



## Complete Summary

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### GUIDELINE TITLE

The role of cytoreductive nephrectomy in metastatic renal cell cancer: a clinical practice guideline.

### BIBLIOGRAPHIC SOURCE(S)

Fleshner N, Waldron T, Winquist E, Lukka H, Genitourinary Cancer Disease Site Group. The role of cytoreductive nephrectomy in metastatic renal cell cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Apr 10. 19 p. (Evidence-based series; no. 3-8-3). [12 references]

### GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

## COMPLETE SUMMARY CONTENT

SCOPE  
METHODOLOGY - including Rating Scheme and Cost Analysis  
RECOMMENDATIONS  
EVIDENCE SUPPORTING THE RECOMMENDATIONS  
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS  
QUALIFYING STATEMENTS  
IMPLEMENTATION OF THE GUIDELINE  
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT  
CATEGORIES  
IDENTIFYING INFORMATION AND AVAILABILITY  
DISCLAIMER

## SCOPE

### DISEASE/CONDITION(S)

Metastatic renal cell cancer

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
Treatment

### **CLINICAL SPECIALTY**

Nephrology  
Oncology  
Surgery

### **INTENDED USERS**

Physicians

### **GUIDELINE OBJECTIVE(S)**

To evaluate the role of cytoreductive nephrectomy in the management of patients with metastatic renal cell cancer

### **TARGET POPULATION**

Patients with metastatic renal cell cancer

### **INTERVENTIONS AND PRACTICES CONSIDERED**

Cytoreductive nephrectomy with interferon-alpha2b immunotherapy

### **MAJOR OUTCOMES CONSIDERED**

- Overall survival
- Progression-free survival
- Response rate
- Adverse effects
- Quality of life

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

### **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

The MEDLINE (1993 through March 2005 week 1), EMBASE (1980 through 2005 week 10), CANCERLIT (1993 through October 2002), and Cochrane Library databases (2004, Issue 4) were systematically searched for relevant papers. MEDLINE and CANCERLIT were searched using the following medical subject headings: "carcinoma, renal cell," "kidney neoplasms," "nephrectomy," and "immunotherapy." EMBASE was searched using the following Excerpta Medica tree

terms: "kidney tumor," "kidney cancer," "nephrectomy," and "immunotherapy." In each database, those subject headings were combined with variations of disease and treatment-specific text words or phrases (e.g., "kidney or renal cell cancer," "nephrectomy," "interferon," "interleukin"). Those terms were then combined with search terms for the following publication types and study designs: randomized controlled trial, controlled clinical trial, meta-analysis, systematic review, and practice guideline.

In addition, the conference proceedings from the annual meetings of the American Society of Clinical Oncology (1995-2005) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guideline Clearinghouse (<http://www.guideline.gov/>) were searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

### **Study Selection Criteria**

Articles were selected for inclusion in this systematic review if they met any of the following criteria:

1. They were published reports or abstracts of randomized controlled trials (RCTs) or meta-analyses comparing cytoreductive nephrectomy plus immunotherapy versus immunotherapy alone in adult patients with metastatic renal cell cancer (RCC) and reported any one of the following outcomes: overall survival and/or progression-free survival, response rate, adverse effects, or quality of life.
2. They were systematic reviews or evidence-based guidelines relevant to the guideline question.

### **NUMBER OF SOURCE DOCUMENTS**

Two randomized controlled trials and one meta-analysis of those two trials form the evidence base of this review.

### **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Expert Consensus (Committee)

### **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

Not applicable

### **METHODS USED TO ANALYZE THE EVIDENCE**

Review of Published Meta-Analyses  
Systematic Review with Evidence Tables

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

The results of randomized controlled trials (RCTs) comparing cytoreductive nephrectomy and immunotherapy to immunotherapy alone in patients with metastatic renal cell cancer (RCC) were not statistically pooled due to the availability of an up-to-date, published meta-analysis of the two eligible RCTs.

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

The Genitourinary Disease Site Group (GU DSG) reviewed the available evidence from two randomized trials comparing cytoreductive nephrectomy and interferon-alpha2b (IFN-a2b) to IFN-a2b alone in patients with metastatic renal cell cancer (RCC), as well as a recently published meta-analysis of those two trials. The overall pooled result, which provides a more precise estimate of the treatment effect because it includes more patients, favours combined treatment with nephrectomy with an improved median survival of 5.8 months compared with immunotherapy alone. This translates to an improvement in one-year survival from 37.1% to 51.9%. The survival curves from that analysis do not seem to flatten, indicating a modest prolongation in survival with eventual progression and death due to renal cell cancer in most patients. Although the survival impact was statistically significant, actual regression of metastatic lesions were rare (approximately 6%) and not significant between the two treatment groups. Nephrectomy was associated with a low operative death rate (1.4%) and a high percentage of patients without surgical complications (76%) who went on to receive treatment with IFN-a2b (>90%).

Both trials applied very selective patient eligibility criteria. Further, it took seven years to accrue patients in the larger Southwest Oncology Group (SWOG) trial, suggesting selection bias was likely operating during the patient recruitment process of that trial. As a result, the findings of both randomized controlled trials (RCTs) are applicable to a select group of patients with metastatic renal cell cancer and should not be generalized to other patient subgroups. Selective patients include those with clear cell subtype of renal cell cancer with no evidence of brain metastases, and a performance status of 0 or 1. Members of the Genitourinary Disease Site Group agreed that these criteria require that prior to surgery all patients considered for this treatment approach should have a mandatory biopsy to determine histological subtype, imaging be performed to rule out brain metastases, and performance status be reassessed to ensure no decline in performance status has occurred. There is evidence from retrospective studies that patients with solitary metastases, particularly to lung and bone, can achieve durable complete remission with nephrectomy in conjunction with metastectomy. Data from the Southwest Oncology Group and European Organization for the Research and Treatment of Cancer (EORTC) trials cannot confirm or refute these findings as neither trial included metastectomy as part of treatment.

Although no difference in response rates to IFN-a2b between trial arms was observed in either trial, the Genitourinary Disease Site Group thought it was

important to emphasize that it cannot be assumed that the benefits of nephrectomy are the same without IFN- $\alpha$ 2b, or with another type of immunotherapy such as interleukin-2 (IL-2). Treatment should mimic the approach administered to patients in the Southwest Oncology Group and European Organization for the Research and Treatment of Cancer trials, which consisted of IFN- $\alpha$ 2b 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 or completion of 52 weeks of therapy.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

Not applicable

## **COST ANALYSIS**

A formal cost analysis was not performed and published cost analyses were not reviewed.

## **METHOD OF GUIDELINE VALIDATION**

External Peer Review  
Internal Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

### **Internal Review**

Prior to submission of this evidence-based series report for external review, the report was reviewed and approved by the Program in Evidence-Based Care (PEBC) Report Approval Panel, which consists of two members including an oncologist, with expertise in clinical and methodological issues. Key issues raised by the Panel included only editorial changes; changes were made to the introduction and results section of the systematic review in order to provide clarification.

### **External Review**

Following review and discussion of sections 1 and 2 of this evidence-based series and review and approval of the report by the PEBC Report Approval Panel, the Genitourinary Disease Site Group (GU DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Feedback was obtained through a mailed survey of 94 clinicians in Ontario (medical oncologists and urologists). The survey consisted of items evaluating the methods, results, and interpretation used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on November 11, 2005. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The GU DSG reviewed the results of the survey.

## RECOMMENDATIONS

### MAJOR 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 (Eastern Collaborative Oncology Group [ECOG] 0 or 1)
- Patients without evidence of brain metastases

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by two randomized controlled trials and a meta-analysis of those two trials.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

- 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.

### POTENTIAL HARMS

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.

## QUALIFYING STATEMENTS

### 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.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## **INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES**

### **IOM CARE NEED**

Living with Illness

### **IOM DOMAIN**

Effectiveness

## **IDENTIFYING INFORMATION AND AVAILABILITY**

### **BIBLIOGRAPHIC SOURCE(S)**

Fleshner N, Waldron T, Winquist E, Lukka H, Genitourinary Cancer Disease Site Group. The role of cytoreductive nephrectomy in metastatic renal cell cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Apr 10. 19 p. (Evidence-based series; no. 3-8-3). [12 references]

### **ADAPTATION**

Not applicable: The guideline was not adapted from another source.

### **DATE RELEASED**

2006 Apr 10

### **GUIDELINE DEVELOPER(S)**

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

### **GUIDELINE DEVELOPER COMMENT**

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

### **SOURCE(S) OF FUNDING**

Cancer Care Ontario  
Ontario Ministry of Health and Long-Term Care

### **GUIDELINE COMMITTEE**

Provincial Genitourinary Cancer Disease Site Group

## **COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE**

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

The authors disclosed potential conflicts of interest relating to this systematic review and none were declared.

## **GUIDELINE STATUS**

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## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

## **AVAILABILITY OF COMPANION DOCUMENTS**

The following are available:

- The role of cytoreductive nephrectomy in metastatic renal cell cancer: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Apr 10. Various p. (Practice guideline; no. 3-8-3. Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This NGC summary was completed by ECRI on June 8, 2006. The information was verified by the guideline developer on June 26, 2006.

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