Review

Radiotherapy With Curative Intent in Patients With Early-stage, Medically Inoperable, Non–Small-cell Lung Cancer: A Systematic Review

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Abstract

Patients with early-stage non–small-cell lung cancer (NSCLC) who are unable to undergo surgery can be offered radiation therapy (RT). Previously, conventional RT was offered; however, newer techniques such as stereotactic body RT (SBRT) have become available. The objective of the present systematic review was to investigate the effectiveness of RT with curative intent in patients with early-stage medically inoperable NSCLC. MEDLINE, EMBASE, and the Cochrane Library were searched for studies comparing stereotactic RT with curative intent compared with observation or other types of RT for early-stage, medically inoperable, NSCLC. Comparisons of radiation dosing or fractionation schedules for SBRT were included. We include 4 systematic reviews and 52 observational studies. The evidence suggests that SBRT compared with observation or other forms of RT, such as accelerated hypofractionated RT, 3-dimensional conformal RT, conventional fractionated RT, external beam RT, proton beam therapy, and carbon ion therapy, could have similar or improved results in survival or local control, with similar or fewer adverse effects. Evidence also suggests that local tumor control and survival were associated with the biologically effective dose (BED) for SBRT. Several studies suggested a cutoff of approximately 100 BED correlated significantly with patient outcomes. The presented evidence suggests that SBRT compared with other forms of RT is a reasonable treatment option for patients with medically inoperable early-stage NSCLC.

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Introduction

Non–small-cell lung cancer (NSCLC) is the most prevalent type of lung cancer.[1] Surgical resection of early-stage (stage I, II) NCSLC is the standard against which other treatments are measured. A subset of these patients will be unable to tolerate surgery because of their age or medical comorbidities.[2] The latter include abnormal underlying cardiovascular and/or pulmonary function. Such patients were previously offered conventional radiotherapy (RT; 60-66 Gy in 1.8-2.0 Gy fractions) or were observed without receiving specific cancer therapy. The outcomes for each of these approaches have not been ideal, with 2-year survival < 40% using either conventional RT or observation and local control of only 40% to 50% with conventional RT.[3,4]

Stereotactic RT is a high-precision radiation delivery technique of a few (or even a 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, the accuracy and precision of treatment planning and delivery become critical. Stereotactic body RT (SBRT) and stereotactic ablative RT were considered synonymous for the purposes of the present systematic review and referred to as SBRT from this point onward.

Because the outcomes for patients with early-stage NSCLC who were observed or were given conventional RT have not been ideal, the objective of the present review was to investigate the effectiveness of

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SBRT compared with other RT techniques used with curative intent in patients with early-stage NSCLC who are medically inoperable. To make recommendations as a part of a clinical practice guideline on the use of RT with curative intent,[5] Cancer Care Ontario's (CCO's) Program in Evidence-Based Care, together with CCO's Lung Cancer Disease Site Group and the Radiation Treatment Program, developed this evidentiary base. Based on the objectives of the present review, we derived the research questions outlined below.

1. What is the effectiveness of SBRT compared with other RT techniques used with curative intent in patients with early-stage NSCLC who are unable to undergo surgery?
2. What are the most effective dose and/or fractionation schedules for curative-intent RT using SBRT?

Materials and Methods

CCO's Program in Evidence-Based Care produces evidence-based guidance documents using the methods of the Practice Guidelines Development Cycle, which involves development of recommendations based on evidence from this systematic review, in consultation with clinical experts, followed by internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.[6] This evidentiary base was developed using a planned 2-stage method. If $\geq$ 1 existing systematic reviews were identified that addressed the research questions, those systematic reviews were included in the evidentiary base. A search of the primary data would focus on those areas not covered by existing systematic reviews.

Search for Existing Systematic Reviews

A search for systematic reviews was conducted within the Cochrane Library, MEDLINE, and EMBASE databases from January 1985 to July 2015. Systematic reviews were included if they had addressed either of the research questions and had reported on the sources searched. A priori, we decided that the main comparison would be SBRT against other forms of RT; therefore, the systematic reviews were required to have focused on SBRT and either compared it with other RT techniques or examined the most appropriate dose or fractionation schemes for SBRT. The results were limited to studies published in English. The identified systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) tool[7] to determine whether existing systematic reviews met a minimum threshold for methodologic quality and could be considered for inclusion in the evidence base.

Search for Primary Published Data

Search Strategy. The published data were searched using MEDLINE (1985 through July 16, 2015), EMBASE (1985 through July 16, 2015), the Cochrane Database of Systematic Reviews (2007 to March 2014), the Cochrane Central Register of Controlled Trials (2007 to April 2014), and the Database of Abstracts of Reviews of Effects (2007 to first quarter of 2014). In addition, the proceedings of the meetings of the American Society of Clinical Oncology (2007-2014), American Society of Therapeutic Radiology and Oncology (2007-2013), and European Society for Radiotherapy and Oncology (2007-2014) were searched for relevant abstracts. The reference lists of the studies deemed eligible for inclusion were scanned for additional citations.

The search of the electronic databases combined disease-specific terms (lung carcinoma, non–small-cell lung cancer, NSCLC), disease stage-specific terms (early stage, medically inoperable) and treatment-specific terms (radiation, stereotactic, hypofractionation) for all study designs (Supplemental Appendix 1; available online).

Study Selection Criteria and Process. Inclusion Criteria

The studies were considered eligible for inclusion in the present systematic review if they met the following criteria:

1. Studies that included full reports or abstracts of randomized controlled trials (RCTs) or full reports of comparative trials with $>$ 50 participants. The interventions considered were stereotactic RT with curative intent compared with observation or other types of RT for early-stage, medically inoperable NSCLC. Comparisons between radiation dosing or fractionation schedules for SBRT were included.
2. Studies that included patients with a tumor size $<$ 5 cm (ie, stage T1 or T2a), node-negative (ie, N0), medically inoperable NSCLC.
3. Studies that reported data on survival, local control, adverse events, or quality of life.

Exclusion Criteria

The exclusion criteria were as follows:

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

A review of the titles and abstracts that resulted from the search was conducted by 1 of us (E.V.). For those items that warranted full-text review, the same reviewer (E.V.) reviewed each item in collaboration with a second reviewer (E.Y., Y.U., P.E., C.F., M.E.), if uncertainty was present.

Data Extraction and Synthesis and Assessment of Study Quality. All eligible studies underwent data extraction independently by a research methodologist (E.V.), with all extracted data and information subsequently audited by an independent auditor. Ratios, including hazard ratios, were expressed such that a ratio $<$ 1.0 indicated a survival benefit favoring nonstereotactic RT and a ratio $>$ 1.0 indicated a survival benefit favoring stereotactic RT.

An assessment of study quality was performed for all the included primary studies by 1 methodologist (E.V.). Cohort studies were assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool.[8]

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

Results

Search for Existing Systematic Reviews

Thirteen systematic reviews were considered for inclusion.[9-21] Two were excluded because they were abstracts only.[9,16] Although the 11 remaining reviews had different inclusion criteria, 2 reviews were included because they had performed a meta-analysis using