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**Guideline 7-21 REQUIRES UPDATING**

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

# Radiotherapy with Curative Intent in Patients with Early Stage, Medically Inoperable, Non-Small Cell Lung Cancer

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**An assessment conducted in November 2021 indicated that Guideline 7-21 REQUIRES UPDATING. It is still appropriate for this document 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)**

**Guideline 7-21 is comprised of 5 sections. You can access the summary and full report here:**
**https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31811**



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# Radiotherapy with Curative Intent in Patients with Early Stage, Medically Inoperable, 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**

To investigate the effectiveness of radiotherapy with curative intent in patients with early stage non-small cell lung cancer (NSCLC) who are medically inoperable.

**TARGET POPULATION**

Adult patients with potentially curable, early stage (Stage I or II) NSCLC (without nodal involvement or metastases), and who are deemed medically inoperable or refuse surgery.

**INTENDED USERS**

Radiation planning and treatment providers, oncologists, thoracic surgeons, respirologists, diagnostic assessment groups, and other healthcare providers involved with lung cancer.

NOTE: Stereotactic body radiation therapy (SBRT) and stereotactic ablative radiation therapy are considered synonymous for the purposes of this guideline and will be referred to as SBRT from this point on.

**RECOMMENDATIONS**

**Recommendation 1**
SBRT with curative intent is an option that should be considered for patients with early stage, node-negative, medically inoperable NSCLC.

***Qualifying Statements for Recommendation 1***

- The planning process and treatment delivery for SBRT require the use of advanced technology to maintain an appropriate level of safety due to the high dose per fraction. Consistent patient positioning and four-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 require further clinical studies. More randomized controlled trials are required.

**Recommendation 2**
Recommended fractionation schemes for SBRT should have a $BED_{10(LQ)}$ of ≥100.[1]

***Qualifying Statements for Recommendation 2***

[1] BED = biological effective dose; LQ = linear quadratic

- Tumour size and proximity to critical central[2] structures [1] requires consideration when determining the dose fractionation due to increased risk of treatment-related adverse events associated with centrally located tumours.
- ***Examples*** of dose/fractionation schemes used in the studies included (see Table 4-2):

| Location | Total dose (Gy)/# of fractions | $BED_{10}$ |
|---|---|---|
| **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 |

- Evidence showed consistent tumour control and survival outcomes using the above schedules. Ongoing trials may yield new evidence regarding optimal stereotactic dosing schedules and recommended doses different than those listed above.
- Based on the current evidence and the opinion of the authors, radiation doses of $BED_{10(LQ)}$ >146 may significantly increase toxicity and should be avoided.
- Although the use of radiation dosages expressed as a biological effective dose has been advocated, it is important to understand the limitations of determining radiation BED using the linear quadratic model for the extreme-hypofractionated schemes used in SBRT.



[2] Central tumours refer to tumours within a 2 cm radius of the distal trachea and proximal bronchial tree.

# Radiotherapy with Curative Intent in Patients with Early Stage, Medically Inoperable, Non-Small Cell Lung Cancer

## Section 2: Guideline – Recommendations and Key Evidence

**GUIDELINE OBJECTIVES**

To investigate the effectiveness of radiotherapy with curative intent in patients with early stage non-small cell lung cancer (NSCLC) who are medically inoperable.

**TARGET POPULATION**

Adult patients with potentially curable, early stage (Stage I or II) NSCLC (without nodal involvement or metastases), and who are deemed medically inoperable or refuse surgery.

**INTENDED USERS**

Radiation planning and treatment providers, oncologists, thoracic surgeons, respirologists, diagnostic assessment groups, and other healthcare providers involved with lung cancer.

NOTE: Stereotactic body radiation therapy (SBRT) and stereotactic ablative radiation therapy are considered synonymous for the purposes of this guideline and will be referred to as SBRT from this point on.

**RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE**

| **Recommendation 1** |
|---|
| SBRT with curative intent is an option that should be considered for patients with early stage, node-negative, medically inoperable NSCLC. |
| ***Qualifying Statements for Recommendation 1*** |
| • The planning process and treatment delivery for SBRT requires the use of advanced technology to maintain an appropriate level of safety due to the high dose per fraction. Consistent patient positioning and four-dimensional analysis of tumour and critical structure motion during simulation and treatment delivery are essential.<br>• Preliminary results for proton beam therapy have been promising but require further clinical studies. More randomized controlled trials are required. |
| ***Key Evidence for Recommendation 1*** |
| There were no randomized trials comparing SBRT with other forms of radiotherapy or observation. One meta-analysis of non-comparative studies [2] and eight comparative retrospective cohort studies [3-10] compared radiotherapy with observation or other forms of radiotherapy such as accelerated hypofractionated radiation therapy, three-dimensional conformal radiotherapy, conventional fractionated radiation therapy, external beam radiation therapy, and proton beam therapy and carbon ion therapy. The evidence was considered to be very low quality due the potential increase in risk of bias associated with retrospective designs. However, all of the studies consistently demonstrated that SBRT had similar or better effects on survival or local control compared with observation or alternative radiotherapy techniques with similar or fewer adverse effects compared with alternative radiotherapy techniques. The meta-analysis by Grutters et al. (2010) found that conventional radiotherapy had lower two-year (53%, 95% confidence interval [CI], 46% to 60%) and five-year (20%, 95% CI, 15% to 24%) overall survival rates and lower two-year (67%, 95% CI, 59% to 76%) and five-year (44%, 95% CI, 31% to 56%) disease-specific survival rates compared with |

SBRT (two-year overall survival: 70%, 95% CI, 63% to 77%, p<0.001; five-year overall survival: 42%, 95% CI, 34% to 50%, p<0.001; two-year disease-specific survival: 83%, 95% CI, 75% to 92%, p=0.006; five-year disease-specific survival: 63%, 95% CI, 50% to 75%, p=0.045) [2].

***Interpretation of Evidence for Recommendation 1***

Although the evidence was from retrospective cohort studies, the consistency of the results led the Working Group to believe that the potential benefits in overall survival and local control with SBRT compared with observation and other radiotherapies, especially older conventional therapy treatments, outweighed the potential harms associated with SBRT for medically inoperable patients with early stage NSCLC. Therefore, they considered SBRT to be a recommended treatment option for this patient population.

**Recommendation 2**

Recommended fractionation schemes for SBRT should have a $BED_{10(LQ)}$ of ≥100.[3]

***Qualifying Statements for Recommendation 2***

- Tumour size and proximity to critical central[4] structures require consideration when determining the dose fractionation due to increased risk of treatment-related adverse events associated with centrally located tumours.
- ***Examples*** of dose fractionation schemes used in the studies included (see Table 4-2):

| Location | Total dose (Gy)/# of fractions | $BED_{10}$ |
|---|---|---|
| **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 |

- Evidence showed consistent tumour control and survival outcomes using the above schedules. Ongoing trials may yield new evidence regarding optimal stereotactic dosing schedules and recommended doses different than those listed above.
- Based on the current evidence and the opinion of the authors, radiation doses of $BED_{10(LQ)}$ >146 may significantly increase toxicity and should be avoided.
- Although the use of radiation dosages expressed as a biological effective dose has been advocated, it is important to understand the limitations of determining radiation BED using the linear quadratic model for the extreme-hypofractionated schemes used in SBRT.

***Key Evidence for Recommendation 2***

Twelve retrospective observational studies investigated the most appropriate BED cut off associated with patient outcomes [11-22]. Again, these studies were considered to be very low quality due to their retrospective designs. A meta-regression by Zhang 2011, found a significant overall survival benefit at two years and three years with the delivery of medium BED (83.2 to 106 - two-year: 76%, 95% CI, 62% to 92%; three-year: 64%, 95% CI, 57% to 71%)

[3] BED = biological effective dose; LQ = linear quadratic

[4] Central tumour refers to tumours within a 2 cm radius of the distal trachea and proximal bronchial tree

1. Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, et al. Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer. J Clin Oncol. 2006;24(30):4833-9..

or medium to high BED (106 to 146 - two-year: 68%, 95% CI, 61% to 76%; three-year: 63%, 95% CI, 56% to 71%) compared with high BED (>146 - two-year: 56%, 95% CI, 50% to 63%, p<0.001; three-year: 50%, 95% CI, 43% to 57%, p<0.001) or low BED (<83.2) at three years only (three-year: 52%, 95% CI, 44% to 62%, p<0.005) [23]. The occurrence of severe adverse events of grades 3 to 5 was only significantly different between the low and high BED groups. This suggested that medium or medium to high doses may be the most optimal dose ranges. The cut-off, however, was difficult to determine. Several studies suggested a cut-off of approximately 100 BED was significantly correlated with patient outcomes [11,13-16,20]; however, other studies, including the Zhang 2011 meta-regression, did not show this association [12,18,19,21,23].

***Interpretation of Evidence for Recommendation 2***

Although there was variability in results using a BED cut-off of approximately 100, the largest studies suggested that a BED close to 100 was associated with overall survival and local control [11,13-16,20]. The Working Group 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 associations with patient outcomes with BED cut-offs of 100, 105, and 106 [11,13-16,20]. They selected the lowest value since the Zhang 2011 meta-analysis found that medium values between 83.2 and 106 had significantly better survival compared with lower doses [23].

Many of the included studies assigned doses based on the size and location of the tumour. This was based on a study by Timmerman in 2006 that suggested that an increase in the damage to critical structures and incidence of serious adverse events and toxicity had been found in patients with centrally located tumours when higher dose fractionation schemes were used [1]. Delivering lower doses with a minimum of 100 BED to central tumours did not predict inferior overall survival, local control, or increased toxicity compared with peripheral tumours [24]. Therefore, these factors should be taken into consideration when deciding on the dose or fractionation schedule.

Although the Working Group advocated the use of radiation doses expressed as a BED, it is important to understand the limitations of determining radiation BED using the linear quadratic model for the extreme-hypofractionated schemes used in SBRT. The linear quadratic model has been used as a convenient, slightly simplified, model to calculate effective dose when treating tumours with conventional fractionated radiation therapy. At such high-dose fractions, other models of tissue injury have been suggested [25-27]. As such, users should exercise caution when using BED models in comparing different SBRT schemes.

**IMPLEMENTATION CONSIDERATIONS**

The Working Group considered these recommendations to be the current standard of care and thus would be feasible to implement. They believe the outcomes valued in this guideline would align with patient values and that patients would view these recommendations as acceptable.

**RELATED GUIDELINES**

- 7-18 Positron Emission Tomography in Radiation Treatment Planning for Lung Cancer.
- 7-12 Altered Fractionation of Radical Radiation Therapy in the Management of Unresectable Non-Small Cell Lung Cancer.

# Radiotherapy with Curative Intent in Patients with Early Stage, Medically Inoperable, Non-Small Cell Lung Cancer

## Section 3: Guideline Methods Overview

*This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.*

**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, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

**GUIDELINE DEVELOPERS**

This guideline was developed by the Radiation with Curative Intent in Medically Inoperable Patients with Non-small Cell Lung Cancer GDG (Appendix 1), which was convened at the request of the Radiation treatment program along with the Lung Disease Site Group.

The project was led by a small Working Group of the Radiation with Curative Intent in Medically Inoperable Patients with Non-small Cell Lung Cancer GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in radiation oncology, medical oncology, and health research methodology. Other members of the Radiation with Curative Intent in Medically Inoperable Patients with Non-small Cell Lung Cancer GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

**GUIDELINE DEVELOPMENT METHODS**

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [28,29]. This process includes a systematic review, interpretation of the evidence by the Working Group who then draft 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 PEBC uses the AGREE II framework [30] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature

to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

**Search for Existing Guidelines**

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation, using the ADAPTE framework [31], or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), National Guideline Clearinghouse, and Inventory of Cancer Guidelines.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network.

Only guidelines published in English after 2008 were considered. Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument [30]. This search yielded five practice guidelines [18,32-35]. The Working Group decided that proceeding with a new systematic review that included the latest research was warranted due to the relatively frequent release of information and a need to focus on treatment. Existing guidelines were either not up to date, or addressed a broader scope than was required by this treatment guideline.

## GUIDELINE REVIEW AND APPROVAL

**Internal Review**

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

**External Review**

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

**ACKNOWLEDGEMENTS**

The Radiation with Curative Intent in Medically Inoperable Patients with Non-small Cell Lung Cancer GDG would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Patrick Cheung, Sheila McNair, Hans Messersmith, Gunita Mitera, Gordon Okawara, Raymond Poon, Kenneth Schneider, Marko Simunovic, Cindy Walker-Dilks, Pardraig Warde, and Eric Winquist for providing feedback on draft versions.
- Andrea Bezjak for participating on the Working Group of this guideline in the early stages of development.
- Terence Tang for conducting a data audit.
- Sara Miller for copy editing.

# Radiotherapy with Curative Intent in Patients with Early Stage, Medically Inoperable, Non-Small Cell Lung Cancer

## Section 4: Systematic Review

**INTRODUCTION**

Lung cancer is the third most common cancer in both men and women in Canada (14%) [36]. Lung cancer represented 13% of the 65,000 cancer cases diagnosed in 2009 in Ontario [37]. In Ontario, there were 8211 new cases reported in 2009 [37]. Despite a significant overall decline in cancer mortality rates, lung cancer remained the leading cause of cancer death with a relative five-year survival of 17% and a mortality rate of 40.2/100,000 person-years in 2015 in Canada [36]. An estimated 20,900 related deaths occurred due to lung cancer in 2015 in Canada [36].

Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer [37]. Surgical resection of early stage (Stage I, II) NCSLC is the standard against which other treatments are measured. A subset of these patients is unable to tolerate surgery because of their age or medical comorbidities [38]. These include abnormal underlying cardiovascular and/or pulmonary function. These patients were previously offered conventional radiotherapy (60 to 66 Gy in 1.8 to 2.0 Gy fractions) or were observed without specific cancer therapy. Outcomes for each of these approaches have not been ideal, with two-year survival less than 40% with either conventional radiation and observation, and local control of only 40% to 50% with conventional radiation therapy [39,40].

Stereotactic radiation therapy is a high-precision radiation delivery technique of a few (or even single) high-dose fractions to small targets or volume of disease. It is characterized by a steep dose-gradient beyond the target volume and as such, accuracy and precision of treatment planning and delivery become critical. Stereotactic body radiation therapy (SBRT) and stereotactic ablative radiation therapy are considered synonymous for the purposes of this guideline and will be referred to as SBRT from this point on.

Because the outcomes for patients with early stage NSCLC who were observed or were given conventional radiation have not been ideal, the objective of this guideline was to investigate the effectiveness of radiotherapy with curative intent in patients with early stage NSCLC who are medically inoperable. In order to make recommendations as part of a clinical practice guideline on the use of radiotherapy with curative intent, the Radiation Treatment Program, together with the Lung Cancer Disease Site Group, developed this evidentiary base. Based on the objectives of the guideline, the Working Group derived the research questions outlined below.

**RESEARCH QUESTIONS**

1. What is the effectiveness of radiotherapy with curative intent in patients with early stage NSCLC who are unable to undergo surgery?
2. What are the most effective dose/fractionation schedules for curative intent radiotherapy?

**METHODS**

The Program in Evidence-Based Care produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [29]. This evidentiary base was developed using a planned two-stage method, summarized here and described in more detail below.

1. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews were identified that addressed the research questions, then those systematic reviews were included in the evidentiary base.
2. Systematic review of the primary literature: This search would focus on those areas not covered by existing systematic reviews.

**Search for Existing Systematic Reviews**

A search for systematic reviews was carried out on the topic of radiation treatment with curative intent in patients with medically inoperable NSCLC. This search was conducted within the Cochrane library, MEDLINE, and EMBASE databases from January 1985 to July 2015. Systematic reviews were included if they addressed either of the research questions and reported on the sources searched. *A priori*, the Working Group decided that the main comparison would be SBRT against other forms of radiotherapy; therefore, the systematic reviews had to focus on SBRT and either compare it with other radiotherapies or examine the most appropriate dose or fractionation schemes for SBRT. Results were limited to articles published in English. Identified systematic reviews were assessed using the AMSTAR tool [41].

**Search for Primary Literature**

***Literature Search Strategy***

The literature was searched using MEDLINE (1985 through July 16, 2015), EMBASE (1985 through July 16, 2015), the Cochrane Database of Systematic Reviews (OVID CDSR: March 2014), the Cochrane Central Register of Controlled Trials (OVID CCTR: April 2014), and the Database of Abstracts of Reviews of Effects (OVID DARE: 1st quarter 2014). In addition, the proceedings of the meetings of the American Society of Clinical Oncology (ASCO: 2007 to 2014), the American Society of Therapeutic Radiology and Oncology (ASTRO: 2007 to 2013), and the European Society for Radiotherapy and Oncology (ESTRO: 2007 to 2014) were searched for relevant abstracts. Reference lists of studies deemed eligible for inclusion were scanned for additional citations.

The literature search of the electronic databases combined disease-specific terms (lung carcinoma, non-small cell lung cancer, NSCLC, etc.) along with disease stage-specific terms (early stage, medically inoperable) and treatment-specific terms (radiation, stereotactic, hypofractionation) for all study designs (Appendix 2).

***Study Selection Criteria and Process***

*Inclusion Criteria*

Articles were eligible for inclusion in this systematic review if they met the following criteria:

1. Studies included full reports or abstracts of randomized controlled trials (RCTs) or other comparative trials with more than 50 participants. Interventions considered were stereotactic radiation treatment with curative intent compared with observation or other types of radiotherapy for early stage, medically inoperable, NSCLC. Comparisons between radiation dosing or fractionation schedules for SBRT were included.
2. Studies included patients with a tumour size less than 5 cm (i.e., T1 or T2a), node-negative (i.e., N0), medically inoperable NSCLC.
3. Studies reported data on survival, local control, adverse events, or quality of life.

*Exclusion Criteria:*

1. Interventions were combined with limited surgery or chemotherapy.
2. Radiation therapy was not used with curative intent or as second-line treatment.

A review of the titles and abstracts that resulted from the search was conducted by one reviewer (EV). For those items that warranted full-text review, one reviewer (EV) reviewed each item in collaboration with a second reviewer (EY, YU, PE, CF, ME) if uncertainty existed.

***Data Extraction and Assessment of Study Quality and Potential for Bias***

All eligible studies underwent data extraction independently by a research methodologist (EV), with all extracted data and information subsequently audited by an independent auditor. Ratios, including hazard ratios (HR), were expressed such that a ratio <1.0 indicated a survival benefit favouring non-stereotactic radiation therapy; conversely, a survival benefit that favoured patients treated with stereotactic radiation therapy was expressed by a HR >1.0.

An assessment of study quality was performed for all the included primary literature by one methodologist (EV). Cohort studies were assessed using A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI) [42].

**Synthesizing the Evidence**

A meta-analysis was not planned because of the variability in dose and fractionation schedules and the inconsistent SBRT procedures due to evolving technologies in the field.

**RESULTS**

**Search for Existing Systematic Reviews**

Thirteen systematic reviews were considered for inclusion [2,23,25,26,43-51]. Two were excluded because they were abstracts only [43,47]. Although the 11 remaining reviews had different inclusion criteria, two reviews were included because they performed meta-analysis using non-comparative data [2,23]. Their results could be used to support or refute conclusions drawn from the comparative data from the primary literature. Two other reviews were included because they examined the most appropriate metrics to use when comparing the dosage effects of SBRT on patient outcomes [25,26]. The evidence from the primary literature compared different dose schedules; however, there are several ways to calculate dose and these two reviews compared different dose formulae. One review included recommendations; however, only the highlights from their systematic review were presented and the full document was available only in French. Therefore, this review was used only as a source for references [45].

**Search for Primary Literature**

***Literature Search Results***

A total of 7944 English and foreign-language studies were identified. Seven hundred fifty-five were selected for full-text review. Of those, 52 met the pre-defined eligibility criteria for this systematic review (Tables 4-1 and 4-2) [3-22,52-83]. In some cases, patients that refused surgery or had tumours larger than five centimeters with early stage NSCLC were included in the study. The percentage of these patients was included in the evidence tables if reported. The search flow diagram is available in Appendix 3.

**Table 4-1. Studies selected for inclusion comparing SBRT with other radiotherapy regimens or observation.**

| Study | Study design | Treatment type | Sample size | Median/mean age (range) | Fraction dose (Gy) | Fraction number | Total dose | Overall treatment time (weeks) | % tumours <5 cm or ≤T2a | % medically inoperable | Median f/u in months (range) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Borst 2009 [3] | Retro | SBRT | 128 | NR | 6-12 | 4-8 | 35-60 | NR | NR | NR | 16.1 |
| | | CFRT | 142 | NR | 2-2.25 | 27-42 | 60.8-94.5 | NR | NR | NR | 13.0 |
| Jeppesen 2013 [4] | Retro | SBRT | 100 | 73.3 (52-88) | 15-22 | 3 | 45-66 | 1.3 | NR | 100 | 35.4 (8.8-90.5) |
| | | Conventional radiation | 32 | 70.4 (51-87) | 2-2.29 | 35-40 | 80 | 7-8 | NR | 100 | 129 (16.9-173) |
| Koshy 2015 [5] | Retro | SBRT | 773 | NR | NR | NR | NR | NR | NR | NR | 21 (11-43) |
| | | Conventional radiation | 5375 | NR | 1.8-2 | NR | 60 | NR | NR | NR | |
| | | Observation | 6888 | NR | NA | NA | NA | NA | NA | NA | |
| Lanni 2011 [6] | Retro | SBRT | 45 | 76 (63-90) | 12 | 4-5 | 48-60 | NR | 97.8 (1NR) | 100 | 36 |
| | | EBRT | 41 | 76 (53-85) | NR | 23-47 | 29-70 | NR | 97.6 (1NR) | 100 | |
| Lucas 2014 [7] | Retro | SBRT | 81 | 74 (66-78) | 8-20 | 2-5 | 36-60 | NR | 100 | 94 | 29.4 (11.6-40.4) |
| | | AHRT | 79 | 69 (65-79) | 2.25-4.11 | 17-30 | 60-72.3 | NR | 84.7 | 76 | 19 (8.5-34.2) |
| Shirvani 2012 [8] | Retro | SBRT | 124 | 75 | NR | NR | NR | NR | 100 | NR | 38.4 |
| | | Conventional radiation | 1613 | | NR | NR | NR | NR | 100 | NR | |
| | | Sublobar resection | 1277 | | NR | NR | NR | NR | 100 | NR | |
| | | Lobectomy | 6531 | | NR | NR | NR | NR | 100 | NR | |
| | | Observation | 1378 | | NR | NR | NR | NR | 100 | NR | |
| Tong 2015 [9] | Retro | SBRT | 30 | 74.7 (66-83) | 14-20 | 3 | 42-60 | NR | 100 | 100 | 12 |
| | | 3D-CRT | 38 | 75.7 (65-82) | 2 | 30 | 60 | 6 | 100 | 100 | |
| Widder 2011 [10] | Pro SBRT with historical 3D-CRT cohort | SBRT | 202 | 76 (46-93) | 7.5-20 | 3-8 | 60 | NR | NR | 100 | 13 |
| | | 3D-CRT | 27 | 71 (47-82) | 2 | 35 | 70 | NR | 100 | 100 | |

Abbreviations: AHRT, accelerated hypofractionated radiation therapy; 3D-CRT, three-dimensional conformal radiotherapy; CFRT, conventional fractionated radiation therapy; EBRT, external beam radiation therapy; f/u, follow-up; NA, not applicable; NR, not reported; pro, prospective; retro, retrospective; SBRT, stereotactic body radiation therapy

**Table 4-2. Studies selected for inclusion to advise on the most effective dose/fractionation schedules.**

| Study | Study design | Doses & selection criteria (sample size) | Median/mean age (range) | Overall treatment time (weeks) | % tumours < 5 cm or ≤T2a | % medically inoperable | Median f/u in months (range) |
|---|---|---|---|---|---|---|---|
| Allibhai 2013 [52] | Pro | For tumours ≤3 cm: 48 Gy in 4<br>For tumours >3 cm: 54-60 Gy in 3<br>For tumours <2 cm adjacent to mediastinum:<br>60 Gy in 8 or 50 Gy in 10 (185) | 74.8 | 1.5 | 97.3 | 100 | 15.2 (6-76) |
| Barriger 2012 [53] | Retro | 24-72 Gy in 3-5 (143) | 74 (45-100) | NR | NR | 100 | 17 (0.3-89) |
| Baumann 2006 [54] | Retro | 30-48 Gy in 2-4 (138) | 74 (56-90) | NR | NR | 96 | 33 (1-107) |
| Bongers 2011 [55] | Retro | For peripheral tumours: 60 Gy in 3<br>For broad contact with chest wall:<br>60 Gy in 5<br>For central tumours:<br>60 Gy in 8 (500) | 74 (42-92) | NR | 100 | 75 | 33 (13-86) |
| Bradley 2010 [56] | Pro | For peripheral tumours: mean 54 Gy in 3<br>For central tumours: mean 45 Gy in 5 (91) | 71 (31-93) | 1-1.4 | 63.7 (22 NR; 6 with T1N0M1) | 91.2 | 18 (6-42) |
| Chang 2014 [57] | Retro | For central tumours: 50 Gy in 4 (82) or 70 Gy in 10 (18) | 73 (50-93) | NR | 80.2 (19.8 NR; 19% had isolated recurrence) | NR | 30.6 (9.4-92.6) |
| Chang 2012 [58] | Retro | 50 Gy in 4 (130) | 74 (48-91) | 0.6 | 100 | 74 | 26 (6-78) |
| Davis 2015 [11] | Retro | Median 54 Gy in 3 (723) | 76 (41-95) | NR | 70 (30 NR) | 67 | 12 (1-87) |
| Factor 2014 [12] | Retro | For central tumours: Mainly 48 Gy in 4<br>For peripheral tumours: Mainly 60 Gy in 3 (74) | 78.5 (56-93) | 0.6 | 100 | NR | For local control: 14.4<br>For overall survival: 18.8 |

| Study | Study design | Doses & selection criteria (sample size) | Median/mean age (range) | Overall treatment time (weeks) | % tumours < 5 cm or ≤T2a | % medically inoperable | Median f/u in months (range) |
|---|---|---|---|---|---|---|---|
| Fischer-Valuck 2013 [59] | Retro | For peripheral tumours: 60 Gy in 5 (49)<br>For central tumours: 48 Gy in 4 (13) | 72.6 (27-92) | Median 1.1 (range, 0.1-3.9) | 70.9 (29.1 NR) | NR | 28 (4-78) |
| Grills 2012 [13] | Retro | Ranged from 20 Gy in 1 to 64 Gy in 8, see paper for details (483); dose based on location | 74 (42-92) | NR | NR; 1 had local recurrence | 87 | 15.6 (1.2-87.6) |
| Guckenberger 2013 [14] | Retro | Median 37.5 Gy (range, 12.0-64.0) in 3 (range, 1-20) (582); dose based on tumour size and location | 72.2 (30.9-92.4) | NR | 100 | NR | Mean 21.4 (NR-144) |
| Guckenberger 2013 [60] | Retro | 18-64 Gy in 1-15 (191) | 76 (45-93) | NR | 99.5 | NR | NR |
| Hayashi 2014 [61] | Retro | For peripheral tumours: 48 Gy in 4 (60)<br>For central tumours: 60 Gy in 10 (21) | 80 (64-93) | 2-3 | 100 | 75 | 29 (5-84) |
| Hoppe 2008 [62] | Retro | 60 Gy in 3 (36), 44-48 Gy in 4 (14) | 79 (60-94) | NR | 100 | NR | 6 (3-18) |
| Inoue 2013 [63] | Retro | 48 Gy in 4 (30), 45 to 50 Gy in 4 (79); dose based on tumour size | 78 (47-90) | 0.6-1 | 72.5 (27.5 NR) | NR | 25 (4-72) |
| Kelley 2015 [64] | Retro | For peripheral tumours: Median 48 Gy in 4 (67) | 79 (60-92) | NR | 78 (22 NR) | 100 | 24.5 (2.4-50.3) |
| Kestin 2014 [15] | Retro | Median 54 Gy in 3 (483) | 74 (42-94) | NR | 99 (1 NR) | 89 | 15.6 |
| Kohutek 2015 [16] | Retro | For peripheral tumours: 54-60 Gy in 3<br>For central tumours: 45-50 Gy in 5<br>For tumours within 1 cm of chest wall: 48 Gy in 4<br>(211) | 77 (51-95) | NR | 99.1 | NR | 25.2 (4.3-75.2) |
| Kopek 2009 [65] | Retro | For peripheral tumours: 67.5 in 3 (26)<br>For central tumours: 45 Gy in 3 (62) | 72.8 (47.1-88.5) | 0.7-1.1 | 58 (40.9 NR) | 100 | 44 (1.6-96.5) |

| Study | Study design | Doses & selection criteria (sample size) | Median/mean age (range) | Overall treatment time (weeks) | % tumours < 5 cm or ≤T2a | % medically inoperable | Median f/u in months (range) |
|---|---|---|---|---|---|---|---|
| Koshy 2015 [17] | Retro | Median 54 Gy (range, 36-80 Gy) in 3 (range, 3-10) (498) | NR | NR | 67.1 (32.9 NR) | 100 | 68 (58-74) |
| Lagerwaard 2008 [66] | Retro | For peripheral tumours: 60 Gy in 3 (93) or 60 in 5 (99)<br>For central tumours: 60 Gy in 8 (27) | 73 | NR | 59 (41 NR) | 81 | 12 (3-44) |
| Lee 2013 [18] | Retro | For peripheral tumours: 45 Gy in 3 or 60 Gy in 5<br>For central tumours: 50 Gy in 5 or 56 Gy in 7 (58) | 73 (48-90) | 0.4-1.4 | 98.3 | 65.5 | 23.8 (1.5-77.2) |
| Mak 2015 [19] | Retro | Close to chest wall: 50-60 Gy in 5<br>All other tumours: 54 Gy in 3 (75) | 74 (46-93) | NR | 98.7 | 100 | 18.8 |
| Marwaha 2014 [67] | Retro | Based on size and location:<br>50 Gy in 5, 60 Gy in 3, 30 or 34 Gy in 1 (342) | 74 (43-94) | NR | NR | 100 | 17.6 (0-84) |
| Matsuo 2012 [68] | Retro | For peripheral tumours: 48 Gy in 4 (74) | 77 (63-88) | Median 0.7 (0.6-1.7) | 100 | 50 | 31.4 (4.2-65.0) |
| Mutter 2012 [69] | Retro | 40-60 Gy in 3-5 (126); dose based on location | 77 (55-95) | Median 1 (0.6-2.7) | 96.8 | NR | 16 (3-43) |
| Olsen 2011 [70] | Retro | For peripheral tumours: 54 Gy in 3 (111)<br>For central tumours: 45 Gy in 5 (8) or<br>50 Gy in 5 (11) | 75 (31-92) | 54 Gy in 3: median 1.1 (0.7-3.6)<br>45 Gy in 5: median 2.4 (1.6-4)<br>50 Gy in 5: median 2 (1.6-2.3) | 95.4 | 90 | 54 Gy in 3: 13<br>45 Gy in 5: 11<br>50 Gy in 5: 16 |
| Onishi 2007 [20] | Retro | 18-75 Gy in 1-22 (257); high dose excluded for spinal cord | 74 (39-92) | <3.6 | 63.8 (36.2 NR) | 61.5 | 38 (2-128) |
| Ricardi 2014 [21] | Retro | For peripheral tumours: 48-60 Gy in 3-8 (196) | 75 (48-91) | NR | 100 | 92.3 | 30 |
| Rosen 2014 [71] | Retro | Based on location and tumour size:<br>48 Gy in 4 (20)<br>60 Gy in 5 (59) | 73 (27-92) | NR | 75 (25 NR) | 100 | 27 (4-82) |

| Study | Study design | Doses & selection criteria (sample size) | Median/mean age (range) | Overall treatment time (weeks) | % tumours < 5 cm or ≤T2a | % medically inoperable | Median f/u in months (range) |
|---|---|---|---|---|---|---|---|
| Satoh 2014 [72] | Retro | 48 Gy in 4 (65), 60 Gy in 10 (4), 70 Gy in 10 (19) | Male 77.9 (60-90)<br>Female 78.6 (58-89) | NR | 100 | NR | 33 (7-79) |
| Schanne 2015 [73] | Retro | For peripheral tumours: Median 60 Gy in 3 (476)<br>For central tumours: 58.3 Gy in 5 (90) | 71.6 (31-92) | Peripheral: median 0.7 (0.3-4.1)<br>Central: median 1.1 (0.1-5.1) | 94.7 (5.3 NR) | NR | 18.8 (mean) |
| Shibamoto 2012 [74] | Pro | 44 Gy in 4 (4), 48 Gy in 4 (124), 52 Gy in 4 (52); dose based on tumour size | 77 (29-89) | Median 1.7 (1.3-3) | 71.1 (28.9 NR) | 66.7 | 36 |
| Shirata 2012 [75] | Retro | 48 Gy in 4 (45), 60 Gy in 8 (29), 60 Gy in 15 (7); dose based on location | 77 (54-90) | 0.6-3 | 77.8 (22.2 NR) | NR | 30.4 (0.3-78.5) |
| Shultz 2014 [76] | Retro | Based on tumour size: 25-60 Gy in 1-5 (117) | 77 (42-93) | NR | 73 (27 NR) | NR | 17 (3-74) |
| Sibley 1998 [77] | Retro | Median 64 Gy (50-80 Gy) in 1.2 bid to 3 Gy qd (141) | 70 (46-95) | Median 6.3 | 54 (46 NR) | 100 | 24 (7-132) |
| Stanic 2014 [78] | Retro | For peripheral tumours: 54 Gy in 3 (55) | 72 (48-89) | 2 | 80 (20 NR) | 100 | NR |
| Stephans 2009 [79] | Retro | 50 Gy in 5 (51) or 60 Gy in 3 (35); central only received 50 Gy in 5 | 73 (48-89) | 50 Gy in 5: 0.7<br>60 Gy in 3: 1.1-2 | 73.4 (26.6 NR) | 100 | 15.3 (1.9-47.6) |
| Suzuki 2014 [22] | Retro | Based on tumour location: 48-60 in 3-10 (383) | NR (47-93) | NR | NR | 78.3 | 39 |
| Taremi 2012 [80] | Pro | For peripheral tumours: 48 Gy in 4, 54 Gy in 3, 60 Gy in 3<br>For central tumours: 60 Gy in 8, 50 Gy in 10 (108) | 72.6 (48.3-90) | NR | 75.4 (24.6 NR) | 100 | 19.1 (1-55.7) |
| Ueki 2015 [81] | Retro | By tumour location: 48-60 Gy in 4-8 (157) | 77.5 (56-89) | NR | 100 | NR | 39.5 |
| Videtic 2014 [82] | Retro | For peripheral tumours: 30 Gy in 1 (55), 34 Gy in 1 (25) | 30 Gy in 1: 75 (48-91), 34 Gy in 1: 73 (53-84) | 8-14 days | 100 | 100 | 30 Gy in 1: 18.7 (1.8-43.0), 34 Gy in 1: 17.8 (0.1-39.4) |

| Study | Study design | Doses & selection criteria (sample size) | Median/mean age (range) | Overall treatment time (weeks) | % tumours < 5 cm or ≤T2a | % medically inoperable | Median f/u in months (range) |
|---|---|---|---|---|---|---|---|
| Woody 2012 [83] | Retro | 60 Gy in 3, 50 Gy in 5, 48 Gy in 4, 50 Gy in 10 (102) | 71.5 | 0.6-1.7 | NR | 100 | 25.5 mean (12-55) |

Abbreviations: bid, twice daily; f/u, follow-up; Gy, Grays; NR, not reported; Pro, prospective; qd, four times daily; retro, retrospective

***Study Design and Quality***

*Quality of Systematic Reviews*

The systematic reviews were assessed using AMSTAR (Table 4-3) [41]. The quality of the systematic reviews was considered to be low to moderate. This was mainly because the quality of the included studies was not assessed and, therefore, was not taken into consideration when the conclusions were formulated. Furthermore, the Chi and Kong reviews only searched one database [25,26]. Given the lack of comparative RCTs, most of the studies included in these reviews were prospective or retrospective cohorts even though data collection may have been done prospectively. As such, the inherent limitations of retrospective designs should be taken into consideration when reviewing evidence from these studies.

**Table 4-3. AMSTAR evaluation of included systematic reviews.**

| ITEM | Chi et al 2013 [25] | Grutters et al 2010 [2] | Kong et al 2014 [26] | Zhang et al 2011 [23] |
|---|---|---|---|---|
| **1.** Was an 'a priori' design provided? | Y | Y | Y | Y |
| **2.** Was there duplicate study selection and data extraction? | N | Y | Y | Y |
| **3.** Was a comprehensive literature search performed? | N | Y | N | Y |
| **4.** Was the status of publication (i.e., grey literature) used as an inclusion criterion? | Y | Y | N | Y |
| **5.** Was a list of studies (included and excluded) provided? | N | N | N | N |
| **6.** Were the characteristics of the included studies provided? | Y | Y | Y | Y |
| **7.** Was the scientific quality of the included studies assessed and documented? | N | N | N | N |
| **8.** Was the scientific quality of the included studies used appropriately in formulating conclusions? | N | N | N | N |
| **9.** Were the methods used to combine the findings of the studies appropriate? | N | Y | Y | Y |
| **10.** Was the likelihood of publication bias assessed? | N | N | N | Y |
| **11.** Was the conflict of interest stated? | Y | N | Y | Y |
| TOTAL AMSTAR POINTS | 4 | 6 | 5 | 8 |

Abbreviations: N = no; Y = yes

*Quality of Primary Studies*

The quality of the primary studies was assessed using ACROBAT-NRSI (Appendix 4). The quality of the 52 observational studies was considered to be very low. Only four of the studies were prospective [52,56,74,80] and blinding was not reported in most of the papers. As such, most studies were at an increased risk of bias in the selection of participants into the study, in the measurement of interventions and outcomes, and in the selection of the reported results. Furthermore, many of the studies did not adjust for potential confounders such as tumour stage or location.

**Outcomes**

***Question #1:*** **What is the effectiveness of radiotherapy with curative intent in patients with early stage NSCLC who are unable to undergo surgery?**

***Systematic reviews***

Grutters et al. (2010) compared SBRT with conventional radiotherapy, proton therapy, and carbon ion therapy using meta-regression, adjusting for the percentage of medically inoperable patients [2]. Age, percentage of small tumours (<3 cm), and median follow-up were not found to be effect modifiers. Only single-arm observational studies were available for the meta-regression. They found that conventional radiotherapy had lower two-year (53%, 95% confidence interval [CI], 46% to 60%) and five-year (20%, 95% CI, 15% to 24%) overall survival rates and lower two-year (67%, 95% CI, 59% to 76%) and five-year (44%, 95% CI, 31 to 56%) disease-specific survival rates compared with SBRT (two-year overall survival: 70%, 95% CI, 63% to 77%, p<0.001; five-year overall survival: 42%, 95% CI, 34% to 50%, p<0.001; two-year disease-specific survival: 83%, 95% CI, 75% to 92%, p=0.006; five-year disease-specific survival: 63%, 95% CI, 50% to 75%, p=0.045). There were no significant differences in survival rates among SBRT, proton therapy, and carbon ion therapy. However, they suggested five-year outcomes be interpreted with caution due to the limited length of follow-up. They also found that SBRT studies reported more adverse events including grades 3/4 pneumonitis, grades 3/4 irreversible dyspnea, grades 3/4 esophagitis, and treatment-related death, compared with conventional radiotherapy or proton or carbon ion therapies. However, all of the treatment-related deaths after SBRT came from one study that had a high biological effective dose (BED) and included peripherally located tumours. Furthermore, the studies that used proton or carbon therapies had smaller sample sizes than the SBRT studies. Statistical comparisons could not be made due to the low number of events.

***Primary studies***

Eight cohort studies [3-10] compared SBRT with observation or other forms of radiation treatments including accelerated hypofractionated radiation therapy, three-dimensional conformal radiotherapy, conventional fractionated radiation therapy, and external beam radiation therapy (Tables 4-4 and 4-5). In all studies, patients treated with SBRT were found to have at least the same or better local control or survival compared with patients who received other forms of radiotherapy or observation. In terms of adverse events, few statistical comparisons were made due to the low number of events, but in studies where statistical comparisons were made, there were lower adverse events for SBRT compared with the alternate therapy.

**Table 4-4. Comparisons of survival, local control/recurrence, and toxicity for different radiotherapy regimens or observation.**

| Study | Treatment type | Local control (%) | Survival (%) | Median overall survival in months (95% CI) | Toxicity |
|---|---|---|---|---|---|
| Borst 2009 [3] | SBRT | NR | NR | NR | No difference between treatments in incidence of radiation pneumonitis for any of the six dose ranges covering 4 Gy each. However, statistical power limited due to lower number of patients at higher dose range. |
| | CRFT | NR | NR | NR | |
| Jeppesen 2013 [4] | SBRT | 5-year: 83 | Cancer-specific survival: 61 | 36.1 | <table><tr><td></td><td>SBRT (%)</td><td>Con R (%)</td></tr><tr><td>Esophagitis</td><td>0</td><td>1(3)</td></tr><tr><td>Dyspnea</td><td>0</td><td>0</td></tr><tr><td>Coughing</td><td>0</td><td>0</td></tr></table> No difference in decline of lung function measured by $FEV_1$ |
| | Conventional radiation | 78 (p=0.48) | Cancer-specific survival: 31 (p=0.09) | 24.4 (p=0.02) | |
| Koshy 2015 [5] | SBRT | NR | 3-year overall survival: 48 | NR | NR |
| | Conventional radiation | NR | 40 (p=0.001) | NR | |
| Lanni 2011 [6] | SBRT | 3-year: 88 | 3-year overall survival: 71 | NR | NR |
| | EBRT | 66 (p=0.10) | 42 (p<0.049) | NR | |
| Lucas 2014 [7] | SBRT | 2-year: 92.5<br>3-year: 87.7 | NR | 38.4 (29.7-51.6) | <table><tr><td></td><td>SBRT (%)</td><td>AHRT (%)</td></tr><tr><td>Grade 3 toxicity</td><td>3(4)</td><td>0</td></tr><tr><td>Bleeding</td><td>0</td><td>1 (1)</td></tr><tr><td>Pneumonitis (grades 1&2)</td><td>3(4)</td><td>8(10)</td></tr><tr><td>Chronic pain</td><td>5(6)</td><td>5(6)</td></tr><tr><td>Rib fracture</td><td>0</td><td>1(1)</td></tr><tr><td>Complications resolved</td><td>2(3)</td><td>9(11)</td></tr></table> |
| | AHRT | 2-year: 79.5 (p=0.11)<br>3-year: 71.7 | NR | 35 (22-48.3) (p=0.59) | |
| Shirvani 2012 [8] | SBRT<br>Conventional radiation<br>Observation | NR | Cancer-specific survival: SBRT better than conventional radiation HR 1.56 (0.67-3.59) p=0.30 Adjusted for age & grade HR 1.59 (0.67-3.80) p=0.30 SBRT better than observation HR 3.88 (1.78-8.43) p<0.001 adjusted for tumour size HR 3.90 (1.76-8.61) p<0.001 | SBRT better than conventional radiation HR 1.97 (1.31-2.96) p=0.001 Adjusted for age & grade HR 1.96 (1.28-3.00) p=0.002 SBRT better than observation HR 2.10 (1.37-3.08) p<0.001 adjusted for tumour size HR 2.03 (1.34-3.07) p<0.001 | NR |
| Widder 2011 [10] | SBRT | 2-year: 95 | Cancer-specific survival: 89 | 72 | NR |

| Study | Treatment type | Local control (%) | Survival (%) | Median overall survival in months (95% CI) | Toxicity |
|---|---|---|---|---|---|
| | 3D-CRT | 78 | 67 | 48 (p=0.02) | |

Abbreviations: AHRT, accelerated hypofractionated radiation therapy; 3D-CRT, three-dimensional conformal radiotherapy; CFRT, conventional fractionated radiation therapy; CI, confidence interval; EBRT, external beam radiation therapy; $FEV_1$, forced expiratory volume in 1 s; HR, hazard ratio; NR, not reported; SBRT, stereotactic body radiation therapy

## Table 4-5. Comparisons of outcomes using regression for different radiotherapy regimens or observation.

| Study | Variables compared | Variables in multivariable analysis | Statistically significant treatment variables |
|---|---|---|---|
| Jeppesen 2013 [4] | SBRT<br>Conventional radiation | Overall survival:<br>SBRT, gross tumour volume <25 $cm^3$, adenocarcinoma, sex, smoker, performance score >1 | Overall survival:<br>Better for SBRT |
| Koshy 2015 [5] | SBRT<br>Conventional radiation<br>Observation | Overall survival:<br>Gender, comorbidities, T stage, age at diagnosis, histology, race/ethnicity, insurance status, facility type, facility volume, year of diagnosis, treatment method | Overall survival:<br>SBRT better than observation HR 0.67 (0.61-0.73) p<0.0001<br>Conventional radiation better than observation HR 0.77 (0.74-0.80) p<0.0001) |
| Tong 2015 [9] | SBRT<br>3D-CRT | Radiation pneumonitis:<br>Radiation therapy techniques, pre-forced expiratory volume during first second/forced vital capacity | Radiation pneumonitis:<br>higher for 3D-CRT |
| Widder 2011 [10] | SBRT<br>3D-CRT | Overall survival:<br>Treatment method, World Health Organization performance score, tumour size, Charlson comorbidity index<br><br>Global quality of life, physical functioning, dyspnea:<br>Mean baseline score between treatments, change per year between treatments | Overall survival:<br>Better for SBRT<br><br>Physical functioning:<br>Change per year better for SBRT |

Abbreviations: 3D-CRT, three-dimensional conformal radiotherapy; HR, hazard ratio; SBRT, stereotactic body radiation therapy

***Question #2:*** **What are the most effective dosing/frequency schedules for curative intent radiotherapy?**

***Systematic reviews***

Zhang et al. (2011) performed a meta-regression using observational studies to assess the impact of the BED of SBRT on overall survival, cancer-specific survival, and local control rate [23]. The only characteristic that was found to significantly influence the regression coefficient and was corrected for in their model was the percentage of patients with tumours smaller than 3 cm. They divided studies into four dose groups based on the quartile of included studies. These included low (<83.2), medium (83.2 to 106), medium to high (106 to 146), and high (>146). They found a significant overall survival benefit at two years and three years with the delivery of medium BED (two-year: 76%, 95% CI, 62% to 92%; three-year: 64%, 95% CI, 57% to 71%) or medium to high BED (two-year: 68%, 95% CI, 61% to 76%; three-year: 63%, 95% CI, 56% to 71%) compared with high BED (two-year: 56%, 95% CI, 50% to 63%, p<0.001; three-year: 50%, 95% CI, 43% to 57%, p<0.001) or low BED at three years only (three-year: 52%, 95% CI, 44% to 62%, p<0.005). Also, three-year cancer-specific survival for medium BED (80%, 95% CI, 72% to 88%) was higher compared with low BED (70%, 95% CI, 57% to 85%, p=0.016) but lower compared with high BED (90%, 95% CI, 69% to 1%, p=0.0067). No significant differences were found among dose groups for local control rate, nor were any differences found when a cut-off of 100 BED was used. The occurrence of severe adverse events of grades 3 to 5 was only significantly different between the low and high BED groups.

Two systematic reviews examined the most appropriate metrics for what dose to use when calculating the effects of SBRT on patient outcomes. Chi et al. (2013) performed a systematic review to investigate the best α/β ratio for the BED calculation [25]. They included 24 studies and found the strongest correlations between BED and local control (p=0.007) or BED and two-year overall survival (p=0.073) when an α/β ratio of 20 Gy was used, suggesting that an α/β ratio of >10 Gy may be more appropriate for the prediction of BED dose response in early stage lung cancer. The 2014 systematic review by Kong et al. included 19 studies, and found that total dose multiplied by dose per fraction was predictive of local control, whereas BED had no significant association [26]. This suggests that total dose multiplied by dose per fraction may be a more appropriate metric than BED to estimate the effects of SBRT. However, the authors from both systematic reviews caution that these results need to be validated in future studies.

***Primary studies (Tables 4-6 and 4-7)***

Twenty-four cohort articles [19,22,52,54,56,57,59,61,63-67,70-77,79,80,82] compared different doses or fractions or BED as a continuous variable and their impact on patient outcomes. Many of the studies used the location or size of the tumour as criteria for administering different dosages, with central tumours receiving lower doses than peripheral tumours, but this was not adjusted for in their analyses. Only Bradley et al. (2010) adjusted for location in a multivariable analysis and found that a higher maximum dose of ≥67 Gy led to fewer local recurrences compared with maximum doses <67 Gy [56]. Allibhai et al. (2013) also controlled for tumour diameter in a multivariable analysis and found that increasing dose regimens were associated with greater overall survival, cause-specific survival, and local relapse-free survival [52]. Likewise, Taremi et al. adjusted for tumour size in a multivariable analysis and found dose to be associated with overall survival [80]. In a multivariable analysis by Kopek et al. (2009) that adjusted for T stage, no difference was found in overall survival between patients that had a total dose of 45 Gy in three fractions versus 67.5 Gy in three fractions [65]. Olsen et al. 2011 found no difference in overall survival using multivariable analysis, controlling for tumour volume, among 54 Gy in three fractions, 45 Gy in five fractions or 50 Gy in five fractions; however, 45 Gy in five fractions was a significant predictor of local

failure [70]. Using univariable analysis, Hayashi et al. (2014) found that neither tumour location nor total dose (48 Gy in four fractions versus 60 Gy in 10 fractions) was correlated with overall survival [61]. For centrally located tumours, Chang et al. (2014) found no difference in overall survival, progression-free survival, local recurrence, regional recurrence, or distant metastasis in patients who had received 50 Gy in four fractions compared with patients who had received 70 Gy in 10 fractions [57]. Likewise, Schanne et al. (2012) found no association between the maximum dose (range, 30 to 86.2 Gy) and overall survival, disease-free survival, and freedom from local progression in patients with centrally located tumours [73].

Twelve retrospective studies [11-22] assessed optimal BED cut-offs. A study using multivariable analyses that controlled for stage, found that patients who received doses with a BED ≥106 had higher overall survival and freedom from local progression than patients who received a BED of <106 [14]. Similarly, Grills et al. (2012) found that a BED cut-off of 105 was associated with local recurrence using regression analysis and adjusting for tumour volume [13]. Furthermore, Onishi et al. (2007) found that local recurrence rates were lower and five-year overall survival rates were higher for patients who received a BED ≥100 compared with a BED of <100 [20]. Likewise, Kestin et al. (2014) and Kohutek et al. (2015) found associations between a cut-off of 100 BED or 105 BED and local control, but not overall survival [15,16]. Conversely, Lee et al. (2013), Ricardi et al. (2014), Mak et al. (2015) and Factor et al. (2014) did not find an association between BED cut-offs of 101, 101.7, 106, or 151.2, respectively, and local relapse-free survival, distant metastasis-free survival, cause-specific survival, local control, or overall survival [12,18,19,21]. Most of these studies had small sample sizes [12,18,19]. For T2 tumours, Davis et al. (2015) [11] found an association between a BED of <105 and local failure but not overall survival, and Koshy et al. (2015) [17] found higher overall survival for patients with T2 tumours that received BED doses of >150.

For adverse effects, several studies examined the impact of dose on chest wall toxicity including chest wall pain or pneumonitis. Stephans et al. (2009) found significantly higher chest wall toxicity for patients receiving 60 Gy in three fractions compared with 50 Gy in five fractions [79]. Bongers et al. (2011) reported that different fractionation schemes in which 60 Gy was delivered in three, five, or eight fractions based on location was not a significant factor for chest wall toxicity [55]. Likewise, Fischer-Valuck et al. (2013) found no difference in chest toxicity between 48 Gy in four fractions compared with 60 Gy in five fractions [59].

Using Cox regression multivariable analysis, Creach et al. (2012) found that only the percentage of the chest wall receiving 40 Gy versus other doses from 20 to 65 Gy was predictive of chest wall pain [84]. Using multivariable logistic analysis, Woody et al. (2012) reported that a modified equivalent dose that accounts for dose inhomogeneity and fractionation differences was associated with chest wall pain [83]. For peripheral tumours, Mutter et al. (2012) found that a volume of chest wall ≥70 $cm^3$ receiving 30 Gy was correlated with chest wall pain [69].

Several studies found an association between mean lung dose or the dose received by lung volume and pneumonitis. Barriger et al. (2012) found that a mean lung dose >4 Gy and a lung volume receiving at least 20 Gy but not 10 Gy or 5 Gy of radiation was associated with grade 2 to 4 pneumonitis [53]. Using Cox regression multivariable analysis, Chang et al. (2012) found that an ipsilateral lung volume of ≥6.3% receiving 40 Gy (the highest dose entered in the model) was associated with grade 2 to 3 pneumonitis [58]. Matsuo et al. (2012) reported that only V20 and V25 were associated with pneumonitis of grade 2 or higher [68]. Similarly, Inoue et al. (2013) found that the mean lung dose and V20 were significantly higher in patients with grade 2 or 3 pneumonitis compared with those with grade 0 or 1 pneumonitis [63]. Ueki et al. (2015) also found that V5, V15, V20, V25, and the mean lung dose were predictive of grade 2 or higher pneumonitis [81]. However, two studies using regression analysis did not find an association between mean lung dose or V20 and pneumonitis [61,78].

Other adverse events were also investigated. Grills et al. (2012) found that rib fractures were associated with higher BED [13]. The threshold value for a significant increase in fracture rate appeared to be at a BED of 132 (11% versus 5%, p=0.007). Guckenberger et al. (2013) found no association between dosimetric variables and changes in pulmonary function [60]. Hoppe et al. (2008) reported that a maximum skin dose of 50% or higher of the prescribed dose was associated with increased skin toxicity [62].

**Table 4-6. Comparisons of overall survival, local control, and toxicity to advise on the most effective dose/fractionation schedules.**

| Study | Doses compared | Local control (%) | Median overall survival in months (95% CI) | Toxicity |
|---|---|---|---|---|
| Davis 2015 [11] | BED <105<br>BED 105-149<br>BED ≥150 | For T2 tumours (p=0.011):<br>BED <105 = 43%<br>BED 105-149 = 74%<br>BED ≥150 = 95 %<br>No difference for T1 tumours | For T2 tumours:<br>BED <105 = 17<br>BED 105-149 = 32 (p=0.062)<br>No difference for T1 tumours | NR |
| Olsen 2011 [70] | For peripheral tumours: 54 Gy in 3<br>For central tumours: 45 Gy in 5 or 50 Gy in 5 | 54 Gy in 3 = 91<br>45 Gy in 5 = 50<br>50 Gy in 5 = 100<br>(p=0.46) between 50 Gy in 5 and 54 Gy in 3<br>(p=0.006) between combined 50 Gy in 5 and 54 Gy in 3 vs 45 Gy in 5 | 54 Gy in 3 = 34<br>45 Gy in 5 = 14<br>50 Gy in 5 = Not reached<br>(p=0.21) between 50 Gy in 5 and 54 Gy in 3<br>(p=0.016) between combined 50 Gy in 5 and 54 Gy in 3 vs 45 Gy in 5 | From Creach 2012 [84]<br>On multivariable analysis using logistic regression, % of chest wall receiving 30, 35, or 40 Gy was most predictive of chest wall pain.<br>On multivariable analysis using Cox regression, only % of chest wall receiving 40 Gy was predictive of chest wall pain. |
| Stephans 2009 [79] | 50 Gy in 5 or 60 Gy in 3 | 50 Gy in 5 = 97.3<br>60 Gy in 3 = 100 (p=0.536) | At 1-year: 50 Gy in 5 = 83.1%<br>60 Gy in 3 = 76.9% (p=0.680) | <table><tr><td></td><td>50 Gy in 5 (%)</td><td>60 Gy in 3 (%)</td></tr><tr><td>Grade 2 radiation pneumonitis</td><td>1</td><td>1</td></tr><tr><td>Grade 3 radiation pneumonitis</td><td>0</td><td>0</td></tr><tr><td>Chest wall toxicity</td><td>2(4)</td><td>7(18) p=0.028</td></tr></table><br>No difference in pulmonary function test changes by fractionation group |

Abbreviations: BED, biological effective dose, CI, confidence interval; Gy, Grays

**Table 4-7. Comparisons of outcomes using regression to advise on the most effective dose/fractionation schedules.**

| Study | Dosimetric variables compared | Variables in multivariable analysis using Cox proportional hazard model | Statistically significant dosimetric variables associated with better outcomes | Other analysis |
|---|---|---|---|---|
| Allibhai 2013 [52] | Dose regimen as ordinals of 50 Gy in 10 fractions < 60 Gy in 8 fractions < 50 Gy in 5 fractions < 52.5 Gy in 5 fractions < 48 Gy in 4 fractions < 54 Gy in 3 fractions < 60 Gy in 3 fractions | LRFS, RRFS, DRFS, NLRFS, overall survival, CSS, DFS:<br>Age, dose regimen, ECOG, sex, tumour diameter, gross tumour volume, planning target volume, T-category | LRFS, overall survival, CSS:<br>Increasing dose regimen<br>No dosimetric variables were significant for the remaining outcomes | No significant association between rate of radiation pneumonitis and dosimetric values such as V20 and mean lung dose |
| Barriger 2012 [53] | Mean lung dose (≤4 Gy and >4 Gy), V5 (≤20% and >20%), V10 (≤12% and >12%), V20 (≤4% median and >4%) | NR | NR | Mean lung dose and V20 but not V5 or V10 were associated with grade 2-4 pneumonitis |
| Baumann 2006 [54] | 30-48 Gy or < and >55.6 Gy | NR | NR | No correlation between dose and local control or overall survival rates<br>No difference in risk of local failure between < and >55.6 Gy groups<br>Significant advantage in survival for >55.6 Gy group ($p<0.0018$) |
| Bongers 2011 [55] | For peripheral tumours:<br>60 Gy in 3 fractions<br>For broad contact with chest wall:<br>60 Gy in 5 fractions<br>For central tumours:<br>60 Gy in 8 fractions | NR | NR | On univariable analysis fractionation scheme was not a significant factor for chest wall toxicity |

| Study | Dosimetric variables compared | Variables in multivariable analysis using Cox proportional hazard model | Statistically significant dosimetric variables associated with better outcomes | Other analysis |
|---|---|---|---|---|
| Bradley 2010 [56] | Maximum dose: < and ≥ 67 Gy, total prescription dose, fraction size | Local recurrence:<br>Age, sex, race, performance status, biopsy, location, tumour dimension, T stage, poor lung function, fraction size, total prescription dose, gross tumour volume, planning target volume, maximum dose<br>Overall survival:<br>Age, sex, performance status, biopsy, location, tumour dimension, T stage, poor lung function, fraction size, total prescription dose, gross tumour volume, planning target volume, maximum dose, secondary cancer, distant metastasis<br>Nodal or distant metastases:<br>Age, sex, performance status, biopsy, location, histology primary site, tumour dimension, T stage, poor lung function, fraction size, total prescription dose, gross tumour volume, planning target volume, pneumonitis | Local recurrence:<br>Maximum dose<br>Overall survival:<br>None<br>Nodal or distant metastases:<br>Total prescription dose | Higher maximum doses (≥67 Gy) led to higher rates of local tumour control (p=0.07) |
| Chang 2014 [57] | 50 Gy in 4 fractions or 70 Gy in 10 fractions | Unclear | Radiation pneumonitis grade 2-3:<br>Mean bilateral lung dose >6, V20 of >12%, ipsilateral V30 of >15% | For overall survival, progression-free survival, local recurrence, regional recurrence, and distant metastasis, there were no differences between 50 Gy in 4 and 70 Gy in 10 |
| Chang 2012 [58] | Total lung volume (= right plus left lungs minus gross tumour volume), ipsilateral lung volume (= lung containing lesion to be treated minus gross tumour volume) | Radiation pneumonitis:<br>Total lung volume, mean dose to total lung volume, ipsilateral lung volume, mean dose to ipsilateral lung volume | Radiation pneumonitis:<br>Ipsilateral lung V40 ≥6.3% | NR |
| Factor 2014 [12] | BED >106 or ≤106 | NR | NR | On univariable analysis, BED at a cut-off of 106 did not predict local control or overall survival |

| Study | Dosimetric variables compared | Variables in multivariable analysis using Cox proportional hazard model | Statistically significant dosimetric variables associated with better outcomes | Other analysis |
|---|---|---|---|---|
| Fischer-Valuck 2013 [59] | For peripheral tumours:<br>60 Gy in 5 fractions<br>For central tumours:<br>48 Gy in 4 fractions | NR | NR | Overall survival, local failure, distant metastasis were not different on univariable analysis by radiation dose<br>No relationship between radiation dose and toxicity |
| Grills 2012 [13] | Prescription $BED_{10}$ < and ≥ 105 | Local recurrence:<br>Prescription $BED_{10}$, elapsed days during SBRT, gross tumour volume maximum dimension | Local recurrence:<br>Prescription $BED_{10}$ | Mean prescription $BED_{10}$ for rib fracture versus none was 124 versus 141 ($p<0.001$)<br>Prescription $BED_{10}$ had an area under the curve of 0.659 ($p=0.001$) for rib fracture, with an optimal receiver operator characteristic cut point of 132 for a fracture rate of 11% versus 5 % ($p=0.007$) |
| Guckenberger 2013 [14] | Planning target volume-encompassing dose $BED_{10}$ < and ≥ 106, dose inhomogeneity (planning target volume-encompassing dose/maximum dose) < and ≥ 80% | Overall survival:<br>Performance status, clinical stage, baseline forced expiratory volume in 1 second, biopsy status, planning target volume-encompassing dose, SBRT procedures/institution and year<br>Freedom from local progression:<br>Clinical stage, biopsy status, staging fluoro-deoxy-glucose positron emission tomography, histology, planning target volume-encompassing dose, dose inhomogeneity, image-guided radiotherapy, SBRT procedures/institution and year | Overall survival:<br>Planning target volume-encompassing dose<br>Freedom from local progression:<br>Planning target volume-encompassing dose | NR |
| Guckenberger 2013 [60] | Mean lung dose, absolute and relative V5-V70 of the lungs, mean planning target volume dose | NR | NR | No relationship was found between the dosimetric variables and changes in post-treatment pulmonary function test using linear regression analysis, receiver operating characteristic analysis and Lyman's normal tissue complication probability model |
| Hayashi 2014 [61] | For peripheral tumours:<br>48 Gy in 4 fractions<br>For central tumours:<br>60 Gy in 10 fractions | NR | NR | In univariable analysis, total dose was not a predictor of overall survival<br>V20 and mean lung dose were not correlated with radiation pneumonitis |

| Study | Dosimetric variables compared | Variables in multivariable analysis using Cox proportional hazard model | Statistically significant dosimetric variables associated with better outcomes | Other analysis |
|---|---|---|---|---|
| Hoppe 2008 [62] | 60 Gy in 3 fractions vs 44-48 Gy in 4 fractions | NR | NR | Using Fisher's exact test, there was no difference in skin toxicity between the different doses<br>Maximum back skin dose ≥50% of prescribed dose on the planning scan was associated with skin toxicity grade ≥2 (p=0.02) |
| Inoue 2013 [63] | 48 Gy in 4 fractions, 45 to 50 Gy in 4 fractions | NR | NR | No difference in local control or overall survival between the different dose prescriptions<br>Mean lung dose (p=0.002) and volume of lung receiving 20 Gy (p=0.003) were higher in patients with radiation pneumonitis Grade 2/3 than in those with radiation pneumonitis grade 0/1 |
| Kelley 2015 [64] | For peripheral tumours: Median 48 Gy in 4 fractions | NR | NR | In univariable analysis, BED was not a predictor of disease-free survival or overall survival |
| Kestin 2014 [15] | BED cutpoint 105 or as a continuous variable | NR | Local recurrence:<br>BED as a continuous variable | A $BED_{10}$ >105 and $PTV_{mean}$ BED > 125 had significantly higher local control than lower doses (p=0.001) |
| Kohutek 2015 [16] | $BED_{10}$ <100 or ≥100 | NR | NR | BED was not a significant predictor in univariable analysis for overall survival but was correlated with local control (p=0.01) |
| Kopek 2009 [65] | For peripheral tumours:<br>45 Gy in 3 fractions or 67.5 in 3 fractions<br>For central tumours:<br>45 Gy in 3 fractions | Overall survival:<br>Sex, histology, WHO performance status, age-adjusted Charlson Co-morbidity Index, total dose, T-stage | None | NR |
| Koshy 2015 [17] | BED ≥150 and <150 | Overall survival:<br>Gender, comorbidities, T stage, age at diagnosis, histology, BED, race/ethnicity, insurance status, facility type, facility volume, year of diagnosis | Overall survival:<br>BED ≥150 | BED ≥150 was a significant predictor of overall survival for patients with T2 tumours (p<0.0001) but not for patients with T1 tumours |

| Study | Dosimetric variables compared | Variables in multivariable analysis using Cox proportional hazard model | Statistically significant dosimetric variables associated with better outcomes | Other analysis |
|---|---|---|---|---|
| Lagerwaard 2008 [66] | $BED_{10}$ of 180, 132, and 105 | NR | NR | In univariable analysis, BED was not associated with overall survival, local progression-free survival, regional progression-free survival, distant progression-free survival, DFS |
| Lee 2013 [18] | $BED_{10}$ <101.7 or ≥101.7 | NR | NR | In univariable analysis, $BED_{10}$ was not associated with LRFS, distant metastasis-free survival, or CSS |
| Mak 2015 [19] | >54 Gy or ≤ 54 Gy<br>BED ≥151.2 or <151.2 | NR | NR | In univariable analysis, dose and BED were not associated with recurrence or cancer-specific survival |
| Marwaha 2014 [67] | 50 Gy in 5 fractions, 60 Gy in 3 fractions, 30 or 34 Gy in 1 fractions | NR | NR | In univariable analysis, radiation fractionation and total dose were not associated with nodal failure patterns |
| Matsuo 2012 [68] | Mean lung dose, V5, V10, V15, V20, V25, V30, V35, V40 | NR | NR | Using the recursive partitioning method, V25 (p=0.019) and V20 (p=0.030) were significant factors for radiation pneumonitis (≥ grade 2) |
| Mutter 2012 [69] | Volume exposed to a given dose were constructed for values of dose from 0 to the maximum dose in the total population at intervals of 1 Gy | Chest wall pain:<br>Prescription dose, number of fractions | Chest wall pain:<br>None | A volume of chest wall ≥70 $cm^3$ receiving 30 Gy (V30) significantly correlated with Grade ≥2 chest wall pain (p<0.001) |
| Olsen 2011 [70] | For peripheral tumours:<br>54 Gy in 3 fractions<br>For central tumours: 45 Gy in 5 fractions or<br>50 Gy in 5 fractions | Local recurrence:<br>Age, sex, race, treatment duration, biopsy performed, smoker, surgical candidate, tumor volume, treatment with 45 Gy in 5 fractions<br>Overall survival:<br>Age, sex, race, treatment duration, biopsy performed, smoker, surgical candidate, tumor volume, prescription dose group, performance status, distant metastasis | Local recurrence:<br>45 Gy in 5 fractions<br>Overall survival:<br>None | Overall survival statistics at years 1 and 2 were 92% and 85%, respectively, for operable patients, compared with 81% and 61% for inoperable patients, with no significant difference between the groups on log–rank test (p=0.088) |

| Study | Dosimetric variables compared | Variables in multivariable analysis using Cox proportional hazard model | Statistically significant dosimetric variables associated with better outcomes | Other analysis |
|---|---|---|---|---|
| Onishi 2007 [20] | BED ≥100 vs < 100 | NR | NR | Local recurrence rates lower for BED ≥100 (8.4%) vs <100 (42.9%, p<0.01)<br>Overall 5-year survival higher for BED ≥100 (53.9%; 95% CI, 46-61.8%) vs <100 (19.7%; 95% CI, 5.9-33.4%) |
| Ricardi 2014 [21] | $BED_{10}$ >100 vs ≤100 | NR | NR | In univariable analysis, BED was not a significant predictor of local recurrence, disease-free survival, overall survival or cancer-specific survival |
| Rosen 2014 [71] | 48 Gy in 4 fractions vs 60 Gy in 5 fractions | NR | NR | In univariable analysis, dose was not a predictor of overall survival (p=0.101) |
| Satoh 2014 [72] | $BED_{10}$ 96-119 | NR | NR | In univariable analysis, BED was a significant predictor of DFS (p=0.005) but not of overall survival |
| Schanne 2015 [73] | maximum dose for central tumours of 30-86.2 Gy | Overall survival, disease-free survival, freedom from local progression:<br>Maximum dose, availability of staging PET/CT | Overall survival, disease-free survival, freedom from local progression:<br>None | There was a significant association between freedom from local progression and maximum dose (cut-off 70 Gy, p=0.05) |
| Shibamoto 2012 [74] | 48 Gy in 4 fractions vs 52 Gy in 4 fractions | NR | NR | No difference in local control between 48 Gy in 4 fractions vs 52 Gy in 4 fractions (p=0.060) |
| Shirata 2012 [75] | 48 Gy in 4 fractions, 60 Gy in 8 fractions, 60 Gy in 15 fractions | Local control:<br>Age, sex, T factor, histology, planning target volume, minimum dose for planning target volume, BED calculated from prescribed dose, BED calculated from minimum dose | Local control:<br>BED calculated from prescribed dose, minimum dose for planning target volume | NR |
| Shultz 2014 [76] | $BED_{10}$ | Overall survival:<br>BED using linear quadratic, contact with pleura adjacent to mediastinum, maximum standard uptake value | Overall survival:<br>none | In univariable analysis, BED was not associated with freedom from distant metastasis, freedom from regional progression, freedom from local progression |

| Study | Dosimetric variables compared | Variables in multivariable analysis using Cox proportional hazard model | Statistically significant dosimetric variables associated with better outcomes | Other analysis |
|---|---|---|---|---|
| Sibley 1998 [77] | >64 Gy vs ≤64 Gy | CSS:<br>Histology, incidental diagnosis, age, pack-years of smoking, radiotherapy dose, treatment volume<br>Local failure:<br>Age, size, histology, chronic obstructive pulmonary disease, incidental diagnosis, cough, dyspnea, pain, hemoptysis, weight loss, pack-years of smoking, radiotherapy dose, radiotherapy volume | None | NR |
| Stanic 2014 [78] | Mean dose to whole lung, V5, V10, V20 | NR | NR | In logistic regression analysis, mean dose to whole lung, V5, V10 and V20 were not correlated with pneumonitis |
| Stephans 2009 [79] | 50 Gy in 5 fractions vs 60 Gy in 3 fractions | NR | NR | No difference in actuarial rates of distant metastasis, local control, and overall survival by fractionation regimen<br>In univariable analysis, fractionation scheme was not a significant factor for overall survival<br>No difference in pulmonary function test changes by fractionation group<br>Chest wall toxicity was higher in 60 Gy group (7/38 lesions, 18%) compared with 50 Gy group (2/56 lesions, 4%, p=0.028)<br>This difference persisted when central lesions were excluded (7/38 vs 2/49, p=0.039) |
| Suzuki 2014 [22] | BED | Overall survival, local control:<br>Age, sex, WHO performance status, BED at periphery of planning target volume, operability, forced expiratory volume at one second at baseline, gross tumour volume | Overall survival:<br>None<br>Local control:<br>BED at periphery of planning target volume | Using receiver operator curve analysis, an optimal cut off of 86.4 BED was determined in predicting local failure |
| Taremi 2012 [80] | 60 gy in 3 fractions vs 54 Gy in 3 fractions vs 48 Gy in 4 fractions vs 60 Gy in 8 fractions vs 50 Gy in 10 fractions | Overall survival:<br>Tumour size, dose, female | Overall survival:<br>Dose | NR |

| Study | Dosimetric variables compared | Variables in multivariable analysis using Cox proportional hazard model | Statistically significant dosimetric variables associated with better outcomes | Other analysis |
|---|---|---|---|---|
| Ueki 2015 [81] | BED, fraction number (8 vs 4), V5, V10, V15, V20, V25, mean lung dose | NR | NR | In univariable analysis, BED and fraction number were not significant predictors of radiation pneumonitis, but V5, V15, V20 V25 and mean lung dose were significant predictors of ≥ grade 2 pneumonitis |
| Videtic 2014 [82] | 30 Gy vs 34 Gy | NR | NR | There was no difference in toxicity, local failure, overall survival or lung cancer-specific survival between the doses |
| Woody 2012 [83] | Modified equivalent uniform dose | Chest wall pain:<br>Modified equivalent uniform dose, body mass index | Chest wall pain:<br>Modified equivalent uniform dose | With a volumetric parameter of 7.5 and an α/β ratio of 3 Gy, a modified equivalent uniform dose at a cutoff of 203 Gy in 2 had a 75% sensitivity and 80% specificity in predicting chest wall pain |

Abbreviations: BED, biological effective dose; CSS, cause specific survival; DFS, disease-free survival; DRFS, distant relapse-free survival; ECOG, Eastern Cooperative Oncology Group status; Gy, Grays; LRFS, local relapse-free survival; NLRFS, nonlocal relapse-free survival; NR, not reported; PET/CT, positron emission tomography/computed tomography; $PTV_{mean}$, mean planning target volume; RRFS, regional relapse-free survival; SBRT, stereotactic body radiation therapy; WHO, World Health Organization

***Ongoing, Unpublished, or Incomplete Studies***

The US National Institutes of Health's clinical trial registry (http://www.clinicaltrials.gov) was searched on October 15, 2015. Many ongoing trials investigating curative radiotherapy in early stage medically inoperable NSCLC were identified (Table 4-8). Also, 20 unpublished abstracts from non-randomized studies were found during the literature search [85-104]. This guideline does not make recommendations on treatment offered in these trials.

**Table 4-8. Ongoing trials of stereotactic radiation therapy in early stage, medically inoperable NSCLC**

| Protocol ID | Study details |
|---|---|
| Proton Stereotactic Body Radiation Therapy for Early-Stage Non-Small Cell Lung Cancer<br>NCT01525446 | In this study, the investigators are evaluating the safety and effectiveness of proton-based SBRT for early-stage NSCLC located in the periphery of the lung. |
| A Phase I/II Trial of Stereotactic Body Radiation Therapy (SBRT)<br>NCT00591838 | The purpose of this study is to use SBRT in patients with early stage lung cancer and find out what effects (good and bad) SBRT has on their cancer. |
| Stereotactic Body Radiotherapy (RT) for Non-Small Cell Lung Cancer<br>NCT01480973 | MRI assessment of post-radiation change following stereotactic body RT for NSCLC: a pilot study |
| Risk-adapted Stereotactic Body Radiotherapy for Early Non-Small Cell Lung Cancer Using the VERO Stereotactic Body Radio Therapy System<br>NCT02224547 | The purpose of this study is to perform prospective data analysis on tumour response in terms of local tumour control after 2 years, potential acute and late toxicity and survival in patients with non-metastatic, NSCLC treated by radiotherapy that are medically inoperable due to coexisting comorbidities or that refuse surgery. SBRT regimens used will be 4 fractions of 12 Gy or 3 fractions of 17 Gy depending on tumour location in a risk-adapted approach. |
| Risk Adapted SABR (SABR) in Stage I NSCLC And Lung Metastases (sbrtlungfff)<br>NCT01823003 | This study is designed to evaluate the safety of Stereotactic Ablative Radiotherapy (SBRT) in selected patients with stage I NSCLC or metastatic lung cancer to demonstrate the feasibility and risks of using an ablative dose-adapted scheme with FFF beams. |
| Phase II Trial of Individualized Lung Tumor Stereotactic Ablative Radiotherapy (iSABR)<br>NCT01463423 | The purpose of this study is to evaluate the effectiveness of individualizing the dose of radiation used to treat lung tumours with SABR based on tumour-specific factors. |
| Stereotactic Body Radiotherapy Versus Conventional Radiotherapy in Medically-Inoperable Non-Small Lung Cancer Patients (LUSTRE)<br>NCT01968941 | Eligible and consenting patients will be randomly allocated to receive stereotactic body radiotherapy (SBRT) or conventional radiotherapy (CRT) in a 2:1 ratio. Radiotherapy will be administered as soon as possible following randomization and subjects will be followed for 5 years post-randomization for cancer recurrence, toxicity and survival. The primary outcome is local control (LC). The trial will be conducted at 16-20 clinical centres throughout Canada. |
| LungTech: Stereotactic Body Radiotherapy (SBRT) of Inoperable Centrally Located NSCLC<br>NCT01795521 | The main purpose of this trial is to assess the effectiveness of IG-SBRT (Image guided stereotactic body radiotherapy) in patients with medically inoperable early stage, centrally located NSCLC and in those who are not willing to undergo surgical treatment. |

Abbreviations: IG, image guided; MRI, magnetic resonance imaging

## DISCUSSION

Evidence from retrospective observational studies suggest that SBRT compared with observation or other forms of radiotherapy treatments such as accelerated hypofractionated radiation therapy, three-dimensional conformal radiotherapy, conventional fractionated

radiation therapy, external beam radiation therapy, proton beam therapy, and carbon ion therapy may have similar or improved results in patient outcomes of survival or local control with similar or fewer adverse effects [3-10,86,88,90,91,94,96,98,100,101]. In the absence of RCTs, this evidence suggests that SBRT compared with other forms of radiotherapy is a reasonable treatment option for patients with medically inoperable early stage lung cancer.

SBRT involves the delivery of extremely large fraction sizes for each treatment. This requires much stricter treatment planning and delivery criteria compared with conventional radiotherapy. Rigorous quality assurance protocols must be followed in order to achieve intended results. Immobilization, imaging, planning, and treatment require a coordinated effort among the radiation oncologist, the medical physicist, the medical dosimetrist, and the radiation therapist [105].

Many of the included studies assigned doses based on the size and location of the tumour. This was based on a study by Timmerman et al. in 2006 that suggested that an increase in the damage to critical structures and incidence of serious adverse events and toxicity had been found in patients with centrally located tumours when higher dose fractionation schemes were used [1]. Park et al. (2015) showed that delivering lower doses to central tumours with a minimum of 100 BED did not predict inferior overall survival, local control, or toxicity compared with peripheral tumours [24]. Therefore, these factors should be taken into consideration when deciding on the dose or fractionation schedule.

Evidence from observational studies also suggested that local tumour control and survival was associated with the BED. A meta-regression by Zhang et al. (2011) found a significant overall survival benefit at two years and three years with the delivery of medium (83.2 to 106) or medium to high BED (106 to 146) compared with low (<83.2) or high BED (>146) [23]. The occurrence of severe adverse events of grades 3 to 5 was only significantly different between the low and high BED groups. This suggested that medium or medium to high doses may be the most optimal dose ranges. The BED cut-off, however, was difficult to determine. Several studies suggested a cut-off of approximately 100 BED was significantly correlated with patient outcomes [11,13-16,20]; however, other studies, including the Zhang et al. (2011) meta-regression, did not show this association [12,18,19,21,23], although most of these studies had small sample sizes.

There were several limitations associated with this review. These include the fact that the conclusions were drawn from mainly retrospective observational studies, which were at a higher risk of bias. The comparative studies varied in the doses and fractionation schedules and the specific techniques used for SBRT (e.g., linear accelerator, CyberKnife® system, and helical TomoTherapy®). Furthermore, the treatments were sometimes administered at different points in time. For example, conventional radiotherapy was an older technique compared with the newer technique of SBRT. Also, many of the studies comparing different doses or fractionation schedules did not adjust for possible confounders such as tumour location or stage. The conclusions drawn from this systematic review were consistent with the recommendations reported by Boily et al. (2015) [45].

Although the use of radiation dosages expressed as a BED has been advocated, it is important to understand the limitations of determining radiation BED using the linear quadratic model for the extremely hypofractionated schemes used in SBRT. The linear quadratic model has been used as a convenient, slightly simplified model to calculate effective dose when treating tumours with conventional fractionated radiation therapy. At such a high dose per fraction, other models of tissue injury have been suggested [25-27]. As such, users should exercise caution when using BED models in comparing different SBRT schemes.

## CONCLUSIONS

Stereotactic radiation therapy is now emerging as the current treatment of choice for patients with early stage, medically inoperable, NSCLC. The comprehensive evidentiary base compiled suggests that it is a valid treatment option that should be offered to patients with this disease. Ongoing trials will continue to review dosing for marginal gains in effectiveness. Future research should focus on establishing the most effective location-specific dose/fractionation schemes, explore the effectiveness of other radiation modalities (e.g., proton), and determine the comparative effectiveness of stereotactic radiation combined with standard surgical treatment for operable cases with early stage NSCLC.

# Radiotherapy with Curative Intent in Patients with Early Stage, Medically Inoperable, Non-Small Cell Lung Cancer

## Section 5: Internal and External Review

**INTERNAL REVIEW**

The guideline was evaluated by the Guideline Development Group (GDG) Expert Panel and the Program in Evidence-Based Care (PEBC) Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

**Expert Panel Review and Approval**

Of the 24 members of the GDG Expert Panel, 21 (88%) members cast votes in December 2015. Of those that cast votes, 21 approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

**Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.**

| Comments | Responses |
|---|---|
| 1. Since the search date of this systematic review, two phase II randomized controlled trials have been published. One was the RTOG 0915 trial, which compared 48 in 4 with 34 in 1 for peripheral NSCLC. The second (in abstract form) was presented at IASLC WCLC 2016, the Scandinavian SPACE trial, which compared stereotactic body radiation therapy (SBRT) (45/3) with conventional radiation therapy (RT) (70/35). The SPACE trial showed no difference in local control or survival but with better quality of life/convenience with SBRT. RTOG suggested a single fraction SBRT should be tested further. | The Working Group is aware of these trials. The results from these trials will not change the recommendations. The trials will be included in any future updates of this guideline. |
| 2. I did not see NCIC BR.25 reported in this document, which showed that hypofractionated accelerated RT has fairly good local control at two years, similar to SBRT. | We did not include this trial because it did not have SBRT as one of the comparators. |
| 3. I think that we should be clear that the biological effective dose (BED) question and the majority of the literature data are largely based on SBRT for peripherally located lung cancer. I think that while it has been written that dose-fractionation should be carefully considered in centrally located NSCLC, this should be clarified. First, it should be defined here what is centrally located disease (the Timmerman no-fly zone only, or including proximity to mediastinum, descending thoracic aorta, etc). Second, there have been recent abstracts/papers on central and ultra-central NSCLC where there have been some grade 5 toxicities. RTOG 0813 was | A definition for centrally located tumours has been added.<br>The papers mentioned in the second comment are either an abstract or an ongoing trial and therefore their results have not been included. |

| | |
|---|---|
| recently presented at ASTRO and IASLC WCLC and there were not an insignificant number of grade 3 to 5 toxicities with 50 to 60 Gy in five fractions. LUNGtech (which you cited) has recently opened and will be the largest prospective trial of 60 Gy in 8 fractions for central tumours. | |
| 4. I think the document should be separated into peripheral and central NSCLC, and have a wider range of potential dose fractionations, particularly for central disease, including conventional fractionation schemes like 60 Gy in 15 fractions or lower dose/fraction. | The dose/fractionation schemes are only examples of possible schedules and are not an exhaustive list. |
| 5. The qualifying statement for recommendation 1 should include use of image-guided radiation therapy. | The Working Group believed that image guidance is part of SBRT and need not be specifically repeated. The words "during simulation and treatment delivery" were added to this qualifying statement to make it clearer. |

**RAP Review and Approval**

Three RAP members, including the PEBC Director, reviewed this document in December 2015. The RAP conditionally approved the document on December 16, 2015. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

**Table 5-2. Summary of the Working Group's responses to comments from RAP.**

| Comments | Responses |
|---|---|
| 1. It is unclear what the current standard was for these patients. | In the past, observation and conventional radiotherapy were used. This has been made more explicit in the introduction. |
| 2. Why did the systematic review show more adverse events for the studies using SBRT whereas the comparative primary literature found the opposite? | An explanation for the higher proportion of adverse events after SBRT found in the systematic review has been explained more thoroughly. |
| 3. In the objective statement, perhaps a term such as "value" or "effectiveness" rather than "role" should be used. | This has been changed. |
| 4. If conventional radiation should not be used for these patients, this should be stated. | There was not enough evidence to make this statement or to actually state that SBRT is the preferred option. SBRT is a reasonable option and should be considered. |

**EXTERNAL REVIEW**

**External Review by Ontario Clinicians and Other Experts**

***Targeted Peer Review***

Seven targeted peer reviewers from Ontario who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Four agreed to be the reviewers (Appendix 1). Four responses were received. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

**Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.**

| Question | Reviewer Ratings (N=4) | | | | |
|---|---|---|---|---|---|
| | Lowest Quality (1) | (2) | (3) | (4) | Highest Quality (5) |
| **1. Rate the guideline development methods.** | 0 | 0 | 0 | 2 | 2 |
| **2. Rate the guideline presentation.** | 0 | 0 | 0 | 3 | 1 |
| **3. Rate the guideline recommendations.** | 0 | 0 | 2 | 1 | 1 |
| **4. Rate the completeness of reporting.** | 0 | 0 | 2 | 0 | 2 |
| **5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?** | 0 | 0 | 1 | 2 | 1 |
| **6. Rate the overall quality of the guideline report.** | 0 | 0 | 1 | 1 | 2 |
| | Strongly Disagree (1) | (2) | Neutral (3) | (4) | Strongly Agree (5) |
| **7. I would make use of this guideline in my professional decisions.** | 0 | 0 | 0 | 2 | 2 |
| **8. I would recommend this guideline for use in practice.** | 0 | 0 | 0 | 2 | 2 |
| **9. 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.<br>• This guideline provides a good understanding of how to prescribe this therapy to patients.<br>• 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 5-4. Responses to comments from targeted peer reviewers.**

| Comments | Responses |
|---|---|
| 1. Should the recommendation be more strongly worded towards SBRT being the preferred or recommended approach rather than "an option", especially for straightforward peripherally located tumours? | The Working Group believed this recommendation is strongly worded because the word "should" is used, rather than "may" be considered. |
| 2. This guideline is also relevant to those patients who are operable, but refuse surgery, so somehow that should be incorporated too. | Patients who refuse surgery are included in the target population. |
| 3. The comment in the recommendation stating that immobilization and four-dimensional analysis for planning and delivery is important | The qualifying statement was changed from, "Adequate immobilization of the patient and four-dimensional analysis of tumour and critical structure |

| | |
|---|---|
| might be better described as 'not only important, but mandatory'. | motion during simulation and treatment delivery are important." to "Consistent patient positioning and four-dimensional analysis of tumour and critical structure motion during simulation and treatment delivery are essential." |
| 4. Currently the recommendations state that SBRT is an option and there is a suggested listing of fractionation schemes. It would have been great if other relevant recommendations were included such as what are the radiation treatment planning considerations that we should be mindful of, i.e., dose-volume histograms (DVHs) to review, the relevant DHV limits, and normal tissue low-dose considerations, etc. Along with that, recommendations on how best to manage side effects for this group with such an RT prescription should also be included. Adding these to the current recommendations would provide the user with a more fulsome picture of things to consider when faced with this population of patients. | This was outside the scope of this guideline. |
| 5. In terms of comparative studies, Sunnybrook has just published a propensity score matched analysis, comparing SBRT versus accelerated hypofractionation in Radiotherapy and Oncology in 2016: http://www.ncbi.nlm.nih.gov/pubmed/26795773. Should this be included in the guideline? | The Working Group is aware of this trial. The results from this trial will not change the recommendations. This trial will be included in any future updates of this guideline. |
| 6. Comments on lack of data on functional outcomes and quality of life from studies reviewed would be worthwhile. | There is a lack of data on these outcomes and have not been included in our research questions. |

***Professional Consultation***

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. Any health-care provider with an interest in lung cancer in the PEBC database was contacted by email to inform them of the survey. One hundred two professionals who practice in Ontario and 19 who practice outside of Ontario were contacted. Twenty (17%) responses were received. Six stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 14 people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

**Table 5-5. Responses to four items on the professional consultation survey.**

| | Number (%) | | | | |
|---|---|---|---|---|---|
| **General Questions: Overall Guideline Assessment** | Lowest Quality (1) | (2) | (3) | (4) | Highest Quality (5) |
| **1. Rate the overall quality of the guideline report.** | 0 | 0 | 0 | 6 (43) | 8 (57) |
| | Strongly Disagree (1) | (2) | (3) | (4) | Strongly Agree (5) |

| | | | | | |
|---|---|---|---|---|---|
| **2. I would make use of this guideline in my professional decisions.** | 0 | 0 | 3 (21) | 6 (43) | 5 (36) |
| **3. I would recommend this guideline for use in practice.** | 0 | 0 | 1 (7) | 4 (29) | 9 (64) |
| **4. What are the barriers or enablers to the implementation of this guideline report?** | • The review is thorough and comprehensive.<br>• It would be helpful if there were patient awareness and education for this guideline.<br>• The limitation really is the quality of the available source evidence the guidelines are based upon.<br>• The barriers are primarily related to the availability of the technology and expertise to offer SBRT.<br>• 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. | | | | |

**Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.**

| Comments | Responses |
|---|---|
| 1. There is no mention about what staging needs to be done to exclude N1 or N2 disease. Many of these patients are at high risk for invasive biopsies. Do they require a tissue diagnosis? Do they require invasive mediastinal staging? Can computed tomography and positron emission tomography imaging be acceptable in these medically unfit patients? | This was outside the scope of this guideline. |
| 2. It might be helpful if the top-line recommendations were explicit in discussing the other options for these patients and how they compare (e.g., other radiotherapy techniques). We can read this and see that SBRT is an option, but is it the preferred option? Is there a preferred option? Are there other options? Some of this is captured in the detailed body of the report but I think it needs greater priority in the report. | The Working Group believed there was not enough evidence to recommend SBRT as the preferred option. |
| 3. I was disappointed that the RTOG trial looking at single fraction RT (34 Gy in 1) was left out. I realize it was published after the search date but it was an important trial. | The Working Group is aware of this trial. The results from this trial will not change the recommendations. This trial will be included in any future updates of this guideline. |

| | |
|---|---|
| 4. The concept of not using regimens with a BED > 146 was a bit confusing. As you show in the document, there is tremendous experience with 54 Gy in 3 which falls into this category. Many of us use this dose/fractionation without any issues. Toxicity depends on the size of tumour and proximity to organs at risk such as chest wall. | This recommendation is based on the best available evidence. Future studies may provide more clarity on this issue. |
| 5. The comments mention the appropriateness of SBRT as an option but there is no discussion of the potential convenience for shorter treatment durations or of the potential advantages of scheduling shorter treatment course. Did any study report on patient satisfaction of resource utilization? | This was outside the scope of this guideline. |

**CONCLUSION**

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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**Appendix 1: Affiliations and Conflict of Interest Declarations.**

In accordance with the PEBC Conflict of Interest (COI) Policy, the Members of the Radiation with Curative Intent in Medically Inoperable Patients with Non-small Cell Lung Cancer Working Group, Expert Panel, Report Approval Panel and Target Peer Reviewers were asked to disclose potential conflicts of interest.

| Name and Affiliation | Declarations of interest |
|---|---|

| **Working Group** | |
|---|---|
| Conrad Falkson<br>Radiation Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Emily Vella<br>Health Research Methodologist<br>Program in Evidence-Based Care, Cancer Care Ontario, Hamilton, ON | None declared |
| Edward Yu<br>Radiation Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Medhat El-Mallah<br>Radiation Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Yee Ung<br>Radiation Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Peter Ellis<br>Medical Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Robert Mackenzie<br>Health Research Methodologist<br>Program in Evidence-Based Care, Cancer Care Ontario, Hamilton, ON | None declared |
| **Lung Cancer Disease Site Group Expert Panel** | |
| Adrien Chan<br>Medical Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Susanna Cheng<br>Medical Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Ronald Feld<br>Medical Oncologist<br>Lung Cancer Disease Site Group | None declared |
| John Goffin<br>Medical Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Richard Gregg<br>Medical Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Swati Kulkarni<br>Medical Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Sara Kuruvilla<br>Medical Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Scott Laurie<br>Medical Oncologist<br>Lung Cancer Disease Site Group | None declared |

| | |
|---|---|
| Natasha Leighl<br>Medical Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Andrew Robinson<br>Medical Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Mark Vincent<br>Medical Oncologist<br>Lung Cancer Disease Site Group | • Has received $5,000 or more in a single year as a consultant for Eli Lilly, Roche, Boehringer Ingelheim, Astra Zeneca<br>• Has received research support as a principal or co-investigator from Roche Canada |
| Penny Bradbury<br>Medical Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Robert MacRae<br>Radiation Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Andrew Pearce<br>Radiation Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Kevin Ramchandar<br>Radiation Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Anand Swaminath<br>Radiation Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Mojgan Taremi<br>Radiation Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Alexander Sun<br>Radiation Oncologist<br>Lung Cancer Disease Site Group | None declared |
| Abdollah Behzadi<br>Surgeon<br>Lung Cancer Disease Site Group | None declared |
| Donald Jones<br>Surgeon<br>Lung Cancer Disease Site Group | None declared |
| Richard Malthaner<br>Surgeon<br>Lung Cancer Disease Site Group | None declared |
| Donna Maziak<br>Surgeon<br>Lung Cancer Disease Site Group | None declared |
| Kazuhiro Yasufuku<br>Surgeon<br>Lung Cancer Disease Site Group | None declared |
| Robert Zeldin<br>Surgeon | None declared |

| | |
|---|---|
| Lung Cancer Disease Site Group | |
| **Report Approval Panel** | |
| Melissa Brouwers<br>Director<br>Program in Evidence-Based Care,<br>Cancer Care Ontario, Hamilton, ON | None declared |
| Marko Simunovic<br>Surgeon<br>Juravinski Cancer Centre | None declared |
| Eric Winquist<br>Medical Oncologist<br>London Regional Cancer Program<br>London Health Sciences Centre | None declared |
| **Target Peer Reviewers** | |
| Patrick Cheung<br>Radiation Oncologist<br>Sunnybrook Odette Cancer Centre | As the president of his medical corporation, he bills OHIP for all medical services, including radiotherapy treatment planning/delivery for early stage lung cancer |
| Gunita Mitera<br>Departments of Radiation Therapy and Radiation Oncology<br>Sunnybrook Odette Cancer Centre<br>University of Toronto | None declared |
| Gordon Okawara<br>Radiation Oncologist<br>Hamilton Health Sciences<br>Juravinski Cancer Centre | None declared |
| Kenneth Schneider<br>Radiation Oncologist<br>Windsor Regional Cancer Centre | None declared |

**Appendix 2: Literature Search Strategy**

**Ovid EMBASE (1985 to 2014 Week 19)**

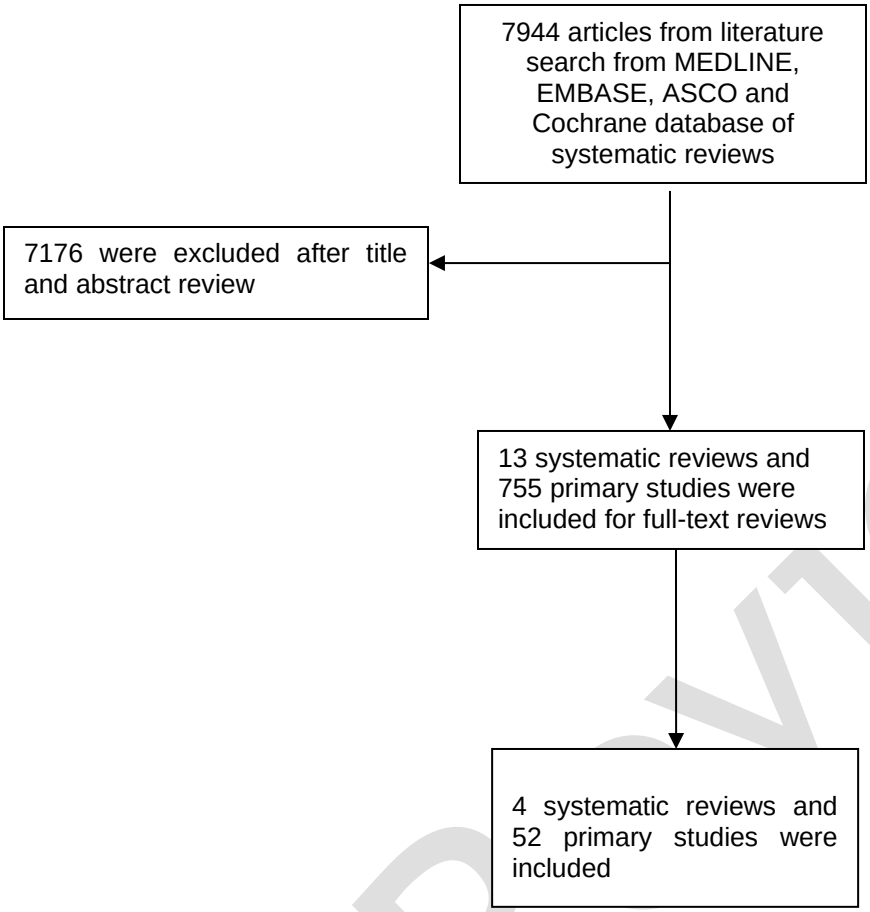
1. exp lung tumour/ or lung non small cell cancer/
2. nsclc.ti,ab.
3. (lung and (cancer$ or neoplasm$ or carcinoma$ or malignan$ or tumo?r$)).ti,ab.
4. Or/1-3
5. Inoperable cancer/
6. Early cancer/
7. (inoperable or early stage$).mp.
8. (stage adj2 (I or Ia or Ib or II or IIa or IIb or "1" or 1a or 1b or "2" or 2a or 2b)).ti,ab.
9. Or/5-8
10. Exp cancer radiotherapy/
11. Exp radiotherapy/
12. *lung non small cell cancer/rt
13. dose fractionation.ti,ab.
14. Radiotherapy.ti,ab.
15. Stereotactic.ti,ab.
16. Sbrt or sabr.ti,ab.
17. Hypofraction:.ti,ab.
18. Radiation therapy.ti,ab.
19. Or/10-18
20. 4 and 9 and 19
21. (editorial or note or letter or erratum or short survey).pt. or letter/
22. 20 not 21
23. limit 22 to English language

**Ovid MEDLINE (1985 to April Week 5, 2014), MEDLINE In-Process & Other Non-Indexed Citations (May 12, 2014), MEDLINE Daily Update (May 12, 2014), Cochrane Databases of Systematic Reviews (CDSR: March 2014), Cochrane Central Register of Controlled Trials (CCTR: April 2014), Database of Abstracts of Reviews of Effects (DARE: 1st quarter 2014)**

1. exp lung neoplasm/ or carcinoma, non-small-cell lung/
2. nsclc.ti,ab.
3. (lung and (cancer$ or neoplasm$ or carcinom$ or malignan$ or tumo?r$)).ti,ab.
4. Or/1-3
5. (inoperable or early stage$).mp.
6. (stage adj2 (I or Ia or Ic or II or IIa or IIb or "1" or 1a or 1b or "2" or 2a or 2b)).ti,ab.
7. 5 or 6
8. exp radiotherapy/
9. exp dose fractionation/
10. carcinoma, non-small-cell lung/rt
11. exp radiation dosage/
12. dose fractionation.ti,ab.
13. Radiotherapy.ti,ab.
14. Stereotactic.ti,ab.
15. Sbrt or sabr.ti,ab.
16. Hypofraction:.ti,ab.
17. Radiation therapy.ti,ab.

18. Or/8-17
19. 4 and 7 and 18
20. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
21. 19 not 20
22. limit 21 to English language
23. animal/
24. human/
25. 23 not 24
26. 22 not 25

**Appendix 3: PRISMA Flow Diagram**



## Appendix 4. Quality of Included Studies

**Risk of bias judgements for eligible non-randomized studies by the Cochrane Collaboration Tool.**

| Study | Bias due to confounding | Bias in selection of participants into the study | Bias in measurement of interventions | Bias due to departures from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result | Overall |
|---|---|---|---|---|---|---|---|---|
| **TECHNIQUE** | | | | | | | | |
| **Borst 2009 [3]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Moderate risk | Serious risk | Serious risk |
| **Jeppesen 2013 [4]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Low risk | Serious risk | Serious risk |
| **Koshy 2015 [5]** | Moderate risk | Moderate risk | Moderate risk | Low risk | No information | Low risk | Serious risk | Serious risk |
| **Lanni 2011 [6]** | Moderate risk | Moderate risk | Moderate risk | Low risk | No information | Moderate risk | Serious risk | Serious risk |
| **Lucas 2014 [7]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Shirvani 2012 [8]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Tong 2015 [9]** | Moderate risk | Moderate risk | Moderate risk | Moderate risk | No information | Moderate risk | Serious risk | Serious risk |
| **Widder 2011 [10]** | Moderate risk | Serious risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **DOSE** | | | | | | | | |
| **Allibhai 2013 [52]** | Serious risk | Serious risk | Low risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Moderate risk | Serious risk |
| **Barriger 2012 [53]** | Serious risk | Moderate risk | Moderate risk | Low risk | Moderate risk | Moderate risk | Serious risk | Serious risk |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Baumann 2006 [54]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Bongers 2011 [55]** | Serious risk | Serious risk | Moderate risk | Low risk | No information | Moderate risk | Serious risk | Serious risk |
| **Bradley 2010 [56]** | Moderate risk | Moderate risk | Moderate risk | Low risk | Moderate risk | Moderate risk | Moderate risk | Moderate risk |
| **Chang 2014 [57]** | Moderate risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Chang 2012 [58]** | Moderate risk | Moderate risk | Moderate risk | Low risk | No information | Moderate risk | Serious risk | Serious risk |
| **Davis 2015 [11]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Factor 2014 [12]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Fischer-Valuck 2013 [59]** | Serious risk | Serious risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Grills 2012 [13]** | Serious risk | Serious risk | Moderate risk | Low risk | No information | Moderate risk | Serious risk | Serious risk |
| **Guckenberger 2013 [14]** | Moderate risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Guckenberger 2013 [60]** | Moderate risk | Moderate risk | Moderate risk | Low risk | Moderate risk | Moderate risk | Serious risk | Serious risk |
| **Hayashi 2014 [61]** | Moderate risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Hoppe 2008 [62]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Moderate risk | Serious risk | Serious risk |
| **Inoue 2013 [63]** | Serious risk | Serious risk | Moderate risk | Low risk | Moderate risk | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Kelley 2015 [64]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Kestin 2014 [15]** | Moderate risk | Moderate risk | Moderate risk | Low rik | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Kohutek 2015 [16]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Kopek 2009 [65]** | Serious risk | Serious risk | Moderate risk | Low risk | Moderate risk | Low risk | Serious risk | Serious risk |
| **Koshy 2015 [17]** | Moderate risk | Moderate risk | Moderate risk | Low risk | Moderate risk | Low risk | Serious risk | Serious risk |
| **Lagerwaard 2008 [66]** | Serious risk | Serious risk | Moderate risk | Low risk | Moderate risk | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Lee 2013 [18]** | Serious risk | Serious risk | Moderate risk | Low risk | Moderate risk | Moderate risk | Serious risk | Serious risk |
| **Mak 2015 [19]** | Moderate risk | Moderate risk | Moderate risk | Low risk | Moderate risk | Moderate risk | Serious risk | Serious risk |
| **Marwaha 2014 [67]** | Serious risk | Serious risk | Moderate risk | Low risk | No information | Moderate risk | Serious risk | Serious risk |
| **Matsuo 2012 [68]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Moderate risk | Serious risk | Serious risk |
| **Mutter 2012 [69]** | Serious risk | Serious risk | Moderate risk | Low risk | No information | Moderate risk | Serious risk | Serious risk |
| **Olsen 2011 [70]** | Serious risk | Serious risk | | | | Low risk for OS; moderate risk for other outcomes | Serious risk | |
| **Onishi 2007 [20]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Ricardi 2014 [21]** | Moderate risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Rosen 2014 [71]** | Serious risk | Serious risk | Moderate risk | Low risk | No information | Low risk | Serious risk | Serious risk |
| **Satoh 2014 [72]** | Moderate risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Schanne 2015 [73]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Shibamoto 2012 [74]** | Serious risk | Serious risk | Low risk | Low risk | Moderate risk | Moderate risk | Moderate risk | Serious risk |
| **Shirata 2012 [75]** | Serious risk | Serious risk | Moderate risk | Low risk | No information | Moderate risk | Serious risk | Serious risk |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Shultz 2014 [76]** | Moderate risk | Serious risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Sibley 1998 [77]** | Moderate risk | Moderate risk | Moderate risk | Low risk | Serious risk | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Stanic 2014 [78]** | Serious risk | Moderate risk | Moderate risk | Low risk | No information | Moderate risk | Serious risk | Serious risk |
| **Stephans 2009 [79]** | Moderate risk for chest wall toxicity; serious risk for other outcomes | Serious risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Suzuki 2014 [22]** | Serious risk | Serious risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Taremi 2012 [80]** | Serious risk | Serious risk | Low risk | Serious risk | No information | Low risk | Moderate risk | Serious risk |
| **Ueki 2015 [81]** | Moderate risk | Serious risk | Moderate risk | Low risk | No information | Moderate risk | Serious risk | Serious risk |
| **Videtic 2014 [82]** | Moderate risk | Moderate risk | Moderate risk | Low risk | No information | Low risk for OS; moderate risk for other outcomes | Serious risk | Serious risk |
| **Woody 2012 [83]** | Moderate risk | Serious risk | Moderate risk | Low risk | Moderate risk | Moderate risk | Serious risk | Serious risk |

Abbreviations: OS, overall survival