Evidence-based Series #7-4 Version 2 -IN REVIEW

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

Use of Preoperative Chemotherapy With or Without Postoperative Radiotherapy in Technically Resectable Stage IIIA Non-Small Cell Lung Cancer

Members of the Lung Cancer Disease Site Group

An assessment conducted in December 2016 placed Evidence-based Series (EBS) 7-4 Version 2 IN REVIEW. This means that it is undergoing review for currency and relevance. The Lung Cancer Disease Site Group has determined that it is still appropriate for this document to continue to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document.

(PEBC Assessment & Review Protocol)

This document is available on the CCO website and is comprised of the following 3 sections:

Section 1: Clinical Practice Guideline (ENDORSED)
Section 2: Systematic Review
Section 3: Document Review Summary and Tool

Release Date: May 16, 2013

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PEBC Report Citation (Vancouver Style): Members of the Lung Cancer Disease Site Group. Use of preoperative chemotherapy with or without postoperative radiotherapy in technically resectable stage

Guideline Report History

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Members of the Lung Cancer Disease Site Group

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

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 3: Document Review Summary and Tool for a summary of updated evidence published between 2002 and 2012, and for details on how this Clinical Practice Guideline was ENDORSED.

Report Date: May 16, 2013

Guideline Question

Should preoperative (neoadjuvant) cisplatin-based chemotherapy, with or without postoperative radiotherapy, be offered to patients with technically resectable stage IIIA non-small cell lung cancer (NSCLC), in order to improve survival? Resectability should be determined preoperatively by a thoracic surgeon.

Target Population

These recommendations apply to adult patients with technically resectable Stage IIIA NSCLC, as determined by a thoracic surgeon.

Recommendations

- Stage IIIA non-small cell lung cancer (NSCLC) has a number of different presentations including T3N0 (tumour with chest wall involvement without lymph node involvement) and N2 disease (mediastinal lymph node involvement on the same side of the mediastinum as the primary tumour). Although the surgical approach to patients with stage IIIA disease varies, it is generally accepted that T3N0 tumours should be managed by primary surgical resection. The role of surgery for patients who have histological evidence of N2 disease,
however, is controversial. Many surgeons regard the presence of N2 disease as a contraindication to surgery.

- There is evidence from four small randomized controlled trials (12 to 32 patients per treatment arm) that for patients with technically resectable stage IIIA NSCLC, the use of preoperative cisplatin-based chemotherapy and postoperative radiotherapy results in superior survival compared with surgery and postoperative radiotherapy. Whether the benefits of chemotherapy can be generalized to patients who do not receive postoperative radiotherapy cannot be determined from the existing trials.

- Although the interpretation of these trials is made difficult by their small size and presence of retrospectively identified imbalances in prognostic factors, the available evidence leads the Lung Cancer Disease Site Group (DSG) to recommend that preoperative chemotherapy and postoperative radiotherapy be offered to patients with technically resectable, histologically confirmed N2 disease for whom surgery is planned.

Methods
Entries to MEDLINE (through March 2002), CANCERLIT (through March 2002) and Cochrane Library (through Issue 1, 2002) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (through 2001) were systematically searched for evidence relevant to this practice guideline report. Evidence that has emerged in the most recent review of the literature is currently being reviewed by the Lung Cancer DSG. The guideline will be revised in 2002 to incorporate the relevant new evidence.

Evidence was selected and reviewed by four members of the Cancer Care Ontario Practice Guidelines Initiative’s Lung Cancer DSG and methodologists. This practice guideline report has been reviewed and approved by the Lung Cancer Disease Site Group, which comprises medical and radiation oncologists, pathologists, surgeons, epidemiologists, a psychologist, and a medical sociologist. A community representative was present at one meeting during which this recommendation was discussed.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Cancer Care Ontario Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence
- Four small randomized controlled trials (RCTs) were available for review when this guideline report was originally developed. Of the four trials, two are completed and fully published, one is published in abstract form, and one is closed and reports an interim analysis. Although the RCTs used appropriate clinical trials methodology, including planned interim analyses and early stopping rules, retrospective review revealed imbalances between the treatment arms for subsets of stage IIIA disease and for prognostic factors. These factors and the small size of each study limit the interpretation of the results.

- The data from two of the four trials were not combined because the data were not mature in one case and not extractable in the other. The two fully published, completed trials reported a survival benefit for patients treated with preoperative chemotherapy ± postoperative radiotherapy compared with patients who received no preoperative chemotherapy. One trial reported a median survival of 26 months for preoperative
chemotherapy versus eight months for control (p<0.001). A second trial reported an estimated median survival of 64 months for preoperative chemotherapy plus surgery versus 11 months for control (p<0.008) and three-year survival of 56% versus 15% for the two treatment groups respectively. A pooled analysis of two-year survival data from the two completed RCTs yielded an odds ratio for death of 0.18 (95% CI, 0.06 to 0.51) in favour of preoperative chemotherapy.

- There was no difference in postoperative mortality in the trials reviewed. Toxicities associated with chemotherapy were limited primarily to neutropenic fever, nausea and vomiting.
- Since the release of the original guideline two randomized controlled trials published in abstract form were reviewed by the Lung Cancer DSG. Both studies reported no difference in median survival time, and one study reported no difference in the two-year survival rate. Methodologic problems existed in both these studies: in one study, patients in the immediate surgery group who were inoperable received the same chemoradiotherapy regimen as did patients in the combined modality group, and the other study was closed prematurely because of low accrual.

Related Guidelines
- #7-1: Postoperative Adjuvant Chemotherapy and/or Radiation Therapy in Stage II and IIIA Completely Resected NSCLC.

Funding
The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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