LOCALLY ADVANCED RENAL CELL CA

Advanced Urology Course
2015
Outlines of presentation

- IVC thrombosis
  - IVC thrombectomy – level of thrombus
  - How to investigate patients suspected to have IVC or RV thrombosis
  - Metastatic risk at presentation
  - Indication for bypass
  - What is circulatory arrest
  - Principle of IVC thrombectomy

- Lymphadectomy during radical nephrectomy
  - Evidence from literature
  - Potential indication
Introduction

- 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.


- In a large prospective analysis by Karakiewicz et al. including 3907 patients with RCC, 32.1% presented with stage T3 and 1.7% with stage T4 disease.

<table>
<thead>
<tr>
<th>T3a</th>
<th>Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or invades perirenal and/or renal sinus fat (peripelvic), but not beyond Gerota’s fascia</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3b</td>
<td>Tumour grossly extends into the vena cava below the diaphragm</td>
</tr>
<tr>
<td>T3c</td>
<td>Tumour grossly extends into vena cava above the diaphragm or invades the wall of the VC</td>
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<tr>
<td>T4</td>
<td>Tumour invades beyond Gerota’s fascia (including contiguous extension into the ipsilateral adrenal gland)</td>
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<table>
<thead>
<tr>
<th>TNM stage grouping</th>
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<tbody>
<tr>
<td>Stage I T1 N0 M0</td>
</tr>
<tr>
<td>Stage II T2 N0 M0</td>
</tr>
<tr>
<td>Stage III T3 N0 M0</td>
</tr>
<tr>
<td>Stage IV T4 Any N M0</td>
</tr>
<tr>
<td>Any T Any N M1</td>
</tr>
</tbody>
</table>
Prognosis

• Prognosis of locally advanced RCC is poor.

• Despite radical nephrectomy, there is a significant risk of recurrence and progression in comparison to localized RCC.

• The estimated 10-yr cancer-specific survival (CSS) rates:

<table>
<thead>
<tr>
<th>Stage</th>
<th>pT1</th>
<th>pT2</th>
<th>pT3a</th>
<th>pT3b</th>
<th>pT3c</th>
<th>pT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>80 - 90</td>
<td>55 -66</td>
<td>36</td>
<td>26</td>
<td>25</td>
<td>12</td>
</tr>
</tbody>
</table>

RCC Patient Survival Rates by Tumor Stage

![RCC 5yr Survival Rate](image)

Metastatic risk at presentation

- About a third of those patients with IVC thrombus have metastases.

- The involvement of the adrenal gland is associated with a significantly decreased survival rate and often accompanied by distant metastasis.

- Large retrospective series report a 1.7–15.0% incidence of pT4 RCC, the majority of which were associated with synchronous metastases.

- 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.
Locally advanced RCC

- Surgery
- Adrenalectomy
- Lymphadenectomy
- Involvement of adjacent organs
- Partial nephrectomy
- Minimally invasive versus open nephrectomy
- Inferior vena cava involvement
Surgery

- Radical nephrectomy is the gold standard of treatment for locally advanced RCC.

- 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.

Adrenalectomy

- Locally advanced tumour stage and upper-pole tumour are recognized as risk factors for adrenal gland involvement.

- The involvement of the adrenal gland is associated with a significantly decreased survival rate and often accompanied by distant metastasis. Frequency of ipsilateral adrenal involvement is < 10% of cases.

- Routine ipsilateral adrenalectomy in locally advanced RCC does not seem to improve cancer-specific survival (CSS).

- Suggest preserving the adrenal gland unless adrenal gland involvement is suspected on CT scans or surgical aspect. Sawai et al. [25] were able to demonstrate that CT can rule out adrenal involvement in most cases.
Involvement of adjacent organs

- 9.1% of all patients with locally advanced RCC had an invasion of adjacent organs.


- Large retrospective series report a 1.7–15.0% incidence of pT4 RCC, the majority of which were associated with synchronous metastases.

  Karakiewicz et al. (2007)
  Margulis et al. (2007)

- Radical en bloc resection is mandatory. Complete resection can be challenging, retrospective results show an acceptable morbidity, with durable DFS in a significant portion of patients
Partial nephrectomy

• Only few studies examined the role of partial nephrectomy in cases of locally advanced RCC.

• T3a/b RCC - showed acceptable oncologic results and renal function outcomes.

Kolla et al.

• NSS in locally advanced RCC can be considered in carefully selected patients or imperative cases when tumour control is not compromised.
Minimally invasive surgery

• Minimally invasive surgery is an established option in small renal masses, with comparable oncologic outcomes to open approaches.

• 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.

  Bensalah et al, Hammond et al, Guzzo et al

• 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.
RCC with venous thrombus

• IVC involvement:
  • 4 – 10% occurrence
  • More common on the right because of a shorter renal vein
  • Half of the IVC thrombi are infra-hepatic
  • 10% of them are located in the right atrium
  • 55 – 68% 5-year survival if no nodal or distant metastases

• Aggressive surgical resection is widely accepted as the default management option for patients with VTT.
Tumor thrombus is either at the entry of the RV or within the IVC < 2 cm from the confluence of the RV and IVC. Thrombus extends within the IVC > 2 cm above the confluence of the RV and IVC but still remains below the hepatic veins. Thrombus involves the intrahepatic IVC. The size of the thrombus ranges from a narrow tail that extends into the IVC to one that fills the lumen and enlarges the IVC. Thrombus extends above the daphragm or into the right atrium.
Novick staging system.

Classification of tumour thrombus level into the IVC

Nesbit et al.

<table>
<thead>
<tr>
<th>Level</th>
<th>Extension</th>
</tr>
</thead>
<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 intrahepatic IVC and suprahepatic IVC but not into the atrium</td>
</tr>
<tr>
<td>IV</td>
<td>Into the atrium</td>
</tr>
</tbody>
</table>

IVC = inferior vena cava.
How to investigate patients suspected to have IVC or RV thrombosis (RVT)²

• Imaging is a crucial step in the management of RCC with IVC thrombus by providing the information necessary to determine the best surgical approach for a given patient.

• Evaluating the proximal extent, volume of tumour thrombus, and potential of caval wall invasion.

  • US
  • CT
  • MRI
  • Vena cavography
  • Transoesophageal echocardiography
Sensitivity and specificity

• US in detecting tumour thrombus below the level of the insertion of the hepatic vein has a sensitivity of 68%. In addition, prior studies would suggest that in >40% of cases, the IVC is not fully visualised by US.

• MDCT has a sensitivity of 93% and a specificity of 80% in delineating the extent of tumour thrombus. Nazim et al. concluded that MDCT has 97% specificity for detecting tumour thrombus in the renal vein and IVC.

• MRI has proven to be the most effective in detecting IVC tumour thrombus, with a sensitivity level of 96 – 100%.
  • The advantage of MRI is that it offers multiplanar anatomical views with detailed images clearly showing the relationship of the thrombus to the liver, heart, and other vital structures, while delivering no radiation to the patient.
Imaging: EUA Guidelines

• The extent of an IVC thrombus can be identified by abdominal ultrasonography and computed tomography, the sensitivity of magnetic resonance imaging is superior to these techniques and is now the gold standard for assessing the level of IVC thrombus.


• Inferior vena cavography is not often used.

• During surgery, transoesophageal echocardiography (TOE) ultrasonography enables real-time visualization of the thrombus.
Surgery for IVC thrombus in RCC

• The prognostic value of involvement of the IVC still remains uncertain because of the many controversies in the current literature

• In one of the largest published studies a higher level of thrombus was not associated with increased tumour dissemination to LNs, perinephric fat or distant metastasis.

• Thus, all patients with non-metastatic disease and VTT, and an acceptable performance status, should be considered for surgical intervention, irrespective of the extent of TT at presentation (LE: 3).

The evidence base for different surgical strategies

- Minimal access techniques resulted in significantly shorter operating time compared with traditional median sternotomy.

- Pre-operative embolisation was associated with increased operating time, blood loss, hospital stay and peri-operative mortality in patients with T3 RCC.

- No significant differences in oncological and process outcomes were observed between cardiopulmonary bypass with deep hypothermic circulatory arrest or partial bypass under normothermia or single caval clamp without circulatory support.

- No surgical method was shown to be superior for the excision of VTT. The surgical method was dependent on the level of TT, and the grade of occlusion of the IVC.

- The role of IVC filters and bypass procedures remain uncertain.
Principle of IVC thrombectomy\textsuperscript{4}

- 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.
thrombectomy

- Level I tumor thrombus (TT) - requires only limited liver mobilization. Vascular isolation can be obtained using clamps on the contralateral renal vein and the IVC without any circulatory support.

- Level II TT - 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.

- Level IV TT - a hepatic vascular exclusion is necessary. This procedure requires complete liver mobilization, often accompanied by the Pringle manoeuvre. After mobilization 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.
...thrombectomy

- Level IV TT - Extensive access requiring complete liver mobilization and cardiopulmonary bypass (CPB) or even deep hypothermic circulatory arrest may be necessary.

- The use of CPB improves immediate control of blood loss, but it is associated with higher overall blood loss, a greater rate of coagulopathy, and longer operative times.

- If tumour thrombus invades the IVC, partial or complete resection with adequate surgical margins is necessary. The reconstruction can be performed by patch angioplasty or tubular graft. The patch can consist either of polytetra- fluoroethylene or autogenous pericardium.
Indication for bypass$^5$

- For complex supradiaphragmatic and atrial tumor thrombi—Level III and IV TT
- Accomplished using cardioplegia-induced cardiac arrest and cardiopulmonary bypass to maintain perfusion of other organs.
What is circulatory arrest?\textsuperscript{6}

- A cessation of blood circulation by temporally stopping CPB flow during certain procedure, used intentional profound total-body hypothermia to protect vital organs.

- Deep hypothermic circulatory arrest (DHCA) is a technique that involve cooling of the body of the patients and stopping blood circulation in order to obtain optimal operating conditions while providing cerebral protection.

- Safe period:
  - Most patient will tolerate 30 min of circulatory arrest at 18\textdegree{}C without significant neurological impairment.
  - > 40 min there is marked increase in the incidence of brain injury
  - > 60 min, majority of patients will suffer irreversible brain injury
CPB with / or without DHCA

CPB without DHCA

- DISADVANTAGES: reduced visualization and exposure of the IVC and the RA within the surgical field, higher risk of warm hepatic and renal ischemia, higher risk of pulmonary embolism (PE), ischemic liver, and acute tubular necrosis.

CPB with DHCA

- ADVANTAGES: bloodless surgical field with reduced risk of cellular spreading, PE, and fatal hemorrhage; there is reduced risk of warm hepatic and renal ischemia, reduced risk of incomplete tumor excision, and there is optimal visualization of the IVC lumen (in particularly of the hepatic vein) and of the RA.
Incision

Noguchi K, et al.
Reflect the liver medially to et control of the IVC both above and below the TT
Level II TT

Control of the contralateral RV and the IVC both above and below the TT
Level IV TT

IVC thrombosis

RCC
Complications

- Radical nephrectomy with removal of a thrombus from the IVC may be associated with major perioperative morbidity (up to 70%) and mortality (3–16%).
- The complication rates increase with the higher extension of the caval thrombus. The most common complication is significant blood loss.
- Reported transfusion amounts vary between 3 and 70 units. The average blood loss is higher in patients with left-sided tumors and with higher levels of IVC thrombus.
IVC Thrombosis: Prognosis

- Although IVC thrombus implies a worse biologic behavior, it does not ultimately affect long-term prognosis.

- Most of the patients with non-metastatic RCC and renal vein or IVC tumor thrombus can have high progression-free, cancer-specific, and overall survival rates.

- Three questions have been extensively discussed in the literature concerning the impact of IVC thrombus removal on survival:
  1. impact of thrombus removal in non-mRCC and the adverse factors for survival
  2. the level of thrombus and its impact on survival
  3. the impact of thrombus removal in metastatic RCC

(1) The impact of thrombus removal in non-metastatic RCC and the adverse factors for survival

- Poor prognosis is also expected in patients with a macroscopic thrombus in the large vessels.
- Surgical removal of an IVC thrombus in a patients with non-metastatic RCC should always be attempted to improve survival.

<table>
<thead>
<tr>
<th>Author/reference</th>
<th>Year</th>
<th>No.</th>
<th>Survival</th>
</tr>
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<tbody>
<tr>
<td>Skinner [5]</td>
<td>1989</td>
<td>43</td>
<td>5-yr OS 57%</td>
</tr>
<tr>
<td>Galzer [12]</td>
<td>1996</td>
<td>18</td>
<td>5-yr OS 57%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-yr CSS 60%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Renal vein 66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IVC 29%</td>
</tr>
<tr>
<td>Kim [19]</td>
<td>2004</td>
<td>81</td>
<td>3-yr CSS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal vein 36%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>IVC 35%</td>
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<td></td>
<td></td>
<td></td>
<td>T3c 12%</td>
</tr>
<tr>
<td>Lubahn [18]</td>
<td>2006</td>
<td>44</td>
<td>5-yr OS 56%</td>
</tr>
<tr>
<td>Ciancio [15]</td>
<td>2007</td>
<td>56</td>
<td>2-yr PFS 53%</td>
</tr>
<tr>
<td>Wagner [24]</td>
<td>2007</td>
<td>1192</td>
<td>Median survival, mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal vein: 52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IVC below diaphragm: 25.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IVC above diaphragm: 18</td>
</tr>
</tbody>
</table>

OS = overall survival; CSS = cancer-specific survival; IVC = inferior vena cava; PFS = progression-free survival.
The adverse prognostic features for patients with VT

1. Perinephric extension of RCC
2. Lymph node metastasis
3. Incomplete tumor or thrombus excision
4. Invasion of the IVC wall
(2) The impact of the level of tumor thrombus on survival

- The TNM staging of T3b and T3c is based on the assumption that a higher level of tumor thrombus is associated with a worse prognosis.

- Patients with more extensive thrombus propagation tend to have tumors of a higher grade and a more advanced local stage.

- The presence of IVC invasion, not the level of TT, was identified as an independent prognostic factors in some series.
(3) The impact of thrombus removal in metastatic RCC

- These patients are usually symptomatic, removal of the thrombus, may relieve symptoms and provide a better quality of life.

- However, life expectancy, performance status, and comorbidity should all be taken into account.

- The overall survival rate of patients with IVC thrombus was similar regardless of metastatic status, and metastatic patients with thrombus who underwent surgery had a significantly better response to immunotherapy than those treated non-operatively.

- Thus, the combination of cytoreductive surgery and immunotherapy has an important role in the treatment of patients with renal vein thrombus and a potential role for those with IVC thrombus.
Surgery in mRCC with TT

• Verghe et al. do not advise radical nephrectomy for metastatic disease and thrombus of the IVC, believe that the limited chance of survival of longer survival doesn’t justify the morbidity of such an extensive operation.

• Lambert et al. found patients with metastatic disease did not experience any added morbidity or mortality compared to patients without metastatic disease.
LYMPHADENECTOMY
Lymph Node Dissection

• The role of lymph node dissection (LND) for renal cell carcinoma remains controversial.

• LND in low-risk disease had no benefit in a randomized clinical trial, LND in patients with high-risk disease improves stage assessment and may prolong survival.

• Management of clinically positive lymph nodes (cN+)
  • In the presence of clinically positive LNs (cN+), LND is always justified.
  • However, the extent of LND is controversial.

Regional LN dissection: Potential Indications

• The decision to perform LND at the time of radical nephrectomy has been based on clinical suspicion of lymph node involvement.

• LND at the time of nephrectomy is not associated with significantly increased morbidity, routine LND is not warranted in all patients with RCC.

• Risk of lymph node involvement can be estimated based on radiographic images or clinical prediction models pre-operatively and may also be suspected based on intraoperative assessment of the primary tumor or retroperitoneal lymph nodes.

• At present, intraoperative frozen section and sentinel node techniques should be considered investigational for LND planning.
• **T1 – T2**
  - LND offers extremely limited staging information and no benefit in terms of decreasing disease recurrence or improving survival (level 1 evidence).
  - if additional risk factors (sarcomatoid features, presence of coagulative tumor necrosis, and high Fuhrman grade) are present, the risk of LNI significantly increases and potentially makes LND a valid surgical addition (level 2 evidence).

• **cT3–T4N0 or cT_{any}N1**
  - the majority of the retrospective nonrandomized trials suggest a possible benefit of regional LND on cancer-specific survival.

• **M1**
  - Surgery with regional LND in patients who are candidates for debulking and potential subsequent systemic treatment (level 2 evidence)
Fig. 1 – Rational algorithm for selection of renal cell carcinoma patient candidates for lymph node dissection (LND) at the time of radical nephrectomy. * = when technically feasible; # = palpable nodes at surgery, larger tumors, sarcomatoid features, presence of coagulative tumor necrosis, and high Fuhrman grade.
Regional LN

1. Right Hilar
2. Paracaval
3. Interaortocaval
4. Paraaortic
5. Left Hilar
Location of positive LN based on side of primary tumor

Reported percentage represents frequency of involved location in patients with lymph node–positive disease.
Extent of lymph node dissection: The choice of the anatomic template

• While there is no consensus on the anatomic extent of LND for RCC, it is reasonable that a template should be based on the primary lymphatic drainage of the kidney and the location of metastatic disease noted in surgical series.

• The suspected primary lymphatic drainage from the right kidney are the paracaval, precaval, retrocaval, and inter-aortocaval lymph nodes.

• The primary lymphatic drainage for the left kidney are the para-aortic, preaortic, retroaortic, and interaortocaval lymph nodes [16].
Lymph node dissection should include:

(a) for the **right kidney**, the paracaval, retrocaval, and precaval nodes from the adrenal vein to the level of the inferior mesenteric artery.

(b) for the **left kidney**, the paraaortic and preaortic nodes from the crus of the diaphragm to the inferior mesenteric artery.

(c) Interaortocaval nodes should always be removed as well when extended LND is sought.

- If disease is confirmed within the interaortocaval nodes, a complete retroperitoneal LND is recommended to define the full extent of metastatic lymph node involvement.
Number of lymph nodes that should be retrieved

- No study found a straight correlation between number of nodes removed and CSS. Therefore, any recommendation regarding the adequate extent of LND in RCC management is based on a low level of evidence.
Locally Advanced RCC EAU 2015
Conclusions and recommendations

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
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<tbody>
<tr>
<td>In patients with locally advanced disease due to clinically enlarged LNs the survival benefit of LND is unclear. In these cases LND can be performed for staging purposes.</td>
<td>3</td>
</tr>
<tr>
<td>Low quality data suggest that tumour thrombus in non-metastatic disease should be excised.</td>
<td>3</td>
</tr>
<tr>
<td>Tumour embolisation or IVC filter do not appear to offer any benefits.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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<tbody>
<tr>
<td>In patients with clinically enlarged LNs, LND can be performed for staging purposes or local control.</td>
<td>C</td>
</tr>
<tr>
<td>Excision of the kidney tumour and caval thrombus is recommended in patients with non-metastatic RCC.</td>
<td>C</td>
</tr>
</tbody>
</table>
Locally advanced unresectable RCC

• In patients with non-resectable disease, embolisation can control symptoms, including gross haematuria or flank pain.


• The use of neoadjuvant targeted therapy to downsize tumours is experimental and cannot be recommended outside controlled clinical trials.
Conclusion

- RCC with IVC involvement poses a surgical challenge.
- A radical surgical approach in locally advanced RCC is still mandatory.
- A successful removal of the tumor thrombus in the renal vein and IVC may result in improved long-term survival rates for more than half of the affected patients.
- Removal of the IVC thrombus in the metastatic setting, provides a better quality of life and may prolong survival.
- In high-risk patients, LND should be considered to obtain more accurate staging and because some indirect evidence exists that there may be a survival benefit.
THANK YOU