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PRACTICE GUIDELINE

Guideline for radiotherapy with curative intent in patients with early-stage medically inoperable non-small-cell lung cancer

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ABSTRACT

Objectives For this guideline, we investigated the effectiveness of radiotherapy with curative intent in medically inoperable patients with early-stage non-small-cell lung cancer (NSCLC).

Methods The guideline was developed by Cancer Care Ontario's Program in Evidence-Based Care and by the Lung Cancer Disease Site Group through a systematic review of mainly retrospective studies, expert consensus, and formal internal and external reviews.

Recommendations

- Stereotactic body radiation therapy (SBRT) with curative intent is an option that should be considered for patients with early-stage, node-negative, medically inoperable NSCLC.

  Qualifying Statements
  - Because of the high dose per fraction, the planning process and treatment delivery for SBRT require the use of advanced technology to maintain an appropriate level of safety. Consistent patient positioning and 4-dimensional analysis of tumour and critical structure motion during simulation and treatment delivery are essential.
  - Preliminary results for proton-beam therapy have been promising, but the technique requires further clinical study.

- Recommended fractionation schemes for SBRT should result in a biologically effective dose of 100 or greater by the linear quadric model, choosing an α/β value of 10 [$BED_{10(LQ)} \geq 100$].

  Qualifying Statements
  - Because of the increased risk of treatment-related adverse events associated with centrally located tumours, consideration of tumour size and proximity to critical central structures is required when determining the dose and fractionation.
  - Examples of dose–fractionation schemes used in the included studies have been provided.
  - Based on the current evidence and the opinion of the authors, radiation doses at $BED_{10(LQ)}$ greater than 146 might significantly increase toxicity and should be avoided.
  - Determination of the radiation BED by the linear quadratic model has limitations for the extreme hypofractionated schemes used in SBRT.

Key Words Early-stage disease, inoperable tumours, non-small-cell lung cancer, stereotactic body radiation therapy, stereotactic ablative radiation therapy, clinical practice guidelines

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INTRODUCTION

Non-small-cell lung cancer (NSCLC) is the most common type of lung cancer[1]. The standard treatment for patients with early-stage NSCLC is surgery; however, some patients are unable to undergo surgery because of medical comorbidities such as abnormal underlying cardiovascular or pulmonary function[2]. Patients with early-stage NSCLC who are medically inoperable were previously offered conventional radiotherapy [RT (60–66 Gy in 1.8–2.0 Gy fractions)] or were observed without specific cancer treatment. The outcomes for such patients were not ideal, with 2-year survival being less than 40% with either conventional radiation or observation, and local control being only 40%–50% with conventional RT[3,4].

Stereotactic RT uses specialized equipment to position patients so that high-dose fractions can be delivered precisely to a small target or volume of disease. The technique requires complex treatment planning to ensure the accuracy and precision of treatment delivery that is characterized by a steep dose gradient beyond the target volume. Stereotactic body RT (SBRT) and stereotactic ablative RT are considered synonymous for the purposes of this guideline and will be referred to as SBRT from this point forward.

Because outcomes for patients with early-stage NSCLC receiving observation or conventional radiation have not been ideal, Cancer Care Ontario's Radiation Treatment Program, together with its Lung Cancer Disease Site Group (DSG), developed the present guideline containing recommendations for the use of RT with curative intent in medically inoperable patients with early-stage NSCLC.

METHODS

The development of this guideline used the methods of the practice guidelines development cycle[5,6]. The process included a systematic review with interpretation of the evidence by the authors, who then drafted recommendations based on the evidence and expert consensus; internal review by content and methodology experts; and external review by Ontario clinicians and other stakeholders. The authors had expertise in radiation oncology, medical oncology, and health research methodology.

Further details of the methods and findings of the systematic review that informed these recommendations have been published elsewhere[7]. Briefly, MEDLINE, EMBASE, and the Cochrane Library were searched for studies comparing stereotactic radiation treatment with curative intent, observation, and other types of RT for early-stage medically inoperable NSCLC. Comparisons of radiation dose or fractionation schedules for SBRT were included. Preplanned study selection criteria were used to screen the literature. Studies were assessed for quality using the ROBINS-I tool (Risk of Bias in Non-randomized Studies of Interventions, http://www.riskofbias.info).

Internal Review

For the guideline document to be approved, at least 75% of the Lung Cancer DSG have to vote on whether they approve the document, and of those that vote, 75% have to approve the document. The Lung Cancer DSG consists of experts in radiation oncology, medical oncology, and surgical oncology in Ontario. In addition, the Program in Evidence-Based Care's (PEBC's) Report Approval Panel, a 3-person panel with methodology expertise, had to approve the document.

External Review

Two processes were used to obtain feedback on the approved draft guideline from content experts and target users. In the targeted peer review, 7 individuals with content expertise were identified by the authors and were asked to review and provide feedback on the guideline document. In the professional consultation, health care providers with an interest in lung cancer in the PEBC database were contacted and asked to complete a brief online survey about the guideline recommendations. That consultation was intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

RESULTS

The authors held teleconferences to develop and approve the recommendations through informal consensus. Each recommendation took into consideration evidence from the systematic review.

Internal Review

On 18 November 2015, the draft guideline was sent to the Lung Cancer DSG members for approval. Of the 24 members of the Lung Cancer DSG, 21 (88%) voted. Of those 21 voters, 21 (100%) approved the document. Also, 3 Report Approval Panel members, including the PEBC Director and 2 methodology experts, reviewed and approved the draft guideline in December 2015.

External Review

After approval of the document at internal review, the authors circulated the draft document to external review participants for review and feedback. Of the 7 experts in radiation oncology contacted, 4 agreed to be targeted peer reviewers and provided feedback. Table I summarizes the survey results.

In the professional consultation, 102 professionals who practice in Ontario and 19 who practice outside Ontario were contacted. Responses were received from 20 (17%) of the professionals, including from 6 who stated that they did not have an interest in the topic or were unavailable to review the guideline at the time. Table II summarizes the results of the survey responses from the small sample of 14 professionals.

PRACTICE GUIDELINE

The present report integrates available evidence from observational studies found in the systematic review[7] with feedback obtained through the external review process, and has obtained final approval from the Lung Cancer DSG and the Report Approval Panel of the PEBC. The target population for the guideline consists of adult patients with potentially curable early-stage (stage I or II) NSCLC (tumours < 5 cm, without nodal involvement or metastases) who are deemed

medically inoperable or who refuse surgery. The intended users of the guideline are radiation planning and treatment providers, oncologists, thoracic surgeons, respirologists, diagnostic assessment groups, and other health care providers involved with lung cancer.

Recommendation 1

Stereotactic body RT with curative intent is an option that should be considered for patients with early-stage, node-negative, medically inoperable NSCLC.

Qualifying Statements

Because of the high dose per fraction, the planning process and treatment delivery for SBRT require the use of advanced technology to maintain an appropriate level of safety. Consistent patient positioning and 4-dimensional analysis of tumour and critical structure motion during simulation and treatment delivery are essential.

Preliminary results for proton-beam therapy have been promising, but the technique requires further clinical study. More randomized controlled trials are required.

TABLE I Responses to nine items on the targeted peer reviewer questionnaire

Question	Reviewer ratings (*n*=4)				
	Lowest quality (1)	**(2)**	**(3)**	**(4)**	**Highest quality (5)**
Rate the guideline development methods.	0	0	0	2	2
Rate the guideline presentation.	0	0	0	3	1
Rate the guideline recommendations.	0	0	2	1	1
Rate the completeness of reporting.	0	0	2	0	2
Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	1	2	1
Rate the overall quality of the guideline report.	0	0	1	1	2
	Strongly disagree (1)	**(2)**	**Neutral (3)**	**(4)**	**Strongly agree (5)**
I would make use of this guideline in my professional decisions.	0	0	0	2	2
I would recommend this guideline for use in practice.	0	0	0	2	2

What are the barriers or enablers to the implementation of this guideline report?

- This guideline needs to be disseminated to the intended audience or users.
- This guideline provides a good understanding of how to prescribe this therapy to patients.
- All radiation programs are not, as yet, equipped or positioned with the developed expertise to implement lung SBRT based on the guideline and should acquire that expertise in the setting of clinical trials using SBRT in order that a high level of quality assurance is used to move in this direction. Otherwise, patients who are candidates should be offered referral to programs where lung SBRT has been adopted with acceptable quality assurance for planning and treatment delivery.

TABLE II Responses to four items on the professional consultation survey

General questions	Overall guideline assessment [*n* (%)]				
	Lowest quality (1)	**(2)**	**(3)**	**(4)**	**Highest quality (5)**
Rate the overall quality of the guideline report.	0	0	0	6 (43)	8 (57)
	Strongly disagree (1)	**(2)**	**(3)**	**(4)**	**Strongly agree (5)**
I would make use of this guideline in my professional decisions.	0	0	3 (21)	6 (43)	5 (36)
I would recommend this guideline for use in practice.	0	0	1 (7)	4 (29)	9 (64)

What are the barriers or enablers to the implementation of this guideline report?

- The review is thorough and comprehensive.
- It would be helpful if there were patient awareness and education for this guideline.
- The limitation really is the quality of the available source evidence the guidelines are based upon.
- The barriers are primarily related to the availability of the technology and expertise to offer SBRT.
- There seems to be sufficient uncertainty to warrant the collection and analysis of further data from monitoring and assessing patients post treatment, to address the evidence gaps that are mentioned. My belief is that many patients would be very willing to participate if requested to do so on an anonymous basis.

Key Evidence

No randomized trials have compared SBRT with other forms of RT or with observation. One meta-analysis of noncomparative studies[8] and eight retrospective cohort studies[9–16] compared SBRT with observation or with other forms of RT such as accelerated hypofractionated RT, 3-dimensional conformal RT, conventionally fractionated RT, external-beam RT, and proton-beam or carbon-ion therapy. The evidence was considered to be very low quality because of the potential increase in the risk of bias associated with retrospective designs. However, all studies consistently demonstrated that, compared with observation or alternative RT techniques, SBRT was associated with similar or better survival or local control and with similar or fewer adverse effects (for comparisons with alternative RT techniques). The meta-analysis by Grutters *et al.*[8] found that, compared with SBRT, conventional RT was associated with lower rates of overall survival (OS) at 2 years {53% [95% confidence interval (CI): 46% to 60%] vs. 70% [95% CI: 63% to 77%], $p < 0.001$} and 5 years [20% (95% CI: 15% to 24%) vs. 42% (95% CI: 34% to 50%), $p < 0.001$] and with lower rates of disease-specific survival at 2 years [67% (95% CI: 59% to 76%) vs. 83% (95% CI: 75% to 92%), $p = 0.006$] and 5 years [44% (95% CI: 31% to 56%) vs. 63% (95% CI: 50% to 75%), $p = 0.045$][8].

Interpretation of the Evidence

Although the evidence came from retrospective cohort studies, the consistency of the results led the DSG to believe that the potential benefits in OS and local control with SBRT compared with observation and with other RT techniques, especially older conventional RT techniques, outweighed the potential harms associated with SBRT for medically inoperable patients with early-stage NSCLC. They therefore considered SBRT to be a recommended treatment option for this patient population.

Recommendation 2

Recommended fractionation schemes for SBRT should result in a biologically effective dose of 100 or greater by the linear quadric model, choosing an α/β value of 10 [$BED_{10(LQ)} \geq 100$].

Qualifying Statements

Because of the increased risk of treatment-related adverse events associated with centrally located tumours, consideration of tumour size and proximity to critical central structures is required when determining dose and fractionation.

Examples of dose–fractionation schemes from the studies included in the systematic review can be found in Table III[7]. Evidence from the use of those schemes showed consistent tumour control and survival outcomes. Ongoing trials might yield new evidence about optimal stereotactic schedules and recommended doses that are different from those presented in the systematic review.

Based on the current evidence and the opinion of the authors, radiation doses at $BED_{10(LQ)}$ greater than 146 might significantly increase toxicity and should be avoided.

Although the use of radiation doses expressed as BEDs has been advocated, it is important to understand the limitations of the linear quadratic model in determining radiation BEDs for the extreme hypofractionated schemes used in SBRT.

TABLE III Examples of dose–fractionation schemes used in the studies included in the systematic review

Location	Total dose (Gy)	Fractions (*n*)	BED_{10}
Peripheral			
	60	3	180
	54	3	151.2
	55	5	115.5
	48	4	105.6
	66	3	211.2
	60	5	132
Central			
	50	5	100
	48	4	105.6
	60	8	105

BED_{10} = biologically effective dose by the linear quadric model, choosing an α/β value of 10.

Key Evidence

Twelve retrospective observational studies investigated the most appropriate BED cut-off in association with patient outcomes[17–28]. Again, the studies were considered to be very low quality because of their retrospective design. A meta-regression by Zhang *et al.*[29] found a significant OS benefit at 2 years and 3 years with the delivery of a medium BED [83.2–106 (2-year: 76%; 95% CI: 62% to 92%; 3-year: 64%; 95% CI: 57% to 71%)] or a medium-to-high BED [106–146 (2-year: 68%; 95% CI: 61% to 76%; 3-year: 63%; 95% CI: 56% to 71%)] compared with a high BED [>146 (2-year: 56%; 95% CI: 50% to 63%; $p < 0.001$; 3-year: 50%; 95% CI: 43% to 57%; $p < 0.001$)] or a low BED at 3 years only [<83.2 (3-year: 52%; 95% CI: 44% to 62%; $p < 0.005$]. The occurrence of severe adverse events of grades 3–5 was significantly different only between the low and high BED groups. That observation suggests that medium or medium-to-high BEDs might be the most optimal. However, the cut-off was difficult to determine. Several studies suggested that a BED cut-off of approximately 100 is significantly correlated with patient outcome[17,19–22,26]; however, other studies, including the meta-regression by Zhang *et al.,* did not show that association[18,24,25,27,29].

Interpretation of the Evidence

Although variability in the results with the use of a BED cut-off of approximately 100 was evident, the largest studies suggested that a BED close to 100 was associated with OS and local control[17,19–22,26]. The DSG believed that recommending a minimal BED threshold would maximize the beneficial outcomes associated with SBRT without increasing harm. They chose to use 100 as the BED threshold because most of the larger cohort studies found an association of patient outcomes with BED cut-offs of 100, 105, and 106[17,19–22,26]. The DSG selected the lowest value because the Zhang meta-analysis found that, compared with lower values,

medium values between 83.2 and 106 were associated with significantly better survival[29].

Many of the included studies assigned the dose based on the size and location of the tumour. That approach is based on a 2006 study by Timmerman *et al.*[30], which suggested that an increase in damage to critical structures and in the incidence of serious adverse events and toxicity had been found in patients with centrally located tumours when higher dose–fractionation schemes were used. Delivering lower doses, with a minimum BED of 100, to central tumours (compared with peripheral tumours) did not predict inferior OS, local control, or increased toxicity[31]. Those factors should therefore be taken into consideration when deciding on the dose or fractionation schedule.

Although the DSG advocated the use of radiation doses expressed as a BED, it is important to understand the limitations of using the linear quadratic model to determine radiation BED for the extreme hypofractionated schemes used in SBRT. The linear quadratic model has been used as a convenient—and slightly simplified—model to calculate effective dose when treating tumours with conventional fractionated RT. At SBRT's high-dose fractions, other models of tissue injury have been suggested[32–34]. Users should therefore exercise caution when using BED models in comparisons of various SBRT schemes.

UPDATES

All PEBC documents are maintained and updated as described in the PEBC Document Assessment and Review Protocol.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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