Treatment of Locally Advanced Renal Cell Carcinoma

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Abstract

Context: Locally advanced renal cell carcinoma (RCC) is associated with a poor prognosis despite radical surgery. The surgical approach can differ according to tumour size, location, and vascular involvement. The development of molecular targeted therapies aroused new interest in adjuvant and neoadjuvant strategies.

Objective: The aim of this article was to review trends in surgical approaches for locally advanced RCC as well as to discuss the role of targeted therapies in an adjuvant and neoadjuvant setting.

Evidence acquisition: A PubMed search performed in September 2011 was used to identify relevant literature regarding locally advanced RCC.

Evidence synthesis: An aggressive surgical approach is essential in locally advanced RCC. Nevertheless, the necessity of simultaneous ipsilateral adrenalectomy and extended lymphadenectomy in RCC is put into question. The presence of a tumour thrombus in the inferior vena cava requires special surgical techniques for thrombus control. The role of adjuvant and neoadjuvant molecular targeted therapies is investigated in ongoing trials. Phase 3 results of an adjuvant tumour cell vaccine are promising.

Conclusions: Radical surgical resection remains mandatory in locally advanced RCC. The role of adjuvant and neoadjuvant therapy in these patients remains unknown until the data from ongoing trials become available.

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1. Introduction

Renal cell carcinoma (RCC) represents approximately 2–3% of all malignant diseases [1]. The incidence is highest in Western countries, whereas the lowest rates are reported in Asia and Africa [1]. The estimated incidence of RCC in Europe was 71 600 cases, with a mortality rate of 31 000 deaths in 2008 [2]. In Europe, the incidence has steadily risen over the past decades [3].

Locally advanced RCC is defined by the TNM classification as stage T3 and T4, with involvement of the renal vein, vena cava, peripelvic and perirenal fat, adrenal gland, or invasion beyond Gerota’s fascia [4]. In a large prospective analysis by Karakiewicz et al. [5], including 3907 patients with RCC, 32.1% presented with stage T3 and 1.7% with stage T4 disease.

There is no doubt that the treatment of choice for locally advanced RCC is surgery because of significantly increased cancer-specific survival (CSS) [6,7]. Nevertheless, the prognosis of locally advanced RCC is poor [8,9]. Despite radical nephrectomy (RN), there is a significant risk of recurrence and progression in comparison to localised RCC. The estimated 10-yr CSS rates are 80–96%, 55–66%, 36%, 26%, 25%, and 12% for patients with a primary tumour classification of pT1, pT2, pT3a, pT3b, pT3c, and pT4, respectively [10]. Considering these results, there is a need for proper adjuvant therapy as well as a neoadjuvant approach in cases where surgery is challenging.
The development of molecular targeted therapeutics in RCC has changed the standard care for patients with metastatic disease. Their superiority over immunotherapy is proven [11,12,13,14], but the role of adjuvant and neoadjuvant targeted therapy in locally advanced RCC remains unclear. A tumour cell vaccine has already shown positive effects in adjuvant therapy [13]; phase 3 trials in adjuvant targeted therapies as well as phase 2 trials in neoadjuvant targeted therapies are mainly pending.

Radiation has no significance in therapy for advanced RCC because of the disease’s resistance to radiation. Studies investigating adjuvant and neoadjuvant radiation in advanced RCC did not show an improvement in overall survival (OS) or disease-free survival (DFS) [14,15].

2. Radical nephrectomy

The gold standard of treatment for locally advanced renal tumours is RN [8,16–18]. Improved outcome using a standardised surgical procedure was first described by Robson et al. [19]. According to this standardised technique, RN consists of removing the kidney, including perinephritic fat, Gerota’s fascia, the adrenal gland, as well as extensive lymphadenectomy of the para-aortic and paracaval nodes from the diaphragm to the bifurcation of the aorta [19]. But with a consistent, limited prognosis of locally advanced RCC, the radicalism of this approach, which is associated with significant morbidity, has been questioned. Consequently, different adaptations of the classical technique have been introduced and investigated.

2.1. Adrenalectomy

Routine ipsilateral adrenalectomy has been part of RN since the procedure was first described by Robson et al. [19]. Locally advanced tumour stage and upper-pole tumour are recognised as risk factors for adrenal gland involvement [20]. Nevertheless, the incidence of ipsilateral adrenal involvement is rare at 1–5% [20–22]. Even in patients with high-risk features such as locally advanced tumours with tumour thrombus or upper-pole tumour, the frequency of ipsilateral adrenal involvement is \( \leq 10\% \) of cases [21].

The involvement of the adrenal gland is associated with a significantly decreased survival rate and often accompanied by distant metastasis [4]. In a retrospective analysis of 1087 patients who underwent nephrectomy, 27 patients were identified as having adrenal involvement. These patients had a median survival of 12.5 mo, with a 0% 5-yr-survival rate [23]. This poor prognosis was included in the new TNM classification of 2009 and categorised the adrenal gland involvement as T4. In contrast, routine ipsilateral adrenalectomy in locally advanced RCC does not seem to improve CSS [20,21,24]. Furthermore, asynchronous adrenal metastasis is just as likely to occur in the contralateral gland as in the ipsilateral adrenal gland [21]. Weight et al. [21] concluded that if the rationale of resecting the ipsilateral adrenal gland were to remove micrometastasis, the contralateral adrenal gland should be removed, as well. In addition, routine removal of the ipsilateral gland puts the patient in risk for adrenal insufficiency if asynchronous contralateral adrenal gland metastasis occurs [21]. Therefore, the authors suggested preserving the adrenal gland unless adrenal gland involvement is suspected on computed tomography (CT) scans or surgical aspect. Sawai et al. [25] were able to demonstrate that CT can rule out adrenal involvement in most cases.

The preservation of the adrenal gland in the absence of CT-observed morphologic or macroscopic invasion should be taken into consideration. If the adrenal gland has to be removed unilaterally, there is no proof of hormonal disadvantages for the patient [26]. If asynchronous contralateral adrenal gland metastasis occurs, the patient has a risk of adrenal insufficiency.

2.2. Lymphadenectomy

The role of lymph node dissection (LND) in locally advanced RCC remains uncertain. The only randomised prospective trial investigating whether to perform RN with or without LND did not show any survival advantage [27]. However, the trial has been criticised because it included preferably low-stage tumours with a negligible risk for nodal involvement [28].

In a retrospective analysis of 1087 patients, 129 (14%) patients presented with lymph node metastases [29]. The incidence of patients presenting with regional nodal metastases in the absence of distant disease was \(<5\%\). Lymph node metastases were correlated to higher T-stage, younger age, and larger primary tumour, and patients were more likely to have metastatic disease. Regarding survival rates, there was a significant benefit for patients with lymph node metastases who underwent LND and adjuvant immunotherapy. Giuliani et al. [30] even reported a 5-yr survival rate of 52% after RN with LND in patients with metastatic lymph node involvement.

There is a lack of standardisation of LND in RCC, and the lymph drainage of RCC remains unpredictable. Crispen et al. [31] analysed dissected lymph nodes from 169 high-risk patients in which 38% presented lymph node metastases. Based on the recorded localisation of lymph node metastases, the authors recommend removing the paracaval and interaortocaval lymph nodes in patients with right-sided tumours and the para-aortic and interaortocaval lymph nodes in patients with left-sided tumours. The available evidence suggests that extended lymphadenectomy in patients with locally advanced RCC might be beneficial when technically feasible.

2.3. Involvement of adjacent organs

In the series from Robson et al. [19], 9.1% of all patients with locally advanced RCC had an invasion of adjacent organs. Today, large retrospective series report a 1.7–15.0% incidence of pT4 RCC, the majority of which were associated with synchronous metastases [5,17,18]. When the tumour involves adjacent organs, radical en bloc resection is mandatory. In case of positive surgical margins, the risk of local recurrence or distant metastasis is high [8]. Even
though complete resection can be challenging, retrospective results show an acceptable morbidity, with durable DFS in a significant portion of patients [17,18].

2.4. Partial nephrectomy

Only few studies examined the role of partial nephrectomy in cases of locally advanced RCC. In a recent retrospective analysis by Margulis et al. [32], 26 patients with an imperative and elective indication for nephron-sparing surgery (NSS) and T3a/b RCC were reviewed. In this cohort, the CSS was equivalent to the results of RN. In addition, a small series by Kolla et al. [33] showed acceptable oncologic results and renal function outcomes in seven patients with T3b stage tumours. Angermeier et al. [34] reviewed nine patients with venous tumour involvement who had undergone NSS. Five patients had no evidence of recurrence after a medium follow-up of 33.2 mo, four died of metastatic disease, and two patients developed local recurrence. Therefore, NSS in locally advanced RCC can be considered in carefully selected patients or imperative cases when tumour control is not compromised [33].

2.5. Minimally invasive versus open nephrectomy

Minimally invasive surgery is an established option in small renal masses, with comparable oncologic outcomes to open approaches [35]. The standard procedure of larger renal masses is still open surgery. Nevertheless, there is a trend towards laparoscopic nephrectomy in selected cases of locally advanced RCC [36].

In a matched comparison of laparoscopic versus open RN in T3 RCC, Bensalah et al. [37] showed comparable oncologic outcomes in the intermediate follow-up. Recent publications confirm the feasibility of the laparoscopic approach in cases of renal vein involvement [36,38]. A first series of five patients with vena caval tumour thrombectomy by robot-assisted surgery was published by Abaza [39].

These publications demonstrate an obvious trend towards minimally invasive laparoscopic or robot-assisted surgery. However, in locally advanced RCC, surgery can be challenging, especially using a minimally invasive approach, and therefore should be performed only by an experienced surgeon. Longer-term follow-up data are required for general acceptance of these methods into urologic practice [40].

3. Inferior vena cava involvement

The potential for extension into the venous system is one of the unique clinical features of RCC [41]. The incidence of an invasion to the inferior vena cava (IVC) occurs in 4–15% [41,42]. The prognostic value of involvement of the IVC still remains uncertain because of the many controversies in the current literature [43–45]. In a large retrospective analysis of 1192 patients who underwent nephrectomy for pT3b and pT3c RCC, the OS was statistically different for patients with a tumour thrombus in the renal vein compared to those with IVC involvement [45]. Despite this difference, the level of tumour thrombus in the IVC did not significantly affect long-term OS in patients with RCC [45]. Russo [46] assumes that even highly successful resection of the renal tumour and its thrombus would not affect the poor outcome for those patients.

The extension of the tumour thrombus in the IVC can be classified into four levels (Table 1). Accurate staging of the tumour–thrombus extension is essential for determining the appropriate surgical approach. If CT is limited in its ability to define thrombus extension, magnetic resonance imaging as a noninvasive diagnostic tool should be preferred. Angiography or transoesophageal echocardiography can be used as complementary modalities, as well [16,42].

In a prospective analysis of long-term survival in patients with RCC extending to the IVC, tumour thrombus level was identified as an independent prognostic factor [44]. The CSS was significantly higher in patients with an infrahepatic thrombus level than in those with a thrombus at the level of the hepatic veins or higher [44]. The surgical approach depends on the thrombus level, as the most important step during surgery is the early control of the tumour thrombus to avoid embolism. A level 1 tumour thrombus requires only limited liver mobilisation [47]. Vascular isolation can be obtained using clamps on the contralateral renal vein and the IVC without any circulatory support [48]. In patients with level 2 thrombus, it can be beneficial to first perform the nephrectomy, allowing better access and exposure of the IVC. The thrombus can subsequently be removed by anterior cavotomy [49].

If the thrombus reaches the level of the hepatic veins (level 3), a hepatic vascular exclusion is necessary. This procedure requires complete liver mobilisation, often accompanied by the Pringle manoeuvre [9,48,49]. After mobilisation of the liver, vascular cross-clamps are applied across the suprahepatic, infrahepatic IVC, and contralateral renal vein. The liver is pushed to the left for exposure of the IVC. The IVC can be opened along its anterolateral aspect to the level of the hepatic veins, and the thrombus can be removed en bloc [49].

<table>
<thead>
<tr>
<th>Level</th>
<th>Extension</th>
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<tbody>
<tr>
<td>I</td>
<td>From the renal vein into the infrahepatic IVC for 1–2 cm</td>
</tr>
<tr>
<td>II</td>
<td>&gt;2 cm from the renal vein but no farther than the subhepatic IVC</td>
</tr>
<tr>
<td>III</td>
<td>Into the infrahepatic IVC and suprahepatic IVC but not into the atrium</td>
</tr>
<tr>
<td>IV</td>
<td>Into the atrium</td>
</tr>
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IVC = inferior vena cava.
suprahepatic IVC. A vascular cross-clamp or tourniquet can then be applied to block the IVC below the cavoatrial junction. Afterwards, the thrombus can be removed by cavotomy [48,49].

If tumour thrombus invades the IVC, partial or complete resection with adequate surgical margins is necessary [48]. The reconstruction can be performed by patch angioplasty or tubular graft. The patch can consist either of polytetrafluoroethylene or autogenous pericardium [48].

4. Targeted therapy

Trials on the use of adjuvant immunotherapy did not show an OS or relapse-free survival benefit [50]. However, the development of molecular targeted therapies aroused new interest in adjuvant and neoadjuvant strategies in locally advanced RCC.

In recent years, several targeted therapies have become available for first- and second-line use in metastatic disease. These modalities include the tyrosine kinase inhibitors (TKI) sorafenib, sunitinib, and pazopanib; the monoclonal antibody bevacizumab (plus interferon [IFN]); and the mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus [51]. Their benefit in OS and progression-free survival (PFS) in the metastatic setting is proven [12,51]; their role in adjuvant or neoadjuvant therapy in locally advanced RCC remains unclear, but trials are ongoing.

4.1. Neoadjuvant therapy

Neoadjuvant therapy in locally advanced RCC may be of interest because of a possible reduction in the primary tumour size. This reduction may lead to a less extensive and potentially nephron-sparing procedure or even enable resection of a previously inoperable tumour. Four ongoing phase 2 trials on neoadjuvant therapy in locally advanced RCC investigating potential influence on OS and PFS have been identified (Table 2).

In a retrospective setting, Cost et al. [52] evaluated the effect of neoadjuvant therapy on vena cava tumour thrombus. Twelve patients received sunitinib, nine received bevacizumab, three received temsirolimus, and one patient received sorafenib. Analysis revealed minimal effect on the tumour thrombus level and failed to demonstrate a significant impact on the surgical approach. Interestingly, only the administration of sunitinib showed measurable thrombus regression [52]. Cowey et al. [53] investigated neoadjuvant administration of sorafenib in a prospective, nonrandomised pilot trial that included patients with locally advanced and metastatic RCC. Sorafenib was given a median of 33 d prior to surgery. In the majority of patients, a decrease in the primary tumour size was observed, and the median tumour shrinkage was 9.6%. Two patients even met the criteria for partial response using Response Evaluation Criteria in Solid Tumours (RECIST) criteria.

Silberstein et al. [54] undertook a prospective pilot study of sunitinib prior to surgery in 12 patients with locally advanced or centrally located tumours. Sunitinib was administered for 4 wk followed by a washout phase of 2 wk before NSS. All patients experience a decrease in the primary tumour size, with a mean reduction in maximum diameter of 21%. There was no negative effect in outcome or surgical procedure, and there were no severe adverse effects from sunitinib administration. Present data are encouraging, but further investigations are necessary to evaluate whether tumour shrinking can influence the surgical approach significantly (nephrectomy vs NSS) and whether neoadjuvant therapy can influence PFS and OS.

4.2. Adjuvant therapy

In the absence of distant metastasis, the indication for adjuvant medical therapy is unclear. To decide whether to initiate adjuvant therapy, risk classification may be useful. Two retrospectively validated prognostic nomograms exist for establishing the risk of relapse after resected advanced RCC: the stage, size, grade and necrosis (SSIGN) score and the University of California, Los Angeles, Integrated Staging System (UISS). The UISS categorises patients according to TNM stage (1 to IV), Eastern Cooperative Oncology Group performance status, and Fuhrman grade [55]. A recent comparison of SSIGN and UISS postulates a slightly superiority for the SSIGN [56]. Nevertheless, the UISS might be more practicable because not every pathology report includes a coagulative necrosis description. These tools can be useful for deciding whether to administer adjuvant therapy.

Earlier attempts using adjuvant immunotherapy with INF or interleukin have failed to show an improvement in OS or relapse-free survival [57]. In the era of molecular targeted therapies and autologous tumour cell vaccines, an encouraging change has occurred. In locally advanced RCC after nephrectomy with no clinical signs of metastasis, evidence for the use of adjuvant therapy is missing. Nevertheless, the results of two randomised phase 3 studies with tumour cell vaccines are already available.

A randomised trial investigating adjuvant therapy for locally advanced RCC in the absence of distant metastases

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Estimated enrolment</th>
<th>Treatment</th>
<th>Primary outcome</th>
<th>Expected primary completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00480935</td>
<td>30</td>
<td>Sunitinib 4 wk prior to surgery</td>
<td>Radiologic response rate</td>
<td>September 2012</td>
</tr>
<tr>
<td>NCT01070186</td>
<td>30</td>
<td>Sunitinib 4 wk prior to surgery</td>
<td>Clinical recurrence</td>
<td>May 2014</td>
</tr>
<tr>
<td>NCT01361113</td>
<td>40</td>
<td>Pazopanib 12 wk prior to surgery</td>
<td>Clinical recurrence disease response</td>
<td>June 2014</td>
</tr>
<tr>
<td>NCT01263769</td>
<td>24</td>
<td>Axitinib 12 wk prior to surgery</td>
<td>Objective response rate disease response</td>
<td>February 2014</td>
</tr>
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addresses an autologous tumour cell vaccine (Reniale, LipoNova, Hanover, Germany) [13]. In this phase 3 trial, 558 patients scheduled for RN were randomised either to receive autologous renal tumour cell vaccine (six intradermal applications at 4-wk intervals postoperatively) or to no adjuvant therapy (control group). The 5-yr PFS rate was 77.4% in the vaccine group and 67.8% in the control group, respectively. Furthermore, the vaccine was well tolerated, with a low incidence of adverse events. A recent update of the study has shown a significant improvement in OS, especially in pT3 tumours [58].

The autologous, tumour-derived heat-shock protein (glycoprotein 96)–peptide complex (vitespen [Oncophage, Antigenics, New York, NY, USA]) was used in another phase 3 vaccine trial after nephrectomy in locally advanced RCC [59]. After a follow-up of 1.9 yr, there was no significant difference in OS. Nevertheless, the RFS and OS in patients with T1, T2, and T3a disease were better, even if not statistically significant. At this time, six phase 3 trials are investigating the role of adjuvant targeted therapy in high-risk patients after nephrectomy (Table 3).

Although five studies evaluate multiple TKIs and mTOR inhibitors as adjuvant medications, only one study uses an antibody therapy. The ARISER trial (NCT00087022) is a randomised, double-blind, phase 3 study to evaluate adjuvant cG250 (WX-G250; Rencarex, Wlex, Munich, Germany) treatment against placebo in patients who have undergone surgery but are at high-risk for RCC recurrence. Girentuximab is a chimeric monoclonal antibody that binds to carbonic anhydrase IX (G250 antigen), which is a cell-surface antigen expressed in 95% of RCC [60]. The antibody fulfills two major tasks: It provides excellent biolocalisation, and it can induce natural killer cells to kill tumour cells in vitro via antibody-dependent cellular cytotoxicity. Girentuximab is given once weekly intravenously over 15 min. The primary outcome of the trial is DFS. An estimated 864 patients will be enrolled, and the primary completion date is September 2013.

### 5. Conclusions

A radical surgical approach in locally advanced RCC is still mandatory. Nevertheless, the preservation of the adrenal gland should be taken into consideration in the absence of CT-proven morphologic or macroscopic suspicion of invasion. The role of extended lymphadenectomy remains unclear, but there seems to be a benefit for patients undergoing LND in locally advanced RCC in retrospective trials. Therefore, regarding the limited morbidity of lymphadenectomy in RCC, it should be conducted, if feasible.

The significance of targeted therapy in the neoadjuvant and adjuvant settings in locally advanced RCC is still pending in ongoing trials. The autologous tumour cell vaccine Reniale could already be proof of a significantly better 5-yr PFS rate in a phase 3 trial. In the neoadjuvant setting, some retrospective studies have shown a reduction in primary tumour size using targeted therapy, but prospective trials are still missing.

### Conflicts of interest

The authors have nothing to disclose.

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None.

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