1. Introduction

Approximately 210,000 new cases of kidney cancer are diagnosed in the world each year, accounting for just under 2% of all cancers [1]. It is estimated that in 2002, there were approximately 86,000 new cases of kidney cancer in Europe and approximately 45,000 deaths from this disease [1]. According to the National Cancer Institute, the highest incidences of kidney cancer occur in the United States, Canada, Northern Europe, Australia, and New Zealand. The lowest incidences are found in Thailand, China, and the Philippines. Several types of carcinomas can develop in the kidneys; renal cell cancer (RCC), which includes clear-cell, papillary, and chromophobe cancer types, is the most common form of kidney cancer. RCC is expected to account for approximately 3% of newly diagnosed malignancies in the United States in 2006 and it is estimated that >10,000 people in the United States will die of this disease [2].
Typically, about 30% of patients with RCC present with metastatic disease, although this rate may drop considerably with the widespread use of thin-slice computed tomography (CT) scans. Patients with metastatic disease have an extremely poor prognosis, with a 5-yr survival rate of generally <2% [3]. If detected at an early stage, RCC can be treated successfully with radical or partial nephrectomy; however, metastatic disease develops in 20–30% of patients following nephrectomy [3]. Other treatment options are limited because RCC is generally resistant to chemotherapy and radiation therapy, and only infrequent responses are achieved with immunotherapy agents such as interferon-α (IFN-α) and interleukin-2 (IL-2) [4,5]. In this article, we present three clinical scenarios and discuss the optimal management of RCC in these patients.

2. Clinical scenario I: a patient with a renal mass and inferior vena cava thrombus

The initial presentation of the patient with a renal mass and inferior vena cava (IVC) thrombus in the first clinical scenario is shown in Box 1.

2.1. Value of imaging as an initial diagnostic technique

The first question to ask when presented with a patient such as the one described is, which imaging technique is best? In a meeting of 746 specialists [6], an audience poll revealed that approximately two-thirds of urologists and oncologists who responded would recommend a CT scan for this patient, with the remainder recommending either ultrasound or magnetic resonance imaging (MRI). In this clinical scenario, a CT scan was performed but MRI and other diagnostic procedures would also have been possible options. MRI is slightly more sensitive than CT and, because it can accurately predict a thrombus in most patients, is often the procedure of choice when trying to stage a thrombus. For example, in a study of 220 patients who underwent radical nephrectomy for RCC, MRI accurately detected a thrombus in 98% of cases [7]. Continued advances in CT and MRI technology should expand the role of preoperative imaging and could potentially, through earlier and more accurate staging, improve the cure rate of renal cancer.

2.2. Impact of tumour thrombus on RCC

RCC invades the venous system to different degrees in 4–9% of cases [8] and can include extension into the renal vein or the IVC (level I), extension above the diaphragm (level II), or extension into the atrium (level III) [9]. This invasion of the venous system, or “tumour thrombus”, is associated with a more advanced stage and is a more aggressive disease than that found in nonmetastatic RCC cases. Five-year survival rates for nonmetastatic RCC with tumour thrombus range from approximately 20% to almost 70% after surgical resection [10]. Interestingly, tumour thrombus is not associated with an adverse prognosis as long as complete surgical resection is possible. In one of the largest studies published to date, the long-term survival of 153 patients with tumour thrombus was evaluated [9]. This study placed a particular emphasis on survival outcome of patients with different levels of tumour thrombus. The overall 10-yr cancer-specific survival for patients with IVC tumour thrombus was 30% for level I, 19% for level II, and 29% for level III (Fig. 2); however, there was no statistically significant difference between the three IVC levels \( p = 0.48 \) [9]. In addition, the 10-yr survival of patients classified as T3b with renal vein wall involvement was significantly greater after surgical resection than that of patients with IVC level I who also underwent surgery. This study suggests that tumour thrombus in the IVC can be treated and cured surgically in approximately one-third of patients, assuming it is not associated with any other factors indicative of poor prognosis. Other factors, such as the presence of distant or lymph node metastases and higher grade tumours would also influence prognosis.

2.3. Treatment options for patients with IVC thrombus

Surgery is the only curative treatment option for RCC and radical nephrectomy of the tumour-bearing kidney with thrombectomy remain the treatment of choice in patients with IVC involvement [11]. Radical nephrectomy with thrombectomy has also been
shown to improve overall survival for a small number of patients with metastasis, tumour thrombus, and Eastern Cooperative Oncology Group performance status 1 (Fig. 3) [8]. In view of recent advances in the management of RCC, is there also a role for laparoscopy, adjuvant therapy, or embolisation in the management of patients with IVC thrombus?

Laparoscopic radical nephrectomy is now an established surgical procedure worldwide and is associated with reduced morbidity compared with open radical nephrectomy. In light of this, the European Association of Urology (EAU) renal cancer treatment guidelines now recommend that for patients with T1-2 RCCs, laparoscopic radical nephrectomy should be performed in preference to open radical nephrectomy in centres that have laparoscopic expertise [12]. However, the patient in this clinical scenario has stage cT3b disease and, except for radical open nephrectomy with thrombectomy, few surgical options exist. Cardiopulmonary bypass has been used as an adjunct to removing cavoatrial tumour thrombus with and without hypothermic circulatory arrest [13]. For tumours just below the diaphragm, venovenous bypass can be a useful technique to decrease perioperative morbidity and when control of the vena cava is required above the hepatic veins, the Pringle manoeuvre can be used [13]. Other intraoperative techniques include hypotensive anaesthesia with vasodilation and colloid administration, and transoesophageal echocardiography [13]. In our scenario, the patient underwent radical nephrectomy with IVC thrombectomy without any form of bypass or Pringle manoeuvre.

For this patient, study data suggest that the role of adjuvant immunotherapy would be limited; in a study involving 77 patients diagnosed with N0, M0

Fig. 1 – Computed tomography scan of the patient in clinical scenario I, which revealed a large right renal tumour (stage cT3b, N0, M0) filling the inferior vena cava and extending to below the hepatic veins.
disease, those with IVC involvement had a poorer response to adjuvant immunotherapy (mostly IL-2-based therapy) than renal vein or patients without thrombus [8]. The EAU guidelines state that “outside of controlled clinical trials, there is no indication for adjuvant therapy following surgery” [12].

So what is the current role for embolisation in this situation? Tumour embolisation alone is limited to certain patients, for example, those with gross haematuria who are not fit for surgical intervention or prior to surgical resection of large paravertebral metastases [12]. It should be noted that gross haematuria with severe and acute anaemia, as occurs in this patient, is not a typical or frequent complication of IVC involvement. Preoperative tumour embolisation has also frequently been used in highly vascular, large renal cancers, within 24 h prior to resection. When a vascular thrombus is present, some surgeons believe embolisation may help reduce thrombus bulk and ease removal.

2.4. Clinical scenario summary

Standard treatment for a patient with RCC and IVC involvement is radical nephrectomy with thrombectomy. This is reflected in an audience poll in a meeting of 746 specialists [6], which revealed that most respondents (64% of urologists, 50% of radiation oncologists, 100% of medical oncologists, and 100% of clinical oncologists) would recommend a nephrectomy with thrombectomy for this patient. The patient actually underwent embolisation followed by surgery but a positive lymph node was identified after surgery and the patient died within 6 mo.

3. Clinical scenario II: a patient with metastatic RCC

The initial presentation of the patient in the second clinical scenario is shown in Box 2.
3.1. Immunotherapy treatment options for patients with metastatic RCC

The patient in the second clinical scenario has a poor prognosis and positive lymph nodes. The experience of one large institution in treating >300 patients with metastatic RCC suggests that the presence of positive lymph nodes is a significant predictor of failure to respond to immunotherapy treatment [14]. At this institution, objective response with adjuvant IL-2–based immunotherapy was 30% in node-negative patients and 11% in node-positive patients. However, median survival in patients with negative or positive lymph node status more than doubled following treatment with adjuvant immunotherapy (28 and 10.8 mo in patients with negative and positive lymph nodes, respectively) compared with no adjuvant immunotherapy (12 and 4.5 mo, respectively).
For most patients with metastatic disease, tumour nephrectomy is palliative and other systemic treatments are often necessary. IL-2, which is approved for patients like the one in this clinical scenario, and IFN-α have yielded response rates of 10–20% and although long-term survival is only achieved in a few patients, these responses are clearly superior to chemotherapy [5]. Other interleukins (IL-4, IL-6, and IL-12) have limited activity.

A clinical standard for this metastatic patient would be to combine nephrectomy with immunotherapy. Two randomised controlled trials, the Southwest Oncology Group (SWOG) trial 8949 [15] and the European Organisation for Research and Treatment of Cancer (EORTC) trial 30947 [16] investigated whether nephrectomy performed prior to treatment with IFN-α2b prolonged overall survival compared with IFN-α2b alone. Both trials recruited previously untreated patients with metastatic RCC and good performance status. After about 1 yr of follow-up, patients undergoing nephrectomy and receiving IFN-α2b survived approximately 3 and 10 mo longer than patients receiving IFN-α2b alone in the SWOG and EORTC trials, respectively. As would be expected, the best results were achieved in patients with low-volume, pulmonary metastatic disease and a good performance status.

3.2. The role of lymphadenectomy

There is no accepted standard approach for the management of lymph nodes at the time of nephrectomy. A number of studies found no difference in survival between patients who had no or limited lymph node dissection for all stages of RCC [17–19]. Other studies found no difference in survival for low-risk patients but demonstrated a survival advantage for high-risk patients and/or patients with metastatic disease treated with lymphadenectomy [20,21].

A retrospective analysis of the National Surveillance, Epidemiology and End Results database reviewed the impact of lymphadenectomy and nodal burden in patients with RCC and it was concluded that extensive lymphadenectomy does not appear to improve the cancer-specific survival rate for patients undergoing radical nephrectomy for RCC [22]. The role of lymphadenectomy as a therapeutic option in a patient with RCC and lymph node metastases is unclear and further research is required before routine lymphadenectomy can be justified.

3.3. Novel, targeted agents for the treatment of metastatic RCC

Most patients with RCC have clear-cell histology and this develops particularly in patients with genetic alterations within the von Hippel-Lindau tumour suppressor gene (VHL) [23]. Inactivation of the VHL gene can result in accumulation of hypoxic-inducible factor, which, in turn, leads to the activation of several pathways that facilitate the progression of RCC (Fig. 5). Multiple blockade of vascular endothelial growth factor and platelet-derived growth factor with oral multitargeted tyrosine kinase inhibitors has the potential to suppress tumour growth. Two tyrosine kinase inhibitors, sunitinib and sorafenib, are approved by the Food and Drug Administration in the United States for the treatment of metastatic RCC.

![Fig. 5 - Molecular pathophysiology of clear-cell renal cell cancer (RCC). Inactivation of the tumour suppressor gene von Hippel-Lindau (VHL) results in an absence of VHL gene product, pVHL. Cells lacking pVHL accumulate high levels of hypoxic-inducible factor (HIF), which is known to activate several pathways that facilitate the progression of RCC through angiogenesis (mediated by vascular endothelial growth factor [VEGF] and platelet-derived growth factor [PDGF], through erythropoietin, a glycoprotein hormone that increases red cell production, and increased metabolism in Glut-1 and transforming-growth factor [TGF]-α stimulation of autocrine growth).](image-url)
A phase 3 international trial involving 746 patients with advanced clear-cell carcinoma demonstrated that sunitinib as a first-line treatment improved progression-free survival and was well tolerated when compared with the standard care of IFN-α [24]. Progression-free survival was 47 wk for the sunitinib group compared with 25 wk for the IFN-α group; response rates were 25% and 5% for the sunitinib and IFN-α groups, respectively. In a pivotal study of sorafenib, the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET), 905 patients with advanced RCC were randomised to receive sorafenib or placebo [25]. In TARGET, progression-free survival was 5.5 mo with sorafenib versus 2.8 mo with placebo, an approximate 50% reduction in risk. As yet, there is no significant improvement in overall survival. Based on encouraging findings from these trials, these novel agents are being integrated into multiple experimental approaches for the treatment of metastatic RCC.

Additional agents such as axitinib (AG013736) and AZD2171 are also under investigation. Axitinib is a novel small-molecule inhibitor of the tyrosine kinase portion of the vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptors. In a phase 2 trial, axitinib has demonstrated activity in cytokine-refractory, metastatic RCC (n = 52) with a response rate of 46% [1,26]. Therapy was well tolerated with manageable toxicity. Treatment-related grade 3/4 adverse events included hypertension (12%), aggravated hypertension (6%), diarrhoea (6%), fatigue (6%), and limb pain (4%); 6% of patients discontinued treatment as a result of an adverse event. A phase 2 study is ongoing to determine the activity and efficacy of axitinib in patients with advanced/refractory RCC who previously failed sorafenib-based therapy [1,27]. AZD2171 is a selective, reversible tyrosine kinase inhibitor of VEGF receptors 1, 2, and 3. One ongoing multicentre phase 2 study in patients with advanced/refractory RCC is evaluating AZD2171 in terms of objective response rate and safety [28].

3.4. Clinical scenario summary

The second clinical scenario describes a patient with a poor prognosis and positive lymph nodes. In this situation, many clinicians would opt for radical nephrectomy plus adjuvant therapy. For example, in a meeting of 746 specialists [6], an audience poll revealed that 69% of respondent urologists, 43% of respondent radiation oncologists, and 50% of respondent clinical oncologists would recommend a radical nephrectomy plus adjuvant therapy for the patient described in this clinical scenario. EAU guidelines recommend tumour nephrectomy combined with IFN-α for metastatic RCC patients with good performance status [12].


The initial presentation of the patient in the final clinical scenario is outlined in Box 3.

4.1. Supportive care in patients medically unsuitable for nephrectomy

Nephrectomy is a major surgical procedure and carries a significant risk (11–40%) of morbidity [29]. The patient described in this clinical scenario was obese, had several different comorbidities and renal failure, and had previously received warfarin. Given her history, the patient would most likely require dialysis and be at significant risk of morbidity if she were to undergo surgery, so it is important to consider alternative management strategies.

Supportive care is an option, although there are only limited data available on the natural history of renal tumours as most are removed soon after diagnosis (Table 1) [30]. In one study that represents the largest published cohort of patients treated conservatively (patients were either unfit or unwilling to undergo radical nephrectomy and were not offered alternative therapies), no patient proceeded to nephrectomy [31]. In the study, 36 patients (mean age, 76.1 yr) who were treated conservatively were identified from a database of 421 patients with RCC.

### Box 3. Presentation of patient in clinical scenario III

- 62-yr-old obese woman with gross haematuria and other urinary symptoms (frequency, urgency, dysuria, and occasional suprapubic discomfort with voiding).
- Previous frequent smoker.
- Patient had right nephrectomy 30 yr earlier for stone disease.
- Patient had previous diagnoses of osteoarthritis, peptic ulcer disease, atrial fibrillation (previously received warfarin for 8 mo), and cerebrovascular accident.
- Noncontrasted computed tomography (CT) of the abdomen and pelvis (Fig. 6) revealed a 6-cm left anterior lower-pole renal mass in a nodular kidney.
- Haematocrit 27.5, platelets 480, liver function test normal, creatinine 1.6 mg/dl, calcium 7.4, chest CT and x-ray both negative.
- Patient developed acute renal failure (creatinine 5.0 mg/dl), was rehydrated, and creatinine level reduced to 3.9 mg/dl.
Median follow-up was 24 mo and, of the 36 patients, 13 died, 8 of an unrelated illness and 5 of an unknown cause with no radiologic evidence of progression but severe comorbidity. This study in particular highlights that using a conservative, symptomatic approach in the management of selected patients, namely, the elderly or those with severe comorbidity, has little or no impact on life expectancy.

Table 1 – Clinical data for patients who have received supportive care as primary treatment of RCC [30]

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of lesions</th>
<th>Mean lesion size, cm</th>
<th>Mean tumour growth, cm/yr</th>
<th>Mean follow-up interval, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosniak</td>
<td>1995</td>
<td>40</td>
<td>1.68</td>
<td>0.36</td>
<td>39</td>
</tr>
<tr>
<td>Oda</td>
<td>2002</td>
<td>16</td>
<td>2.0</td>
<td>0.54†</td>
<td>25</td>
</tr>
<tr>
<td>Kassouf</td>
<td>2004</td>
<td>29</td>
<td>3.27</td>
<td>0.49</td>
<td>32</td>
</tr>
<tr>
<td>Volpe</td>
<td>2004</td>
<td>32</td>
<td>2.48</td>
<td>0.10</td>
<td>35</td>
</tr>
<tr>
<td>Wehl</td>
<td>2004</td>
<td>29</td>
<td>1.83</td>
<td>0.12</td>
<td>32</td>
</tr>
<tr>
<td>Kato</td>
<td>2004</td>
<td>18</td>
<td>1.98</td>
<td>0.42</td>
<td>27</td>
</tr>
<tr>
<td>Chawla and Uzzo</td>
<td>2004</td>
<td>34</td>
<td>3.08</td>
<td>0.21</td>
<td>34</td>
</tr>
</tbody>
</table>


† Median lesion size.
In the absence of other prognostic factors, tumour growth measurement can be beneficial for initial conservative management of selected patients with small renal tumours [32], with no patient progressing to metastatic disease in the series.

4.2. Radical, partial, or laparoscopic partial nephrectomy?

Partial nephrectomy (nephron-sparing) is an effective treatment for RCC in selected adult patients and compared with radical nephrectomy there is no difference in cancer-specific survival for patients with single, small, and clearly localised tumours (T1 tumours) [33,34]. Furthermore, in patients with tumours ≤4 cm in diameter, cancer-specific survival following partial nephrectomy is significantly better than in those patients with larger tumours [35,36]; although no randomised clinical trial has shown that partial nephrectomy is superior to radical nephrectomy, retrospective data suggest that there is no difference in cancer-specific outcomes. The ongoing EORTC 30904 study is expected to clarify whether there is any difference in outcome between these two approaches. Our patient had a larger tumour of 6 cm; therefore, if surgery were possible, the prognosis for our patient would not be as favourable as that for a patient with a smaller tumour.

Laparoscopic partial nephrectomy is now a recognised viable alternative to open partial nephrectomy, although most of the data available in the literature come from one single institution. Data from the Cleveland Clinic Foundation were collected prospectively from 500 laparoscopic partial nephrectomies [37]. In the first 100 patients with a minimum of 3 yr of follow-up, overall survival was 86% and cancer-specific survival 100%. However, data are limited in the high-risk population of patients with a tumour in their only remaining kidney (as in the clinical scenario). The largest study of this type reported in the literature involved 22 patients undergoing partial laparoscopic nephrectomy for a tumour in a single kidney [38]. At a median follow-up of 2.5 yr, overall survival was 91% and cancer-specific survival was 100%. Although laparoscopic partial nephrectomy can be performed effectively and safely in selected patients with a tumour in a single kidney, any such surgery for the patient in the clinical scenario presented here would be deemed to be high risk in terms of postsurgical morbidity. Such surgery in this scenario is best performed open because complication rates tend to be lower. Even for renal masses smaller than that presented in this clinical case, laparoscopic partial nephrectomy is typically limited to carefully selected patients in selected centres.

4.3. Cryoablation or radiofrequency ablation?

When surgery may not be an option and there is a preference for a “treatment approach,” there is a growing body of literature demonstrating that, when properly applied, ablation technologies such as cryoablation and radiofrequency ablation are effective in the local control of RCC. Rather than surgically removing tumours, ablation aims to destroy them in situ. In a retrospective study of 48 patients undergoing renal cryoablation, with a 64-mo median follow-up, median lesion size was 2.6 cm and 12.5% of patients were diagnosed with persistent disease during the follow-up period [39]. After a single cryoablation procedure, the cancer-specific survival rate was 100% and the cancer-free survival rate was 87.5%. Cancer-free survival improved to 97.5% after a repeat procedure, suggesting that cryoablation of renal neoplasms can lead to acceptable long-term disease-free survival. Radiofrequency ablation has also been shown to have a high success rate [40,41], but it should be noted that ablation procedures are generally restricted to small tumours of <5 cm in diameter. Therefore, for the patient in the clinical scenario described here, ablation (cryoablation or radiofrequency) is probably not a valid treatment approach. It is important to monitor ablation outcomes carefully via radiography and to take into account the learning curves involved with these investigational approaches, because they can affect clinical outcome.

4.4. Clinical scenario summary

For patients unsuitable for surgery, alternative management strategies have to be considered. Supportive care appears to be an option particularly in the elderly or those with severe comorbidity. However, in a meeting of 746 specialists [6], an audience poll revealed that only 2% of respondents would recommend this approach in the described clinical scenario. Most respondents (65%) would recommend a partial nephrectomy; this included 66% of respondent urologists, 100% of respondent radiation oncologists, and 33% of clinical oncologists. Ablation technologies can provide benefit in patients with tumours <5 cm but in this clinical scenario, where the tumour was 6 cm, the patient received supportive care following discussion of all potential options and outcomes.

5. Conclusions

Surgery is the most effective treatment option for patients with nonmetastatic, localised RCC and
patients with low-stage, low-grade tumours have a favourable long-term prognosis. Advances in partial nephrectomy make this surgical approach attractive for patients with low-risk RCC and, with improvements in technology, less-invasive techniques involving laparoscopy are now established as valid treatment options. Active surveillance of small renal masses, with delayed therapy for patients whose disease progresses, is an experimental approach that can be considered for the elderly or patients with significant comorbidity. For patients with large tumours, regional lymph node involvement, or IVC tumour thrombus, complete tumour resection can be challenging and, in a significant number of patients, surgical resection alone is not sufficient to prevent disease recurrence or progression. To date, adjuvant therapies have been largely ineffective, although IL-2 is approved in selected patients. In the past decade, an increased understanding in the biologic mechanisms that contribute to oncogenesis have led to the development of promising new targeted agents that may have a future role in the management of patients with RCC.

Conflicts of interest

Professor Thomas Keane is a member of the Speakers’ Bureau for Cytogen, AstraZeneca, Auxillium and Sanofi. He is a consultant for Valera and Auxillium and has received a research grant from Cytogen. Mr David Gillatt has worked as a paid consultant and attended advisory boards for AstraZeneca. Dr Christopher Evans has no conflict of interest with respect to this article. Professor Andrea Tubaro is a consultant for Astellas. He has attended advisory boards for Novartis and Pfizer and has been a speaker for AstraZeneca.

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