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## Evidence-based Series #3-8-3: Section 1

# The Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Cancer: A Clinical Practice Guideline

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Developed by the Genitourinary Cancer Disease Site Group

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### Question

What is the role of cytoreductive nephrectomy in the management of patients with metastatic renal cell cancer? The outcomes of interest are overall survival and/or progression-free survival, response rate, adverse effects, and quality of life.

### Draft Recommendations

- Cytoreductive nephrectomy is recommended to improve overall survival in appropriately selected patients with metastatic renal cell cancer planned to receive interferon-alpha2b immunotherapy. Appropriately selected patients include:
  - Patients with a primary tumour of clear cell histology amenable to surgical extirpation and a low risk of perioperative morbidity.
  - Patients with good performance status (ECOG 0 or 1).
  - Patients without evidence of brain metastases.

### Qualifying Statements

- Biopsy of a primary or metastatic site to determine histology should be performed prior to consideration of cytoreductive nephrectomy.
- In the two trials reviewed for this guideline:
  - Only patients with good performance status were included. Therefore, performance status should be reassessed prior to surgery to ensure that no major decline in performance status has occurred.
  - Patients with brain metastases were excluded. Therefore, imaging of the brain should be performed prior to surgery in patients considered candidates for cytoreductive nephrectomy.
  - Patients with tumour thrombus involving the inferior vena cava below the level of hepatic veins were included.

- Cytoreductive nephrectomy was studied in combination with interferon-alpha2b. It cannot be assumed that the benefits of cytoreductive nephrectomy are the same if patients do not receive postoperative immunotherapy.
- Immunotherapy consisted of interferon-alpha2b initiated within one month of nephrectomy, escalated to a dose of  $5 \times 10^6$  IU/m<sup>2</sup> subcutaneously thrice weekly, and continued until disease progression, unacceptable toxicity despite dose modifications, or completion of 52 weeks of therapy. It cannot be assumed that the benefits of cytoreductive nephrectomy are the same with other forms of immunotherapy.
- They did not address nephrectomy combined with metastectomy for patients with single solitary metastases, or palliative nephrectomy for alleviation of symptoms.

### **Key Evidence**

- Two randomized controlled trials comparing cytoreductive nephrectomy and interferon-alpha2b with interferon-alpha2b alone in patients with metastatic renal cell cancer, and one meta-analysis of those two trials, form the evidence base of this review.
- The two trials identified, Southwest Oncology Group Trial 8949 (n=241) and European Organization for the Research and Treatment of Cancer Trial 30947 (n=83), were identical with respect to patient eligibility and trial design. Overall survival and response to interferon-alpha2b were designated as the primary and secondary endpoints in both trials. Data on the complications of nephrectomy and interferon toxicity were also reported in each trial report. The meta-analysis pooled data on overall survival and response (n=331).
- In both trials, responses to interferon-alpha2b were not significantly different between trial arms. The pooled response rates were 6.9% and 5.7% (p=0.60) for nephrectomy and interferon-alpha2b and interferon-alpha2b alone, respectively.
- In both trials, median survival times were significantly longer in patients treated with nephrectomy. The pooled median survival time for patients treated with nephrectomy and interferon-alpha2b was 13.6 months versus 7.8 months in patients treated with interferon-alpha2b alone (p=0.002). Nephrectomy was associated with a 31% reduction in the risk of death (pooled hazard ratio=0.69, 95% confidence interval, 0.55-0.87) compared with interferon-alpha2b alone.
- Nephrectomy and interferon-alpha2b combined therapy were well tolerated in the majority of patients. In the largest trial, 78% of patients experienced no complications related to nephrectomy, 16% experienced moderate complications, and 5% experienced more severe complications. Cardiac toxicity and postoperative infection both occurred in 2% of patients. There was one postoperative death in each trial. Myelotoxicity, nausea, anorexia, and neurological and psychological disorders were the most common toxicities associated with interferon-alpha2b in the smaller trial; those toxicities lead to dose reductions in 32% of patients.

### **Treatment Alternatives**

Patients with metastatic renal carcinoma may be managed with other approaches including:

- Best supportive care.
- Standard immunotherapy approaches including interferon-alpha.
- High-dose interleukin-2 in the context of a clinical trial or investigational setting.
- Novel agents in the setting of a clinical trial.

## Future Research

- A number of novel molecularly targeted therapies are currently being assessed in clinical trials for metastatic renal carcinoma. Metastatic renal carcinoma patients should be encouraged to participate in clinical trials to identify more effective treatments.

## Related Guidelines

- Practice Guideline Report #3-8-1: *The Use of Interferon-alpha for the Treatment of Patients with Locally Advanced or Metastatic Renal Cell Cancer* (in progress).
- Practice Guideline Report #3-8-2: *The Use of Interleukin-2 for the Treatment of Patients with Locally Advanced or Metastatic Renal Cell Cancer* (in progress).

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