Surgical Management of Metastatic and Locally Recurrent Kidney Cancer: Does it Make Sense?

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Surgery in the Setting of Metastatic Renal Cell Carcinoma
Role of Cytoreductive Nephrectomy

• Pioneering work of Dr Flanigan and colleagues effectively demonstrating the improvement in overall survival in patients with metastatic RCC treated with cytoreductive nephrectomy (in the context of interferon immunotherapy)

• Combined analysis of SWOG 8949+85 and EORTC 30947 demonstrated a 5.8 month overall survival advantage with cytoreductive immunotherapy and immunotherapy

Role of Cytoreductive Nephrectomy

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Role of Cytoreductive Nephrectomy

- A subsequent retrospective study conducted by Choueiri et al. assessing role of surgery in current TKI era
- A retrospective cohort of 314 patients treated with cytoreductive nephrectomy followed by anti-VEGF therapy
- Cytoreductive nephrectomy was associated with a median overall survival of 19.8 months versus 9.4 months if not performed prior to TKI (P<0.01)
Role of Cytoreductive Nephrectomy

- On multivariate analysis, this overall survival benefit for cytoreductive nephrectomy persisted (P=0.04)
- In subgroup analyses, patients in the poor risk (Motzer categories) had only a marginal benefit with surgery (P=0.06)
- Patients with a Karnofsky performance status (less than 80%) had as well only a marginal benefit with surgery (P=0.08)

Role of Cytoreductive Nephrectomy

Role of Cytoreductive Nephrectomy

- Study by Heng et al. evaluating the benefit of cytoreductive nephrectomy (CN) in patients with synchronous metastatic RCC (in present targeted therapy era)
- Retrospective assessment of the International Metastatic Renal Cell Carcinoma Database Consortium
- Median OS of patients undergoing CN versus without CN was 20.6 months vs 9.5 months (P<0.0001)

Heng DY et al. European Urology, 2014
Role of Cytoreductive Nephrectomy

Fig. 1 – Kaplan-Meier curve depicting the overall survival from the initiation of targeted therapy for 1633 metastatic renal cell carcinoma patients who did or did not receive a cytoreductive nephrectomy.

CI = confidence interval; CN = cytoreductive nephrectomy; HR = hazard ratio; OS = overall survival.

Heng DY et al. European Urology, 2014
Role of Cytoreductive Nephrectomy

Table 4 – Overall survival differences in those with and without cytoreductive nephrectomy by number of International Metastatic Renal Cell Carcinoma Database Consortium criteria met

<table>
<thead>
<tr>
<th>No. of IMDC criteria met</th>
<th>No CN OS, mo (n)</th>
<th>CN OS, mo (n)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>92% of patients (65/71) had CN, insufficient number to compare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22.5 (n = 72)</td>
<td>30.4 (n = 178)</td>
<td>0.002</td>
</tr>
<tr>
<td>2</td>
<td>10.2 (n = 143)</td>
<td>20.2 (n = 253)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>10.0 (n = 113)</td>
<td>15.9 (n = 106)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>5.4 (n = 103)</td>
<td>6.0 (n = 67)</td>
<td>0.166</td>
</tr>
<tr>
<td>5</td>
<td>3.6 (n = 36)</td>
<td>2.8 (n = 14)</td>
<td>0.504</td>
</tr>
<tr>
<td>6</td>
<td>25% of patients (3/12) had CN, insufficient number to compare</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall, 1168 of 1658 subjects (70%) had complete information about prognostic factors, nephrectomy, and outcomes and were used in this complete case analysis; the rest were excluded. Shaded rows indicate patient groups that may not benefit from cytoreductive nephrectomy.

CN = cytoreductive nephrectomy; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival.
Which patients should we operate on?

- Symptomatic/palliation
- Good/intermediate and selected poor risk
- Small number/favorable metastatic sites
- Predominant volume of disease in kidney
- Patient, physician, and tumor specific characteristics/anticipated outcomes
Risk categories in mRCC

**Motzer Risk Groups**
- No prior nephrectomy status
- Karnofsky PS < 80%
- Low serum hemoglobin
- High corrected serum calcium
- High serum lactate dehydrogenase

**Heng Criteria**
- Time from diagnosis to treatment less than 1 year
- Karnofsky PS < 80%
- Low serum hemoglobin
- High corrected serum calcium
- High serum neutrophil count
- High serum platelet count


Risk categories in mRCC

**Motzer Risk Groups**

- Risk factors are no prior nephrectomy
- KPS = 80
- low HGB
- high corrected calcium
- high LDH

- 0 risk factors (164 Patients, 30 Alive)
- 1 or 2 risk factors (348 Patients, 23 Alive)
- 3, 4, or 5 risk factors (144 Patients, 1 Alive)

**Heng Criteria**

- Overall Survival (probability)

- Time Since Therapy Initiation (months)

- No. of events/No. at risk
  - Favorable: 11/133, 16/110, 4/62, 2/22, 0/3
  - Intermediate: 61/301, 50/182, 17/82, 2/18, 0/3
  - Poor: 94/152, 19/36, 1/3, 0/1, 0/0


Significant decline in # of surgeries

• Study by Tsao et al. revealing using SEER data that the # of patients undergoing surgery for mRCC declining by 38% in 2008

• On multivariate analysis, decrease use of cytoreductive nephrectomy was associated with advanced age (OR = 0.82), race (black OR = 0.64), hispanic (OR = 0.71), and onset of TKI era (OR = 0.82)

Significant decline in # of surgeries

Fig. 1 The use of CyNx in the United States, 2001–2008 (SEER database). There is a significant cubic trend in CyNx over time; $p = 0.0041$

Significant decline in # of surgeries

**Table. — Nephrectomy Status in Selected Large, Single-Modality Medical Trials**

<table>
<thead>
<tr>
<th>Study Sponsor and Reference</th>
<th>Systemic Therapy</th>
<th>Population Sample Size (No. of Patients)</th>
<th>Nephrectomy Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI11</td>
<td>Interleukin-2 (nonrandomized)</td>
<td>154</td>
<td>100% nephrectomy</td>
</tr>
<tr>
<td>EORTC SWOG1</td>
<td>Nephrectomy plus interferon vs interferon alone</td>
<td>331</td>
<td>Randomized 1:1</td>
</tr>
<tr>
<td>Bayer2</td>
<td>Sorafenib vs placebo</td>
<td>904</td>
<td>94%</td>
</tr>
<tr>
<td>Pfizer3</td>
<td>Sunitinib vs interferon</td>
<td>750</td>
<td>89% (of sunitinib arm)</td>
</tr>
<tr>
<td>Pfizer4</td>
<td>Sunitinib expanded access</td>
<td>4,617</td>
<td>88%</td>
</tr>
<tr>
<td>Wyeth15,16</td>
<td>Temsirolimus vs interferon vs both</td>
<td>416 (counting temsirolimus only and interferon only)</td>
<td>67%</td>
</tr>
<tr>
<td>Novartis17</td>
<td>Everolimus vs placebo</td>
<td>410</td>
<td>96%</td>
</tr>
<tr>
<td>EORTC (Genentech)18</td>
<td>Bevacizumab + interferon vs interferon</td>
<td>649</td>
<td>Required (100%)</td>
</tr>
<tr>
<td>CALGB (Genentech)19</td>
<td>Bevacizumab + interferon vs interferon</td>
<td>732</td>
<td>85%</td>
</tr>
<tr>
<td>GlaxoSmithKline20</td>
<td>Pazopanib vs placebo</td>
<td>436</td>
<td>Required (100%)</td>
</tr>
</tbody>
</table>

NCI = National Cancer Institute, SWOG = Southwest Oncology Group, EORTC = European Organisation for Research and Treatment of Cancer, CALGB = Cancer and Leukemia Group B.
Role of Cytoreductive Nephrectomy

- Recent study by Hanna et al. published in the JCO evaluating the contemporary utilization rates of cytoreductive nephrectomy (CN) in mRCC and reassessing the survival benefit in the current era of targeted therapy
- Data from the NCDB was assessed between 2006 and 2013
- Of 15,390 Pts treated with targeted therapy, only 5,374 (35%) underwent cytoreductive surgery
- Median OS of CN vs non-CN cohorts was 17.1 versus 7.7 months, respectively (P<0.001)

Hanna N et al. JCO, 2016
Role of Cytoreductive Nephrectomy

- Patients who were younger, privately insured, treated at an academic center, and had lower tumor stage and cN0 were more likely to undergo CN
- Survival benefit of CN was +0.7 and +3.6 months who survived $\leq 6$ and $\leq 24$ months, respectively versus no CN

Hanna N et al. JCO, 2016
Role of Cytoreductive Nephrectomy

Fig 1. CONSORT diagram of patient selection within the National Cancer Data Base (NCDB), 2006 to 2013. CN, cytoreductive nephrectomy; ICD, International Classification of Diseases; mRCC, metastatic renal cell carcinoma; PUF, participant user file.

Hanna N et al. JCO, 2016
# Role of Cytoreductive Nephrectomy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AJCC clinical N stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>1.0 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>0.51</td>
<td>0.47 to 0.56</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.56</td>
<td>0.50 to 0.63</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>Year of diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>1.0 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>0.93</td>
<td>0.78 to 1.10</td>
<td>.401</td>
</tr>
<tr>
<td>2008</td>
<td>1.23</td>
<td>1.03 to 1.47</td>
<td>.019</td>
</tr>
<tr>
<td>2009</td>
<td>1.08</td>
<td>0.90 to 1.29</td>
<td>.391</td>
</tr>
<tr>
<td>2010</td>
<td>1.18</td>
<td>0.98 to 1.43</td>
<td>.079</td>
</tr>
<tr>
<td>2011</td>
<td>1.08</td>
<td>0.90 to 1.31</td>
<td>.391</td>
</tr>
<tr>
<td>2012</td>
<td>1.13</td>
<td>0.94 to 1.36</td>
<td>.182</td>
</tr>
<tr>
<td>2013</td>
<td>1.06</td>
<td>0.88 to 1.26</td>
<td>.552</td>
</tr>
</tbody>
</table>

**Abbreviations:** AJCC, American Joint Committee on Cancer; CCI, Charlson comorbidity index; Ref, reference.

Hanna N et al. JCO, 2016
Role of Cytoreductive Nephrectomy

![Graph showing overall survival with and without cytoreductive nephrectomy (CN) status.](image)

**Fig 2.** Kaplan-Meier survival analyses of patients with metastatic renal cell carcinoma treated with targeted therapy stratified according to cytoreductive nephrectomy (CN) status (yes or no), National Cancer Data Base, 2006 to 2012. Data were restricted to 12,995 patients with no missing information on vital status or follow-up time.

Hanna N et al. JCO, 2016
Contemporary outcomes of CN

• Recent retrospective study by Gerschman et al from the Mayo Clinic reporting on the contemporary outcomes of CN at their center over two decades (1990-2009)

• 294 Pts underwent CN at their center, with 15 Pts (5%) reported at least one Clavien grade ≥ 3 early complication

• Of those recommended post surgical systemic therapy, 61% did not receive it within 60 days of surgery (delay was surgery related in only 11%)

• On multivariate analysis, presence of liver metastasis was associated with periop complications (OR = 3.73) and increased LOS (OR = 2.46)

Contemporary outcomes of CN

• On multivariate analysis, MIS approach was associated with earlier administration of systemic Tx (HR = 5.05)
• On a multivariate model incorporating OR parameters, intraop transfusion was associated with periop complications (OR = 1.14) and increased LOS (OR = 1.22) as well the presence of pN1 was associated with increased LOS (OR = 2.12) and delay in initiating systemic therapy (HR = 0.38)

Contemporary outcomes of CN

Fig. 1 – Kaplan-Meier plot of survival free of systemic therapy following cytoreductive nephrectomy.

Why are surgical rates declining?

Emergence of new systemic therapies

Where is the field going?

**Era of personalized therapy**

Management of Locally Recurrent Disease
Locoregional recurrences

• Multicenter study by Russell et al. evaluating the outcomes with the surgical management of isolated nodal recurrences of RCC
• Retrospective study of 22 Pts, with the median time to local recurrence being 31.5 months
• After resection, 10 Pts (46%) had a secondary recurrence at median time of 11.2 months (2 died of disease)
• Overall median PFS was 12.7 months

Figure 1. Nodal recurrence involving contralateral great vessel developed within respective modified Donohue templates. All tumors with contralateral involvement developed in or in addition to recurrence in interaortocaval node group except in 1 patient with right primary lesion and isolated retroaortic recurrence. Percent do not total 100% because 4 patients had multiple nodal recurrence sites. A, 4 patients with left primary tumor. B, 2 patients with right primary tumor.

Locoregional recurrences

Figure 2. Kaplan-Meier curves of PFS after complete RPLND for isolated nodal recurrence. A, in 10 patients with clinically staged T(1-2) N(any)M0 (solid curve) primary and 12 with clinically staged T3N(any)M0 (broken curve) tumors median PFS was 24.8 months with 1 at risk at 5 years and 9.9 months with none at risk at 5 years for T(1-2)N(any)M0 and T3N(any)M0 tumors, respectively. B, in 10 patients with histological clear cell tumors (solid curve) on pathological evaluation at primary recurrence and in 11 with nonclear cell histology (broken curve) at primary recurrence median PFS was 13.4 months with no patients at risk at 5 years and 17.4 months with 1 at risk at 5 years for recurrent clear cell and nonclear cell tumors, respectively.

Locoregional recurrences

- Subsequent study was published as part of a collaboration between Moffitt and the Mayo Clinic
- 50 Pts with isolated nodal recurrences were surgically managed
- The most common site of nodal recurrence was the interaortocaval region (34%)
- At last follow-up, 26 Pts (52%) developed a subsequent recurrence at a median of 9.9 months post-resection
- On multivariate analysis, shorter time to recurrence (≤ 12 months) was the only predictor of disease progression

Russell CM et al. BJU Int, 2015
Locoregional recurrences

Fig. 1 Sites of primary isolated RPLN recurrence for the 35 patients in whom individual LN packets could be identified. (A) 16 patients with left-sided primary tumours. (B) 19 patients with right-sided primary tumours.
Locoregional recurrences

Table 3  Multivariate Cox proportional hazards analyses assessing the association of various clinicopathological features with patients’ risk of progression after resection of RCC RPLN recurrence.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Non-cc RCC histological subtype (ref. cc RCC)</td>
<td>1.44 (0.59–3.52)</td>
<td>0.43</td>
</tr>
<tr>
<td>Nephrectomy stage</td>
<td>1.56 (0.67–3.65)</td>
<td>0.30</td>
</tr>
<tr>
<td>pT3 (ref. pT1–2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN1 status at nephrectomy (ref. pN0/Nx)</td>
<td>1.02 (0.44–2.36)</td>
<td>0.96</td>
</tr>
<tr>
<td>RPLN recurrence ≤12 months after nephrectomy (ref. RPLN &gt;12 months)</td>
<td>3.51 (1.46–8.45)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*cc, clear cell.*

Russell CM et al. BJU Int, 2015
Locoregional recurrences

- Recent retrospective study published by Thomas et al from MDACC assessing treatment outcomes with surgical management of all local retroperitoneal recurrences of RCC
- 102 Pts were identified between study period of 1990 to 2014
- No patients had distant metastatic disease at time of retroperitoneal recurrence surgery
- Median time from nephrectomy to retroperitoneal recurrence was 19 months
- Metastatic progression was observed in 60 Pts (58.8%) post-op (median follow-up was 32 months)
- On multivariate analysis, pathological nodal stage at time of nephrectomy and maximal diameter of retroperitoneal recurrence were predictors of cancer specific mortality

Locoregional recurrences

Figure 2. CSS stratified by RPR surgical margin status (A), time to RPR (B), nodal status at RN (C) and location of RPR recurrence (D) (log rank p = 0.012, 0.04, 0.005 and 0.370, respectively).

### Locoregional recurrences

<table>
<thead>
<tr>
<th>Table 3. Multivariate Cox regression analysis of cancer specific mortality after RPR surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>pN stage at nephrectomy (pN1 vs pNO/Nx)</td>
</tr>
<tr>
<td>Max RPR tumor diameter/cm</td>
</tr>
<tr>
<td>Recurrence less than 1 yr after RN (yes vs no)</td>
</tr>
<tr>
<td>RPR tumor pos pathologica margin (yes vs no)</td>
</tr>
<tr>
<td>Abnormal hemoglobin (yes vs no)</td>
</tr>
</tbody>
</table>
Conclusions

• Surgery has a clear and defined role in the management of metastatic and locally recurrent kidney cancer

• Risk categorization and personalized patient, physician, and tumor characteristics help delineate when surgery should be performed in this setting

• The importance of a multidisciplinary approach to such patients cannot be overemphasized and should be conducted routinely in such cases
The good physician treats the disease; the great physician treats the patient who has the disease.

(William Osler)