Evidence-based Series 3-8-3 EDUCATION AND INFORMATION 2011

The Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Cancer

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Evidence-based Series (EBS) 3-8-3 was reviewed and put in the Education and Information section in September 2011. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol). The EBS consists of:

1. Guideline Report Overview
2. Section 1: Clinical Practice Guideline
3. Section 2: Evidentiary Base
4. Section 3: EBS Development Methods and External Review Process and Results

and is available on the CCO website (http://www.cancercare.on.ca)
PEBC Genitourinary Cancer Disease Site Group page at:
https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/genito-fts/

Release Date: May 15, 2012

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The Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Cancer

Guideline Report History

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EBS 3-8-3 EDUCATION AND INFORMATION 2011

Evidence-based Series 3-8-3 ARCHIVED 2011

The Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Cancer

Guideline Review Summary

Review Date: September 2011

The 2006 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW
Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) in 2006. In September 2011, the PEBC guideline update strategy was applied, and the recommendations were archived. The Summary and Full Report in this version are the same as October 2006 version.

Update Strategy

The PEBC update strategy includes an annual screening of our guidelines and if necessary, an updated search of the literature is completed with the review and interpretation of new eligible evidence by the clinical experts from the authoring panel and consideration of the guideline and its recommendations based on the new available evidence.

Impact on Guidelines and Its Recommendations

During the annual screening process, it was agreed that this document will no longer be maintained by PEBC therefore no update search was conducted. The 2006 guideline and its recommendations on the role of cytoreductive nephrectomy in metastatic renal cell cancer have been ARCHIVED.
Review outcomes definitions.

1. ARCHIVED - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase “ARCHIVED”.

2. ENDORSED - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DEFERRAL - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool.

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.
The Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Cancer: A Clinical Practice Guideline

N. Fleshner, T. Waldron, E. Winquist, H. Lukka, and Members of the Genitourinary Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Genitourinary Cancer Disease Site Group

Report Date: April 10, 2006

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/m² 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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The Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Cancer: A Systematic Review

N. Fleshner, T. Waldron, E. Winquist, H. Lukka, and Members of the Genitourinary Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Genitourinary Cancer Disease Site Group

Report Date: April 10, 2006

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

INTRODUCTION
Renal cell carcinomas account for three percent of all adult solid malignancies (1). It is estimated that, in 2004, 4,300 patients were diagnosed with the disease in Canada (2). At the time of first diagnosis, 45% of patients will present with localized disease, 25% will have locally advanced disease with lymph node or local organ involvement, and the remaining 30% will present with metastases (3).

In the 1980’s, when the fundamentals of surgical oncology were becoming widely disseminated, the general opinion was that surgical removal of the primary tumour had a limited role in metastatic disease since systemic metastases were largely responsible for deaths. In the late 1980’s and early 1990’s, the positive activity of immunotherapy for metastatic RCC became apparent. Small studies and larger phase II cohort studies began to display evidence of tumour response with interferon-alpha (IFN-a) and interleukin-2 (IL-2). The response rates appeared low but were better than what had historically been achieved with cytotoxic chemotherapy. As retrospective analyses of risk factors for response to treatment among those cohorts were performed, consistent data suggested that patients who had a prior nephrectomy achieved superior results with immunotherapy. Debates existed as to the rationale behind that observation, with many believing that this was a by-product of selection bias, while others reasoned that nephrectomy could exert some biological effect on patient survival.

Against that background, the Southwest Oncology Group (SWOG) and the European Organization for the Research and Treatment of Cancer (EORTC) initiated trials of immunotherapy with or without nephrectomy in patients with metastatic RCC. The Genitourinary Cancer Disease Site Group (GU DSG) felt that an evidence-based guideline for this intervention was needed in order to: 1) interpret and disseminate evidence from those trials among urologists in Ontario to ensure surgery is reserved for appropriate patients most likely to benefit from the approach and 2)
to clarify, for both surgeons and their patients, the modest benefits of surgery and the necessity of perioperative immunotherapy.

METHODS

This systematic review was developed by Cancer Care Ontario’s Program in Evidence-based Care (PEBC) using the methods of the Practice Guidelines Development Cycle (4). Evidence was selected and reviewed by three members of the GU DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on the role of cytoreductive nephrectomy in the management of patients with metastatic RCC. The body of evidence in this review is primarily comprised of randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the GU DSG (refer to Section 1). The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

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 Guidelines Clearinghouse (http://www.guideline.gov/index.asp) 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 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.

Synthesizing the Evidence

The results of RCTs comparing cytoreductive nephrectomy and immunotherapy to immunotherapy alone in patients with metastatic RCC were not statistically pooled due to the availability of an up-to-date, published meta-analysis of the two eligible RCTs (5).
RESULTS

Literature Search Results
The literature search identified two RCTs that satisfied the eligibility criteria (6,7). SWOG trial 8949 (7) and EORTC trial 30947 (6) both compared outcomes associated with cytoreductive nephrectomy and IFN-alpha2b (IFN-a2b) versus IFN-a2b alone in patients with metastatic RCC. Summary data from those two trials were recently combined in a meta-analysis (5). The results of both trials and the combined analysis are summarized in this report. No previous systematic reviews or practice guidelines relevant to the guideline question were identified.

Outcomes

Randomized Controlled Trials
SWOG 8949 (n=241) and EORTC 30947 (n=83) were identical with respect to patient eligibility criteria and trial design (Table 1). Both trials recruited previously untreated patients with metastatic RCC and good performance status (SWOG/Eastern Collaborative Oncology Group [ECOG] 0 or 1). The treatment arms of both trials were reported to be well balanced in terms of important patient prognostic variables, with the exception of performance status in the SWOG trial. In that trial, significantly more patients with a worse performance status of 1 were randomized to the IFN-a2b control arm (p=0.04) (58.1%, versus 45% in the nephrectomy arm). Stratification variables, the nephrectomy procedure, and the dosing and timing of IFN-a2b were the same in each trial. Both trials assessed whether nephrectomy performed prior to treatment with IFN-a2b prolonged overall survival and improved response rates to IFN-a2b. Data on IFN-a2b toxicity and complications of nephrectomy were presented in each trial report.

In 2004, a combined analysis of SWOG 8949 and EORTC 30947 was published that was based on summary data (n=331) from each of the trials (5). In that report, data were pooled for the outcomes of overall survival and response.

Table 1: Randomized controlled trials comparing cytoreductive nephrectomy and interferon-alpha2b versus interferon-alpha2b alone in adult patients with metastatic renal cell cancer.

<table>
<thead>
<tr>
<th>Trial Descriptors</th>
<th>SWOG 8949 (7)</th>
<th>EORTC 30947 (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Characteristics</strong></td>
<td>Histologically confirmed metastatic RCC with metastases beyond regional lymphatics, no brain metastases, IVC thrombus below hepatic veins if present</td>
<td>No prior treatment, defined as no prior chemotherapy, hormonal therapy, radiotherapy, or biological response modifying agents</td>
</tr>
<tr>
<td></td>
<td>No prior treatment, defined as no prior chemotherapy, hormonal therapy, radiotherapy, or biological response modifying agents</td>
<td>PS of 0 or 1 (WHO)</td>
</tr>
<tr>
<td><strong>Stratification Variables</strong></td>
<td>PS, presence or absence of lung metastases, presence or absence of measurable disease not to be resected</td>
<td>PS of 0 or 1 (WHO)</td>
</tr>
<tr>
<td><strong>No. Randomized</strong></td>
<td>246</td>
<td>85</td>
</tr>
<tr>
<td><strong>No. Eligible</strong></td>
<td>241</td>
<td>83</td>
</tr>
<tr>
<td><strong>Treatment Arm</strong></td>
<td>Radical nephrectomy + IFN-a2b</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Nephrectomy:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transabdominal, flank, or thoracoabdominal approach; excision of tumour outside Gerota’s fascia; early ligation of renal artery and vein; extent of lymphadenectomy not defined; performed within 4 wks of enrollment</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>IFN-a2b (sc):</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initiated within one month of nephrectomy, escalated to a dose of 5 x 10^6 IU/m^2, 3 times per wk until disease progression or toxicity for a maximum 52 wks</td>
<td></td>
</tr>
<tr>
<td><strong>Control Arm</strong></td>
<td>IFN-a2b</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>IFN-a2b (sc):</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Escalated to a dose of 5 x 10^6 IU/m^2, 3 times per wk until disease progression or toxicity for a maximum of 52 wks</td>
<td></td>
</tr>
</tbody>
</table>
Efficacy Data

Table 2 summarizes the data on overall survival and response from the two randomized trials (6,7) and the combined analysis (5). In the combined analysis, it is unclear whether the authors had access to additional patient data, as the estimates they used were not always the same as what was reported in the original trial reports. Therefore, the combined estimates may not always equate with the individual trial estimates summarized in Table 2. In all three reports, analyses of survival data included all eligible randomized patients according to intent-to-treat.

Response rates varied considerably between the two trials, with more responses observed in the EORTC trial (6). The authors of the SWOG trial attributed the low response rates in their trial to SWOG response criteria being more rigorous than other commonly used criteria. However, response rates were not significantly different between treatment arms in either trial. The pooled analysis of response data also did not detect a significant difference by treatment arm; the pooled response rates were 6.9% for nephrectomy and IFN-a2b compared with 5.7% for IFN-a2b alone (p=0.60) (5).

Both trials assessed overall survival after approximately one year of follow-up. In each trial, median survival times were significantly longer in patients treated with nephrectomy; patients receiving nephrectomy and IFN-a2b survived approximately three months and 10 months longer than control patients in the SWOG and EORTC trials, respectively. Time-to-disease progression was also prolonged in patients treated with nephrectomy in the EORTC trial (median time-to-progression, five months versus three months; p=0.04; hazard ratio for time-to-progression, 0.60; 95% confidence interval [CI], 0.36-0.97) (6). In the combined analysis, the pooled median survival times for patients treated with and without nephrectomy were 13.6 months and 7.8 months (p=0.002), respectively, and the pooled hazard ratio was 0.69 (95% CI, 0.55-0.87), which represents a 31% reduction in the risk of death with surgery. Survival was also analyzed by subgroups defined by each stratification parameter. In each subgroup, nephrectomy was associated with a survival benefit, but there were no differences in the size of the treatment effect among the levels of each subgroup. The authors also report results from a prognostic factor analysis, although the methods and complete results of that analysis were not presented in the published report. Of the three stratification parameters, performance status was the only parameter to have prognostic importance. Survival was significantly longer in patients with a performance status of 0 (p<0.0001) compared with patients with a poorer performance status of 1. The median survival estimates for each performance status group were not reported.

It could be argued that the survival advantage associated with nephrectomy in the larger SWOG trial (and thus the combined analysis as well) may in fact be attributable to the imbalance in performance status between trial arms, since significantly more patients in the IFN-a2b arm had a poorer performance status. The investigators of the trial argue that, since the median survival estimates in each performance group favoured combined therapy, and no significant interaction between treatment group and performance status was detected in a proportional-hazards regression model, it is unlikely that the imbalance influenced the survival outcome of the trial.

Surgical Complications and Interferon Toxicity

In general, nephrectomy and IFN-a2b therapy were well tolerated among patients. Among 98 evaluable patients in the SWOG trial (7), 78% experienced no complications related to surgery, 16% experienced mild to moderate complications, and 5% experienced more severe complications. Cardiac toxicity and postoperative infection both occurred in 2% of patients. There was one reported death in the nephrectomy arm of this trial; that patient had an unresectable tumour and died from wound dehiscence and intrabdominal abscess with peritonitis. The mean duration of hospitalization for patients undergoing nephrectomy was 8.2 days, and the mean time-
to-initiation of therapy with IFN-a2b was approximately 20 days. Among the 210 patients evaluable for IFN-a2b toxicity across treatment groups, 11% percent experienced severe adverse effects, and one patient died as a result of a myocardial infarction attributed to IFN-a2b.

In the EORTC trial (6), surgery and IFN-a2b were also considered manageable by most patients; six patients experienced postoperative complications, and there was one reported postoperative death. There were no significant differences in toxicities observed with IFN-a2b between the two treatment groups; the most frequent toxicities in both groups were myelotoxicity, nausea, anorexia, and neurological and psychological disorders. Those adverse events led to IFN-a2b dose reductions in 32% of patients.

Table 2: Efficacy results from two randomized trials comparing cytoreductive nephrectomy plus interferon-alpha2b versus interferon-alpha2b alone in adult patients with metastatic renal cell carcinoma.

<table>
<thead>
<tr>
<th>Trial Outcome (reference)</th>
<th>Treatment Arms</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nephrectomy + IFN-a2b</td>
<td>IFN-a2b</td>
</tr>
<tr>
<td>SWOG 8949 (7)</td>
<td>n=120</td>
<td>n=121</td>
</tr>
<tr>
<td>Response rate % (CR + PR)</td>
<td>3.3 (0 + 3)</td>
<td>3.6 (1 + 1, plus 1 unconfirmed)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>11.1</td>
<td>8.1</td>
</tr>
<tr>
<td>1-year survival %</td>
<td>49.7</td>
<td>36.8</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>EORTC 30947 (6)</td>
<td>n=42</td>
<td>n=42</td>
</tr>
<tr>
<td>Response rate (CR + PR)</td>
<td>19 (5 + 3)</td>
<td>12 (1 + 4)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>1-year survival %</td>
<td>59.3*</td>
<td>33.7*</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.54 (0.31-0.94)</td>
<td></td>
</tr>
<tr>
<td>Combined Analysis (5)†</td>
<td>n=161</td>
<td>n=163</td>
</tr>
<tr>
<td>Response rate % (CR + PR)</td>
<td>6.9 (3 + 6)</td>
<td>5.7 (2 + 4)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>13.6</td>
<td>7.8</td>
</tr>
<tr>
<td>1-year survival %</td>
<td>51.9</td>
<td>37.1</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.69 (0.55-0.87)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI – confidence interval; CR – complete response; EORTC – European Organization for the Research and Treatment of Cancer; IFN-a2b – interferon-alpha2b, n – number of patients; NR – not reported; PR – partial response; SWOG – Southwest Oncology Group.

*estimated from published survival curve.
†for some outcomes the estimates used in the combined analysis were different from what was reported in the original trial reports; therefore, the combined estimates may not equate with the individual trial estimates (i.e., absolute number of complete and partial responses).

DISCUSSION

The GU DSG reviewed the available evidence from two randomized trials comparing cytoreductive nephrectomy and IFN-a2b to IFN-a2b alone in patients with metastatic 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 RCC 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%).

SYSTEMATIC REVIEW – page 5
Both trials applied very selective patient eligibility criteria. Further, it took seven years to accrue patients in the larger SWOG trial, suggesting selection bias was likely operating during the patient recruitment process of that trial (8). As a result, the findings of both RCTs are applicable to a select group of patients with metastatic RCC and should not be generalized to other patient subgroups. Selective patients include those with clear cell subtype of RCC with no evidence of brain metastases, and a performance status of 0 or 1. Members of the GU DSG 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 (9,10). Data from the SWOG and 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 GU DSG thought it was important to emphasize that it cannot be assumed that the benefits of nephrectomy are the same without IFN-a2b, or with another type of immunotherapy such as IL-2. Treatment should mimic the approach administered to patients in the SWOG and EORTC trials, which consisted of IFN-a2b initiated within one month of nephrectomy escalated to a dose of $5 \times 10^6$ IU/m² subcutaneously thrice weekly and continued until disease progression, unacceptable toxicity or completion of 52 weeks of therapy.

ONGOING TRIALS
The National Cancer Institute’s clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for ongoing trials. No ongoing trials that compared nephrectomy plus immunotherapy versus immunotherapy alone in patients with metastatic RCC were identified.

CONCLUSIONS
In patients with metastatic RCC, cytoreductive nephrectomy followed by immunotherapy with IFN-a2b is associated with a modest survival benefit when compared with IFN-a2b alone. This treatment approach should only be offered to patients who have a primary tumour of clear cell histology with no evidence of brain metastases and good performance status.

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

JOURNAL REFERENCES
A manuscript is in preparation.

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For a complete list of the Genitourinary Cancer Disease Site Group members, please visit the CCO website at http://www.cancercare.on.ca.

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REFERENCES

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

The Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Cancer: Guideline Development and External Review – Methods and Results

N. Fleshner, T. Waldron, E. Winquist, H. Lukka and Members of the Genitourinary Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Genitourinary Cancer Disease Site Group

Report Date: April 10, 2006

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines
Each Evidence-based Series is comprised of three sections.
- **Section 1: Clinical Practice Guideline.** This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
• **Section 2: Systematic Review.** This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.

• **Section 3: Guideline Development and External Review: Methods and Results.** This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

**DEVELOPMENT OF THIS EVIDENCE-BASED SERIES**

**Development and Internal Review**

This evidence-based series was developed by the Genitourinary Cancer Disease Site Group (GU DSG) of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on the role of cytoreductive nephrectomy in the management of patients with metastatic renal cell cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario. The GU DSG is comprised of medical and radiation oncologists, urologists, a pathologist, and methodologists. For a current list of GU DSG members please visit [http://www.cancercare.on.ca/](http://www.cancercare.on.ca/).

**Report Approval Panel**

Prior to submission of this evidence-based series report for external review, the report was reviewed and approved by the 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 by Ontario Clinicians**

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 GU DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations developed by the panel.

**BOX 1:**

**DRAFT RECOMMENDATIONS (approved for external review November 11, 2005)**

**Recommendation**

- Cytoreductive nephrectomy is recommended to improve overall survival in appropriately selected patients with metastatic renal cell cancer planned to receive interferon-alpha-2b 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-alpha-2b. It cannot be assumed that the benefits of cytoreductive nephrectomy are the same if patients do not receive postoperative immunotherapy.
- Immunotherapy consisted of interferon-alpha-2b initiated within one month of nephrectomy, escalated to a dose of 5 x 10^6 IU/m^2 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.

**Methods**

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 above 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.

**Results**

Fifty-seven surveys were received out of the 94 surveys sent (61% response rate). Responses included returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 48 (84%) indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the survey are summarized in Table 1.

**Table 1. Responses to eight items on the practitioner feedback survey.**

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a clinical practice guideline, as stated in the &quot;Choice of Topic&quot; section of the report, is clear.</td>
<td>Strongly agree or agree: 47 (97.9), Neither agree nor disagree: 1 (2.1), Strongly disagree or disagree: 0</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>Strongly agree or agree: 41 (85.4), Neither agree nor disagree: 5 (10.4), Strongly disagree or disagree: 2 (4.2)</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>Strongly agree or agree: 39 (83), Neither agree nor disagree: 6 (12.8), Strongly disagree or disagree: 2 (4.3)</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>Strongly agree or agree: 46 (95.8), Neither agree nor disagree: 2 (4.2), Strongly disagree or disagree: 0</td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>Strongly agree or agree: 44 (91.7), Neither agree nor disagree: 3 (6.3), Strongly disagree or disagree: 1 (2.1)</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>Strongly agree or agree: 37 (77.1), Neither agree nor disagree: 7 (14.6), Strongly disagree or disagree: 4 (8.4)</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>Strongly agree or agree: 29 (61.7), Neither agree nor disagree: 10 (21.3), Strongly disagree or disagree: 8 (17.1)</td>
</tr>
<tr>
<td>If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?</td>
<td>Very likely or likely: 35 (74.4), Unsure: 6 (12.8), Not at all likely or unlikely: 6 (12.8)</td>
</tr>
</tbody>
</table>
Summary of Written Comments

Twenty-two respondents (46%) provided written comments. The main points contained in the written comments were:

1. Six practitioners made comments suggesting they do not believe the efficacy of this treatment approach has been established. Specifically,
   a) Four practitioners were sceptical that a survival benefit of approximately six months would improve the quality of life of patients, especially in light of the adverse effects of treatment. Since quality of life data are not available from the trials it is unclear how clinically significant the observed benefit actually is. One practitioner commented that at least three weeks of the survival time would be spent in hospital post-operatively.
   b) Two practitioners believe that selection bias, especially in the SWOG trial, contributed to the outcome of the trials, and therefore, believe more trials are required to confirm the benefit of this treatment approach.

2. A number of comments were suggested modifications to the draft recommendations or the body of the report. The suggested changes were as follows:
   a) Two practitioners disagreed with the requirements that patients should undergo routine biopsy; one practitioner thought biopsy is not necessary if the lesion is obviously vascular, while another practitioner noted that the yield of CT scans of the head in the absence of clinical symptoms is low, therefore this type of investigation should not be routine.
   b) One practitioner thought the draft recommendations were too broad and require more explicit direction as to “how much metastatic disease”.
   c) One practitioner wondered why the recommendations are only applicable to patients with clear cell-type RCC; another practitioner thought this treatment approach should also be offered to patients with mixed and granular cell-type RCC.
   d) One practitioner thought the recommendations are reasonable if one accepts that cytoreductive nephrectomy is not the same as palliative nephrectomy. Many patients with advanced disease are considered for nephrectomy for palliation of bleeding, pain, IVC thrombosis extension etc. The distinction may not be apparent to all readers of the guideline, and therefore it is suggested that it appear somewhere in the report.
   e) One practitioner suggested the discussion of molecularly targeted therapies under Future Research should be moved to the Treatment Alternatives section because of the strength of benefit in the absence of other alternatives and immunotherapy failures.

3. Other comments, relating to immunotherapy, were as follows:
   a) One practitioner commented that while there appears to be some benefit to combination nephrectomy and IFN-a2b in a select group of patients with metastatic RCC, an important question is whether the addition of IFN-a2b is any better than nephrectomy alone. Although this question cannot be answered by this report it must be considered before guidelines are considered. Another practitioner commented that there was not much discussion within the report of the non-effect of IFN-a2b.
   b) Two practitioners were concerned with the cost/funding of IFN-a2b therapy.
   c) Based on observations of patients, one practitioner thought cytoreductive nephrectomy may be used prior to systemic IL-2 even though the randomized trials have not examined the effect of this treatment approach. It was suggested that a discussion of IL-2 trials might be of benefit.

4. Other comments were as follows:
   a) It was suggested by one practitioner that cytoreductive nephrectomy may also benefit symptomatic patients.
   b) Two practitioners had comments related to guidelines themselves. One practitioner believes this type of work to be valuable, educational, and helps guide practice
approaches, however is also of the opinion that guidelines can be dangerous tools that often create too rigid a framework often considered gospel by non-medical players (e.g., legal, parliamentary). Flexibility in patient care should be considered a very important aspect to an individual’s practice. Another practitioner commented that publishing a definitive guideline on this topic could take away clinical judgement and force urologists to make inappropriate decisions for their patients. Instead, it was suggested that patients continue to enter onto protocols involving new agents.

c) Two practitioners commented that the guideline and systematic review were very good, comprehensive, and excellent analyses of the available literature.

**Modifications/Actions**

1. Regarding comments that the efficacy of this treatment approach has not been established:
   a) Unfortunately, there are no quality of life data available from the randomized trials to quantify the clinical significance of the six month survival benefit observed. However, in light of the low morbidity observed with combined treatment in the larger SWOG trial (78% of patients experienced no complications related to nephrectomy, 16% experienced moderate complications, and 5% experienced more severe complications) and the short post-operative period associated with the nephrectomy procedure (six days or two or three days with laparoscopic surgery) the GU DSG believes combined treatment improves the quality of life of selected patients offered the approach.
   b) It is possible that selection bias was operating in the SWOG trial since it took over seven years to recruit patients to the trial; this issue is discussed on p. 6 in the Discussion section of the systematic review. However, it is important to note that the EORTC trial confirmed the results of the SWOG trial.

2. Regarding suggestions or changes to the wording of the draft recommendations or body of the full report:
   a) Clear cell histology was an eligibility criterion for entry onto both trials reviewed in this report. Since a biopsy is the only method of identifying tumour histology, the GU DSG believes this testing should be mandatory to identify appropriate patients likely to receive benefit. A CT should also be performed to rule out the presence of metastases even in the absence of clinical symptoms.
   b) The degree of metastatic involvement was not described in either trial reviewed in this report; rather, performance status was used as a surrogate measure for extent of metastases. Performance status is addressed in the guideline recommendations.
   c) See the GU DSG’s response regarding clear cell histology in 2 (a).
   d) The GU DSG agrees with this comment, and has added text to the last qualifying statement of the recommendations to address this issue.
   e) A fourth bullet has been added to the Treatment Alternatives section to address this point.

3. Regarding the comments related to immunotherapy:
   a) This point is addressed in the second qualifying statement (fourth sub-bullet) of the guideline recommendations, and the non-effect of IFN-a2b (related to objective response rates) is discussed in the Discussion section of the systematic review.
   b) While important, cost and funding issues are beyond the scope of this report; these issues are considered by the Drug Quality and Therapeutics Committee.
   c) It cannot be assumed that the benefits observed with nephrectomy and IFN-a combined treatment are the same if nephrectomy is combined with other forms of immunotherapy (including IL-2). This point is addressed in the second qualifying statement (fifth sub-bullet) of the guideline recommendations and in the Discussion section of the systematic review.
4. Regarding the other comments:
   a) See the GU DSG’s response regarding palliative nephrectomy in 2 (d).

RELATED PRINT AND ELECTRONIC PUBLICATIONS


REFERENCES
