Locally advanced renal cell carcinoma

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Abstract

Despite the observed stage migration and earlier detection of renal masses, patients still present with locally advanced renal cell carcinoma. These patients represent a difficult oncologic challenge. Despite our ability to do surgical resection to cure the disease, survival often remains limited. In this paper, we describe the role and indication for surgical resection for patients with enlarged retroperitoneal lymph nodes, invasion of adjacent organs, invasion into the vena cava or locally recurrent disease. The development of new strategies, including effective drugs to be used in association with surgical resection, will clearly be an essential step to further improve the outcome of these patients.

Renal cell carcinoma (RCC), one of the most lethal urologic cancers, accounts for 3% of all adult malignancies, and more than 40% of patients with RCC will die of their disease. Surgery remains the most curative treatment option for patients with localized RCC. Pathological stage, tumour grade and lymph-node status are independent predictors of progression-free and overall survival in patients with RCC. Patients with low-stage and low-grade RCC tend to have a more favourable outcome than patients presenting with metastatic disease. This finding remains true, despite the use of a combination of aggressive surgical resection and immunotherapy or, more recently, targeted therapy. Patients with locally advanced RCC also have a significant risk of disease recurrence and progression, despite complete surgical resection. Included in this category of locally advanced RCC are patients with inferior vena cava (IVC) involvement, extension to adjacent organs (stage T4) retroperitoneal lymph-node involvement and local recurrence after radical surgery. In this paper, we review the outcome of patients with locally advanced RCC and the role of surgery in these challenging patients.

IVC involvement

Tumour thrombus extending into the IVC occurs in 4%–10% of patients with RCC. Aggressive surgical resection with radical nephrectomy and IVC thrombectomy can potentially cure up to 70% of these patients (Table 1).

A number of pathological factors help predict the outcomes of patients with RCC and IVC thrombus. Tumour confined to the kidney and free-floating tumour thrombus have good prognoses, whereas perinephric fat invasion, lymph-node involvement and caval-wall invasion are associated with a poor prognosis.

For many years, the level of tumour thrombus extension was associated with the prognosis of patients with pT3b RCC. Although this factor may play an indirect role in reflecting the local extent of the tumour, local extension, more than thrombus length, predicts postoperative recurrence. Sweeney and colleagues demonstrated the impact of local extension with invasion of perinephric fat on patients with pT3b RCC. In their review, the median survival of patients with IVC involvement decreased from 33 months to 10 months if they had perinephric fat invasion. Similar findings were reported by both Ficarra and Artibani and Thompson and colleagues who concluded that perinephric fat invasion had an independent prognostic impact on the cancer-specific survival of patients with IVC involvement. This factor seems to have a greater impact on disease-specific survival than the level of IVC thrombus. Both authors proposed that stage pT3 RCC be reclassified to include invasion of perinephric fat as an independent factor and that this be incorporated in the pT3 TNM staging system so that patients could be better stratified, relative to their real risk for recurrence of the disease.

The prognostic significance of the cephalad extent of the IVC thrombus has been a source of controversy. Most series suggest that the incidence of either local or systemic progression is higher in patients with level III or level IV IVC thrombus. Many authors associated this finding with reduced survival. Other reports, however, suggest that patients with level IV IVC thrombus can be cured with surgical resection, provided that the tumour is otherwise confined to the kidney.
Surgical planning remains an integral and important part of the management of RCC with IVC involvement. Accurate staging of the extent of IVC thrombus is essential to properly plan the surgical approach (Fig. 1). Therefore, imaging plays a crucial role. Traditionally, a CT scan was used to diagnose renal vein and IVC thrombus, but a CT scan was often limited in its ability to accurately define the cephalad extent of the thrombus. Transesophageal echocardiography, transabdominal colour flow Doppler ultrasonography or cavography have been used as complementary imaging modalities, when needed, to define the exact extent of renal vein or IVC involvement. MRI is an accurate diagnostic tool for the delineation of the cephalad extent of the tumour thrombus; however, recent data suggest that multiplanar CT scan may approach the accuracy of MRI for identification and characterization of IVC thrombus. Although contrast venography is highly accurate, its invasive nature precludes its use; it is now reserved for the rare cases in which MRI or a CT scan would be contraindicated or equivocal.

### Table 1. Five-year survival for patients with RCC and IVC thrombus

<table>
<thead>
<tr>
<th>Authors (and date)</th>
<th>No. of patients</th>
<th>M0, %</th>
<th>M1, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novick et al(^{11*}) (1990)</td>
<td>43</td>
<td>64</td>
<td>11</td>
</tr>
<tr>
<td>Swierzewski et al(^{12}) (1994)</td>
<td>100</td>
<td>64</td>
<td>20</td>
</tr>
<tr>
<td>Quek et al(^{13}) (2001)</td>
<td>99</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>Zisman et al(^{14}) (2003)</td>
<td>100</td>
<td>72</td>
<td>N/A</td>
</tr>
<tr>
<td>Blute et al(^{15}) (2004)</td>
<td>191</td>
<td>59</td>
<td>15</td>
</tr>
</tbody>
</table>

RCC = renal cell carcinoma; IVC = inferior vena cava; M0 = no metastasis; M1 = distant metastasis; N/A = not available.

*3-year survival.

The surgical approach to patients with IVC involvement is mostly dictated by the cephalad extent of the thrombus. The choice of incision (midline, subcostal or chevron) remains the preference of the individual surgeon. Surgical techniques include mobilization of the kidney and early ligation of the arterial blood supply to the kidney. This initial manoeuvre often results in a reduction of the size of the tumour thrombus, facilitating the rest of the surgery. To properly control the involved portion of the IVC for patients with level I and II thrombus, ligation of all lumbar veins, followed by sequential clamping of the caudal IVC, contralateral renal vein and cephalad IVC, is required. The renal vein ostium is then opened and excised to extract, en bloc, the tumour thrombus. For patients with level III caval thrombus, mobilization of the caudate lobe of the liver allows exposure and access to the infrahepatic IVC. This manoeuvre provides access to the cephalad extent of the thrombus and allows the surgeon to safely clamp the IVC below the hepatic veins. If the thrombus extends above the hepatic veins and below the diaphragm, a liver transplant technique with complete liver mobilization, as described by Ciancio and others, will safely expose the hepatic veins. This manoeuvre facilitates mobilization and exposure of the entire infradiaphragmatic IVC and allows safe excision of more extensive tumour thrombus. A Pringle manoeuvre and selective occlusion of the hepatic veins may be necessary, with control of the IVC above the liver.

In patients with level IV tumour thrombus, cardiopulmonary bypass with or without hypothermic circulatory arrest has been used to facilitate excision of the tumour thrombus. This approach allows safe excision of extensive tumour thrombus, but is associated with increased risk of coagulopathy, cerebrovascular accidents and myocardial infarction.

Preoperative renal angiography and embolization is practised in some centres when tumour thrombus shows distinct vascularity. This approach often reduces the size of the tumour thrombus and venous pressure within the kidney and tumour, and may facilitate surgical excision of the renal tumour and thrombus. This approach will occasionally reduce the size of the tumour thrombus from level III to II, or from level IV to III. This reduction can therefore facilitate tumour resection and may limit surgical morbidity.

**Fig. 1.** Clinical staging of tumour thrombus.
In cases in which the tumour thrombus invades the wall of the vena cava, aggressive resection of the caval wall to achieve negative surgical margins is necessary to avoid local recurrence and improve survival. When complete occlusion with absence of flow in the IVC is present before surgery, en bloc resection with ligation of the IVC may facilitate complete tumour excision and limit the chance of leaving residual disease in areas with unrecognized tumour invasion into the wall of the vena cava. IVC grafting or reconstruction may be required in some cases to avoid partial caval occlusion after extended resection of part of the IVC. Radical nephrectomy with IVC thrombectomy, however, remains a morbid procedure; since operative mortality rates are 5%–10%, patients must be carefully selected for this procedure.

**Locally invasive RCC (T4 disease)**

On rare occasions, RCC occurs with direct invasion into adjacent organs (T4 disease). Liver, spleen, colon, pancreas, diaphragm and duodenum are usually compressed by the RCC and rarely invaded because these tumours are often encapsulated. Invasion of adjacent organs is usually associated with poor prognosis. Pain often occurs when the RCC invades the posterior abdominal wall or nerve roots. The poor prognosis associated with pT4 disease is also frequently associated with grade or performance status. In fact, Lam and colleagues, using the University of California Los Angeles integrated staging system, or UISS, classified T4 RCC in their high-risk group, with a median time to recurrence of only 9.5 months, regardless of grade or performance status. These reports reinforce the clinical behaviour of these advanced cancers that generally have a poor prognosis and require close follow-up for timely treatment.

An aggressive surgical approach with en bloc resection of involved adjacent organs is the only potentially curative treatment. Nearly 90% of patients with pT4 RCC died of disease progression within 1 year if they were treated with incomplete resection or debulking. However, understanding of the biology and natural history of these locally advanced cancers is based on a very limited number of small retrospective series of patients with T4 disease. These clinical series described a limited 5%–18% 5-year survival.

The role of radiation therapy for locally invasive RCC remains unclear. Stein and others suggested that adjuvant radiotherapy was beneficial. However, subsequent studies that randomized patients with locally advanced RCC to either adjuvant radiotherapy or observation have shown no survival benefit of adjuvant radiotherapy and potential nonnegligible gastrointestinal morbidity. Obviously, an effective adjuvant treatment strategy is required for this patient population. So far adjuvant cytokine therapy has failed to demonstrate a benefit. New studies are being done to evaluate the potential benefit of tyrosine-kinase inhibitors as an adjuvant therapy for this high-risk patient population. Until an effective treatment strategy with survival benefit is identified, early diagnosis with aggressive and complete surgical resection remains the best therapeutic option for these patients.

**Regional lymph-node dissection**

Regional lymph-node metastasis in patients with RCC is associated with a poor prognosis and decreased survival. Unlike some other genitourinary cancers, the lymphatic drainage of the kidneys is not accurately defined. Debate about the potential benefits of routine regional and extended lymph-node dissection continues. In recent years, lymph-node dissection for urologic cancers has been revisited; many centres are now proposing more extensive dissection for diseases such as bladder cancer to improve cancer control. Urologists are very familiar with the therapeutic benefit of lymph-node dissection for the management of testes and penile cancers. The European Organization for Research and Treatment of Cancer’s trial (EORTC 30881) prospectively examined the impact of routine lymph-node dissection at the time of nephrectomy. Only 3.3% of patients had unsuspected lymph-node metastasis identified by routine lymph-node dissection. Given the low incidence of nodal metastasis undetected by preoperative imaging studies, the preliminary findings of this trial failed to support the benefit of routine lymphadenectomy at the time of nephrectomy. In a retrospective review, Pantuck and colleagues also failed to demonstrate a difference in either local or distant recurrence-free survival for patients who underwent routine lymphadenectomy at the time of nephrectomy.
The ability to further select patients at high risk of nodal metastasis would allow proponents of lymph-node dissection to better identify patients likely to benefit from this approach. Blute and colleagues identified risk factors that predicted lymphatic involvement in patients with RCC. These factors included the presence of a high Fuhrman grade, sarcomatoid component, histologic tumour necrosis, tumour size larger than 10 cm and pathological stage T3 or T4 disease. The incidence of lymph-node involvement in their series increased to 10% if 2 or more of these factors were present, but was only 0.6% when fewer than 2 factors were identified. Although many reports do not support routine lymph-node dissection, Canfield and others evaluated 54 patients with N+M0 disease and concluded that patients with N1 disease survived significantly longer than those with N2 disease (median 37.5 mo and 14.5 mo, respectively), suggesting a potential benefit of lymph-node dissection in this rare clinical presentation of patients with metastasis to a single lymph node. If hilar lymph nodes are the first level of metastasis, a properly executed radical nephrectomy that includes the hilar and adjacent paracaval or para-aortic lymph nodes could provide a potential curative benefit. Currently, however, the need for routine extended lymphadenectomy for all patients is not justified.

Although the role of lymph-node dissection in clinical N0 disease remains limited, patients with metastatic disease undergoing cytoreductive nephrectomy may have a different clinical outcome. Pantuck and others demonstrated a benefit of complete excision of lymph nodes for patients with metastatic disease who were undergoing cytoreductive nephrectomy. This finding reinforces the role and potential clinical benefit of aggressive surgical resection for patients undergoing cytoreductive nephrectomy. At least in this limited clinical presentation, retrospective data support the potential benefit of extended lymph-node dissection to completely remove all retroperitoneal disease.

**Local recurrence after treatment of RCC**

Local recurrence of RCC after radical nephrectomy remains a rare event. Published series report that between 2% and 4% of patients with RCC will develop a local recurrence after radical nephrectomy. Stephenson and others reported a 1.6% incidence of local recurrence among 495 patients who underwent a radical nephrectomy. Of these 495 patients, only 0.6% had an isolated local recurrence without systemic disease. These findings were similar to those of most reported series in which the majority of patients with local recurrence also had systemic disease at diagnosis; only 40% of patients had true isolated local recurrences. Few pathological features have been proposed as risk factors that predict an increased risk of local recurrence of the disease. These include increasing T stage or node-positive disease in some, but not all, series. Many series clearly identified the presence of locally recurrent disease in all pathological stages.

Not all patients with locally recurrent disease will be symptomatic at presentation. The presence of symptoms leading to the discovery of a local recurrence varies widely from 7% to 73%. Most authors would agree that a large proportion of patients diagnosed with an isolated local recurrence were detected during routine abdominal imaging. The majority of the published series are limited by small numbers of patients and retrospective analysis; however, Schroder and others and Master and others were able to identify a correlation between the time to recurrence and the likelihood of surviving this disease. In both series, the subset of patients who died had a mean time to recurrence of 16 months, compared with 79 and 83 months for patients who survived. These findings reinforce the well-known heterogeneity of the characteristics of RCC and its clinical behaviour.

Currently, treatment of locally recurrent disease in the absence of systemic disease should be surgical resection. An aggressive surgical resection can provide up to 30% 5-year disease-free survival. However, complete surgical resection with negative surgical margins is crucial and en bloc resection of adjacent organs should be done to achieve this goal. Both Tanguay and others and Sandhu and others confirmed that positive surgical margins indicate a poor prognosis and will negatively influence local and distant disease-free survival. These findings reinforce the importance of proper planning for surgery, during which urologists must be ready to proceed with wide excision and resection of adjacent organs to achieve complete surgical resection of the
tumour with negative margins. Failing to do so will likely result in recurrent disease and decreased survival. It is not surprising, then, that most published series report complication rates ranging from 18% to 47%. Although many of the published reports support the potential benefit associated with an aggressive surgical approach, the role of either systemic therapy or radiation therapy remains to be defined. So far, most authors report that disease control with both treatment modalities used alone is reduced. However, this finding may be the result of the retrospective nature of this reported experience and the bias associated with patient selection and referral for possible surgical resection. Radiation therapy may be of value for palliation of symptomatic local recurrence for patients who are not surgical candidates.

Local recurrence after nephron-sparing surgery for RCC has been reported for 1.4%–10% of patients. The main risk factor is advanced T stage disease. Most local recurrences after partial nephrectomy are likely the result of unrecognized tumour multicentricity or new tumour development, rather than a true failure of treatment. Patients with an isolated local recurrence after partial nephrectomy should be treated as if they have a new RCC, with either repeated partial nephrectomy, ablative therapies or completion nephrectomy.

**Conclusion**

Locally advanced RCC remains a challenge for urologists. However, all the tools developed and our better ability to predict outcomes for our patients can be used to select patients for whom novel therapeutic agents can potentially play a role. Many patients with tumour thrombus extending into the IVC or invasion into adjacent organs are destined to have recurrence of their disease. With the development of new therapeutic targets, adjuvant regimens will likely emerge as viable options for our patients.

The role of regional lymph-node dissection has also been debated over the years. Clearly, in the absence of radiological or clinical enlargement of lymph nodes, routine lymphadenectomy at the time of nephrectomy has no role. Complete lymphadenectomy may have a role in the treatment of patients with limited lymph-node involvement or during cytoreductive nephrectomy. In conclusion, the clinical outcome of patients with locally advanced RCC can be further improved, and combined approaches may offer benefit in the future.

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This article has been peer reviewed.

**Competing interests:** None declared.

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