Guideline 7-3 Version 3

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

Treatment of Patients with Stage III (N2 or N3) Non-Small Cell Lung Cancer

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Section 1: Recommendations

The complete guideline is available on the CCO website: https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/lung-ebs/, and includes a summary of the key evidence associated with each recommendation, the guideline development methods, the evidence review and a summary of the review process.

For information about this document, please contact Dr. A. Swaminath, the lead author, through the PEBC via:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopi@mcmaster.ca

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Treatment of Patients with Stage III (N2 or N3) Non-Small Cell Lung Cancer

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES
The objective of this guideline is to determine the most effective therapy for stage III (N2 or N3) non-small cell lung cancer (NSCLC).

TARGET POPULATION
The target population includes adult patients with clinical or pathological stage III NSCLC (N2 or N3). Patients with stage III NSCLC due to T4 N0, T4 N1, or T3 N1 are not necessarily appropriately managed with these recommendations.

INTENDED USERS
This guideline is targeted for oncologists and thoracic surgeons involved in the treatment of patients with stage III NSCLC.

RECOMMENDATIONS

<table>
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<tr>
<th>Recommendation 1</th>
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<tbody>
<tr>
<td>Concurrent chemoradiation should be used for curative-intent treatment of patients with unresectable, lymph node-positive (N2 or N3) stage III NSCLC.</td>
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<tr>
<td>- There is insufficient evidence to recommend a specific concurrent chemotherapy regimen. Reasonable treatment options include cisplatin combined with one of etoposide, vinorelbine, vinblastine, or pemetrexed and carboplatin combined with paclitaxel. Chemotherapy regimens should be similar to those given in randomized clinical trial protocols.</td>
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<tr>
<td>- A standard dose fractionation of 60 to 66 Gy given in fractions of 2 Gy once per day over six weeks is recommended. Dose escalation beyond 66 Gy with conventional fractionation is not recommended.</td>
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<td>- Hyperfractionated radiotherapy regimens that do not result in acceleration of the treatment course, even though the total nominal radiotherapy dose may be modestly increased, are not recommended.</td>
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<tr>
<td>- Routine use of induction chemotherapy prior to concurrent chemoradiotherapy is not recommended; however, this treatment paradigm can be considered for the management of bulky tumours to allow for radical planning after chemotherapy response.</td>
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Qualifying Statements for Recommendation 1

- Parameters to determine suitability for chemoradiation or other treatment options include but are not limited to performance status, weight loss, and comorbidities.
- Increased toxicity, particularly esophagitis and hematologic events, is associated with the addition of chemotherapy to radiotherapy.
- Although the impact of increasing the predicted biologic equivalent dose via accelerated radiotherapy regimens is unclear, further study of accelerated hypofractionated regimens is of interest to optimize the therapeutic ratio of
treatment, particularly in the context of advanced imaging, radiotherapy planning, and treatment delivery.

- Consolidation chemotherapy is generally not recommended. It is unclear whether patients who received carboplatin/paclitaxel as concurrent therapy should receive it as consolidation therapy.
- Depending on a patient’s response to chemoradiation, surgery as salvage or completion of definitive treatment (preferably by lobectomy) may be an option in a subset of patients and should be discussed at a multidisciplinary case conference. Factors to consider include whether the cancer is potentially technically resectable, patient performance status, and patient preferences.

### Recommendation 2

In patients with potentially resectable (single-station, micrometastatic disease to N2) NSCLC, either definitive chemoradiation therapy or induction therapy followed by surgery (preferably lobectomy) is recommended over either surgery or radiation alone and should be discussed at a multidisciplinary case conference, taking into consideration patient preferences.

### Qualifying Statements for Recommendation 2

- Decisions to pursue surgical resection after induction should be made following restaging investigations and reevaluation of patients’ suitability for surgery.
- Induction therapy includes chemotherapy regimens as listed in Recommendation 1 in combination with a minimum dose of 45 Gy up to a maximum of 60 Gy.
- Primary surgical resection followed by adjuvant therapy is generally not recommended. There may be certain circumstances where it may be technically appropriate (e.g., bulky tumour and single-station, microscopic involvement) and should be discussed at a multidisciplinary case conference.

### Recommendation 3

For patients with unresectable, stage III (N2 or N3) NSCLC who cannot tolerate concurrent chemoradiation, one of the following options is recommended after a full discussion of the benefits, limitations, and toxicities of therapy:

- Sequential chemotherapy followed by radical radiation
  - Increasing the biologic equivalent dose using accelerated hyperfractionated radiotherapy following induction chemotherapy may be considered.
- Radical radiotherapy alone
  - A minimum dose of 60 Gy is recommended.
  - Options for altered fractionation schedules may include hyperfractionation (lower dose per fraction over the standard treatment duration), accelerated fractionation (conventional fraction size and same total dose, given in a shorter period of time), accelerated hyperfractionation (combination of these two), and hypofractionation (higher dose per fraction and fewer fractions).
  - Options for specific altered fractionation schemes may include 40 to 45 Gy/15 daily fractions (hypofractionation), 69.6 Gy/58 fractions twice daily (hyperfractionation), 54 Gy/36 fractions three times daily over 12 consecutive days (continuous, hyperfractionated, accelerated radiotherapy, accelerated...
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hyperfractionation), and 60 Gy/40 fractions three times daily over 18 days (continuous hyperfractionated accelerated radiotherapy weekend-less, accelerated hyperfractionation).

- Radiation for symptom palliation
  - Higher dose/fractionation external beam radiotherapy regimens (e.g., 30 Gy/10 fraction equivalent or greater) are associated with modest improvements in survival and total symptom score and can be used primarily in patients with good performance status. As these improvements are also associated with an increase in side effects or adverse effects, such as radiation esophagitis, various shorter fractionation schedules (e.g., 20 Gy in 5 fractions, 17 Gy in 2 weekly fractions, 10 Gy in 1 fraction) have been demonstrated to provide good symptomatic control with fewer side effects, and can be used for patients requesting shorter treatment courses and/or with poor performance status.

Qualifying Statements for Recommendation 3

- Palliative chemotherapy for patients with stage III disease is not reviewed in this guideline. For a guideline on palliative chemotherapy for locally advanced (stage IIIIB) or metastatic (stage IV) NSCLC disease, please visit the Cancer Care Ontario Web site for the 7-10 version 3 guideline [1].
References

1. Ellis PM, Vella ET, Ung YC. Systemic treatment of advanced non-small cell lung cancer. Toronto (ON): Cancer Care Ontario; Year Month Day. Program in Evidence-Based Care Guideline No.: 7-10 Version 3.