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Guideline 7-13 REQUIRES UPDATING

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

Initial Management of Small Cell Lung Cancer (Limited and Extensive Stage) and the Role of Thoracic Radiotherapy and First-Line Chemotherapy

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An assessment conducted in December 2019 indicated that Guideline 7-13 REQUIRES UPDATING. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

The systemic treatment recommendations have been superseded by the recommendations in the ASCO guideline. Please refer to the ASCO recommendations.

Guideline 7-13 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/49411

Section 1:	**Recommendations**
Section 2:	**Guideline – Recommendations and Key Evidence**
Section 3:	**Guideline Methods Overview**
Section 4:	**Systematic Review**
Section 5:	**Internal and External Review**

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Initial Management of Small Cell Lung Cancer (Limited and Extensive Stage) and the Role of Thoracic Radiotherapy and First-Line Chemotherapy

Recommendations

This is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, the systematic review, and the guideline development process, see the Full Report.

GUIDELINE OBJECTIVES

The objective of this guideline was to make recommendations with respect to thoracic radiotherapy and first-line chemotherapy in the treatment of non-resected patients with small cell lung cancer (SCLC).

As a regular Program in Evidence-Based Care updating process, it was decided to update and combine two guidelines on limited-stage (LS) (stage I, II, and III) SCLC (see Appendix 8) and broaden the scope of the guideline to include extensive-stage (ES) (stage IV) SCLC.

TARGET POPULATION

In keeping with recommendations from the International Association for the Study of Lung Cancer and Cancer Care Ontario, we have transitioned to the use of TNM staging rather than the Veterans Affairs staging of LS versus ES. The target population for this guideline are adult patients with non-resected LS (stage I, II, and III) and ES (stage IV) SCLC who can safely receive definitive radiation.

INTENDED USERS

Clinicians involved in the treatment of non-resected adult patients with LS (stage I, II, and III) and ES (stage IV) SCLC.

RECOMMENDATIONS

The systemic treatment recommendations have been superseded by the recommendations in the ASCO guideline. Please refer to the ASCO recommendations.

Recommendations for Patients with LS (Stage I, II, and III) SCLC

1. Thoracic Radiotherapy

In patients with LS (stage I, II, and III) SCLC, the addition of thoracic radiotherapy to standard chemotherapy is recommended. However, there is no clear evidence to inform definitive recommendations for optimal timing, sequential versus concurrent therapies, and optimal dose or regimen.

a) Optimal Timing

- **Qualifying Statement:**
  - It was the consensus of the Working Group members that consultation of radiation oncology should happen as early as possible to facilitate timely therapy with radiation.

b) Sequential or Concurrent

- **Qualifying Statement:**
    - It was the consensus of the Working Group members that concurrent chemotherapy and radiation would generally be considered the standard of care.

c) Dose or Regimen

- **Qualifying Statement:**
    - Currently, dose escalation studies have not shown a benefit in overall survival.
    - The best outcomes in terms of overall survival have been observed in trials using at least 40 Gy in 15 fractions daily or 45Gy in 30 fractions twice daily (or a biologically equivalent dose).

2. Chemotherapy

Etoposide-cisplatin is the preferred regimen for adults who are being treated with combined modality therapy with curative intent.

- **Qualifying Statement:**
    - Although carboplatin is commonly substituted for cisplatin in the etoposide-cisplatin combination, there are insufficient data from clinical trials to demonstrate equivalent outcomes for overall survival.
    - If bolus etoposide-cisplatin is selected as the treatment of choice, there is evidence from one randomized trial that the optimal sequence of administration of the components of the regimen is cisplatin followed by etoposide. The total dose of etoposide per cycle of chemotherapy should be administered in divided doses given daily over three days [1].
    - While not commonly used as a regimen, it is acceptable to offer the alternation of etoposide-cisplatin with cyclophosphamide-doxorubicin-vincristine; however, if this regimen is used, locoregional radiotherapy should not be delivered concurrently with an anthracycline.

a) Typical chemotherapy dosing and schedules used:

Standard chemotherapy doses should be used. The doses and schedules of administration of these recommended chemotherapy regimens are the following:

LS (maximum of 4-6 cycles):

- Cisplatin 75-100 mg/m^2 intravenously (IV) day 1 and etoposide 80-100 mg/m^2 IV days 1-3, every three weeks.
- Cisplatin 25 mg/m^2 IV days 1-3 and etoposide 100 mg/m^2 IV days 1, 2, and 3, every three weeks.
- Carboplatin area under the curve (AUC) 5-6 day 1 and etoposide 100 mg/m^2 IV days 1, 2, and 3, every three weeks.

Recommendations for Patients with ES (Stage IV) SCLC

1. Thoracic Radiotherapy

In patients with ES (stage IV) SCLC, there is insufficient evidence to recommend the addition of thoracic radiotherapy to standard chemotherapy as a standard practice for survival benefit; however, it could be considered on a case-by-case basis to reduce local recurrence.

- **Qualifying Statement:**
  - The following are examples of subgroups of patients that could be considered for thoracic radiotherapy:
    - Low-volume extra-thoracic disease
    - Residual intra-thoracic disease
  - In cases where thoracic radiotherapy is offered to ES SCLC, there is no clear standard for dose or volumes, with dose regimens in trials including 30 Gy in 10 fractions once a day, 45 Gy in 30 fractions twice a day, and 45 Gy in 15 fractions once a day.

There is no evidence to inform definitive recommendations for optimal timing, sequential or concurrent, or dose or regimen.

2. Chemotherapy

In patients with ES SCLC (stage IV), **a** platinum agent plus etoposide is the preferred regimen for adult patients who are being treated with combined modality therapy. Cisplatin and irinotecan represents an alternative treatment option to this, but is associated with increased rates of adverse events such as diarrhea.

- **Qualifying Statement:**
  - A meta-analysis of seven trials of a platinum-etoposide versus a platinum-irinotecan demonstrated modest improvements in overall survival in patients treated with irinotecan. The magnitude of benefit for overall survival was influenced by one trial from Japan and one trial from Korea and it is unclear whether these results may be extrapolated to North American populations. The combination of cisplatin and irinotecan is associated with increased toxicities such as diarrhea, which need to be weighed against modest improvements in overall survival. The clinical importance of this difference is unclear and irinotecan regimens are not currently funded by Cancer Care Ontario for this indication.

a) Typical chemotherapy dosing and schedules used:

Standard chemotherapy doses should be used. The doses and schedules of administration of these recommended chemotherapy regimens are the following:

- Cisplatin 75 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1, 2, and 3, every three weeks.
- Cisplatin 80 mg/m^2 day 1 and etoposide 80 mg/m^2 days 1, 2, and 3, every three weeks.
- Cisplatin 25 mg/m^2 days 1, 2, and 3 and etoposide 100 mg/m^2 days 1, 2, and 3, every three weeks.
- Carboplatin AUC 5-6 day 1 and etoposide 100 mg/m^2 days 1, 2, and 3, every three weeks.
- Cisplatin 60 mg/m^2 day 1 and irinotecan 60 mg/m^2 days 1, 8, and 15, every four weeks.
- Cisplatin 30 mg/m^2 and irinotecan 65 mg/m^2 days 1 and 8, every three weeks.
- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m^2 days 1, 8, and 15, every four weeks.