed with local RCC and who have two functioning kidneys is radical nephrectomy (RN). However, advances in surgical and imaging techniques over the past several years have created the possibility of applying nephron-sparing surgery or minimally invasive treatment strategies as alternatives to invasive RN [8].

2.1. Partial nephrectomy

Partial nephrectomy (PN) was first advocated in patients with a single kidney or a nonfunctioning contralateral kidney or in patients with or at risk for bilateral RCC. However, the current EAU guidelines on RCC also recommend PN for patients with a solitary tumour <4 cm [8]. Although these guidelines propose that easy-operable tumours of 4–7 cm can be treated with PN, this should be addressed cautiously because it has been shown in a study presented at this year’s EAU meeting that tumour size is positively correlated with aggressiveness even in tumours <4 cm. This study evaluated the pathologic stage of 287 solid kidney tumours <4 cm. It was shown that advanced stage (≥pT3a) was found in 2, 12, and 35 of RCC tumours ≤2 cm, 2.1–3 cm, and 3.1–4 cm, respectively (Fig. 1) [9].

Even though it has been demonstrated that PN in patients with a tumour <4 cm provides recurrence-free and long-term survival rates similar to those observed after RN, data from a retrospective study presented at the AUA meeting in 2006 indicated that urologists are still hesitant to perform PN [10,11]. Using the population-based SEER data, it was shown that of the 14,647 patients surgically treated for primary RCC ≤7 cm between 1988 and 2001, 90.4% underwent RN, whereas only 9.6% were treated with PN. For tumours ≤7 cm, a progressive increase in the use of PN was seen between 1988 (4.6%) and 2001 (17.6%; p < 0.01); nevertheless, PN remained an uncommon treatment strategy, even for small tumours. Among patients with tumours <2 cm, 14% were treated with PN in 1988–1989 versus 42% in 2000–2001 and for tumours 2–4 cm, 5% and 20% underwent PN, respectively (p < 0.01; Fig. 2). Notwithstanding this increased frequency of PN over

![Fig. 1 – The size of renal cell carcinomas (RCCs) correlates with advanced stage (≥pT3a) [9].](image-url)
the two decades, its use remains relatively uncommon, despite its equivalent cancer control and the advantageous functional outcomes associated with the preservation of the renal parenchyma [11].

2.2. Minimally invasive techniques

New and progressive minimally invasive techniques such as laparoscopic cryoablation (LCA) or radiofrequency ablation (RFA) are emerging as alternative therapies for the treatment of small RCCs, especially for patients who are poor candidates for surgical interventions. These procedures consist of the insertion of a probe into the tumour using real-time imaging guidance by ultrasonography, CT, or MRI, and then destroying the tumour with cold (LCA) or heat (RFA) [12]. Although these techniques have the disadvantage compared to traditional surgery in that histopathologic confirmation of complete tumour resection with clear margins is not possible, a great deal of attention was paid to both of these minimally invasive techniques at this year’s urologic meetings.

2.2.1. LCA

LCA is an emerging technique for a select group of patients who preferentially have small (<4 cm), solid, peripheral renal tumours that do not involve the central collecting system [8]. Although several small studies with median follow-up reported promising oncologic outcomes and low complication rates after renal LCA, multicentre studies with long-term follow-up of treated patients are necessary to further validate the efficacy and safety of this new procedure [13–16].

A study presented at AUA 2006 annual meeting assessed the long-term oncologic outcomes in patients treated with LCA between September 1997 and September 2005 [17]. Sixty patients treated with LCA completed at least 5 yr of follow-up (median: 72 mo) that consisted of MRI on postoperative day 1, at 3, 6, and 12 mo, and annually from then on. Furthermore, a needle biopsy was performed in conjunction with the 6-mo scan. The initial indication for treatment was a solitary sporadic RCC in 73% of the patients, with a mean tumour size of 2.3 cm (range: 1–4.5 cm). Three patients (6.7%) developed a local tumour recurrence; two of them remained disease-free on dialysis following nephrectomy. The other patient, however, died 10 mo after nephrectomy on dialysis with no evidence of further disease. Given that the cancer-specific 5-yr survival rate was 100% along with the low incidence of recurrences, it was concluded that LCA is feasible in those patients with small, solitary sporadic tumours [17]. Although the cancer-specific 5-yr survival rate in this study was considered reassuring by the urologic experts, the remark was made that this outcome mainly relies on the skills of the surgeon. It was suggested that they should be proficient in laparoscopic surgery prior to engaging themselves in performing LCA.

Even though the former study may support the use of LCA in a select group of patients, a matched-cohort study by O’Malley and colleagues comparing laparoscopic PN (LPN) and LCA did not favour the use of LCA over LPN for the treatment of small peripheral tumours [18]. In this study, 15 patients who had LCA between May 2003 and July 2005 were compared with an age- and tumour size-matched cohort of 15 patients from a pre-existing database of 104 patients who underwent LPN between July 2002 and July 2005. Surgical outcomes between the two groups were similar; only the LPN group had a
significantly longer operating time \( (p < 0.001) \) and a higher estimated blood loss \( (p = 0.007) \) compared to the LCA group (Fig. 3). There were no recurrences recorded in either of the two groups and both had a similar mean follow-up period of 9.8 and 11.9 mo, respectively. It was concluded that, especially in elderly patients with comorbidities precluding blood loss or renal ischaemia, LCA is a good choice for treatment of small RCCs. Still, in experienced hands, LPN remains the preferred option and should be considered as the definitive treatment of small, sporadic renal tumours [18].

At the closed meeting in Marbella, however, some concerns were expressed regarding this study. It was emphasised that it was a retrospective, small-scale study with a short-term follow-up period and that rather long-term data from a head-to-head prospective large-scale study are needed to bring more insights on whether or not LPN should be favoured above LCA.

### 2.2.2. RFA

Another minimally invasive technique that is currently being evaluated is RFA, which has gained more popularity in recent years. Although RFA was initially proposed for patients unfit for (laparoscopic) surgery due to a poor performance status (American Society of Anesthesiologists [ASA] score of 3 or 4), serious comorbidities, minor renal function, or high-risk for developing additional RCCs, a study presented at the AUA 2006 annual meeting assessed this technique in healthy ASA 1 and 2 patients [8,19,20]. Thirty-seven patients with a mean age of 57 yr (range: 20–84 yr) and a mean tumour size of 2.2 cm (range: 1–4 cm) were treated with either open or laparoscopic RFA. The follow-up period was at least 12 mo with a mean follow-up of 27 mo (range: 12–48 mo). During the postoperative follow-up, no incomplete ablations were detected. Only one patient developed a recurrence at 24 mo. This patient underwent salvage RN, which revealed RCC on final pathology, and is without disease 1 yr later. Four minor complications were reported: three patients with self-limiting neuralgia/paresthesia secondarily related to ablation and one with asymptomatic hydrocalyx detected 18 mo after RFA treatment.

Although these and prior results show that treatment of small RCCs with RFA is feasible and safe in both ASA 1 or 2 and ASA 3 or 4 patients, clearly more data from larger-scale studies with long-term follow-up are needed to further validate these results [20–22]. It has been suggested that for long-term evaluation of the ablative properties and completeness, more adequate long-term oncologic outcomes should be assessed and preferentially compared with PN as a standard [23].

In this respect, a study, presented at the AUA 2006 annual meeting, compared intermediate outcomes of patients diagnosed with cT1a renal tumours who were treated with PN or RFA [24]. Of all patients treated for cT1a RCC between July 1994 and May 2005, 141 patients were selected for this study because they did not present with bilateral synchronous or metachronous tumours, metastatic disease, or hereditary RCC. From these, 53 (37.6%) underwent open or laparoscopic PN, whereas the remaining 88 (62.4%) had either percutaneous or laparoscopic cryoablation. The mean age was 56.5 yr (range: 32–79 yr) in the PN group and 62.6 yr (range: 18–85 yr) in the RFA group, and mean follow-up periods were 3.4 yr (range: 1.3–8.8 yr) and 1.4 yr (range: 6 wk to 3.5 yr), respectively. There were four incomplete ablations and three recurrences in the RFA group. Of these, four had a successful re-ablation, one died of heart failure, and two underwent nephrectomy, revealing residual RCC in one and benign tumour in the other. In the PN group, on the other hand, there were two patients with recurrences of whom one had a new enhancing renal mass and the other was diagnosed with advanced RCC that was treated with nephrectomy. The recurrence-free probability at 3 yr was 97.5% ± 0.83% for the PN group and 95.7% ± 0.71% for the RFA group \( (p = 0.102) \) [24]. It was concluded that PN and RFA have a comparable 3-yr outcome for treatment of cT1a renal tumours; however, the remark was made that to obtain straightforward results on this issue, a head-to-head comparative and randomised long-term study should be performed.

Overall, it can be stated that RN remains the gold standard treatment for localised disease. However, during recent years, there has been a growing tendency towards nephron-sparing and less invasive laparoscopic surgery because these procedures clearly improve the patient’s postoperative quality of life. Given the rising importance of laparoscopic surgery for the treatment of RCC, it was indicated at the “New Horizons in Urology” meeting in Marbella that new residents in urology should be proficient in laparoscopic surgery on completion of their training. With regard to minimally invasive techniques such as LCA and RFA, so far, no studies are available evaluating the long-term oncologic outcomes of these rather new procedures. However, it is believed that these techniques are promising and efforts should be undertaken for further optimisation.

During the closed expert meeting “New Horizons in Urology” held in 2006, the participants were
engaged in an interactive voting procedure to assess their treatment preference on a representative case study suggestive of kidney cancer. The results were discussed and experts in the field of RRC offered comments.

A 61-yr-old woman with hypertension and type 2 diabetes presented to the physician complaining of left flank pain for the last 2 wk. An ultrasound examination showed a peripheral renal mass of approximately 3.5 cm. This finding was further confirmed by CT, which clearly showed a 3.5-cm mass on the periphery, but going into the parenchyma. Preoperative tests showed that she had a normal renal function, normal blood analysis, and no signs of distant lesions on radiographic examination. Additionally, a bone scan was negative. Regarding this issue, the brief comment was made by the expert panel that for small renal masses, like the one presented here, a bone scan is not a routine procedure.

With this background information in mind, the participants from the closed meeting were asked to choose a treatment strategy through interactive voting. The results from this voting procedure are shown in Fig. 4. Forty percent of the participants chose open PN, whereas a surprising 30% went for its laparoscopic counterpart. The remaining persons chose RN, either open or laparoscopic (Fig. 4).

Thus, the majority of the attendees decided on performing an open PN and this procedure was actually performed on the patient. However, the experts reflected on the fact that a large proportion of the urologists voted for LPN. Although a progressive shift from open to laparoscopic surgery has been seen over the past few years, performing LPN remains a challenging procedure due to the risk of converting PN into RN because of technical issues. Therefore, training of new residents should focus on this issue and it was advocated by the author that on completion of their residency, urologists should be able to perform laparoscopic surgery. Finally, the remark was made that still 30% of the attendees to the closed meeting opted for RN. Given the data currently available on treatment of small renal masses, this was regarded as over-treatment by some of the experts.

3. Treatment of advanced and metastatic disease

To date, treatment of metastatic RCC with surgical intervention or immunotherapy has been largely unsuccessful. In patients with limited metastases, nephrectomy and resection of metastatic lesions may be a suitable therapy. Generally, however, the cancer is too widespread and the standard treatment for those patients is immunotherapy with interferon-α (IFN-α) or interleukin 2 (IL-2). Unfortunately, IFN-α or IL-2 administered as a single agent only achieves response rates of 8–26% and 7–23%, respectively [25]. These poor outcomes have emphasised the need for new and more effective treatment strategies.

Over the past several years, the understanding of the molecular and genetic basis of RCC has led to the development of new agents for the treatment of metastatic RCC. Although RCC has several histologic subtypes, 70–80% of all tumours contain clear-cell RCC (ccRCC) morphology of which both sporadic and hereditary forms are associated with mutations in the von Hippel-Lindau (VHL) tumour suppressor gene. Loss of the VHL protein function eventually leads to overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), both of which promote tumour angiogenesis and by consequence contribute to the hyper-vascularisation of RCC [26]. Therefore, novel developments in the treatment of RCC aimed at targeting the VEGF and PDGF pathways with the intention to reverse the physiologic consequences of losing the VHL protein function. In this respect, several new drugs have been developed of which sunitinib, sorafenib, and temsirolimus were extensively discussed at this year’s urologic and oncologic congresses.
3.1. Sunitinib

Sunitinib, also known as SU11248, is a small molecule receptor tyrosine kinase inhibitor (TKI) with both direct antiproliferative and antiangiogenic properties by targeting VEGF, PDGF, KIT, and FLT3 tyrosine kinases [27]. Recently, promising results were obtained in two multicentre, phase 2 trials that assessed the clinical activity and safety of sunitinib as second-line therapy for patients with metastatic RCC who progressed after one prior cytokine therapy [28,29]. In summary, 34–40% of the patients treated with sunitinib achieved a partial response and an additional 27–29% of the patients demonstrated stable disease for ≥3 mo. The median progression-free survival was 8.3–8.7 mo.

A phase 3 clinical trial of sunitinib versus INF-\(\alpha\) as a first-line treatment of metastatic RCC was presented at the ASCO 2006 annual meeting [30] and has recently been published [31]. Between August 2004 and October 2005, 750 patients with metastatic ccRCC were randomised in a 1:1 ratio to receive sunitinib (6-wk cycles: 4 wk 50 mg orally once daily followed by 2 wk off) or IFN-\(\alpha\) (6-wk cycles: subcutaneous injection of 9 million units [MU] given three times weekly). The objective response rate was significantly higher for sunitinib compared to IFN-\(\alpha\) (\(p < 0.000001\); Fig. 5). Moreover, a higher median progression-free survival rate was observed in patients receiving sunitinib (47.3 wk) versus those receiving IFN-\(\alpha\) (24.9 wk) with a hazard ratio of 0.394 (\(p < 0.000001\)). Concerning safety outcomes, only 8% of the patients taking sunitinib withdrew from the study due to adverse events, whereas this was the case for 13% of the patients taking IFN-\(\alpha\) [30]. Although this study suggests that sunitinib is superior to IFN-\(\alpha\) as first-line treatment for patients with metastatic ccRCC, still more data are needed to further confirm these results.

3.2. Sorafenib

Sorafenib, formerly known as BAY 43-9006, is a novel bi-aryl urea initially developed as a specific inhibitor of Raf kinase. More detailed analysis showed that sorafenib also has significant activity against other TKIs involved in tumour progression and neoangiogenesis including VEGFR2 VEGFR3, PDGFR-\(\beta\), FLT3, and c-KIT [32]. So far, two phase 2 studies have shown the antitumour activity of sorafenib and at the EAU 2006 annual meeting results were presented from a double-blind, placebo-controlled phase 3 study [33–35]. These results were recently published [36]. A total of 905 patients diagnosed with advanced ccRCC in whom one prior systemic treatment course had failed were randomised to receive continuous oral sorafenib twice daily or placebo added with the best supportive care. First interim analysis of 769 patients demonstrated that the median progression-free survival time was 24 wk for sorafenib compared to 12 wk for placebo, with a hazard ratio of 0.44 (\(p < 0.000001\)). In addition, 75% of the patients taking sorafenib had not progressed after 3 mo of treatment versus 43% of those on placebo. Therefore, it was concluded that sorafenib significantly prolongs the progression-free survival compared to placebo in patients previously treated for advanced RCC [35].

3.3. Temsirolimus

Temsirolimus (CCI 779) is a specific inhibitor of mammalian target of rapamycin (mTOR), a serine/threonine protein kinase that, through its role as key regulator of the cell cycle, presented itself as a potential target for antitumour therapy [37]. In a phase 2 clinical trial by Atkins et al, 7% of the 111 patients with advanced RCC who were assigned to this single-agent study on temsirolimus obtained an objective response and a minor response was observed in 26% of the patients [38]. The efficacy and safety of temsirolimus was further addressed in a three-arm, randomised, phase 3 study that was presented at the ASCO 2006 annual meeting [39]. In this study, 626 patients with advanced RCC with no prior systemic therapy were randomised at a 1:1:1 ratio to arm 1 (IFN-\(\alpha\) up to 18 MU subcutaneously twice/wk; \(n = 207\)), arm 2 (temsirolimus 25 mg intravenously once/wk; \(n = 209\)), or arm 3 (temsirolimus 15 mg intravenously once/wk + IFN-\(\alpha\) 6 MU subcutaneously twice/wk; \(n = 210\)). Fig. 6 shows the median overall survival rate for the 3 groups based on data from the preliminary interim analysis. Compared to IFN-\(\alpha\) treatment alone, temsirolimus...
was associated with a significant 49.3% increase in the overall survival time ($p = 0.0069$; Fig. 6), whereas this was not the case with the combination treatment. It was concluded that monotherapy with temsirolimus significantly increases the overall survival time in poor-risk patients with advanced RCC compared with IFN-α, whereas this was not observed after treatment with combination therapy (temsirolimus + IFN-α) [39].

Next to sorafenib, sunitinib, and temsirolimus, the monoclonal antibody bevacizumab has been evaluated for its use as second-line therapy in metastatic RCC as well. Although the results that have been gathered on these new drugs are promising, especially because they are more effective than cytokines in the treatment of metastatic RCC, clearly additional data are needed to further validate and confirm these results. Additionally, more research is needed to further improve the current drugs and to develop new therapeutic agents because, so far, no complete response is achieved with antiangiogenic drugs.

4. Conclusions

At the key urologic and oncologic congresses of 2006, many interesting and promising new data were presented. Although an increasing body of evidence supports the implementation of PN as a first-line treatment for localised disease, SEER data from the United States show that PN remains relatively uncommon, even in small RCCs ($<4$ cm). However, urologists performing PN should keep in mind that even in these small tumours, the size of the RCC is positively correlated with advanced stage ($\geq$ pT3a), which implicates a thorough selection of possible candidates.

A great deal of interest was also devoted to minimally invasive techniques. A large study with a 5-yr follow-up period demonstrated that LCA treatment was associated with a high cancer-specific 5-yr survival rate. However, it was suggested that, to achieve this kind of outcome, physicians should be proficient in performing laparoscopic surgery. Therefore, new residents should be qualified to master this technique on completion of their residency, not only to perform LCA, but also for RN and PN. Another study suggested that even though LCA is a good treatment option for small RCCs, especially in elderly people unfit for surgery, LPN should remain the preferred option as definitive treatment of small, sporadic renal tumours. Although RFA is normally reserved for patients at risk for surgery, a 2-yr follow-up study showed that this technique is also safe and feasible in patients with ASA status 1 or 2. Furthermore, a comparison was made between PN and RFA for treatment of cT1a RCC, which showed that both techniques have a comparable 3-yr outcome. Although these data on minimally invasive techniques seem promising, more large-scale, long-term data are needed to further confirm them.

Driven by the poor outcomes of surgical and cytokine-based treatment of advanced RCC and the progress made in elucidating the molecular and genetic basis of RCC, several new agents have been developed including sunitinib, sorafenib, and temsirolimus. It was shown that sunitinib is superior to IFN-α as first-line treatment for patients with advanced ccRCC. Furthermore, a large-scale phase 2 study demonstrated that sorafenib significantly prolongs the progression-free survival compared to placebo in patients previously treated for advanced RCC. Finally, it was demonstrated that single-agent temsirolimus, and not the combination therapy temsirolimus + IFN-α, significantly increases the overall survival compared to IFN-α as first-line treatment in poor-risk patients with advanced RCC. However, more research is needed, not only to further confirm these results, but also to further optimise these new drugs and to develop new therapeutic agents to achieve complete remission in patients with metastatic RCC in the future.

Conflicts of interest

Francesco Montorsi is a paid consultant for Pfizer, Bayer, GSK, AMS, Pierre Fabre and Eli Lilly.
References

