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Evidence-based Series 7-16 Version 4

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

The Role of High Dose Rate Brachytherapy in the Palliation of Symptoms in Patients with Non-Small Cell Lung Cancer

Members of the Lung Cancer Disease Site Group

An assessment conducted in November 2024 deferred the review of Evidence-Based Series (EBS) 7-16 Version 4. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 7-16 Version 4 consists of 4 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/791

Section 1:	**Clinical Practice Guideline (ENDORSED)**
Section 2:	**Systematic Review**
Section 3:	**Guideline Development and External Review**
Section 4:	**Document Assessment and Review**

December 16, 2022

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version October 2005	1966 - 2005	Full Report	Web publication Journal publication	NA
Version 2 May 2013	2005-2012	New data in Appendix A: Document Review Tool	Updated Web publication	2005 recommendations are **ENDORSED**
Version 3 June 2018	2005-September 12, 2017	New data found in Appendix B: Document Review Tool	Updated Web publication	2005 recommendations are **ENDORSED**
Current Version 4 December 2022	2017 to 2022	New data found in Section 4: Document Review Tool	Updated Web publication	2005 recommendations are **ENDORSED**

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Evidence-based Series #7-16: Section 1

The Role of High Dose Rate Brachytherapy in the Palliation of Symptoms in Patients with Non-Small Cell Lung Cancer: A Clinical Practice Guideline

Y Ung, E Yu, C Falkson, A Haynes, WK Evans, and the Lung Cancer Disease Site Group

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

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4 and Appendix A and B for a summary of updated evidence published between 2005 and 2022, and for details on how this Clinical Practice Guideline was ENDORSED.

Report Date: October 25, 2005

Guideline Question

1. Is there a role for high dose rate endobronchial brachytherapy (HDREB) in the palliation of respiratory symptoms in patients with non-small cell lung cancer?
2. If so, what is the optimal dose of HDREB in this setting?

Target Population

The recommendations apply to adult patients with symptomatic endobronchial disease in non-small cell lung cancer.

Recommendations

- For patients with previously untreated, symptomatic, endobronchial non-small cell lung cancer:
  - External beam radiation therapy (EBRT) alone is more effective for palliation **of respiratory symptoms** than HDREB alone.

    June 2018: "Respiratory symptoms" is indicated in the research question and systematic review, and has been added here for clarification.
  - The evidence does not provide conclusive results to suggest that **routine use of** HDREB and EBRT would provide improved symptom relief over EBRT alone.

June 2018: It is the opinion of the Lung Cancer Disease Site Group that HDREB and EBRT might be suitable in selected patients.

- *December 2022: the recommendation "For patients with complete collapse of the lung due to endobronchial obstruction, a surgical core out procedure may be needed before EBRT or EBRT with HDREB" is no longer endorsed because the updated evidence does not show a benefit of this procedure (See Section 4 for details).*

- For patients previously treated by EBRT who are symptomatic with endobronchial obstruction due to recurrent disease, HDREB is recommended, providing that endobronchial brachytherapy is technically feasible.

Qualifying Statements

- This guideline addresses only the use of HDREB for the palliation of symptomatic endobronchial disease and not its use as a radical or adjuvant treatment.
- The occurrence of fatal hemoptysis because of HDREB is a significant risk with that therapy, and occurrence rates as high as 32% of patients have been reported. However, the majority of studies report rates between 4% and 18% of patients.

  June 2018: It is the opinion of the Lung Cancer Disease Site Group that the high rates of fatal hemoptysis were found in older studies; current practice indicates that rates are much lower using CT planning and current doses and fractionation of radiation.
- Improvement of hemoptysis as a result of HDREB ranges from 19% to 100% of patients, with most studies reporting rates of 69% and higher.
- HDREB should be provided by a team of experts that includes radiation oncologists, thoracic surgeons (or physicians with expertise in bronchoscopy), and medical physicists.
- HDREB is only possible if afterloading catheters can be inserted bronchoscopically. Patients with complete endobronchial obstruction are not suitable for HDREB.
- Treatment alternatives to HDREB include EBRT (if not previously irradiated), Nd-YAG laser therapy, photodynamic therapy (PDT), and surgical core-out procedure.
- The optimal dose and fractionation for HDREB for the palliation of symptoms of airway obstruction has not yet been determined. However, commonly used doses include 1000 cGy at 1 cm in a single fraction or 750 cGy at 1 cm in one or two fractions.

  June 2018: It is the opinion of the Lung Cancer Disease Site Group that a dosage of 1000 cGy at 1 cm in a single fraction or 750 cGy at 1 cm in one or two fractions is no longer commonly used, and that current practice favours fractionated treatment instead of a single fraction. The tendency is to use multiple catheters, to use CT planning, and to prescribe the dose to a defined volume rather than an empiric dose.
- HDREB may be effectively combined with other endobronchial treatment modalities such as neodymium-yttrium-aluminum-garnet (Nd-YAG) laser therapy.

Key Evidence

- A total of six small randomized trials were identified. One trial compared EBR with HDREB, each as primary palliative treatments. Three studies randomized patients to either EBR alone or EBR with HDREB, one trial randomized patients to Nd-YAG laser therapy with or without HDREB, and one trial compared two different schedules of HDREB. Sample sizes ranged from 29 and 108 patients.
- One randomized trial compared two different doses and schedules of HDREB (four fractions of 3.8 Gy administered weekly versus two fractions of 7.2 Gy administered every 3 weeks) and obtained similar response rates (36% versus 37%), survival (median, 4.2 versus 4.4

months; one-year, 11% versus 20%), and rates of fatal hemoptysis (22% versus 21%), respectively.

- One randomized trial involving 99 previously untreated patients obtained better overall palliation with EBRT alone compared with HDREB alone (physician preference ratings for EBRT, p=0.09; patient preference ratings for EBRT, p=0.029). The incidence of fatal hemoptysis was comparable in both groups (6% to 8%). Although survival was not a specified endpoint of that study, a significant survival advantage for EBRT alone over HDREB alone (p=0.04) was found (median, 9.4 versus 8.2 months, one-year, 38% versus 22%).
- One randomized trial evaluated HDREB in combination with EBRT to EBRT alone using biologically equivalent doses for both arms. Symptom control for cough was better in patients who were treated with EBRT alone compared to HRDEB and EBRT, and survival at one year was the same in each group.
- Two trials obtained comparable median survival (6.2 versus 6.5 months and 7.0 versus 8.5 months) and incidence of fatal hemoptysis (14% versus 20% and 13% versus 15%) for patients treated with EBRT alone or EBRT with HDREB. Combined treatment improved mean dyspnea scores over time (p=0.02) and atelectasis improved for a significantly greater proportion of patients with prior atelectasis in the combined group (57% versus 35%, p=0.009), although individual symptom scale scores were comparable for both treatments. The other trial reported a tendency toward improved local control with combined therapy (p=0.052), but symptom control was not evaluated.
- Median survival (7.4 versus 10.3 months) and incidence of fatal hemoptysis (0 versus 1 patient) were similar for Nd-YAG laser therapy alone or combined with HDREB. The symptom-free period was significantly longer with the combined treatment (8.5 versus 2.8 months, p<0.05), although toxicity and symptom palliation were not reported by treatment group.
- Eighteen non-comparative prospective studies evaluated HDREB in doses ranging from 4 Gy at 2 cm from the source axis twice daily over two days to a single fraction of 20 Gy at 1cm from the source axis. Response rates varied between 20% and 98%, median survival between three and 28 months, and one-year survival between 7% and 78%. Hemoptysis improved for most patients, although fatal hemoptysis occurred in between 4% and 32% of patients.
- Five retrospective studies, involving more than 100 patients, reviewed the role of HDREB alone or in combination with EBRT. Treatment intent varied from palliation to radical, using single dose or fractionated treatments. Symptom improvement ranged from 74% to 94%. The risk of fatal hemoptysis ranged from 3.6% to 8%.

Treatment Alternatives

High dose rate endobronchial brachytherapy can only be given when there is an adequate lumen to allow for insertion of the treatment catheter. If there is complete endobronchial obstruction, then initial therapy could include other treatment modalities such as surgical core out, endobronchial stent for more proximal tumours, Nd-YAG laser therapy, or PDT. Those modalities of therapy could then be followed by HDREB.

Future Research

Future research on the role of HDREB should focus on two objectives:

1. Defining the optimal dose and fractionation as well as defining the physical aspects of radiation delivery (e.g., dose prescription, optimal length, and the effects of catheter curvature on dose).
2. Evaluating the role of combination therapies (e.g., Nd-YAG laser therapy and PDT).

Related Evidence Summary

- Evidence Summary Report #7-15: *The Role of Photodynamic Therapy (PDT) in Patients with Non-small Cell Lung Cancer*.

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Evidence-based Series #7-16: Section 2

The Role of High Dose Rate Brachytherapy in the Palliation of Symptoms in Patients with Non-Small Cell Lung Cancer: A Systematic Review

Y Ung, E Yu, C Falkson, AE Haynes, WK Evans, and the Lung Cancer Disease Site Group

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

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2005 and 2022, and for details on how this Clinical Practice Guideline was ENDORSED.

Report Date: October 25, 2005

QUESTIONS

1. Is there a role for high dose rate endobronchial brachytherapy (HDREB) in the palliation of symptoms in patients with non-small cell lung cancer (NSCLC)?
2. If so, what is the optimal dose of HDREB in this setting?

INTRODUCTION

Brachytherapy is not a new treatment modality, but the development of remote afterloading high dose rate equipment has resulted in the increased use of this treatment option (1,2). High dose rate endobronchial brachytherapy (HDREB) has been defined as brachytherapy capable of delivering greater than 12 Gy/h (>0.2 Gy/min) (3).

A flexible bronchoscope is used to place an intraluminal treatment applicator at the location of the tumour. The applicator is then connected to a high dose rate, remote, after-loading device, which is programmed to advance the radiation source to specific locations within the applicator. That process provides a higher radiation dose at the centre of the tumour than at the periphery, thereby reducing the effect of the radiation on surrounding tissue (1,2).

The treatment can be conducted on an outpatient basis and be both convenient for patients and cost effective for institutions. HDREB has been used as an alternative to, and in

combination with, external beam radiation therapy (EBRT) for the palliation of advanced non-small cell lung cancer (NSCLC). Given the potential for HDREB to provide fast, effective, and convenient relief of symptoms associated with endobronchial disease, the authors felt that an evaluation of this technique for the palliation of symptoms in patients with NSCLC was warranted. This systematic review addresses the role of HDREB in the palliation of symptoms in patients with NSCLC and the optimal dose of HDREB in that setting.

METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (4). Evidence was selected and reviewed by three members of the Lung Cancer Disease Site Group (Lung DSG).

This systematic review is a convenient and up-to-date source of the best available evidence on HDREB for the palliation of advanced NSCLC. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the Lung DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

MEDLINE (1966 through July 2005), EMBASE (1980 through July 2005), CANCERLIT (1975 through March 2002), and the Cochrane Library (2005, Issue 4) databases were searched for evidence relevant to this practice guideline report. "Carcinoma, non-small-cell lung" (Medical subject heading (MeSH)), "Lung Neoplasms" (MeSH), and the phrase "non small cell lung" used as a text word were combined with "brachytherapy" (MeSH), "radiotherapy dosage" (MeSH) and each of the following phrases used as text words: "brachytherapy", "interstitial radiotherapy", "seed implant", "high dose", or "HDR". The initial search did not include restrictions on study design as the literature was expected to be limited. However, subsequent searches included the search terms for the following study designs and publication types: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, controlled clinical trials, clinical trials, comparative studies, follow-up studies, prospective studies, and retrospective studies.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO) (1995-2005) and the American Society for Therapeutic Radiology and Oncology (ASTRO) (2000-2005) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the Web site of the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Articles published as full reports were selected for inclusion in this systematic review of the evidence if they were the following:

1. Randomized clinical trials (RCTs), non-comparative prospective studies, or large retrospective studies involving more than 100 patients evaluating treatment for symptomatic endobronchial disease in patients presenting with primary NSCLC.

2. At least one group in the study had to receive HDREB, either alone or in combination with EBRT, laser therapy, or photodynamic therapy (PDT).
3. Reported data on symptom control, response, survival, or toxicity.

Exclusion Criteria

Articles were excluded if they were:

1. Published in a language other than English.
2. Published in abstract form only.
3. Letters, comments, or editorials.
4. Case studies.

Synthesizing the Evidence

As only three of the six randomized trials compared similar treatments, and all three administered different doses of HDREB, the data were not pooled.

RESULTS

Literature Search Results

Six randomized trials (5-11), 18 non-comparative prospective studies (12-30), and five large retrospective studies (31-36) of HDREB alone or in combination with EBR, neodymium-yttrium-aluminium-garnet (Nd-YAG) laser therapy, or PDT met the eligibility criteria (Table 1). One guideline published by the American Brachytherapy Society in 2001 was identified. A trial by Moghissi et al (37) focused on the treatment of endotracheal or endobronchial obstruction using EBR versus HDREB endobronchial treatment. This trial was excluded as the results were pooled and not reported by treatment arm.

Since it was often difficult to identify if case series reports were based on data collected prospectively or retrospectively, those studies were considered retrospective unless there were clear indications that a study protocol or patient eligibility criteria was pre-specified. Although prospective studies, in particular RCTs, provide the best evidence for the evaluation of different treatments, the view was that large retrospective studies could also provide valuable information relating to treatment toxicity, dosing, and scheduling. Retrospective studies involving more than 100 patients were, therefore, included in the development of this practice guideline.

Table 1. Studies included in this practice guideline report.

Study Type	Number of studies	Reference numbers	Further information found in table
Randomized trials	6	(5-11)	2a and 2b
Non-controlled, prospective studies	18	(12-30)	3a and 3b
Retrospective studies with >100 patients	5	(31-36)	4a and 4b

Outcomes

Practice Guideline

One practice guideline on the role of brachytherapy was found. The recommendations developed by ABS panel members and published by the ABS were based on a literature review, clinical experience, and biomathematical modelling and were reviewed by external experts (2). The guideline included a review of studies involving both low and high dose rate endobronchial brachytherapy, either alone or in combination with EBRT, and focused primarily on indications for treatment and suggested doses for palliative, curative, or interstitial brachytherapy. The

guideline also reviewed the treatment technique of brachytherapy and provided recommendations regarding standardized reporting for symptoms, bronchoscopic response, and radiation bronchitis.

The ABS guideline concluded that palliative brachytherapy should be considered for defined patient populations, particularly those with endobronchial tumours within the lumen that cannot be adequately resected or subjected to further EBRT, and that cause symptoms such as hemoptysis, shortness of breath, or persistent cough. The use of endobronchial brachytherapy as a curative treatment, either alone or as a boost to EBRT, was considered an option for patients with inoperable, occult tumours. A broad range of literature was referenced in the ABS guideline, and although the literature search and selection strategy were not reported, a number of additional studies, including three RCTs, were identified during the development of the current guideline.

Randomized Trials

The six randomized trials involving HDREB are summarized in Tables 2a and 2b (5-11). One trial compared EBR with HDREB, each as primary palliative treatments (9). Three studies randomized patients to either EBR alone or EBR with HDREB (5-7,10), one trial randomized patients to neodymium-yttrium-aluminium-garnet (Nd-YAG) laser therapy with or without HDREB (8), and one trial compared two different schedules of HDREB (11). Across these trials, a total of 491 eligible patients were randomized, with the number of randomized patients per RCT ranging from 29 to 108. None of the trials reported blinding of treatment assignment for researchers or patients, and only one trial described the method of randomization (5). One trial stratified patients by institution, stage and external fractionation schedule (5). Statistical power to detect a significant difference between groups was reported in three trials (5,8,9), although one trial did not meet the target sample size (5). Primary outcomes varied between the trials, and included survival time, response rate of dyspnea, symptom relief, and disease-free progression. Three trials reported that statistical analyses were performed according to intent-to-treat (5,10,11).

The preliminary trial results reported by Sur et al (6) were updated at ASTRO 2004 (7). The trial by Langendijk et al was stopped prematurely due to insufficient patient accrual (5). Stout et al (9) randomized 108 patients with tumours confined to the thorax but reported results only for the 99 patients who were previously untreated. All patients in the study by Chella et al (8) were previously treated with surgery, EBR, or chemotherapy and were not eligible for further conventional treatment. Seven patients receiving EBR alone in the study by Huber et al (10) were treated at other hospitals and were not evaluable. Huber et al (11) also reported interim results for a trial of 93 patients that compared two different schedules of HDREB. The total brachytherapy dose varied from 14.4 Gy to 15.2 Gy, administered in two to four fractions over four to six weeks. The two trials reported by Huber et al (10,11) were not completely independent. Patients in the study involving EBR who had advanced disease and were ineligible for other treatment options (10) were also included in the HDREB scheduling trial (11).

Table 2a. Randomized trials of HDREB: descriptions.

Author, Year (Reference)	Disease Description	No. of Pts Randomized/ Evaluable	Treatment	Follow-up	Comments
Langendijk, 2001 (5)	Inoperable, biopsy proven NSCLC with tumour in main or lobar bronchus.	NR/47 NR/48 Total: 98/95	Radical EBRT: 2.25 Gy/fx x 4 q1w to 45 Gy + 15 Gy boost, or palliative EBRT: 3 Gy/fx x 4 q1w to 30 Gy Radical or palliative EBRT + HDREB of 7.5 Gy @ 1cm q1w x 2	NR	• PS: WHO 0-3 • Stage: I-IIIb (IIIb=55%) • EBRT + HDREB not given on the same day • Previously untreated: 100% • Mean HDREB dose: NR
Sur, 2001 (6) Sur, 2004 (7) [abstract]	Inoperable, biopsy proven NSCLC, luminal disease, no prior treatment.	Total: 65 NR NR	All patients: EBRT: 30 Gy in 10 fx; or 36 Gy in 18 fx; or 40 Gy in 20 fx followed by either: EBRT: 20 Gy in 10 fx over 2w; or HDREB: 12 Gy in 2 fx over 2w @ 1cm	Minimum, 12Mo	• PS: Karnofsky >=60 • Stage: III (IIIb=46%) • Previously untreated: 100% • Mean HDREB dose: NR • Preliminary results from first 26 pts to reach 1 year follow-up
Chella, 2000 (8)	NSCLC involving central airway, SCC 72%.	15/15 14/14	Nd-YAG: 25-45W @ pulses up to 1.2s to a mean total of 1850J Nd-YAG + HDREB of 5 Gy @ 0.5cm q1w x 3	Median, 17.8Mo	• PS: WHO 0-2 • Stage: NR • HDREB given 15-18 days after Nd-YAG in group 2 • Previously untreated: 0% • Mean HDREB dose: NR
Stout, 2000 (9)	Inoperable, histologically proven NSCLC, SCC 82%.	50/NR 49/NR	EBRT: 30 Gy in 8 fx over 10-12 days HDREB: 15 Gy @ 1cm	NR	• PS & Stage: NR • Previously untreated: 100% • Mean HDREB dose: NR
Huber, 1997 (10)	Inoperable, histologically proven NSCLC, SCC 69%.	NR/42 NR/56	EBRT alone: 2-2.5 Gy/day with 4-5fx per week to 50 Gy + 10 Gy booster EBRT + HDREB of 4.8 Gy @ 1cm 1w pre-EBRT and 3w post-EBRT	Median, 30Mo	• PS: Karnofsky > 50 • Stage: I-IV (IIIb/IV=77%) • Previously untreated: 68% • Mean HDREB dose: 7.44 ± 2.6 Gy
Huber, 1995 (11)	Histologically proven lung cancer, SCC 49%.	44/44 (37[1]) 49/49 (36[1])	HDREB(4): 3.8 Gy @ 1cm q1w x 4 HDREB(2): 7.2 Gy @ 1cm q3w x 2	Median, 30Mo	• PS: NR • Stage: I-IV (IIIb/IV=80%) • Previously untreated: 10% • Previous HDREB: HDREB(4)/(2), 11% / 17% • Mean HDREB dose: HDREB(4)/(2), 13.4 ± 5.2 Gy / 13.7 ± 4.4 Gy

Notes: EBRT – external beam radiation therapy, EBT – Endobronchial treatment, fx – fraction(s), Gy – Gray, HDREB – high dose rate endobronchial brachytherapy, J – joules(s), Mo – month(s), Nd-YAG – neodymium-yttrium-aluminum-garnet laser therapy, No – number, NR – not reported, NSCLC – non-small cell lung cancer, PS – performance status, pts – patients, q – every, s – second(s), SCC – squamous cell carcinoma, w – week(s), W – Watts, WHO – World Health Organization.

[1] Evaluable for response.

[a] Patients that received allocated treatment (Moghissi 1999) (5).

Table 2b. Randomized trials of HDREB: results.

Author, Year (Reference)	Response CR/PR (%)	Survival	Toxicity	Symptom Control
Langendijk, 2001 (5)	EBRT: NR EBRT + HDREB: NR	Median 8.5Mo (CI: 5.4-11.6) 7.0Mo (CI: 5.3-8.9) Overall, p=0.21	EBRT vs. EBRT + HDREB Fhem: 13% vs. 15% (p=ns) Unknown cause of death: 2% vs. 13% Bronchopleural fistula: 0% vs. 2% (9Mo post-EBRT)	EBRT vs. EBRT + HDREB Rate of radiological re-expansion for pts with prior atelectasis, 35% vs. 57% (p=0.009) Mean group dyspnea rating over time better for HDREB group (p=0.02)
Sur, 2001 (6) Sur, 2004 (7) [abstract]	EBRT: NR EBRT + HDREB: NR	One-year 29.4% 29.7% p>0.05	No complications in either group	EBRT vs. EBRT + HDREB Median event-free survivals: Any symptoms: 129d vs. 77d, p=0.0090 Dyspnea: 336d vs. 311d, p=0.9158 Cough: 141d vs. 133d, p=0.0464 Hemoptysis: not reached, p=0.2994 Chest pain: 113d vs. 127d, p=0.2768
Chella, 2000 (8)	Nd-YAG: NR Nd-YAG + HDREB: NR	Median 7.4Mo 10.3Mo p=ns	Nd-YAG vs. Nd-YAG + HDREB Fhem: 0% vs. 7% (1pt at 12Mo post-treatment) Reported no morbidity or mortality related to treatment although 6 pts experienced grade 2 or 3 actinic bronchitis	Nd-YAG vs. Nd-YAG + HDREB Symptom-free period in responsive pts, 2.8Mo vs. 8.5Mo (p<0.05) For both treatment arms, Nd-YAG improved stridor in 100% of 9 pts, hemoptysis in 100% of 11 pts, dyspnea in 76% of 21 pts, and cough in 48% of 29 pts. Transient increase in cough in 6 pts.
Stout, 2000 (9)	EBRT: NR HDREB: NR	Median / 1-yr 9.4Mo / 38% 8.2Mo / 22% Overall, p=0.04	EBRT vs. HDREB Fhem: 6% vs. 8% No serious late morbidity occurred	EBRT vs. HDREB (at 8 weeks) Patient-rated symptoms (43 vs. 40 pts, % improved or maintained): Chest pain, 77% vs. 43% (p=0.003) Anorexia, 77% vs. 43% (p=0.003) Tiredness, 65% vs. 30% (p=0.0029) Nausea, 81% vs. 58% (p=0.033) EBRT achieved more re-inflation than HDREB, 60% vs. 18%
Huber, 1997 (10)	EBRT: NR EBRT + HDREB: NR Overall: p=0.052 in favour of combination	Median / 1-yr 6.5Mo / 19% 6.2Mo / 25% Overall, p=0.42	EBRT vs. EBRT + HDREB Fhem: 14% vs. 20% (p=ns)	NR
Huber, 1995 (11)	HDREB(4): 1/15 (ITT: 36) HDREB(2): 0/18 (ITT: 37)	Median / 1-yr 4.2Mo / 11.4% 4.4Mo / 20.4% p=ns	HDREB(4) vs. HDREB(2) Fhem: 22% vs. 21%	NR

Notes: CI – 95% confidence interval, CR – complete response, d – day(s), EBRT – external beam radiation therapy, Fhem – fatal hemoptysis, HDREB – high dose rate endobronchial brachytherapy, ITT – intention to treat, Mo – month(s), NCI-CTC – National Cancer, Institute-Common Toxicity Criteria, Nd-YAG – neodymium-yttrium-aluminum-garnet laser therapy, NR – not reported, ns – not statistically significant, PR – partial response, pt(s) – patient(s), vs. – versus, yr – year(s).

Response

Langendijk et al (5), Sur et al (6,7), and Stout et al (9) did not report treatment response rates. Although Chella et al (8) did not report response rate by treatment group, the Speiser index of obstruction, an alternative measure of response, improved to a similar extent in both treatment groups (from 6.4 to 3.0 for single treatment and from 6.9 to 2.7 for combined treatment). For local control over time, Huber et al (10) found a non-significant difference in favour of EBR combined with HDREB over EBR alone (p=0.052 log rank for 90 evaluable patients). For a subgroup of 62 patients with squamous cell carcinoma, that difference was significant (p=0.007 log rank). In the study by Huber et al (11), response was assessed bronchoscopically and by X-ray for the 73 patients evaluable at three months post-treatment. Response was similar for the two different schedules of HDREB of 2 and 4 fractions, complete response 0% vs 1%, partial response, 18% versus 15%, respectively. The two studies by Huber et al defined partial response differently, with the former study including tumours with more than 50% reduction (10) and the latter study requiring only a 25% reduction in tumour size (11).

Survival

Median survival was similar for patients receiving EBRT with or without HDREB in the study by Langendijk et al (5), although the study did not reach target accrual and may have been underpowered for that comparison. The percentage of patients that reached one year survival was similar in both arms in the Sur et al trial. (7,8) Similarly, in the study by Chella et al (8), median survival was comparable for patients receiving Nd-YAG laser therapy with or without HDREB. Evaluating survival was not one of the aims of the study by Stout et al (9); however, a post-hoc analysis revealed a survival advantage for EBRT alone over HDREB alone (overall, p=0.04). Huber et al (10) reported no significant difference in either median or overall survival for patients receiving EBRT with or without HDREB. A subgroup analysis in the same study for patients with squamous cell carcinomas obtained a non-significant, longer median survival for the combined treatment group (9.2 versus [vs.] 7.6 months for 39 and 29 patients, respectively, p=0.09 log rank). An analysis of the patients that were treated according to protocol found a longer median survival for the combined treatment group (9.9 vs. 6.9 months, p=0.08, number of patients not reported). Two schedules of HDREB, reported by Huber et al (11), evidenced comparable median and one-year survival. For the subgroup of 46 patients with squamous cell carcinoma, median survival was longer for weekly compared with three-weekly treatment (4.4 vs. 2.1 months), although that difference was not significant.

Toxicity

Sur et al (6,7) reported no complications due to treatment for either trial arm. The incidence of fatal hemoptysis was comparable across treatment groups in the five remaining randomized trials, with the lowest rate (0%) obtained for Nd-YAG laser therapy alone (8). The incidence for HDREB varied from 7% of 14 patients when combined with Nd-YAG laser therapy (8) to 20% of 44 patients when administered alone at 3.8 Gy weekly for four fractions (11). Few other toxicities were reported; however, Langendijk et al (5) reported more bronchopleural fistula in the combined treatment group nine months post-EBR (2% vs. 0%), and there were a higher proportion of patients with cause of death unknown in the combined treatment group (13% vs. 2%). Chella et al (8) reported no morbidity or mortality related to treatment although six patients experienced grade 2 or 3 actinic bronchitis.

Symptom control

Four of the six randomized trials assessed symptomatic change (5-9). Langendijk et al (5) assessed palliation with chest X-rays, CT scans, and changes in inspiratory vital capacity. Quality of life (QOL) was evaluated using the European Organization for Research and

Treatment of Cancer (EORTC) general questionnaire, QLQ-C30, and lung cancer module, QLQ-LC13. Comparable responses were obtained for EBR plus HDREB and EBR alone with respect to dyspnea and other respiratory symptoms, including cough, hemoptysis, chest pain, and pain in the arm/shoulder. The results of other QOL dimensions were not reported. A significant difference in favour of the combined treatment group was observed for the mean group dyspnea scores over time (p=0.02). That difference was largely due to the improvement in symptoms experienced by the combined group at two to six weeks post-treatment and was most evident for patients with tumours in the main versus lobar bronchus. By three to six months, the difference had dissipated, and both treatment groups experienced increased dyspnea. Atelectasis improved for a significantly greater proportion of patients in the combined versus single treatment group (57% of 30 patients vs. 35% of 26 patients, p=0.009 for patients with prior atelectasis.

Sur et al (6,7) used the National Cancer Institute Common Toxicity Criteria to rate improvements in dyspnea, cough, hemoptysis, and chest pain. An improvement was defined as the relief of symptomatology by at least one grade from the presenting score and was measured monthly from the time of treatment through each follow-up appointment. The median overall symptom-free survival was significantly longer in the EBR-boost arm compared to the HDREB-boost arm (129 days vs. 77 days, respectively, p=0.0090). Each individual symptom was examined separately, with only median cough-free survival significantly improved for patients that received the EBR boost compared to the HDREB boost (141 days vs. 133 days, respectively, p=0.0464).

Chella et al (8) obtained a significantly longer symptom-free period for patients initially responding to combined Nd-YAG laser therapy and HDREB compared to those responding to Nd-YAG laser therapy alone (8.5 vs. 2.8 months, $p<0.05$), and fewer additional endoscopic treatments were required by the combined treatment group (3 vs.15, $p<0.05$). Across both treatment arms, 76% of patients with dyspnea, 48% of patients with cough and all patients with hemoptysis and stridor had symptom improvement after Nd-YAG. Improvements in lung function tests, including measures of forced expiratory volume in the first second and forced vital capacity, were comparable for both treatment groups.

Patients in the study by Stout et al completed QOL questionnaires (Rotterdam Symptom Checklist and the Hospital Anxiety and Depression Scale), and the physicians rated patient symptoms as none, mild, moderate, or severe (9). Nine key symptoms were combined to provide a measure of overall palliation: cough, hemoptysis, breathlessness, chest pain, dysphagia, anorexia, tiredness, nausea, and hoarseness. Overall palliation was higher with EBR for both physician ratings (91% vs. 76% of patients, p=0.09) and patient ratings (83% vs. 59% of patients, p=0.029). HDREB resulted in more frequent improvement or stability of physician-assessed dysphagia at four weeks (85% vs. 45%, p=0.00085), although there was a higher proportion of missing data in the EBR group (42% vs. 16%). At eight weeks, improvement or stability of symptoms was more frequent with EBR than HDREB, and the difference was significant for the patient-assessed symptoms of chest pain (77% vs. 43%, p=0.003), anorexia (77% vs. 43%, p=0.003), tiredness (65% vs. 30%, p=0.0029), and nausea (81% vs. 58%, p=0.033). However, with the exception of patient-assessed tiredness (p=0.01), those differences had disappeared by the 16-week follow-up. There was a significant difference between physician-rated and patient-rated symptom assessments at eight weeks for breathlessness (p=0.0002), anorexia (p=0.02), tiredness (p=0.003), and nausea (p=0.013), with patients rating symptoms more negatively than physicians. Anxiety and depression were comparable for both treatment groups at eight weeks post-treatment.

Non-controlled, Prospective Studies

Eighteen non-comparative prospective studies were identified (Tables 3a and 3b). Across these trials, a total of 1069 patients were enrolled, with the number per trial ranging from 15

to 117. The percentage of patients evaluated out of those enrolled, ranged from 80% to 100%. The patient inclusion and exclusion criteria differed for each trial. Patients included generally had recurrent, primary symptomatic bronchogenic carcinoma, although disease stage, tumour histology, and performance status varied among trials. Some trials also included a small number of patients with metastatic lung tumours. Two studies focused on patients with malignant airway occlusion, although 77% (27) and 80% (14), respectively, of patients had a primary lung tumour. Studies varied in the percentage of patients that had received previous EBR, ranging from no previous EBR (15,18) to all patients having received previous EBR (16,19,20,25,26,28,30). Seven studies reported Nd-YAG laser therapy prior to HDREB for 2% to 45% of patients (17,20,22-25,28,29). The criteria used to assess symptom control differed across trials and the reliability and validity of the methods used is not clear. The methods used for symptom assessment included asking the patient to rate improvement, using questionnaires, and using a numerical scale developed by Speiser and Spratling (24). However, five trials did not report how symptoms were assessed (14,15,21,26,30). Non-comparative trials are more susceptible to bias and the subjective outcomes used in these trials should be interpreted with the limitations of this study design in mind.

Anacak et al (15) enrolled 30 previously-untreated NSCLC patients in a trial of combination HDREB and EBRT. In the study reported by Gejerman et al (14), 41 patients with locally advanced lung cancer or metastatic cancer with endobronchial obstruction or extrabronchial tumour were treated with combination HDREB and EBRT. Three studies treated patients with a single application of HDREB (17,22,29). In the study by Burt et al (29), only patients whose symptoms were likely to respond to brachytherapy were enrolled (e.g., those with hemoptysis, dyspnea or cough), and a majority were previously untreated (94%).

In two studies that included patients with recurrent carcinoma, HDREB applications were administered to tumours confined to the bronchial lumen (19,26). In both studies, the majority of patients were treated according to the protocol (67% and 88% of 81 and 24 patients, respectively). Freitag et al (12) treated inoperable patients with PDT 2mg/kg six weeks prior to five fractions of 4Gy at weekly intervals.

Ofiara et al (16) reported results separately for the 20 patients with endoluminal tumours and the 10 patients with submucosal infiltration or extrinsic compression. Six of the patients in that study were also included in the report by Hernandez et al (20) (personal communication, May 2002). Perol et al (18) treated 19 patients with endobronchial lesions of ≤1cm. In the study by Trédaniel et al (21), the six planned fractions of HDREB were received by 90% of the 29 patients with endoluminal tumours and 41% of the 22 patients with extraluminal tumour extension.

In a case series, Speiser et al (23,24) treated patients on one of three protocols based on patient characteristics and prior treatment: curative (20% patients), palliative (48% patients) and recurrent (32% patients). However, treatment results were not presented by treatment protocol within brachytherapy dose. All of the patients in the curative protocol received concurrent EBRT, as did 43% of the 164 patients in the palliative protocol. Most patients received the scheduled three fractions of treatment (83%), although 6% received more than three treatments.

In the trial by Bedwinek et al (25), the scheduled three fractions were repeated for four patients between four and 10 months after initial brachytherapy. Mehta et al (27) compared data obtained from an earlier study of low dose rate endobronchial brachytherapy with that obtained from a recent study using a hyperfractionated high dose rate schema. Only the data from the high dose rate study is included in Tables 3a and 3b. In a phase II study, Sutedja et al (28) treated intraluminal tumours.

Table 3a. Non-controlled prospective studies of HDREB: descriptions.

Author, Year (Reference)	Disease Description	No. of Pts Enrolled/ Evaluable	HDREB Treatment	Follow-up	Comments
Freitag 2004 (12)	Inoperable or recurrent bronchogenic carcinoma limited to the bronchial wall, SCC 97%	32/32	PDT iv 2mg/kg and HDREB 4 Gy @ 1cm q1w x 5 (HDREB 6w after PDT)	24 Mo (3-46 mos)	• Treatment: 6 w apart and 2nd round of PDT & HDREB if required • PS: NR • Stage: NR
Escobar-Sacristan 2004 (13)	Malignant endobronchial tumour (SCLC 9%), SCC 59%, primary 94%	81/81	5 Gy @ 0.5-1 cm q1w x 4	NR	• Focuses on CR of symptoms in pts • PS: Karnofsky > 60 • Stage: Advanced
Gejerman, 2002 (14)	Endobronchial obstruction and extrabronchial tumours >2.5 cm, SCLC 15%, primary 80%	41/41	5 Gy/w @ 1cm x 3w + EBRT 2.5 Gy/d x 3.5w	NR	• HDREB and EBRT not given on same day • PS: Median Karnofsky, 70 (range, 40-90) • Lung cancer – 33 pts • Lung metastases – 8 pts (colorectal [4], breast, ovary, renal cell carcinoma, sarcoma) • 83% of pts had stage IV disease
Anacak 2001 (15)	Endobronchial tumour with biopsy proven stage III NSCLC	30/30	5 Gy @ 1cm x 3 (frequency NR) + EBRT 60 Gy	Median, 45Mo	• PS: Karnofsky > 60 • Stage: IIIa-b • Previous EBRT: 0% • Mean HDRB dose: NR • HDREB and EBRT not given on same day
Ofiara 1997 (16)	Inoperable, bronchogenic carcinoma with recurrent or persistent symptoms (SCLC 10%), SCC 67%	30/24	8 Gy @ 1cm q2w x 3	NR	• PS: NR • Stage: IIIa-IV • Previous EBRT: 100%, mean dose 43 Gy • Mean HDREB dose: NR
Ornadel 1997 (17)	Recurrent, inoperable bronchogenic carcinoma (SCLC 2%), SCC 70%	117/102	15 Gy @ 1cm	NR	• PS & Stage: NR • Previous EBRT: 79%, median dose 30 Gy • Mean HDREB dose: NR • Nd-YAG – 44%*
Perol 1997 (18) Pilot study	Histologically proven, localized, bronchogenic NSCLC, lesion <1 cm, SCC 84%	19/18	7 Gy @ 1cm q1w x 3-5	Mean, 28Mo (range, 7-49)	• PS: Mean Karnofsky, 78.4 ± 8.9 • Stage: NR • Previous EBRT: 0% • Mean HDREB dose: NR
Delclos 1996 (19)	Recurrent, endobronchial carcinoma (SCLC 6%), SCC 46%	81/81	Intracavity: 15 Gy @ 6mm or 7.5mm q2w x 2	NR	• PS: Karnofsky, 40-90 • Stage: NR • Previous EBRT: 100% • Mean HDREB dose: NR
Hernandez 1996 (20)	Histologically proven, residual or recurrent bronchogenic carcinoma (SCLC 14%), SCC 72%	29/26	7.5 to 10 Gy @ 1cm q2w x 3	NR	• PS: Mean ECOG, 1.9 • Stage (NSCLC): IIIa-IV • Previous EBRT: 100%, mean dose 44 Gy • Mean HDREB dose: 8.05 Gy/session • Nd-YAG – 10%*
Trédaniel 1994 (21)	Endobronchial disease (G1) with extraluminal extension (G2), SCC > 80%	G1: 29/25 G2: 22/21	7 Gy @ 1cm in 2 fx over 2d q15d x 3	Range, 4-23Mo	• PS: Karnofsky > 50, mean 72 to 85.9 • Stage: NR • Previous EBRT: 63%, median dose >55 Gy • Mean HDREB dose: NR
Goldman 1993 (22)	Inoperable, bronchogenic carcinoma with major airway occlusion (SCLC 5%), SCC 80%	20/19	15 Gy @ 1cm	NR	• PS: WHO 0-2 • Stage: NR • Previous EBRT: 20% • Mean HDREB dose: NR • Nd-YAG – 5%*

Speiser 1993 (23) and (24)	Endobronchial carcinoma, inoperable or primary or recurrent, SCC 49%	G1: 47/NR G2: 144/NR G3: 151/NR	MDREB: 10 Gy @ 5mm x 3 HDREB: 10 Gy @ 1cm x 3 HDREB: 7.5 Gy @ 1cm x 3	NR	• PS: Host 0-4 • Stage: T1-3N0-3M0, T4±M1 • Previous EBRT: curative, 0%, palliative, NR, recurrent, 100% • Mean HDREB dose: NR • Nd-YAG – 24%*
Bedwinek 1992 (25)	Biopsy proven, recurrent endobronchial carcinoma	38/27	6 Gy @ 1cm q1w x 3	NR	• PS & Stage: NR • Previous EBRT: 100%, dose ≥ 50 Gy • Mean HDREB dose: NR • Nd-YAG – 24%*
Gauwitz 1992 (26)	Recurrent, primary, bronchogenic carcinoma (SCLC 4%), SCC 54%	24/24	15 Gy @ 6mm (equivalent to 9 Gy at 1 cm) q2w x 2	NR	• PS: ECOG 0-2 • Stage: III (96%) • Previous EBRT: 100%, dose ≥ 55 Gy • Mean HDREB dose: NR
Mehta 1992 (27) Pilot study	Malignant airway occlusion (primary lung tumour, 77%)	31/31	4 Gy @ 2cm BID x 2d	Median, 4.5Mo	• PS: ECOG 0-4 • Stage: NR • Previous EBRT: 30%, median dose 50 Gy • Median HDREB dose: 32 Gy @ 1cm
Sutedja 1992 (28)	Recurrent, endobronchial NSCLC	31/31	10 Gy @ 1cm q2w x 3 maximum	NR	• PS: NR • Stage: III • Previous EBRT: 100% • Mean HDREB dose: NR • Nd-YAG – 45%*
Burt 1990 (29)	Inoperable, advanced symptomatic endobronchial carcinoma (SCLC, 6%), SCC 72%	50/46	15-20 Gy @ 1cm	NR	• PS: NR • Stage: Advanced • Previous EBRT: 2% • Mean HDREB dose: NR • Nd-YAG – 2%*
Fass 1990 (30) Pilot study	Tracheal or bronchial recurrence of advanced NSCLC, prior treatment with EBRT	15/15	5-6 Gy @ 1cm q7-10d x 6 maximum	NR	• PS: NR • Stage: Advanced • Previous EBRT: 100% • Mean HDREB dose: NR

Notes: BID – twice daily, d – day(s), EBRT – external beam radiation therapy, ECOG – Eastern Cooperative Oncology Group, fx – fractions, Gy – Gray, HDREB – high dose rate endobronchial brachytherapy, , LC – Lung Cancer, Mo – month(s), MDREB – medium dose rate endobronchial brachytherapy, Nd-YAG – neodymium-yttrium-aluminum-garnet laser therapy, No – number, NR – not reported, NSCLC – non-small cell lung cancer, PDT – Photodynamic therapy, bw - body weight, PS – performance status, pt(s) – patient(s), q – every, SCC – squamous cell carcinoma, SCLC – small cell lung cancer, w – week(s), WHO – World Health Organization.

* Percentage of all patients in the study who were pretreated with Nd-YAG laser therapy.

Table 3b. Non-controlled prospective studies of HDREB: results.

Author, Year, Reference	Response CR/PR (%)	Survival	Toxicity % pts (No. of pts)	Symptom Control % pts (No. of pts)
Freitag 2004 (12)	24/NR (75%) post PDT 31/NR (97%) post combine tx	Mean 24mos 100% survival 26 pts RTLRF	No severe complications reported	NR
Escobar-Sacristan 2004 (13)	46/33 (98%) at 1 mo post treatment	NR	Bronchospasm, 1% (1/81pts) Post tx bronchial stenosis 1% (1/81pts) Pneumonitis 1% (1/81pts) Bronchial Fistula 1% (1/81pts)	Overall, CR for 85% of symptoms analysed Haemoptysis,96% (23/24) Cough,88% (30/34) Dyspnea,75% (18/24) Expectoration 50% (4/8) Stridor 100% (7/7)
Gejerman, 2002 (14)	NR/NR (ITT: 54%)	Median, 5.2Mo	Odynophagia, 64%	No specific symptom improvements noted. However, 72% of pts reported clinically significant alleviation of their chief complaint with 67% of pts free of their presenting symptom at time of last follow-up or death.
Anacak 2001 (15)	16/7 (ITT: 77%) at 4-6w after EBRT	Median, 11Mo 5-yr, 10% actuarial	Early: Cough and laryngotracheal irritation; Grade I-III radiation bronchitis, 70% (21/30 pts); Grade III acute esophagitis, 7% (2/30 pts) Late: Fhem, 10% (2/19 pts); Bronchial stenosis, 25% (4/16 pts); Esophageal stenosis, 12% (2/16 pts)	Palliation of symptoms at 4-6w post EBRT: Cough, 43% (12/28 pts); Hemoptysis, 95% (20/21 pts); Chest pain, 88% (15/17 pts); Dyspnea, 80% (12/15 pts)
Ofiara 1997 (16)	NR	NR	NR	Symptom improvement at 4w: Hemoptysis, 79% (11/14 pts), $p<0.01$; Cough, 46% (11/24 pts), $p<0.01$; Dyspnea, 33% (8/24 pts); Pneumonitis, 20% (1/5 pts); Atelectasis, 43% (9/21 pts)
Ornadel 1997 (17)	NR	Median, 12Mo	Fhem, 9% (11/117 pts) in total with actuarial risk of 11% at 1 yr and 20% at 2 yrs	No/mild symptoms, pre- vs. 3Mo post tx (includes 102 evaluable patients): Cough, 62% vs. 77%; Dyspnea, 32% vs. 56%; Hemoptysis, 78% vs. 97%; PS, 65% vs. 84%
Perol 1997 (18) Pilot study	Total, 15 (ITT: 79%[1]) at 2Mo	Median, 28Mo 1-yr, 78% 2-yr, 58%	Early: Pneumothorax, 5% (1/19 pts); Bronchial infection, 5% (1/19 pts) Late: Fhem, 11% (2/19 pts); Major necrosis of bronchial wall, 11% (2/19 pts, one also with Fhem); Cause of death unknown, 21% (4/19 pts)	NR
Delclos 1996 (19)	NR	Median, 5Mo	Fatal, 2% (2/81 pts, fistula and tracheal malacia); Pneumothorax, 4% (3/81 pts); Tumour necrosis, 1% (1/81 pt); Tracheal stenosis, 2% (2/81 pts); Hemorrhage, 1% (1/81 pts); Total 11% (9/81 pts)	Symptom improvement (for all patients): Excellent, 32%; Moderate, 31%; Minimal, 21%; Worsening symptoms, 9%

Hernandez 1996 (20)	NR	NR	Nonfatal massive hemoptysis, 3% (1/29 pts); Minor hemoptysis, 21% (6/29 pts); Pneumothorax, 3% (1/29 pts)	Symptom improvement/worsening at 1Mo: Atelectasis, 28% (5/18 pts) / 28% (5 pts); Hemoptysis, 69% (11/16 pts) / 19% (3 pts); Pneumonitis, 25% (3/12 pts) / 59% (7 pts); Dyspnea, 24% (7/29 pts) / 28% (8 pts); Cough, 24% (7/29 pts) / 21% (6 pts); PS, 24% (7/29 pts) / 34% (10 pts)
Trédaniel 1994 (21)	G1: 18/2 (ITT: 69%[1]) G2: 2/8 (ITT: 45%[1]) at 2Mo[2]	Median, G1, NYR G2, 5Mo	<u>Early:</u> Temporary pleuritic pain (no. of pts NR); Bronchial secretions, 6% (3/51 pts); Transient fever/chills, 4% (2/51 pts) <u>Late (G1/G2 of 51 pts):</u> Fhem, 3%/18% (1/4 pts); Fatal massive bronchorrhea, 7%/0% (2/0 pts); Pulmonary abscess, 4% (2pts) total; Mild radiation bronchitis, 10%/18% (3/4 pts)	Complete/partial relief of symptoms: 70% (21/30 pts)
Goldman 1993 (22)	NR	1-yr, 15%	No serious complications reported	Symptom improvement at 6w: Overall, 89% (17/19 pts); Re-expansion of lung, 69% (9/13 pts)
Speiser 1993 (23) and (24)	NR	Mean, Curative, 9.5Mo Palliative, 5.6Mo Recurrent, 6.2Mo	Fhem, G1, 4.2% (2/47 pts), G2, 7.0% (10/144 pts), G3, 8.6% (13/151 pts), overall, 7.3%; Radiation bronchitis/stenosis, G1, 9% (4/47 pts), G2, 12% (17/144 pts), G3, 13% (20/151 pts), overall, 12%[3]	Symptom improvement at 4-8w (based on symptom index, no. of pts not reported): Hemoptysis, >99%; Pneumonia, > 99%; Dyspnea, 86%; Cough, 85%
Bedwinek 1992 (25)	11/11 (ITT: 58%[1]) at 3Mo	Median, 6.5Mo	Fhem, 32% (12/38 pts)	Complete/partial symptom relief Overall, 76% (29/38 pts) Where the major symptom was cough or hemoptysis, 80%, and fever or SOB, 71%
Gauwitz 1992 (26)	NR	Median, 7.4Mo Symptom-free median, 6.0Mo (range, 1.6-9.2)	<u>Early:</u> Bronchospasm, 4% (1/24 pts); Blood-tinged sputum, 12.5% (3/24 pts) <u>Late:</u> Chronic mucosal sloughing, 4% (1/24 pts); Fhem, 4% (1/24 pts)	Symptom improvement: Overall, 88% (21/24 pts); Reaeration of lung, 83% (15/18 pts)
Mehta 1992 (27) Pilot study	NR	Median, 4.0Mo 1-yr, 7% (actuarial)	Tracheovascular fistula, 3% (1/31 pts) No reported cases of fatal hemoptysis	Symptom improvement: Overall, 79% of 203 symptoms; Cough, 73% (19/26 pts); Dyspnea, 75% (18/24 pts); Pneumonia, 71% (10/14 pts); Hemoptysis, 100% (10/10 pts); Chest pain, 75% (6/8 pts); Reaeration of lung, 85% (12/14 pts); ECOG PS mean improved from 2.1 to 1.6
Sutedja 1992 (28)	0/22 (ITT: 71%) at 6w	Median, 7Mo/3Mo for pts with response / no response	Fhem, 32% (10/31 pts); Fistula, 10% (3/31 pts) including 1 fatal and 2 resulting in Fhem	Symptom improvement: Dyspnea for 82% of patients with PR (18/22 pts)

Burt 1990 (29)	NR	Median, 3.5Mo	Early: Transient tracheal stridor, 2% (1/50 pts); Asymptomatic pneumothorax, 2% (1/50 pts). No acute radiation esophagitis or late morbidity reported Fhem, 4% (2/50 pts)	Symptom improvement at 6w: Hemoptysis, 86% (24/28 pts); Dyspnea, 64% (21/33 pts); Cough, 50% (9/18 pts); Lung collapse, 46% (11/24 pts)
Fass 1990 (30) Pilot study	3/NR (ITT: 20%)	NR	Obliterative bronchial fibrosis, 7% (1/15pts) Radiation pneumonitis, 7% (1/15pts) Tracheal perforation, 7% (1/15pts)	Palliation of symptoms: Overall, 71% (10/14 pts) Cough, 67% (4/6 pts); Hemoptysis, 71% (5/7 pts); Atelectasis, 33% (1/3 pts); Dyspnea, 60% (3/5 pts)

Notes: CR – complete response, EBRT – external beam radiation therapy, ECOG – Eastern Cooperative Oncology Group, Fhem – fatal hemoptysis, ITT – intention to treat, Mo – month(s), No. – number, NR – not reported, NYR – not yet reached, PR – partial response, PS – performance status, pt(s) – patient(s), RTLRF – residual tumour and local recurrence free, SOB – shortness of breath, tx – treatment, vs. – versus, w – week(s), yr – year(s)..

[1] Intention to treat response rate calculated by reviewer.

[2] Macroscopic CR reported as 21 and 6 patients for group 1 and 2, respectively.

[3] Radiation bronchitis/stenosis reported as 11% for group 3 in the second report of this study (19).

Response

Nine of the 18 prospective studies (12-15,18,21,25,28,30) reported response rates. Complete response was defined as the complete disappearance of the tumour assessed bronchoscopically or by biopsy, and partial response was defined as, at a minimum, definite but not complete tumour regression, or >50% tumour regression. The lowest reported rate, 20%, was obtained for tracheal or bronchial recurrence of NSCLC treated to a total HDREB dose of 5 or 6 Gy every seven to ten days for a maximum of 6 rounds (21). Patients in that study had received previous EBRT. In both of the latter studies, response was assessed macroscopically and histologically two months after HDREB. The highest rates were 97% and 98%. 98% was obtained with 81 patients with malignant endobronchial tumours treated with HDREB alone (13). 97% was obtained in a study of 32 patients with non-small cell bronchogenic tumours who were treated with a PDT and then with HDREB in weekly intervals at five fractions of 4Gy (12). Perol et al (18) reported that tumour control was maintained for 12 of 16 evaluable patients (75%) at one year. Bedwinek et al (25) obtained a significantly higher complete response rate for tumours <5cm compared with those ≥5cm at three months post-treatment (67% of 12 tumours vs. 0% of five tumours, respectively, p=0.048). The difference was not significant when partial response was taken into account (100% of 12 tumours vs. 60% of 5 tumours, p=0.225). At six weeks post-treatment, Sutedja et al (28) reported a partial response, defined as ≥50% improvement in airway lumen diameter, in all 10 T3N2 tumours and in 12 of 21 T4N3 tumours. The remaining T4N3 tumours were considered non-responsive. All of the patients in the latter two studies had received previous EBRT.

Six additional studies provided an alternative measure of response (16,20,22-24,29). Both Ofiara et al (16) and Hernandez et al (20) included a blinded review of response assessment and defined improvement as ≥25% reduction in endobronchial obstruction assessed bronchoscopically. Ofiara et al reported improvement from baseline in 62% of 24 patients at four weeks post-treatment (16), particularly for peripherally located tumours (71% of 14 patients, p<0.01). In the study by Hernandez et al (20), 42% of 26 patients showed improvement at eight weeks post-treatment. Goldman et al (22) obtained complete or partial clearing of bronchial obstruction, assessed bronchoscopically, for eight and nine of 20 patients (40% and 45%, respectively). In the same study, the mean obstruction index, based on the degree of major airway obstruction weighted according to tumour size, improved post-treatment (6.2 vs. 2.8, p<0.001). Speiser et al (23,24) treated patients on one of three different protocols: curative, palliative or recurrent. The post-treatment reduction in obstruction scores, as a percentage of the initial obstruction scores, were 13%, 16%, and 30% for the curative, palliative,

and recurrent protocols, respectively. Response was assessed at six weeks post-treatment as worse, better, or the same by Burt el al (29), with improvement observed bronchoscopically in 88% of 17 patients and radiographically in 39% of 41 patients.

Survival

Eleven studies reported the median survival, which varied between 3.5 and 28 months following the first HDREB treatment (14,15,17-19,21,25-29). The shortest overall median survival occurred in a study of patients with advanced, symptomatic, bronchogenic carcinoma, 94% of whom were previously untreated (29). The longest median survival was reported in a small study of 19 patients with localized bronchogenic carcinoma, none of whom had received previous EBRT (18). In the study reported by Gejerman et al (14) overall median survival was 5.2 months. The authors also reported longer median survival for the 22 partial and complete responders compared to the 19 non-responders (11 vs. 4.2 months, respectively; p=0.01). Sutedja et al (28) did not report overall median survival but did provide median survival separately for 22 treatment responders (seven months) and nine non-responders (three months). In a similar comparison, Anacak et al (15) observed a longer median survival for patients who attained a complete response compared to those who did not (19 vs. 7 months, respectively; p=0.019). Although not part of the main study conducted by Gauwitz et al (26), all five patients with Eastern Cooperative Oncology Group (ECOG) performance status >2 who were treated on the study protocol died within one month of treatment, while the 24 patients in the main study, with ECOG ≤ 2, had a median survival of 7.4 months. All of the patients in the latter two studies received previous EBRT. Speiser et al (23,24) reported a mean survival of 9.5 months, 5.6 months, and 6.2 months for patients treated according to a curative, palliative, or recurrent protocol, respectively. However, since the mean is more directly affected by extreme values than the median, it is difficult to compare this data with that obtained in the other studies reported.

The one-year survival rate was reported in three studies. The highest rate, 78% of 19 patients, was obtained by Perol et al (18). In the same study, the two-year survival rate was reported as 58%. The lowest one-year survival rate, 7% of 31 patients, was obtained by Mehta et al (27) who administered a unique schedule of HDREB. Seventy-seven percent of the patients had lung tumours, and 74% had metastatic disease. Freitag et al (12) had 100% survival at a mean of 24 months, with 26 (84%) of patients remaining free from residual tumour and local recurrence.

Toxicity

Toxicity was reported to varying degrees in 17 of the 18 prospective studies. Some reported only serious complications (12-14,17,22-25,27,28,30) while others reported minor and early complications as well as late complications (15,18-21,26,29).

Of the serious complications reported, fatal hemoptysis was most common, occurring in nine studies (15,17,18,21,23-26,28,29). The lowest rate was 3% (one of 29 patients with endobronchial disease) following local relapse 11 months after treatment (21). The highest rate was 32% at two to fifty-six weeks post-treatment for 38 patients (25) and at two to twenty-four weeks post-treatment for 31 patients (28). Bedwinek et al (25) found fatal hemoptysis to be more common for left upper lobe tumours (75% of eight tumours) than right upper lobe (28% of eight tumours) or right main stem tumours (30% of 10 tumours). In the study by Sutedja et al (28), seven of the 10 patients with fatal hemoptysis had previously been treated with Nd-YAG laser therapy. The four patients with extraluminal disease who died from hemoptysis between one week and 12 months post-treatment in the study by Trédaniel et al (21) also had previous EBR at a dose >55 Gy. None of those patients had previous laser therapy or cryotherapy. Seven studies reported no cases of fatal hemoptysis (12-14,19,20,22,27), although

Hernandez et al (20) reported massive, non-fatal hemoptysis and minor hemoptysis in 3% and 21%, respectively, of 29 patients.

Other fatal complications included fistula in one of 81 and 31 patients (19,28), tracheal malacia in one of 81 patients (19), and bronchorrhea in two of 51 patients (21). Four deaths among the 19 patients in the study by Perol et al (18) were of unknown cause; therefore, the rate of complications may have been underestimated in that study.

The proportions of patients with serious but non-fatal complications are reported in Appendix 1.

Symptom control

Sixteen studies provided some form of symptom assessment (Table 3b), before and after treatment, although the timing and method of assessment was not always clearly stated (13-17,19-30). With respect to specific symptoms, some level of improvement was generally obtained following brachytherapy for dyspnea, hemoptysis, cough and pneumonia. Improvement in dyspnea ranged from 24% to 89% (13,15-17,20-24,27-30). Cough improvement ranged from 24% to 88% and hemoptysis from 69% to 100% (13,15-17,20-24,27,29,30). Improvement of pneumonitis varied from 20% to 25% (16,20), atelectasis from 28% to 43% (16,20,30) and reaeration of the lung from 69% to 85% (22,26,27,29). Only two studies reported improvement in chest pain, and ranged from 75% of 8 patients (27) to 88% of 17 patients (15). Two studies also reported improvement in pneumonia, ranging from 71% to >99% (23,24,27). Ofiara et al (16) assessed symptoms using scales developed by Speiser and Spratling (24). At four weeks post treatment, patients with submucosal and endoluminal tumours had a significant improvement for hemoptysis ($p<0.05$), and patients with submucosal disease also had significant improvement in cough ($p<0.05$). In addition, significant improvement was observed in cough and hemoptysis for peripherally located tumours, but not for centrally tumours.

General symptom improvement was also reported. Gejerman et al (14) reported that 72% of patients had a clinically significant improvement of their main symptom, with two-thirds of patients free of their presenting symptoms at the time of their last follow-up or death, although the method of assessment was not reported. Delclos et al (19) obtained moderate to excellent symptom improvement in 63% of 81 patients whose initial symptoms included shortness of breath, cough, hemoptysis, chest pain, and pneumonitis, however, 9% of patients indicated that their symptoms worsened. Complete or partial relief of symptoms such as cough, hemoptysis, and dyspnea was reported at four weeks post-treatment in 70% of 30 patients in the study by Trédaniel et al (21). Goldman et al (22) reported that overall symptom improvement was obtained in 89% of 19 patients at six weeks post-treatment, with improvement more frequent for hemoptysis (100%) and dyspnea (89%) than cough (37%). Bedwinek et al (25) recorded the maximum symptom relief reported by patients over a three-month period following their final treatment. Improvement was obtained in 76% of 38 patients with a median duration of symptom relief of five months. Symptom relief was more likely when the major symptom was cough or hemoptysis (80%) compared with fever or shortness of breath (71%). In the study by Gauwitz et al (26), patients were asked specific questions about the severity of symptoms and change in symptomatology following brachytherapy and at every three months thereafter. Overall improvement was obtained for 88% of 24 patients, with a median symptom-free survival of six months. Of the 82 symptoms identified prior to treatment, Mehta et al (27) reported an improvement in 79% following treatment, and Bedwinek et al (25) reported more frequent symptom relief for tumours with diameter <5cm (100% for 15 tumours <5cm compared with 25% for eight tumours with diameter ≥5cm, $p=0.0007$). Escobar-Sacristan et al (13) observed a complete clinical response in 85% of symptoms analysed (hemoptysis, cough, dyspnea, expectoration, and stridor).

Using a self-report questionnaire scored according to an adaptation of the Rotterdam scoring system, Ornadel et al (17) obtained an improvement of at least one grade from baseline, at three months post-treatment, in cough (43% of patients with pre-treatment symptoms), dyspnea (50%, p=0.0063), and performance status (54%, p=0.0417). Hernandez et al (20) scored symptoms based on the Speiser index and reported a significant reduction from baseline at four weeks post-treatment in hemoptysis scores ($p<0.01$). Although improvements were obtained in hemoptysis, pneumonitis, dyspnea, cough, and ECOG performance status, a comparable or greater proportion of patients experienced worsening symptoms for pneumonitis, dyspnea, cough and performance status.

Speiser et al (23,24) reported symptom change as a percentage of the pre-treatment weighted composite symptom score. At baseline, approximately 339 patients had a cough, 325 reported dyspnea, 226 had hemoptysis, and 164 presented with obstructive pneumonia. At four to eight weeks post-treatment, reductions in the symptom index score of >85% were reported for hemoptysis, pneumonia, cough and dyspnea. Using Radiation Therapy Oncology Group (RTOG) criteria, Mehta et al (27) reported post-treatment improvements in cough, dyspnea, pneumonia, hemoptysis, and chest pain. Mean performance status, as measured on the ECOG scale, also improved from 2.1 to 1.6. In the study by Sutedja et al (28), dyspnea improved by at least two grades in 82% of patients following treatment. Burt et al (29) asked patients to rate symptoms as worse, the same or better at six weeks post-treatment and patients reported improvements in hemoptysis, dyspnea, and cough.

Pre-treatment atelectasis was reported in seven studies (16,20,22,26,27,29,30). Hernandez et al (20) assessed atelectasis radiographically and obtained improvement and worsening of that condition in the same proportion of patients, 28%, at one month post-treatment. Complete or partial reaeration of the lung occurred in a higher proportion of patients, between 33% of 24 patients and 85% of 14 patients (22,26,27,29).

Retrospective Studies

Five retrospective studies, each involving more than 100 patients, were reported (31-36) (Tables 4a and 4b). The reports by Gollins et al describe results for the same group of 406 patients (34,35). Two studies primarily involved administration of HDREB alone (33,36), and three involved a combination of EBRT with HDREB (31,32,34,35). The majority of tumours treated were squamous cell (65% to 88%), and the main aim of most retrospective studies was to assess symptom palliation and rate of complications associated with HDREB, alone or in combination with EBRT.

These studies did not yield information suggestive of different outcomes or complications compared to those documented in prospective studies. However, they do suggest that the two most significant complications with HDREB are radiation bronchitis (8.7%-40%) and fatal hemoptysis (3.6%-8%).

Table 4a. Retrospective studies primarily involving HDREB alone or in combination with EBRT: study descriptions.

Author, Year (Ref)	Disease Description	Number of Pts	HDREB/EBRT Treatment	Follow-up	Comments
Muto 2000 (31)	Biopsy proven NSCLC	320 pts treated with EBRT/HDREB G1: 84 G2: 47 G3: 189	G1: 10Gy @ 1cm (75 pts single cath; 9 pts two cath), then EBRT G2: 7Gy x2 @ 1cm (41 single cath; 6 dbl cath), EBRT, HDREB G3: 5Gy x3 @ 0.5-1cm (170 single cath; 19 dbl cath) + EBRT q15fx of HDRB	Range 5-36Mo	PS: KPS>60 Stage: IIIA-IIIB
Hennequin 1998 (32)	Biopsy proven bronchial malignancies (SCLC 2%), SCC 88%	149 total (75% prior EBRT) G1: Palliative HDREB for distant metastases, 47 G2: Radical HDREB for tumours <2cm diameter, 73 G3: EBRT/HDREB for primary, localized tumours, 29	Mostly @ 1cm (range 0.5 to 1.5) G1: 5-7Gy x 4 over 3w + 2 additional fx G2: 7Gy x 5-6 over 5w G3: 5-7Gy x 2 following EBRT 60Gy +/- CT	NR	PS: NR Stage: NR No prior EBRT: 25% Mean HDREB dose: NR
Taulelle 1998 (33)	Stage I-IV lung cancer, 90% with symptoms of endobronchial disease (SCLC 6%), SCC 84%	189 total, (62% prior EBRT) G1: No previous treatment, 22 G2: Acute respiratory distress, 36 G3: Previously treated; residual tumour, 33 G4: Previously treated; recurrent, 87	6-10Gy @ 1 cm q1w x 2-6	Median 32Mo	PS:WHO≥2 (53%) Stage: I-IV (22% IIIB/IV) No prior treatment: 30.7% Mean HDRB dose: NR
Gollins 1996,1994 (34,35)	Inoperable, primary endobronchial or endotracheal SCC 87% NSCLC 6.5%	406 total (same pts reported in both studies) (20% prior EBRT) G1: No previous radiation, 324 G2: Recurrent after EBRT, 65 G3: EBRT + HDREB, 17	15Gy @ 1cm (range 10-20Gy) G3: EBRT dose NR	1.5, 4, and 12Mo	PS: NR Stage: II-IV (81% IV) No prior EBRT: 80% 7 pts previous Nd-YAG laser treatment
Macha 1995 (36)	Recurrent bronchial carcinoma SCC 65% SCLC 9%	365 total (majority had prior EBRT; number NR) G1: Palliative HDREB, 124 G2: Radical HDREB, 241	5Gy @ 1cm x3 (G1) or x4 (G2) q2w G1: HDREB + EBRT, laser, cytotoxic therapy or palliative surgery G2: HDREB alone	NR	PS: NR Stage: NR

Notes: cath – catheter(s), CT – chemotherapy, dbl – double, EBRT – external beam radiation therapy, fx – fraction, G – group, Gy – Gray, HDR(EB) – high dose rate (endobronchial brachytherapy), KPS – Karnofsky performance status, Mo – month(s), Nd-YAG – neodymium-yttrium-aluminum-garnet laser therapy, NR – not reported, NSCLC – non-small cell lung cancer, PS – performance status, pts – patients, q – every, Ref – reference, SCC – squamous cell carcinoma, SCLC – small-cell lung cancer, w – week(s), WHO – World Health Organization.

Table 4b. Retrospective studies primarily involving HDREB alone or in combination with EBRT: study results.

Author, Year (Ref)	Response CR/PR (%)	Survival	Toxicity	Symptom Control
Muto 2000 (31)	PR: 45% (defined as reduction of >1/3 tumour volume 1Mo post-treatment)	Mean from diagnosis 11.1Mo; from last HDREB 9.7Mo (median NR)	40% radiation bronchitis @ 6m (18% G3/4) (highest incidence in G1(80% of pts, p<0.01) 3.6% Fhem (no sig diff between G, p>0.05)	Improvement in dyspnea 90%, cough 82%, hemoptysis 94%, OP 90%
Hennequin 1998 (32)	Overall RR: 79% (133 assessable pts at 4-6 weeks post-HDR). CR: 48% PR: 31%	Median / 2-yr survival: G1, 4.2Mo/ 0% G2, 14.4Mo/ 45% G3, 24.6Mo/ 52%	Early: transient hypoxia, 4% bronchial infection, 5% esophagitis, 2% hypoglycemia, angina, pneumothorax, and bacteremia, all <1%. Late: Fhem, 6.7% (10 pts) + 0.7% non-fatal hemoptysis RB, 8.7% (13 pts, including 1.3% fatal)	Improvement in 60% (44/73 pts) with initial respiratory symptoms
Taulelle 1998 (33)	Overall RR: 79% CR: 54% (n=103) (at 1Mo post-HDR) PR: 24% CR (p=0.0005) and survival (p<0.0001) better for G1	Overall median / 2-yr survival: 7Mo / 10%	Early: not reported in detail Late: overall significant grade 3-4 toxicity, 17% massive hemoptysis, 7% bronchial stenosis, 6% soft tissue necrosis, 4% fistula, 2% pneumothorax, <1% Overall, 22% with asymptomatic RB	Complete symptom relief for: hemoptysis, 74%, dyspnea, 54%, cough, 54% No. of pts with initial symptoms, NR
Gollins 1996,1994 (34,35)	CR in 80% of 25 pts with bronchoscopy at 3m post-tx	Overall: median 5.7Mo/ 2-yr 7.2% G1: 6.5Mo/8.8% G2: 4.3Mo/1.5% (p<0.0001) G3: 6.5Mo/0%	Early: Transient cough common and pain occurred in 1% (5 pts) Fhem, 7.9%	Symptom improvement in G1 pts: stridor 92%, hemoptysis 88%, cough 62%, dyspnea 60%, pain 50%, pulmonary collapse 46%
Macha 1995 (36)	NR	G1: mean 9Mo (limited disease, i.e. confined to thorax); extensive disease 5m G2: mean 23Mo (limited disease) (median NR)	G1: 21% fatal hemorrhage; 2% deaths due to tracheo-esophageal fistula; 5% brain mets; 13% resp failure due to pneumonia G2: NR	Effective palliation in 67% of pts G1: 32% improvement in forced expiratory volume and vital capacity, p<0.001 G2: NR

Notes: CR – complete response, diff – difference, EBRT – external beam radiation therapy, Fhem – fatal hemoptysis, G – group(s), HDR(EB) – high dose rate (endobronchial Brachytherapy), Mo – month(s), No. – number, NR – not reported, OP- obstructive pneumonia, PR – partial response, pts – patients, RB – radiation bronchitis, ref – reference, resp – respiratory, RR – response rate, sig – significant, tx – treatment, yr – year.
1 CR = more than 80% of normal lumen reopened; PR = more than 50% of normal lumen reopened (minimal residual tumour).

DISCUSSION

EBR alone is preferable to HDREB alone as a palliative treatment in previously untreated patients, because EBR provided better overall symptom palliation and fewer patients required retreatment in the one RCT (9) that examined this issue. The primary endpoint of this RCT was palliation and quality of life, but results did demonstrate a significant survival benefit in favour of palliative EBR alone compared to HDREB alone.

One RCT (5) showed that the combination of EBR and HDREB provided superior symptom relief of short duration for the mean scores of dyspnea over time compared with EBR alone in

treatment-naïve patients. Patients with prior atelectasis had significantly improved radiological re-expansion with combined EBR and HDREB compared with EBR alone (57% vs. 35%, respectively, p=0.009). Another RCT by Sur et al (6,7) reported that median symptom-free survival was better for patients that received an EBR boost following EBR compared to patients that received a HDREB boost following EBR (129 days vs. 77 days, respectively, p=0.0090). In addition, cough-free survival was better for the EBR-boost arm. A RCT involving both previously treated and untreated patients showed a trend towards improved local control with the addition of brachytherapy to EBR (10). However, that study did not report on symptom control. Median survival and toxicity were similar for Nd-YAG laser therapy with or without HDREB, although the combined treatment significantly prolonged the symptom-free period and resulted in fewer additional endoscopic treatments (8). The dosages of brachytherapy for those six randomized studies ranged from 3.8 to 15 Gy at 0.5cm to 1cm from the source.

The only reported randomized trial evaluating different dosages and frequency of administration of HDREB alone did not report any differences in either median survival or the incidence of fatal hemoptysis (11). However, the two-dose schedules in that trial may not have been that different (3.8 Gy X 4 = 15.2 Gy vs. 7.2 Gy X 2 = 14.4 Gy). The available evidence makes identifying the optimal dose of HDREB for palliation of endobronchial symptoms impossible, since all RCTs to date have been small, involving less than 100 patients, and each trial has used a different dose/schedule combination.

We reviewed 18 non-comparative, prospective studies to define dose and assess complications. The reported administration schedules varied, with the most common (all prescribed at 1cm from the source) being 24 Gy in three fractions (one of 16 studies), 15-20 Gy in a single fraction (one study), 18 Gy in three fractions (one study), 15 Gy in a single fraction (two studies) or three fractions (two studies), 10 Gy in three fractions (three studies), or 7 Gy in three to five fractions (two studies). Two studies reported a dose of 15 Gy given in two fractions at 6 to 7.5 mm from the source. One study reported a dose of 5-6 Gy at 1cm from the centre of the source given every seven to 10 days to a maximum of six fractions. Another study reported a dose of 4 Gy at 2cm from the central axis of the source given twice daily for two days. The various dose and fractionation schedules used in those prospective studies do not clearly define an optimal dose. The main toxicities reported in the trials (shown in Appendix 1) include radiation bronchitis (17%), fatal hemoptysis (10%), bronchial or tracheal stenosis (4%), bronchial necrosis or fistula formation (3%), pneumothorax (3%), and bronchial/tracheal spasm (2%).

The occurrence of fatal hemoptysis is a significant risk with HDREB. The incidence of fatal hemoptysis in randomized trials ranged from 6% to 14% for EBR alone (5,9,10), 15% to 20% for EBR combined with HDREB (5,10) and 8% to 22% for HDREB alone (9,11). The incidence of fatal hemoptysis was higher for EBR combined with HDREB than EBR alone, although the two studies that reported a statistical comparison did not find a significant difference (5,10). It is not apparent whether fatal hemoptysis is related to tumour progression into pulmonary vessels or the irradiation dose and fractionation scheme administered, since the available evidence does not clearly make the distinction. Two retrospective studies conducted analyses to identify factors related to fatal hemoptysis. In a multivariate analysis by Hennequin et al (32), palliative treatment with four to six fractions of HDREB at 5Gy to 7Gy in patients with distant metastases resulted in a higher rate of fatal hemoptysis than treatment in patients with small tumours of < 2cm or those with localized tumours receiving both EBRT and HDR brachytherapy (p=0.02). Endobronchial tumour length (p=0.004) and therapeutic group (p=0.009) were associated with hemoptysis in a univariate analysis, although age, gender, performance status, histology and tumour location were not significantly associated with fatal hemoptysis. Gollins et al found that repeat HDR brachytherapy in the same location as the first treatment (hazard ratio, 4.38, 95% confidence interval, 1.45 to 13.23) and primary treatment with a combination of EBR and HDR

brachytherapy (hazard ratio, 3.83, 95% confidence interval, 1.05 to 13.93) were both significantly associated with occurrence of fatal hemoptysis. However, the number of patients with fatal hemoptysis and repeat brachytherapy or combination treatment was very small (four and three patients, respectively). Prospective future research will need to clarify the causes of hemoptysis and should attempt to minimize this toxicity.

The optimal dose and fractionation for HDREB for palliation of symptoms has not yet been determined in well designed randomized clinical trials. A reasonable recommendation is to use 1000 cGy at 1cm from the central axis given in a single fraction. Technical factors that may influence dose reduction and the fractionation scheme include the extent of curvature causing overlap and "hot spots" of radiation dose, length of treatment, and previous external beam radiation exposure in the treatment volume. If the distal margin can be evaluated, proximal and distal margins should be 2cm.

Patients that may benefit from HDREB include those who have an endobronchial tumour causing symptoms of dyspnea, hemoptysis, post-obstructive pneumonitis, or intractable cough; minimal extrinsic compression of the bronchi; visible endoluminal disease but not complete endobronchial obstruction; failed previous EBR or are not candidates for further EBR; and have good performance status (i.e., ECOG $\leq$ 2). Patients with poorer performance status caused directly by the endobronchial disease may still be suitable for HDREB.

HDREB can only be given if it is technically feasible. While the catheters can be placed in the main bronchi, lobar bronchi or segmental bronchi, there must be an adequate lumen to allow for afterloading catheters to be inserted bronchospically into the endobronchial lesion. Adequate bronchoscopic visualization beyond the segmental bronchi may be limited and preclude accurate catheter placement, making HDREB not feasible. Patients are not suitable for HDREB if there is complete endobronchial obstruction and a surgical core-out procedure is not possible. Initial therapy could then include other treatment modalities such as Nd-YAG laser therapy or PDT. These modalities of therapy could be followed by HDREB. HDREB may not be appropriate if the patient previously received the maximal tolerated doses of EBR.

This review is limited by the lack of high quality evidence on the role of combination therapies, the optimal dose and fractionation scheme for HDREB, as well the physical aspects of radiation delivery (e.g., dose prescription, optimal length, and the effects of catheter curvature on dose). Randomized controlled trials are needed to address these questions and should be the focus of future clinical research.

CONCLUSIONS

For patients with previously untreated, symptomatic, endobronchial NSCLC, EBR alone is more effective for palliation than HDREB alone. The evidence does not provide conclusive results that HDREB and EBR provide improved relief over EBR alone. Furthermore, for patients with complete collapse of the lung due to endobronchial obstruction, a surgical core-out procedure may be needed before EBR or EBR with HDREB. In addition, for those patients previously treated by EBR who are symptomatic from recurrent disease due to endobronchial obstruction, HDREB is recommended, providing that endobronchial brachytherapy is technically feasible.

Fatal hemoptysis is a significant risk of HDREB, and the majority of studies reported rates between 4% and 18%, with rates as high as 32%. Conversely, the same studies reported improvement of hemoptysis in 19% to 100% of patients, while most studies reported improvement in at least 69% of patients. HDREB demonstrates a significant improvement in hemoptysis in patients with disease amenable to HDREB and the potential risk of fatal hemoptysis should not be regarded as a contraindication in these patients. Clinicians may offer patients HDREB for relief of hemoptysis following a full discussion with the patient of the treatment options, goals of therapy, and potential adverse effects.

ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical _trials/) was searched for reports of new or ongoing trials that involved HDREB for patients with NSCLC.

Protocol ID(s)	Title and details of trial
2003 ASCO Annual Meeting Abstract No: 3630	High dose rate endobronchial brachytherapy in the management of primary and recurrent bronchogenic malignancies. Vattemi E et al (38)
CCT: ISRCTN76769573	A randomized trial comparing external beam radiotherapy alone with external beam radiotherapy plus intraterminal irradiation for palliation of endobroncial symptoms in advanced lung cancer. Posted August 2002.
CCT: ISRCTN66281665	A phase II randomized trial to assess external beam radiotherapy and intraluminal bronchial brachytherapy as re-treatment in patients with lung cancer who have received primary palliative external beam therapy. Posted August 2002.
2000 ASCO Annual Meeting Abstract No: 2002	High dose-rate endobroncial brachytherapy for roentgenographically negative bronchogenic carcinoma. Hayakawa K et al (39) (no study to date has been published)
Int J Rad Oncol Biol Phys. 2001; 51(3 Suppl 1)	Fatal hemoptysis and high dose-rate endobronchial brachytherapy: is there a relationship with clinical or technical parameters. Carvelho HA et al (40) (no study to date has been published)
Int J Rad Oncol Biol Phys. 2000; 48(3 Suppl 1)	High-dose rate brachytherapy (HDT-BT): A prospective randomized trial of two fractionation schedules in the palliative treatment of central lung tumours. Poellinger B et al (41) (no study to date has been published)

CONFLICT OF INTEREST

The members of the Lung DSG disclosed potential conflicts of interest relating to the topic of this evidence-based series. No potential conflicts were declared.

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Appendix 1. Summary of complications reported in non-comparative, prospective studies.

Complication	Pooled % (total number of patients)	Number of studies (References)
Complications reported in more than one study		
radiation bronchitis (includes grade I-III and mild)	17% (69/418)	3 (15,21,23,24)
fatal hemoptysis	10% (70/691)	9 (15,17,18,21,23-26,28,29)
bronchial/tracheal stenosis	4% (7/178)	3 (13,15,19)
bronchial necrosis/ulceration/fistula formation	3% (8/243)	5 (13,18,19,27,28)
pneumothorax	3% (6/179)	4 (18-20,29)
bronchial/tracheal spasm	2% (2/105)	2 (13,26)
Complications reported in a single study		
odynophagia	65% (26/41)	1 (14)
blood-tinged sputum	13% (3/24)	1 (26)
esophageal stenosis	12% (2/16)	1 (15)
esophagitis (grade III)	7% (2/30)	1 (15)
obliterative bronchial fibrosis	7% (1/15)	1 (30)
radiation pneumonitis	7% (1/15)	1 (30)
tracheal perforation	7% (1/15)	1 (30)
bronchial secretions	6% (3/51)	1 (21)
bronchial infection	5% (1/19)	1 (18)
fever/chills	4% (2/51)	1 (21)
massive bronchorrhea	4% (2/51)	1 (21)
pulmonary abscess	4% (2/51)	1 (21)
chronic mucosal sloughing	4% (1/24)	1 (26)
tracheal stridor	2% (1/50)	1 (29)
tracheal malacia	2% (1/81)	1 (19)
tumour necrosis	2% (1/81)	1 (19)
hemorrhage	1% (1/81)	1 (19)
pneumonitis	1% (1/81)	1 (13)

Appendix 2. Summary of fatal hemoptysis and symptom improvement for all trials.

Study (Reference)	Fatal hemoptysis (% of patients)	Symptom improvement (% of patients)
Randomized controlled trials		
Langendijk, 2001 (5)	15%	NR
Sur, 2001 (6)	NR	NR
Chella, 2000 (8)	7%	symptom free period significantly greater in HDREB arm (HDREB, 8.5mo vs. no HDREB, 2.8mo)
Stout, 2000 (9)	8%	symptom improvement better for EBRT
Huber, 1997 (10)	20%	NR
Huber, 1995 (11)	(G1, 22%;G2, 21%	NR
Non-controlled prospective studies		
Freitag, 2004 (12)	0%	NR
Escobar-Sacristan, 2004 (13)	0%	hemoptysis, 96%
Gejerman, 2002 (14)	0%	Main symptom was alleviated in 72%
Anacak, 2001 (15)	10%	hemoptysis, 95%
Ofiara, 1997 (16)	NR	hemoptysis, 79%
Ornadel, 1997 (17)	9%	hemoptysis, 19%
Perol, 1997 (18)	11%	NR
Delclos, 1996 (19)	0%	overall: minimal, 21%; moderate, 31%; excellent, 32%
Hernandez, 1996 (20)	0%	hemoptysis, 69%
Trédaniel, 1994 (21)	HDREB, 3% EBRT+HDREB, 18%	70% complete/partial relief of symptoms
Goldman, 1993 (22)	0%	overall, 89%
Speiser, 1993 (23,24)	7.3% (G1, 4.2%; G2, 7.0%; G3, 8.6%)	hemoptysis, >99%
Bedwinek, 1992 (25)	32%	hemoptysis, 80%; overall, 76%
Gauwitz, 1992 (26)	4%	overall, 88%
Mehta, 1992 (27)	0%	hemoptysis, 100%; overall, 79%
Sutedja, 1992 (28)	32%	dyspnea, 82% of patients with PR
Burt, 1990 (29)	4%	hemoptysis, 86%
Fass, 1990 (30)	NR	hemoptysis, 71%; overall, 71%
Retrospective studies		
Muto, 2000 (31)	3.6%	hemoptysis, 94%
Hennequin, 1998 (32)	6.7%	overall, 60%
Taulelle, 1998 (33)	NR (massive hemoptysis, 7%)	hemoptysis, 74%
Gollins, 1994 & 1996 (34,35)	7.9%	hemoptysis, 88%
Macha, 1995 (36)	G1, 21% massive hemorrhage G2, NR	effective palliation in 67% of patients

Notes: EBRT – external beam radiation therapy, G – group, HDREB – high dose rate endobronchial brachytherapy, mo – months, NR – not reported, PR – partial response, vs. – versus.

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Evidence-based Series #7-16: Section 3

The Role of High Dose Rate Brachytherapy in the Palliation of Symptoms in Patients with Non-Small Cell Lung Cancer: Guideline Development and External Review - Methods and Results

Y Ung, E Yu, C Falkson, AE Haynes, WK Evans, and the Lung Cancer Disease Site Group

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

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2005 and 2017, and for details on how this Clinical Practice Guideline was ENDORSED.

Report Date: October 25, 2005

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) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review*. This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results*. This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Lung DSG of Cancer Care Ontario's PEBC. The series is a convenient and up-to-date source of the best available evidence on HDREB for the palliation of advanced NSCLC, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Disease Site Group Consensus

The application of HDREB for lung cancer requires an adequately trained and experienced team that includes radiation oncologists, thoracic surgeons (or physicians with expertise in bronchoscopy), and medical physicists. While the aim of this evidence-based series was not to review the many technical aspects of the delivery of HDREB, the Lung Cancer DSG recommends that rigorous quality assurance programs be in effect to ensure safety and to provide consistency in reporting dose prescriptions to facilitate comparisons of treatment results.

The analysis of the available evidence does not permit the recommendation of a standard dose or optimal fractionation for HDREB. However, a survey of the provincial cancer centres in Ontario was conducted by one of the guideline authors (Ung) to determine common practice among centres doing HDREB. The consensus recommendation for palliation is to use a prescribed dose of 1000 cGy at 1cm from the central axis given in a single fraction. Technical factors that may influence dose reduction and the fractionation scheme include the extent of curvature causing overlap and "hot spots" of radiation dose, length of treatment, and previous external beam radiation exposure in the treatment volume.

The group of patients that may benefit from HDREB may be defined as those who have:

1. Endobronchial tumour causing symptoms of dyspnea, hemoptysis, post-obstructive pneumonitis, or intractable cough;
2. Minimal extrinsic compression of the bronchi;
3. Visible endoluminal disease but not complete endobronchial obstruction;
4. Failed previous EBRT or those who are not candidates for further external beam radiation;
5. Good performance status (i.e., ECOG $\leq$ 2). Patients with poorer performance status caused directly by the endobronchial disease may still be suitable for HDR brachytherapy.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this evidence-based series, the Lung DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review May 4 2004)

Target Population

- This practice guideline applies to adult patients with symptomatic endobronchial disease in NSCLC.

Recommendations

- For patients with previously untreated, symptomatic, endobronchial NSCLC:
  - EBRT, alone, is more effective for palliation than HDREB, alone.
  - HDREB in combination with EBRT provides more effective palliation for symptoms of hemoptysis, cough, and chest pain than EBRT alone.
    - In patients with significant extrinsic compression of the airways, EBRT is often administered prior to HDREB.
    - In patients with respiratory symptoms caused by endobronchial lesions, HDREB can be administered prior to EBRT.
- For patients who have persistent or recurrent symptomatic airway obstruction due to endobronchial disease after previous EBRT, HDREB provides prompt palliation of obstructive symptoms.
- The occurrence of fatal hemoptysis as a result of HDREB is a significant risk of this therapy and may occur in up to 32% of treated patients.
- The optimal dose and fractionation for HDREB for the palliation of symptoms of airway obstruction has not yet been determined. However, commonly used doses include 1000 cGy at 1cm in a single fraction or 750 cGy at 1cm in one or two fractions.
- HDREB may be effectively combined with other endobronchial treatment modalities such as Nd-YAG laser therapy.

Qualifying Statements

- This guideline only addresses the use of HDREB for palliation of symptomatic endobronchial disease and does not apply to its use as a radical or adjuvant treatment.
- HDREB should be provided by a team of experts that include radiation oncologists, thoracic surgeons (or physicians with expertise in bronchoscopy) and medical physicists.
- HDREB is only possible if afterloading catheters can be inserted bronchoscopically. Patients with complete endobronchial obstruction are not suitable for HDREB.
- Treatment alternatives to HDREB include EBRT (if not previously irradiated), ND-YAG laser therapy, PDT, and surgical core out procedure.

Treatment Alternatives

- HDREB can only be given when there is an adequate lumen to allow for insertion of the treatment catheter. If there is complete endobronchial obstruction, then initial therapy could include other treatment modalities such as surgical core out, endobronchial stent for more proximal tumours, ND-YAG laser, or PDT. These modalities of therapy are usually followed by HDREB.

Methods

Feedback was obtained through a mailed survey of 117 practitioners in Ontario and included 35 medical oncologists, 22 radiation oncologists, 27 surgeons, 32 respirologists, and a hematologist. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on May 7, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung DSG reviewed the results of the survey.

Results

Fifty-three responses were received out of the 117 surveys sent (45.3% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 33 indicated that the report was relevant to their clinical practice, and they completed the survey. Two respondents left that question blank but completed the survey. Key results of the practitioner feedback survey are summarized in Table 5.

Table 5. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of this report, is clear.[1]	30 (88)	3 (9)	1 (3)
There is a need for a clinical practice guideline on this topic.[2]	22 (67)	11 (33)	0
The literature search is relevant and complete.[2]	28 (85)	4 (12)	1 (3)
The results of the trials described in the report are interpreted according to my understanding of the data.[1]	32 (94)	2 (6)	0
The draft recommendations in this report are clear.[1]	32 (94)	2 (6)	0
I agree with the draft recommendations as stated.[1]	31 (91)	2 (6)	1 (3)
This report should be approved as a practice guideline.[1]	29 (85)	3 (9)	2 (6)
	Very likely or likely	**Unsure**	**Not at all likely or unlikely**
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?[1]	17 (50)	6 (18)	11 (32)

[1] One practitioner did not respond to these questions.
[2] Two practitioners did not respond to these questions.

Summary of Written Comments

Nine respondents (26%) provided written comments. The main points contained in the written comments were:

1. One practitioner was concerned that the need for a team approach limits the applicability to some extent.
2. Three practitioners responded that this practice guideline was an informative review of HDREB for NSCLC and provides useful guidance. However, two of these commented that although they see patients with NSCLC, the recommendations apply only to radiation oncologists and thoracic surgeons and not medical oncologists, as the latter are not directly involved in the procedure.

3. One practitioner stated that a study on endobronchial brachytherapy has just been completed, and that the complication rates, including hemoptysis, are much lower than reported in the current guideline. This respondent also indicated that patient selection was the key and that the results of the study will be published in the future.
4. One practitioner was concerned that the practice guideline is based on a small amount of data and that each study used different doses of brachytherapy.
5. One practitioner stated that surgical core-out procedures are a useful adjunct to all forms of endobronchial therapy, whether it is HDREB, PDT, or Nd-YAG laser therapy. This practitioner also stated that they can be helpful even when obstruction is not complete.
6. One practitioner noted that assessment of symptoms using validated tools is essential in the application of new therapies as symptom control is as important an outcome as survival. A guideline should be developed on the assessment and quantification of symptoms.
7. One practitioner was concerned that the guideline was unclear on which patients with previously untreated symptomatic endobronchial NSCLC should get HDREB in addition to EBRT. The practitioner stated that the guideline needs recommendations regarding patient selection for HDREB.

Modifications/Actions

1. The Lung DSG feels that centres that perform HDREB should have a multidisciplinary team to do the procedure, and therefore not all cancer centres will be able to offer HDREB.
2. The Lung DSG agrees that the recommendations are intended to aid radiation oncologists and thoracic surgeons; however, it was important to include in the survey sample all practitioners that see NSCLC patients so that they are aware of HDREB as a treatment option.
3. The Lung DSG acknowledges there are studies that have not been published as of yet; however, only published reports have been included in this practice guideline, and, as a result, the recommendations reflect this. The guideline development process necessitates that updates be done on a consistent basis; therefore, when additional trials are identified they will be incorporated into the existing guideline.
4. The Lung DSG acknowledges that the studies included in the guideline used differing doses of HDREB; however, the recommendations are based on the available evidence as well as expert consensus among centres in Ontario doing HDREB.
5. The Lung DSG states, under "Treatment Alternatives," that surgical core-out is an acceptable treatment option when there is complete endobronchial obstruction.
6. The Lung DSG acknowledges that symptom control is an important outcome especially for NSCLC, and the Group feels that this issue was adequately discussed in the "Results" and "Interpretive Summary" sections.
7. The Lung DSG acknowledges that the recommendations should be clear regarding patient selection. Therefore, the recommendations regarding previously untreated patients were reworded in order to clarify which patients should receive HDREB as palliative treatment.

Practice Guidelines Coordinating Committee Approval Process

This evidence-based series reflects the integration of the draft recommendations with feedback obtained from the external review process. After being approved by the Lung DSG, the series was submitted to the Practice Guidelines Coordinating Committee.

Of the 15 panel members, eight members returned ballots of the reviewed document. However, one panel member is a member of the Lung DSG and was not eligible to review the document. Six panel members approved the document and one member approved the document on condition that changes to one of the recommendations are changed due to the weak evidence supporting it.

Modifications/Actions

Rewording of the recommendations was made to provide a clear and concise interpretation. During the course of revisions the group was made aware that a new abstract had been published which met the inclusion criteria of the guideline. The group was unsure whether the new abstract had been an update of a previous study or a new study. Clarification was required from the author of the study and one of the author's of the guideline made contact. The delay in addressing the PGCC comments was due to the wait in response from the lead author of the published abstract. The most recent abstract was in fact an update of a previous study that had been included in the systematic review. The results were updated in the guideline and the outcomes of the current abstract had changed from the initial publication that in fact there was no significant difference in symptom control in patients when they were treated with high dose rate endobronchial brachytherapy in combination with external beam radiation therapy oppose to external beam radiation therapy alone. This resulted in a change in one of the recommendations.

Final Recommendations

For previously untreated patients with NSCLC, the evidence does not provide conclusive results to suggest that HDREB and EBRT would provide improved relief over EBRT alone.

For patients with complete collapse of the lung due to endobronchial obstruction, a surgical core out procedure may be needed before EBRT or EBRT with HDREB

For patients previously treated by EBRT who are symptomatic from recurrent disease due to endobronchial obstruction, high dose rate endobronchial brachytherapy is recommended providing that endobronchial brachytherapy is technically feasible.

RELATED PRINT AND ELECTRONIC PUBLICATIONS

Ung YC, Yu E, Falkson C, Haynes AE, Stys-Norman D, Evans WK, et al. The role of high-dose-rate brachytherapy in the palliation of symptoms in patients with non-small cell lung cancer: a systematic review. Brachytherapy. 2006;5(3):189-202.

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Ontario Health
Cancer Care Ontario

Evidence-Based Series 7-16 Version 4: Section 4

The Role of High Dose Rate Brachytherapy in the Palliation of Symptoms in Patients with Non-Small Cell Lung Cancer

Document Review Summary

C. Falkson, C. Arinze, and Members of the Lung Cancer Disease Site Group

December 16, 2022

The 2005 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2005. It was endorsed after reviews completed in 2013 (Appendix A) and 2018 (Appendix B).

In December 2020, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (CA) conducted an updated search of the literature. A clinical expert (CF) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. Members of the Lung Cancer Disease Site Group (DSG) (Appendix 1) endorsed the recommendations found in Section 1 (Clinical Practice Guideline) in December 2022.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. Is there a role for high dose rate endobronchial brachytherapy (HDREB) in the palliation of respiratory symptoms in patients with non-small cell lung cancer?
2. If so, what is the optimal dose of HDREB in this setting?

Literature Search and New Evidence

The updated search (January 2017 to May 2022) yielded six full-text publications and two abstracts. An additional search for ongoing studies on ClinicalTrials.gov yielded one potentially relevant ongoing trial. Brief results of these publications are shown in the Document Summary and Review Tool. The search strategy is shown in Appendix 2.

Impact on the Guideline and Its Recommendations

The updated evidence generally supported the existing recommendations. One recommendation pertaining to the need for a surgical core out procedure in patients with endobronchial obstruction is not accurate as this does not occur in practice.

The Expert Panel proposed that the guideline could be endorsed with the removal of that recommendation.

Ontario Health
Cancer Care Ontario

Document Review Tool

Number and Title of Document under Review	7-16 The Role of High Dose Rate Brachytherapy in the Palliation of Symptoms in Patients with Non-Small Cell Lung Cancer
Original Report Date	June 11, 2018 (Version 3) October 25, 2005 (Version 1)
Date Assessed (by DSG or Clinical Program Chairs)	December 4, 2020
Health Research Methodologist	Chika Arinze
Clinical Expert	Dr. Conrad Falkson
Approval Date and Review Outcome (once completed)	December 16, 2022 ENDORSE

Original Question(s):

1. Is there a role for high dose rate endobronchial brachytherapy (HDREB) in the palliation of respiratory symptoms in patients with non-small cell lung cancer?
2. If so, what is the optimal dose of HDREB in this setting?

Target Population:

The recommendations apply to adult patients with symptomatic endobronchial disease in non-small cell lung cancer.

Study Selection Criteria:

Inclusion Criteria:

1. Randomized clinical trials (RCTs), non-comparative prospective studies, or large retrospective studies involving more than 100 patients evaluating treatment for symptomatic endobronchial disease in patients presenting with primary NSCLC.
2. At least one group in the study had to receive HDREB, either alone or in combination with EBRT, laser therapy, or photodynamic therapy (PDT).
3. Reported data on symptom control, response, survival, or toxicity.

Exclusion Criteria:

1. Published in a language other than English.
2. Letters, comments, or editorials.

3. Case studies.

Search Details:

- 2017 to December 2021 Cochrane (Database of Systematic Reviews)
- January 2017 to December 2021 (Medline and Embase)
- January 2017 to May 2022 (Clinicaltrial.org for ongoing trials)

Summary of new evidence:

Of 2550 hits from searches of Medline, Embase, and the Cochrane Database for Systematic Reviews, the full texts of 86 publications were reviewed. Eight articles (6 full-text and 2 abstracts) were retained. The included studies were one RCT, four retrospective studies, and two prospective studies investigating the role of high dose rate brachytherapy in the palliation of symptoms in patients with non-small cell lung cancer. A search of ongoing trials yielded one potential trial.

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	Yes. However, one of the guideline recommendations states that brachytherapy is contraindicated when there is complete obstruction and that is not the case. At the present time, brachytherapy is done despite the obstruction.
2. Does the newly identified evidence support the existing recommendations?	Yes.
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	Yes.

Review Outcome as recommended by the Clinical Expert	ENDORSE with removal of one recommendation statement.
If outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	
DSG/Expert Panel Commentary	• It would be unlikely for a patient with obstructive lesions to receive surgical core out. The recommendation *"For patients with complete collapse of the lung due to endobronchial*

	obstruction, a surgical core out procedure may be needed before EBRT or EBRT with HDREB" should be removed to align with current practice.

Evidence Tables

Author (Ref#) Study Name	Study Design (Median follow-up in months)	Population and number of patients	Result
Xiang 2021(1)	Retrospective ^{125}I brachytherapy + 2nd-line chemo vs. single agent 2nd-line CCRT Med F/U: 21 mos	Stage III–IV NSCLC patients who progressed after first-line CCRT. • ECOG: 0-2 n = 210	**LRR** • The 36 mos LRR was significantly better in the BT arm compared to the CCRT arm: 11.2% vs. 7.4% (*P*<0.05). • There were no statistically significant differences at 48 and 60 mos • PFS: BT arm compared to CCRT arm with 15.1 mos vs. 10.0 mos ○ The mean PFS was significantly better in the BT HR=1.472, (95% CI: 1.097–1.975) *P*<0.01 • OS was 21.2 mos in BT arm vs. 16.2 mos in CCRT arm HR=1.342 (95% CI: 1.005–1.791) *P* = 0.036 **Toxicity** • No serious complications occurred in the two groups. • The BT arm had significantly more tumor related clinical symptoms relief than the CCRT arm (*P*<0.01).
Xiang 2021(2) [ABSTRACT]	Prospective phase I/II HDR-BT + IMRT vs. IMRT + concurrent chemotherapy Med F/U: 55 mos	Patients with LA-NSCLC • Med age: 65 yrs n = 83	Patients treated with a combination of HDR-BT and IMRT had lower adverse reactions and improved survival and QoL outcomes compared to those treated with IMRT. • Total response rate was 92.8%. ○ LRR were 90.0%, 81.0% and 54.5% (1-,2-,3-year, respectively) • DFS: Rates were 68.3%,42.2% and 23.9%. • MFS rates were 73.3%, 50.9% and 39.5%. • OS rates were 90.6%, 70.6% and 62.4%. • Compared to the baseline scores, those treated with HDR-BT had higher QoL score.
Soror 2021(3)	Retrospective (no comparison)	Patients with lung cancer who received palliative HDR-EBIRT • STAGE 1-1V	The combination of HDR and EBIRT in the palliative treatment of lung cancer patients is a safe and effective treatment option • CR at 3 mos was 87.7%

	BT + EBR	• ECOG: 0 – 4 • Med age: 69 yrs n = 347	• Med survival for all patients was 10 mos. o The med survival was significantly longer in those who achieved CR compared to those who did not: 13 vs. 7 mos, *P* = 0.03. • OS at 1 and 2 yrs were 55.2% and 18.3% respectively and 3.5% at 5 yrs. • Symptom relief o Complete clinical symptom relief was seen in 28% o Major relief was 59.7% o Minimal or no relief was reported in 8.6% o Worsening symptoms was reported in 3.7% o Chronic bronchitis was found in 26.8% o Uncontrollable hemoptysis caused death in 7.8%
Patel 2021(4)	Retrospective BT vs. EBR	T1-4 N0 M0 NSCLC undergoing limited resection n = 543	Compared to EBR, BT significantly improved DSS: HR 0.524; (95% CI: 0.303 to 0.908), *P* = 0.021 OS: HR 0.604; (95% CI: 0.380 to 0.961) *P* = 0.033
Yue 2020(5)	Retrospective ^{123}I BT + single-agent CT vs. CCRT Med F/U: 19.06 mos	NSCLC with less than three unilateral lung lesions and without distant metastases • ECOG: 0-2 • Mean age: 71.25 (±7.14) yrs n = 110	The use of brachytherapy in locally advanced NSCLC that progressed after CCRT is effective and safe. Local response and survival rates were significantly better in the BT arm compared to the CCRT arm. • The local RR at 6mos was significantly better in the BT arm compared to the CCRT arm: RR: 39 (78.0%) vs 28 (46.7%) *P*<0.0001 • Med PFS was 15.08±0.85 mos (95% CI:13.42–16.74) vs. 10.03 ±0.53 mos (95% CI: 9.01 to 11.06); *P* = 0.000 • The 1- and 2-year OS rates for BT were 88.00% and 54.00%, respectively, and 71.67%, and 13.33%, respectively for combined chemo arm. • Med OS time was 23.71 ±1.41 mos (95% CI: 20.95 to 26.47) vs. 16.12±0.93 mos (95% CI: 14.31 to 17.93); *P* = 0.000

			• Toxicity: The clinical symptoms of patients in the BT arm were significantly relieved when compared with chemo arm. • There were statistically significant differences in myelosuppression and gastrointestinal responses between the two groups. The severe toxicities of chemotherapy were as follows: ○ Myelosuppression (12.00% vs. 41.67%); p = 0.0006 ○ Gastrointestinal response (8.00% vs. 33.33%); *P* = 0.0014 ○ Fever (10.00% vs. 11.67%); *P* = 0.78 ○ Allergy (12.00% vs. 13.33%); *P* = 0.83 ○ Alopecia (12.00% vs. 16.67%); *P* = 0.49 • Severe complications were not observed in either group
Soror 2019(6)	Retrospective HDR-BT Med F/U= 67.2 mos	Isolated endobronchial tumor recurrence in patients with non-small-cell lung cancer, in whom a surgery or external radiation treatment is not possible. • Med age: 63 n = 126	For patients with endobronchial tumor recurrence and contraindications for surgery and external beam radiotherapy, HDR-EBBT is an effective treatment option with acceptable toxicity • CR at 3 mos was 86.5%. • DFS at 5 yrs was 41.4% • OS at 5yrs was 23.6%. 12.7% of the patients died from massive hemoptysis.
Song 2017(7)	PROSPECTIVE ^{125}I BT (120 Gy) vs. BSC (After one cycle of first-line CT) Med F/U: 16 mos	Locally advanced NSCLC patients treated one cycle of first-line CT. • ECOG: 0-2 n = 32	In patients with locally advanced NSCLC treated with one cycle of first-line chemotherapy, ^{125}I BT improved the survival and QoL compared to best supportive care. Response: • The total tumor response rate was 75.0% vs 0.0%. P<0.01. ○ CR: 43.8% vs. 0.0%; *P* = 0.003 ○ PR: 31.3% vs. 0.0%; *P* = 0.015 ○ PD: 18.8% vs. 81.3%. Survival:

			• Med PFS time 4.80 mos (95% CI: 4.61 to 4.99) vs. 1.35 mos (95% CI: 1.01 to 1.59), *P*<0.001 • Med OS was 9.4±0.30 mos (95% CI: 8.81 to 9.99) vs. 8.4±0.10mos (95% CI: 8.21 to 8.60), *P* = 0.013. Toxicity: No procedure-related deaths occurred for those that received BT. Tumor-related symptoms of patients were significantly relieved, and the QoL was markedly improved in BT group compared to BSC group.
Sur 2017(8) [ABSTRACT]	RANDOMISED EBR + HDRILB vs. EBR	Stage III and IV NSCLC patients with symptomatic endobronchial disease who do not qualify for radical CRT • ECOG: 0-2 • Mean age: 69.8 yrs n = 134	The addition of HDR-BT to EBR was not significantly better than EBR alone: • PFS: HR = 0.68; 95% CI = 0.34, 1.35; *P* = 0.27 • OS: HR = 1.06; 95% CI = 0.73, 1.55; *P* = 0.77. • Symptom improvement at six weeks: 29.9% for EBR + HDRILB vs. 28.4% for EBR; *P* = 0.84

Abbreviations: BSC: Best supportive care; BT: Brachytherapy; CCRT: Concurrent chemotherapy; CI: Confidence interval; CR: Complete responses; CRT: Chemo radiation therapy; CT: Chemotherapy; DFS: Disease free survival; DSS: Disease-specific survival; EBBT: Endobronchial brachytherapy; EBIRT: Endobronchial interventional radiotherapy; EBR: External beam radiation; EBRT: Endobronchial radiotherapy; ECOG: Eastern Cooperative Oncology Group; F/U: Follow up; HDR: High-dose-rate; HDRILB: High dose rate intraluminal brachytherapy; HR: Hazard ratio; IMRT: Intensity-modulated radiotherapy; LA: Locally advanced; LRR: Local response rate; Med: Median; MFS: Metastatic free survival; Mos: Month(s); NSCLC: Non-small-cell lung cancer; OS: Overall survival; PD: Progressive disease; PFS: Progression free survival; PR: Partial response; QoL: Quality of life; RR: Response rate; Yrs: Year(s)

Ongoing Trials

Official Title	Status	Protocol ID	Last Updated
I-125 Seeds Implantation in the Treatment of Recurrent Lung Cancer After Radiotherapy	Recruiting	NCT04071418	May 3, 2021

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1. Xiang Z, Zhong Z, Mu L, Li G, Zhou C, Wang H, et al. The Clinical Value of Computed Tomography (CT)-Guided ¹²⁵I Brachytherapy for Locally Advanced Non-Small Cell Lung Cancer After Progression of Concurrent Radiochemotherapy. Cancer Manag Res. 2021;13:5297-307.
2. Xiang L, Wu JB. The 3-Year Outcome of 3D High-Dose-Rate Brachytherapy in Combination With Regional Metastatic Lymph Nodes Intensity-Modulated Radiotherapy in Peripheral Locally Advanced Non-Small Cell Lung Cancer: A Phase I/II Clinical Trial. International Journal of Radiation Oncology Biology Physics. 2021;111(3 Supplement):e458-e9.
3. Soror T, Kovacs G, Wecker S, Ismail M, Badakhshi H. Palliative treatment with high-dose-rate endobronchial interventional radiotherapy (Brachytherapy) for lung cancer patients. Brachytherapy. 2021;20(6):1269-75.
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7. Song J, Fan X, Zhao Z, Chen M, Chen W, Wu F, et al. ¹²⁵I brachytherapy of locally advanced non-small-cell lung cancer after one cycle of first-line chemotherapy: a comparison with best supportive care. Onco Targets Ther. 2017;10:1345-52.
8. Sur R, Falkson CB, Pan M, Pond G, Wright J, Bezjak A, et al. A Phase 3, Multicenter, Randomized Trial to Evaluate the Symptomatic and Quality of Life Improvements in Lung Cancer Patients Receiving External Beam Radiation With or Without High Dose Rate Intraluminal Brachytherapy. Int J Radiat Oncol Biol Phys. 2017;99(2):S116.

Appendix 1. Affiliations and Conflict of Interest Declarations

Name	Affiliation	Conflict of Interest Declaration
Authors		
Conrad Falkson	Clinical Expert Radiation Oncologist Lung Cancer Disease Site Group	None declared
Chika Arinze	Health Research Methodologist Program in Evidence-Based Care	None declared
Expert Panel		
Abdollah Behzadi	Surgeon Lung Cancer Disease Site Group	None declared
Adrien Chan	Medical Oncologist Lung Cancer Disease Site Group	None declared
Medhat El-Mallah	Radiation Oncologist Lung Cancer Disease Site Group	None declared
Peter Ellis	Medical Oncologist Lung Cancer Disease Site Group	$500 or more in a single year to act in a consulting capacity? “Consulting capacity” includes such work as consultant, investigator, advisory board member, lobbyist, speaker." Honararia for advisory boards from AstraZeneca, BMS, Jannsen, Jazz, Lilly, Takeda, Merck, Novartis, Pfizer, Sanofi
John Goffin	Medical Oncologist Lung Cancer Disease Site Group	None declared
Swati Kulkarni	Medical Oncologist Lung Cancer Disease Site Group	None declared
Mridula Sara Kuruvilla	Medical Oncologist Lung Cancer Disease Site Group	None declared
Robert MacRae	Radiation Oncologist Lung Cancer Disease Site Group	None declared
Donna Maziak	Surgeon Ontario Thoracic Cancers Lead	None declared
Andrew Pearce	Radiation Oncologist Lung Cancer Disease Site Group	None declared
Kevin Ramchandar	Radiation Oncologist	None declared

Andrew Robinson	Medical Oncologist Lung Cancer Disease Site Group	$500 or more in a single year to act in a consulting capacity? “Consulting capacity” includes such work as consultant, investigator, advisory board member, lobbyist, speaker." Merck, Astra Zeneca, Roche, BMS, all <5000
Alexander Sun	Radiation Oncologist Lung Cancer Disease Site Group	
Anand Swaminath	Radiation Oncologist Lung Cancer Disease Site Group	
Julius Toth	Surgeon Lung Cancer Disease Site Group	
Yee Chung Ung	Radiation Oncologist Lung Cancer Disease Site Group	
Kazuhiro Yasufuku	Surgeon Lung Cancer Disease Site Group	
Edward Yu	Radiation Oncologist Lung Cancer Disease Site Group	

Appendix 2. Search Strategy

MEDLINE
1. meta-Analysis as topic.mp.
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
41. carcinoma, non-small-cell lung/
42. non-small cell lung.tw.
43. or/41-42
44. (brachytherapy or (radiotherapy adj dosage)).tw.
45. ((interstitial adj radiotherapy) or brachytherp$ HDR or (seed adj implant) or (high adj dose)).tw.
46. or/44-45
47. 43 and 46

EMBASE
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
4. (systematic adj (review$1 or overview$1)).tw.

5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. carcinoma, non-small cell lung/
37. non small cell lung.tw.
38. or/36-37
39. (brachytherapy or (radiotherapy adj dosage)).tw.
40. ((((((interstitial adj radiotherapy) or brachytherp$ or seed) adj implant) or high) adj dose) or HDR).tw.
41. or/39-40
42. 38 and 41

ASCO
1. ("brachytherapy" AND ("non small cell lung cancer" OR "nsclc"))

CLINICALTRIALS.gov
1. "Brachytherapy" AND "Lung"

DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words “ARCHIVE.”

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary, but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.

APPENDIX A: Previous Document Review, December 11, 2012

Evidence-based Series #7-16: Appendix A

The Role of High Dose Rate Brachytherapy in the Palliation of Symptoms in Patients with Non-Small Cell Lung Cancer

Guideline Review Summary

Review Date: December 11, 2012

The 2002 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

Evidence-based Series History

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2005.

In September 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (EY) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. In December 2012, the Lung Cancer Disease Site Group (DSG) endorsed the recommendations found in Section 1 (Clinical Practice Guideline).

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. Is there a role for high dose rate endobronchial brachytherapy (HDREB) in the palliation of respiratory symptoms in patients with non-small cell lung cancer?
2. If so, what is the optimal dose of HDREB in this setting?

Literature Search and New Evidence

The new search (October 2005 to September 2012) yielded 8 relevant new publications in the following categories: One Randomized Control Trial, one prospective non-comparative trial, five large retrospective trials, one meta-analysis (abstract) and 2 existing guidelines. Brief results of these publications are shown in the Document Assessment and Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations

The new data supports existing recommendations. Hence, the Lung Cancer DSG ENDORSED the 2005 recommendations on the role of High Dose Rate Brachytherapy in the Palliation of Symptom in Patients with Non-Small Cell Lung Cancer.

Document Review Tool

Number and title of document under review	**7-16** **The Role of High Dose Rate Brachytherapy in the Palliation of Symptoms in Patients with Non-Small Cell Lung Cancer**
Current Report Date	**October 25, 2005**
Clinical Expert	**Dr. Edward Yu**
Research Coordinator	**Robert Mackenzie**
Date Assessed	**September 2012**
Approval Date and Review Outcome (once completed)	December 11, 2012 (ENDORSED)

Original Question(s):
1. Is there a role for high dose rate endobronchial brachytherapy (HDREB) in the palliation of symptoms in patients with non-small cell lung cancer (NSCLC)?
2. If so, what is the optimal dose of HDREB in this setting?

Target Population:
The recommendations apply to adult patients with symptomatic endobronchial disease in non-small cell lung cancer.

Study Selection Criteria:
Inclusion Criteria
Articles published as full reports were selected for inclusion in this systematic review of the evidence if they were the following:
1. Randomized clinical trials (RCTs), non-comparative prospective studies, or large retrospective studies involving more than 100 patients evaluating treatment for symptomatic endobronchial disease in patients presenting with primary NSCLC.
2. At least one group in the study had to receive HDREB, either alone or in combination with EBRT, laser therapy, or photodynamic therapy (PDT).
3. Reported data on symptom control, response, survival, or toxicity.

Exclusion Criteria
Articles were excluded if they were:
1. Published in a language other than English.
2. Published in abstract form only.
3. Letters, comments, or editorials.
4. Case studies.

Search Details:
- July 2005 to September 2012 (Medline and Embase, Cochrane Library, ASCO Annual Meeting,and Clinicaltrials.gov)
  - ASCO - ("brachytherapy" AND ("non small cell lung cancer" OR "nsclc"))
  - Clinicaltrials.gov - "Brachytherapy" AND "Lung"

Brief Summary/Discussion of New Evidence:

RANDOMIZED CONTROL TRIALS					
Interventions	**Name of RCT (med F/U)**	**Population (n)**	**Outcomes**	**Brief results**	**References**
EBBT vs EBBT & XRT **Arm A**: XRT 30 gy/10fr/2 weeks & 2 sessions EBBT @ 8 Gy. **Arm B**: XRT 30 gy/10fr/2 weeks & 1 session EBBT @ 10 Gy **Arm C**: EBBT @ single fraction 15gy	Optimal Dose & Fractionation EBBT	n=45	Response rates, duration of symptom palliation, obstruction scores, Qol	Response rates: No sig. difference between arms. • Dyspnea(91%) • cough(84%) • hemoptysis(94%) • Obs. Pneumonia(83%) • Median time to symptom relapse: 4-8 months(all) • Median time to symptom progression 6-11 months(all). • Hemoptysis: shorter palliation arm c ($p<0.01$)	Mallick I. et al 2006
NON COMPARATIVE PROSPECTIVE TRIALS					
Interventions	**Name of RCT (med F/U)**	**Population (n)**	**Outcomes**	**Brief results**	**References**
Weekly HDREB sessions intervals (500-1000 cGy per session) with prior Diodi-laser resection in some cases	Outpatient HDREB	n=35	Response was assessed bronchoscopically, clinically and functionally at the end of treatment and one month after the last HDREB session	Following 2000 cGy HDREB therapy: • dyspnoea decreased (Wilcoxon test, $p=0.049$), and remained significantly improved ($p=0.049$) after 1 month. • Haemoptysis completely disappeared after one month(x^2 Mc-Nemar=4.9; $p=0.027$). • Cough decreased significantly (Wilcoxon test, $p=0.019$) after one month.	Scarda A. et al. 2007

Single dose of at least 20 Gy from a 192Ir source in HDR technique	CT-guided interstitial brachytherapy	n=30	Adverse effects, respiratory effect, tumor control	Adverse effects: • nausea (n = 3, 6%) • minor (n = 6, 12%) and one major pneumothorax (2%) • no changes of vital capacity and forced expiratory volume could be detected • Median follow-up period was 9 months with a local tumor control of 91% at 12 months	Peters N. et al. 2008
single fraction of 20 Gy in percutaneous brachytherapy & hypofractionated from 5 × 5 Gy to 2 × 12.5 Gy in transbronchial brachytherapy.	High-Dose-Rate Brachytherapy for Small-Sized Peripherally Located Lung Cancer	n=12	Adverse effects, recurrence, tumor control, survival	• focal radiation pneumonitis was observed in most patients • Primary recurrence occurred in three patients • local control rate is 88.9% • estimated 5-year survival rate is between 60% and 70%	Imamura F., et al. 2006
LARGE RETROSPECTIVE STUDIES					
Interventions	**Name of RCT (med F/U)**	**Population (n)**	**Outcomes**	**Brief results**	**References**
EBBT with or without palliative external radiation (XRT)	Palliation of endobronchial symptoms in advanced non-small cell lung cancer (NSCLC)	n=95	Symptomatic response rates, duration of symptom palliation, obstruction scores, complications and quality of life outcomes	Improvements Symptomatic response rates: • 93% for dyspnea, 57% complete response • 81% for cough, 19% complete response • 97% haemoptysis, 95% complete response • 91% for obstructive pneumonia, 78%	Mallick I. et al 2007

				complete response • Improvement in the obstruction score: 95.8% cases • Median time to symptom relapse: 4—8 months all symptoms • Median time to symptom progression: 6—11 months. • Quality of life improvement for symptom scores, functional scales, overall	
HDR-EBBT as a part of multimodality therapy	Risk factors, early complication rates (occurring within 3 weeks after the application of brachytherapy) following HDR Brachytherapy in Palliative treatment Lung Cancer	n=761	Early Complications included severe hypoxemia, global respiratory failure, cardiac arrhythmia requiring additional treatment, hemoptysis, pneumothorax, pneumomediastinum, pulmonary edema, tracheoesophageal fistulae, and death. Risk factors included myocardial infarction occurring ≥ 6 months previously, stable hypertension, stable arrhythmias, chronic obstructive pulmonary disease (COPD), stabilized cardiomyopathy, previous external beam radiation therapy (EBRT), previous chemotherapy, and previous interventional pulmonology procedures	*(Statistical significance p=0.001)* • Statistically significant correlation between number of clinical risk factors and complications. • statistically significant correlation between age and complications • No statistically significant correlations were evident between the rate of complications and sex, smoking status, type of lung cancer, and localization of the tumor. • Multivariate analysis identified stable hypertension,	Zarick B. et al. 2010

				controlled arrhythmia, COPD, and stabilized cardiomyopathy as statistically significant risk factors	
Stage III lung cancer patients (ERT in combination with HDR-EB), not treated previously with RT, previously irradiated with full dose curative radiotherapy	HDREB response and toxicity evaluation	n=43 NSCLC (158 total)	symptomatic and endoscopic responses as well as related toxicities	KPS and obstruction scores after the completion of treatments were statistically significant (p = 0.0001 for both) Endoscopic response rate was 86%, including 67% of patients who achieved a complete endoscopic response response rate: • 58% for cough (30% complete response), 77% for dyspnea (76% complete response) • 100% for hemoptysis (92% complete response) • Median survival was 11 months • 2 and 5 year survival rates 25.5% and 9.5%	Ozkok S. et al. 2008
Six fractions of 5 or 7 Gy, usually delivered 1 cm from the source	Long-term results of endobronchial brachytherapy	n=106	complete histologic response rate, local control, overall survival, and cause-specific survival rates	• 63 with a complete histologic response (59.4%) • 23 with a complete macroscopic response (21.8%) • 9 with a partial response (8.5%) • 7 with local progression or no change (7.5%) • Patients with complete macroscopic response had a significantly	Hennequin C. et al. 2007

				shorter mean endobronchial tumor length (1.6cm vs. 2.5 cm, p _ 0.006) and less severe bronchial obstruction (19% vs. 35%, p= 0.02) • Patients whose tumors were visible on CT achieved complete remission less frequently than others (30.8% [4 of 13] vs. 65.6% [59 of 90], p= 0.01) • Local control rate was 60.3% at 24 months and 51.6% at 60 months • The median interval between HDR-EBBT and local failure was 14 months; 6 patients developed local relapse more than_2 years after HDR-EBBT • Median overall survival time - 21.4 months • 2- yr overall survival rate – 47.4%, 5yr overall survival – 24% • 36 deaths (48%) were attributed to the treated lung cancers • Massive hemoptysis occurred _3 months after the procedure in 2 patients	

				• 3 patients developed necrosis of the bronchial wall	
total dose:= 30 Gy vs less, dose per fraction:= 5 Gy vs more, number of catheter(s):1 vs = 2. **(ASCO Absrtact)**	Retrospective review high dose rate brachytherapy (HDR-BT) for early stage non-small cell lung carcinoma	n=226	impact on survival and complications	**SURVIVAL** Two and 5-year survival: overall: 57%, 29% local- relapse free (LRF) 68% LRF survival was better in patients treated with = 2 catheters (p=0.007) **TOXICITY** Pneumothorax 1.3% hemoptysis 6.6% (5% fatal) bronchitis 20%.	Aumont M. et al, 2007
SYSTEMATIC REVIEWS					
Diverse fractionation schedules of palliative HDR EBB, EBRT versus HDR EBB, Combined Nd-YAG laser plus HDR EBB versus Nd-YAG laser alone	Palliative endobronchial brachytherapy for non-small cell lung cancer (Review)	n=577	Symptom response, recurrence, survival.	• Variety o HDR EB fractionation schedules had similar effectiveness in overall survival • A schedule of 7.4 Gy in two fractions appeared to be significantly superior to 3.8 Gy in four fractions per week for local control • Fatal hemoptysis was significantly less frequent with the 7.4 Gy in two fractions schedule group, in one trial; no significant difference was found in the other one • The comparison between EBRT and HDR EBB in patients with untreated	Cardona et al., 2008

				advanced NSCLC favors the use of EBRT. • Findings from one trial suggest that a schedule of two fractions of 7.4 Gy EBB is more effective than one of 3.8 Gy per week four times in prolonging the mean time of local control and reducing the rate of fatal hemoptysis. • For patients previously treated by EBRT and who are symptomatic from recurrent disease because of endobronchial central obstruction, EBB should be considered in selected cases • Conclusion: EBRT alone is more effective for palliation than EBB alone. Not enough conclusive evidence to recommend EBB combination with EBRT, chemotherapy or Nd-YAG laser. • Study comparing YAG laser with HDR EBB may be underpowered.	

ON-GOING CLINICAL TRIALS (Retrieved from clinicaltrial.gov database)				
Interventions	**Official title**	**Status**	**Protocol ID & URL**	**Last Updated**

External Beam Radiation vs. External Beam Radiation (EBR) plus High Dose Rate Intraluminal brachytherapy (HDRIB)	A Phase III, Multi-centre, randomized Trial to Evaluate the Symptomatic and Quality of Life Improvements in Lung Cancer Patients Receiving External Beam Radiation With or Without High Dose Rate Intraluminal Brachytherapy	recruiting	NCT01351116	June 11, 2012

Existing Guidelines

Publishing Group	Recommendation	source
American Society for Radiation Oncology 2011	No defined role for EBB in the routine initial palliative treatment of chest disease has been demonstrated; however, EBB can be a reasonable option for the palliation of endobronchial lesions causing obstructive symptomatology including lung collapse, or for hemoptysis after EBRT failure.	
Guidelines Subcommittee of the Clinical Affairs and Quality Committee of the American Society for Radiation Oncology **(ASTRO)**	No defined role for endobronchial brachytherapy for the routine initial palliative treatment of chest disease has been demonstrated; however, endobronchial brachytherapy remains an option for the palliation of endobronchial lesions causing obstructive symptomatology in the EBRT failure scenario or in locally advanced nonmetastatic cancer patients with endobronchial disease who require lung re-expansion before or in conjunction with radical RT.	

4. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	1. No If Yes, the document will be immediately removed from the PEBC website, and a note as to its status put in its place. **Go to 2**.

5. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No to each, and explain if necessary:	2a. Yes a, 2b. Yes If both are Yes, the document can be **ENDORSED**. If either is No, **go to 3**.
6. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	3. Not Applicable If Yes, a final decision can be **DELAYED** up to one year. If No, **go to 4**.
7. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	4. Not Applicable If Yes, the document needs an **UPDATE**. It can be listed on the website as IN REVIEW for one year. If a full update is not started within the year, it will be automatically **ARCHIVED**. If NO, go to 5.
5. If Q2, Q3, and Q4 were all answered NO, this document should be **ARCHIVED** with no further action.	

Review Outcome	ENDORSE
DSG/GDG Approval Date	December 11, 2012
DSG/GDG Commentary	• Due to limited amount of evidence, it is noted that patient selection may help determine who would be best treated by EBRT, HDREB or both. • Although not found in this review of literature it is noted that EBRT re-treatment is another intervention used for palliation of symptoms in NSCLC.

New References Identified:

1. Mallick I, Sharma SC, Behera D, Ghoshal S, Oinam AS. Optimization of dose and fractionation of endobronchial brachytherapy with or without external radiation in the palliative management of non-small cell lung cancer: a prospective randomized study. Journal of Cancer Research & Therapeutics. 2006;2(3):119-25.
2. Mallick I, Sharma SC, Behera D. Endobronchial brachytherapy for symptom palliation in non-small cell lung cancer--analysis of symptom response, endoscopic improvement and quality of life. Lung Cancer. 2007;55(3):313-8.
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5. Ozkok S, Karakoyun-Celik O, Goksel T, Mogulkoc N, Yalman D, Gok G, et al. High dose rate endobronchial brachytherapy in the management of lung cancer: response and toxicity evaluation in 158 patients. Lung Cancer. 2008;62(3):326-33.
6. Peters N, Wieners G, Pech M, Hengst S, Ruhl R, Streitparth F, et al. CT-guided interstitial brachytherapy of primary and secondary lung malignancies: results of a prospective phase II trial. Strahlentherapie und Onkologie. 2008;184(6):296-301.
7. Hennequin C, Bleichner O, Tredaniel J, Quero L, Sergent G, Zalcman G, et al. Long-term results of endobronchial brachytherapy: A curative treatment? International Journal of Radiation Oncology Biology Physics. 2007;67(2):425-30
8. Cardona AF, Reveiz L, Ospina EG, Ospina V, Yepes A. Palliative endobronchial brachytherapy for non-small cell lung cancer. Cochrane Database of Systematic Reviews. 2008;(2)(CD004284).
9. Imamura F, Ueno K, Kusunoki Y, Uchida J, Yoshimura M, Koizumi M, et al. High-dose-rate brachytherapy for small-sized peripherally located lung cancer. Strahlentherapie und Onkologie. 2006;182(12):703-7.
10. Aumont M, Mahe M, Prevost B, Sunyach M, Peiffert D, Maingon P, Thomas L, Begue M, Willaume D, Lerouge D, Campion L. Exclusive high dose rate brachytherapy (HDR-BT) for early stage non-small cell lung carcinoma: Results of a retrospective study in 226 patients. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 7688.
11. Rodrigues, George, Gregory M. Videtic, Ranjan Sur, Andrea Bezjak, Jeffrey Bradley, Carol A. Hahn, Corey Langer, Keith L. Miller, Benjamin J. Moeller, Kenneth Rosenzweig, and Benjamin Movsas. "Palliative Thoracic Radiotherapy in Lung Cancer: An American Society for Radiation Oncology Evidence-based Clinical Practice Guideline." Practical Radiation Oncology 1 (2011): 60-71.
12. Mazeron JJ, Ardiet JM, Haie-Meder C, Kovacs G, Levendag P, Peiffert D, et al. GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas. Radiotherapy and Oncology. 2009;91(2):150-6.
13. Peters S., Adjei A.A., Gridelli C., Reck M., Kerr K., Felip E., and on behalf of the ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Ann Oncol (2012) 23(suppl 7): vii56-vii64 doi:10.1093/annonc/mds226.
14. Alberta Health Services., Alberta Health Services clinical practice guideline LU-003, Non-small cell lung cancer - stage III. Date Accessed: Oct 4, 2012.

Literature Search Strategy:

MEDLINE

1. meta-Analysis as topic.mp.
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
41. carcinoma, non-small-cell lung/
42. non-small cell lung.tw.
43. or/41-42
44. (brachytherapy or (radiotherapy adj dosage)).tw.
45. ((interstitial adj radiotherapy) or brachytherp$ HDR or (seed adj implant) or (high adj dose)).tw.
46. or/44-45
47. 43 and 46
48. (200507: or 2006: or 2007: or 2008: or 2009: or 2010: or 2011:or 2012).ed.
49. 47 and 48
50. remove duplicates from 49

EMBASE

1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.

3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
4. (systematic adj (review$1 or overview$1)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. carcinoma, non-small cell lung/
37. non small cell lung.tw.
38. or/36-37
39. (brachytherapy or (radiotherapy adj dosage)).tw.
40. ((((((interstitial adj radiotherapy) or brachytherp$ or seed) adj implant) or high) adj dose) or HDR).tw.
41. or/39-40
42. 38 and 41
43. (200507: or 2006: or 2007: or 2008: or 2009: or 2010: or 2011:or 2012).ew.
44. 42 and 43
45. remove duplicates from 44

ASCO
2. ("brachytherapy" AND ("non small cell lung cancer" OR "nsclc"))

CLINICALTRIALS.gov
2. "Brachytherapy" AND "Lung"

OUTCOMES DEFINITIONS

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DELAY** – A Delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.

APPENDIX B: Previous Document Review, June 11, 2018

Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-based Series 7-16: Appendix B

The Role of High Dose Rate Brachytherapy in the Palliation of Symptoms in Patients with Non-Small Cell Lung Cancer

Guideline Review Summary

Yee C Ung, Glenn G Fletcher, and Members of the Lung Cancer Disease Site Group

June 11, 2018

The 2005 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-Based Care in 2005. It was assessed in 2012 and subsequently reviewed and endorsed; results from that review are in Appendix A. In 2016 this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (GGF) conducted an updated search of the literature. One clinical expert (YCU) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Lung Cancer Disease Site Group (Appendix 4-2) voted on the proposal with the following results: Of 29 eligible voters, 10 abstained, and 5 did not vote. Of the 14 who voted, 11 (79%) voted to endorse the document, and 3 (21%) voted to archive the document. More than 75% of votes were to

endorse, therefore the recommendations found in Section 1 (Clinical Practice Guideline) were ENDORSED on June 11, 2018.

Document Review Tool

Number and Title of Document under Review	7-16 Version 2: The Role of High Dose Rate Brachytherapy in the Palliation of Symptoms in Patients with Non-Small Cell Lung Cancer: A Clinical Practice Guideline
Current Report Date	May 23, 2013 [2005, reviewed Dec 2012 and endorsed]
Date Assessed (by DSG or Clinical Program Chairs)	Dec 16, 2016
Health Research Methodologist	Glenn G. Fletcher
Clinical Expert	Yee C. Ung
Approval Date and Review Outcome	June 11, 2018 ENDORSE

Original Question(s):
1. Is there a role for high dose rate endobronchial brachytherapy (HDR-BT) in the palliation of symptoms in patients with non-small cell lung cancer (NSCLC)?
2. If so, what is the optimal dose of HDREB in this setting?

Target Population:
The recommendations apply to adult patients with symptomatic endobronchial disease in non-small cell lung cancer.

Study Selection Criteria:
Articles published as full reports were selected for inclusion in this systematic review of the evidence if they were the following:
1. Trials evaluating treatment for symptomatic endobronchial disease in patients presenting with primary NSCLC: limited to randomized clinical trials (RCTs), non-comparative prospective studies, large retrospective studies involving more than 100 patients
2. At least one group in the study had to receive HDR-BT, either alone or in combination with external beam radiotherapy (EBRT), laser therapy, or photodynamic therapy (PDT).
3. Reported data on symptom control, response, survival, or toxicity.

Excluded: abstracts, letters, comments, editorials, case studies, non-English publications

Search Details:

2005
MEDLINE (1966 through July 2005), EMBASE (1980 through July 2005), CANCERLIT (1975 through March 2002), and the Cochrane Library (2005, Issue 4):

(Carcinoma, non-small-cell lung/ or Lung Neoplasms/ or (non small cell lung).tw) and (brachytherapy/ or radiotherapy dosage/ or (brachytherapy or interstitial radiotherapy or seed implant or high dose or HDR).tw)

The initial search did not include restrictions on study design as the literature was expected to be limited. However, subsequent searches included the search terms for the following study designs and publication types: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, controlled clinical trials, clinical trials, comparative studies, follow-up studies, prospective studies, and retrospective studies.

Other
American Society of Clinical Oncology (ASCO) conferences(1995-2005)
American Society for Therapeutic Radiology and Oncology conferences (ASTRO) (2000-2005)
The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp)
National Guidelines Clearinghouse (http://www.guideline.gov/index.asp)

2012 REVIEW

- July 2005 to September 2012 (Medline and Embase, Cochrane Library, ASCO Annual Meeting,and Clinicaltrials.gov): systematic reviews, meta-analyses, guidelines, RCTs
- ASCO - ("brachytherapy" AND ("non small cell lung cancer" OR "nsclc"))
- Clinicaltrials.gov - "Brachytherapy" AND "Lung"

Note: the search strategy did not include non-RCT trials

2017/2018 REVIEW
Due to the changes in search strategy between the original guideline and the 2012 review (which did not include non-RCTs), a more comprehensive search without restriction on study design was used (see Appendix 4-1). MEDLINE and Embase were searched for the period 2005-September 12, 2017. Abstracts were excluded as per the original study selection criteria and conference abstracts were therefore not searched.

Summary of new evidence: See summary and tables following this form.

8. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	NO
9. Does the newly identified evidence support the existing recommendations?	YES
10. Do the current recommendations cover all relevant subjects addressed by the	YES

evidence? (i.e., no new recommendations are necessary)	
Review Outcome as recommended by the Clinical Expert	ENDORSE
If the outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	The OCOG-2011-BRACHY (NCT01351116) trial has been completed but not yet published. It is an RCT comparing EBRT + HDR brachytherapy vs EBRT.
DSG/GDG Commentary	Some modifications were made to the recommendations and qualifying statements to align them with current practice.

Results of Literature Search

Ten studies found in the literature search are summarized in Table 4-1 [1-10]. Preliminary results of the studies by Niemoeller et al [2] and Kelly et al [10] were included in the original PEBC guideline (see Huber et al, 1995 [11] and Delclos et al, 1996 [12], respectively). The literature search also found 4 systematic reviews as summarized in Table 4-2 [13-16], and 14 guidelines (17 publications) as summarized in Table 4-3 [17-33].

The only randomized trial is by Neimoeller et al. Response and tumour control were evaluated by bronchoscopic exam and chest radiograph; respiratory symptoms such as cough and dyspnea were not reported. In this final analysis, 2 fractions (14.4 Gy total) compared to 4 fractions (15.2 Gy total) resulted in longer duration of tumour control; fatal hemoptysis also appeared lower, although the difference was not significant (12.2% vs 18.3%, p=0.34).

The other studies consistently show that brachytherapy improves respiratory symptoms compared to no treatment. Most of the studies were for palliation of obstructive symptoms in patients with tumours that could not be treated by resection or EBRT (often due to prior EBRT). The study by Canak (subsets reported by Canak et al [9] and by Zaric et al [8]) suggest greater improvement and for longer duration with multimodal treatment. Nd:YAG laser + HDR-BT + EBRT was better than Nd:YAG alone, while Nd:YAG + HDR-BT + EBRT was better than HDR-BT + EBRT. This study does not allow any conclusions about the relative role of HDR-BT as it was used together with EBRT. No trials with direct comparison of brachytherapy to other modalities of treatment were found.

The Cochrane review on palliative endobronchial brachytherapy [16] concluded that EBRT alone was better than HDR-BT alone for palliation, but there was insufficient evidence for addition of HDR-RT to EBRT. The OCOG-2011-BRACHY trial (NCT01351116) mentioned as ongoing in the previous assessment of this guideline has recently been completed and publication is expected this year. This trial may provide the most definitive evidence on whether or not addition of brachytherapy to EBRT is beneficial for quality of life and symptom control in patients for whom EBRT is not contraindicated. It expected to not be sufficiently powered for survival outcomes and will not answer the question of whether biologically equivalent doses of endobronchial brachytherapy plus EBRT versus EBRT alone is equivalent since the endobronchial brachytherapy group gets a higher dose of RT.

The American College of Chest Physicians guideline on treatment of cough in patients with lung cancer [17] is based primarily on a Cochrane review on interventions for cough in cancer [15] and suggests the use of endobronchial brachytherapy in suitable patients for whom surgery, chemotherapy or EBRT are not indicated. Other guidelines also place brachytherapy as a suitable option to be used or considered, along with other potential treatments, including Nd:YAG laser, photodynamic therapy, endobronchial debulking, and stenting. The GEC-ESTRO

handbook [23] states that “brachytherapy is one of the most efficient methods in overcoming difficulties in breathing that is caused by endobronchial obstruction in palliative treatment of bronchus cancer”. Other reviews and guidelines suggest use of HDR-BT be limited to patients for which other treatments are not appropriate or have failed.

Several trials and reviews have noted fatal hemoptysis as a serious adverse effect of brachytherapy. It is more likely with higher radiation dosage. The American Brachytherapy Society guideline [24] indicates best practice is to obtain a CT scan to identify applicator position and determine proximity to organs at risk, particularly blood vessels, so that complications, particularly massive hemoptysis, can be decreased. Technical considerations or practice standards are addressed in guidelines by the American College of Radiology/American Brachytherapy Society [26] and by the American Society for Radiation Oncology [28,29].

Impact on the Guideline and Its Recommendations

The new evidence as summarized in this assessment was limited, but supports the existing recommendations. Technical issues such as optimum dose and fractionation were not addressed in the existing recommendations but were included in qualifying statements. The guideline notes that “defining the optimal dose and fractionation as well as defining the physical aspects of radiation delivery (e.g., dose prescription, optimal length, and the effects of catheter curvature on dose)” are areas for future research. These have not been addressed in this review. The opinion of the Lung Cancer DSG is that current practice favours fractionated treatment instead of a single fraction, prescribed to a defined volume, with a tendency to use multiple catheters and CT planning. The qualifying statement has been modified to reflect this change in practice. Other guidelines summarized in this section (see Table 4-3) cover aspects of radiation delivery in more detail.

Fatal hemoptysis was a serious adverse effect in several studies in the systematic reviews and mentioned several times in the key evidence accompanying the existing recommendations. The opinion of the Lung Cancer DSG was high rates of fatal hemoptysis reported were due to higher doses than in current use and the qualifying statement has been modified to reflect this opinion. Other guidelines suggest this can be reduced with CT treatment planning. The user should still be aware of the possibility of fatal hemoptysis and consider in treatment planning ways to minimize this risk.

Table 4-1. Clinical Studies

Trial name, location, publication	Type of study	# pts	Additional stage or pt information	Treatment	Results	Notes
Goldberg, 2015 [1]	Prospective No comparison group	98	Locally advanced, inoperable lung cancer	HDR-BT for palliation of obstructive symptoms Various doses (5-10 Gy/fraction; 5-28 Gy total) and number of fractions (1-4)	97/98 patients had cough, hemoptysis, dyspnea, and pain on presentation (1 pt unknown) Authors indicate brachytherapy had effective and sustained palliation of QoL measures at 4-5 months, but no data were reported	Symptom-free survival data appear to actually be symptom-free duration as they are better than OS (which is not possible if survival data)
Niemoeller, 2013 [2]	RCT	142	Endobronchial tumours: advanced centrally located with preferential endoluminal growth; palliative context (exclusion of EBRT, surgery, chemotherapy as treatment options, although most had prior treatment)	HDR-BT: 14.4 Gy in two fractions vs 15.2 Gy in four fractions	2-fraction group vs 4-fraction group: similar 1-y OS (21.1% vs 11.4%, median 18 weeks vs 19 weeks, n.s.), longer local tumour control duration (mean 37 weeks vs 11 weeks, p≤0.015), and less fatal hemoptysis (12.2% vs 18.3%, p=0.34, ns) in 2-fraction group	Additional pts and longer term follow-up of the study by Huber et al, 1995 ([11], in original PEBC guideline)
De Aquino Gorayeb, 2013 [3]	Prospective observational	78	Palliative intent due to malignant endobronchial obstruction; 83% had lung cancer	HDR-BT: 22.5 Gy in three fractions; a few pts had 3-4 fractions of 5 Gy due to risk of hemoptysis; EBRT and HDR-BT in sequence if obstruction had significant extrinsic component	87.2% of pts had improvement in symptoms Median performance status improved or remained stable in 93.6% of pts Of patients with initial symptom, improvement in obstruction score in 74.3% (p<0.0001), dyspnea (57.4%, p<0.0001), cough (33.9%, p=0.005), infection (80%, 0.001), and hemoptysis	Study supports efficacy of HDR brachytherapy in palliation of symptoms of airway obstruction

Trial name, location, publication	Type of study	# pts	Additional stage or pt information	Treatment	Results	Notes
					(100%, p<0.0001). Corresponding percentages that became worse are 1.5%, 1.6%, 3.4%, 0%, 0%)	
Santini, 2012 [4]	Not stated, but appears to be prospective	27	Advanced lung cancer with central airway obstruction; 78% lung cancer, rest other cancers	HDR-BT as palliative treatment, 1-4 fractions of 7-7.5 Gy	Significant improvement in all pts with hemoptysis, 25% cough, 40% dyspnea, and 77% obstruction. After treatment no pts had Grade 3 or 4 symptoms	
Skowronek, 2009 [5]	Retrospective observation of course of the disease	648	Advanced lung cancer with endobronchial obstruction and intensive dyspnoea; disqualified from radical treatment (surgery, EBRT) due to advanced clinical stage	Palliative HDR-BT. 22.5 Gy in three fractions vs 10 Gy in one fraction; placed in group according to clinical stage and Zubrod-ECOG-WHO score	88.4% had some subjective improvements (subsidence of all symptoms) at 4 weeks 17.4% had complete remission and 71% had partial remission of the tumour At one year, OS 34.8%, 14.5% had clinical improvement (mainly dyspnoea) Both treatments showed similar efficiency in overcoming breathing difficulties	As pt characteristics were used to determine treatment, the outcomes for the two groups cannot be directly compared
Zorlu, 2008 [6]	Unclear (prospective or retrospective)	21	Recurrent lung carcinoma after EBRT	Palliative HDR-BT 10 Gy in 1 fraction (9 pts) or 15 Gy in 1 fraction (12 pts)	81% had improved performance and reduced symptoms 10/14 (71%) dyspneic pts recovered clinically with accompanying radiological downstaging 4/5 pts (80%) with hemoptysis had relief Median symptomatic downstaging was 45 days 1 pt with fatal hemorrhage 1 pt with bronchospasm and intrabronchial edema	

Trial name, location, publication	Type of study	# pts	Additional stage or pt information	Treatment	Results	Notes
Kubaszewska, 2008 [7]	Retrospective	270	Symptomatic endobronchial recurrence of previously irradiated lung cancer (prior HDR-BT or other treatment)	HDR-BT, 8 or 10 Gy per fraction (1-4 fractions depending on pt, disease, and pretreatment factors; 80% received 1 fraction)	Symptomatic response rates: 76% dyspnea, 77% cough, 92% hemoptysis, 82% post-obstructive pneumonia By endoscopic exam (1-3 months after treatment): 80% response rate Median duration of palliation was 5 months	
Zaric, 2007 [8] Part of large scale study by Canak	Prospective, non-randomized	178	Lung cancer pts, stage IIIA-IV, centrally located tumours, unresectable or inoperable, obstruction score >8	Nd:YAG laser reception + HDR-BT + EBRT vs HDR-BT + EBRT HDR-BT: 2 fractions of 7 Gy EBRT: 40 Gy (2x5 fractions) All received cisplatin + etoposide	Significant improvement in both groups; improvement was greater in Nd:YAG laser group (dyspnoea, thoracic pain, body weight loss, ECOG status, time to progression, OS)	Study is mainly on effect of Nd:YAG laser; cannot separate role of brachytherapy from other treatments. Laser group had more stage IIIB (90.7% vs 74.1%) and stage IV (7.2% vs 4.9%) cancers
Canak, 2006 [9]	Prospective, non-randomized	64	Lung cancer, Karnofsky Index ≤50, TMN stage IIIB or IV	Nd:YAG laser + HDR-BT+EBRT (n=44) vs Nd:YAG laser (n=20) HDR-BT: 2 fractions of 7 Gy	Laser only: improvement in all parameters (cough decrease 25%, not significant, p=0.69) Laser + HDR-BT + EBRT: improvement in all parameters (cough, dyspnoea, hemoptysis, thoracic pain, Karnofsky Index, body weight loss, atelectasis, post-obstructive pneumonia) Decrease in dyspnoea, hemoptysis were greater in combined group.	Group that received laser-only treatment was due to technical problems in radiation department

Trial name, location, publication	Type of study	# pts	Additional stage or pt information	Treatment	Results	Notes
					Disease-free period and survival rate significantly longer in combined treatment group ($p \leq 0.0005$)	
Kelly, 2000 [10]	Series of consecutive pts at M.D. Anderson Cancer Center	175	Palliation of symptoms by relapsed or persistent endobronchial tumours (primary lung cancer)	HDR-BT; most pts received 30 Gy in 2 fractions	66% of pts had symptomatic improvement; of these 32% were much improved and 34% slightly improved; 78% objective response rate determined by repeat bronchoscopy Actuarial rate of 5% for fatal hemoptysis, and 13% for complications at 1 year	Includes 74 pts previous reported ([12], in original PEBC guideline)
Ongoing						
NCT01351116 OCOG-2011-BRACHY	RCT	134		EBRT + HDR-BT vs EBRT EBRT 20 Gy in 5 daily fractions; HDR-BT 14 Gy in 2 fractions	Outcomes: symptom improvement, QoL, OS	Complete Jan 2017 but not yet published. Principal investigator: Ranjan Sur at Juravinski Cancer Centre

EBRT, external beam radiotherapy; HDR-BT, high-dose-rate (endobronchial) brachytherapy; Nd:YAG, neodymium-doped yttrium aluminum garnet ($Nd:Y_3Al_5O_{12}$) laser; PEBC, Program in Evidence-Based Care; pts, patients; n.s., not significant; OS, overall survival; QoL, quality of life

Table 4-2. Meta-Analyses and Systematic Reviews

Source	Publication type and search	Topic	Patients	Trials included	Conclusions, other
Youroukou, 2017 [13]	Systematic review Medline, Cochrane, PubMed 1995-2014	Brachytherapy in lung cancer to reduce recurrence and for palliation for inoperable disease	849	8 studies (849 pts) on palliative endobronchial brachytherapy, 2 studies (96 pts) on I-125 interstitial brachytherapy	Symptom improvement with good tolerance and good response rates. Brachytherapy for inoperable symptomatic disease can give symptom improvement. Prospective trials needed.
Colt, 2017 [14]	UpToDate Reviews and evidence-based recommendations Medline, Cochrane, Clinical Evidence, AHRQ, list of 400 journals, conference proceedings are used but no explicit statement for a particular review, no search terms, time period, summary of results				Use HDR-BT for palliation of obstructive symptoms caused by large central airway tumors that are not amenable to surgical resection and/or external beam radiation; or if pts cannot tolerate or fail other local ablative therapies including Nd:YAG laser, argon laser, or cryotherapy Patients with acute life threatening symptoms of airway obstruction that need immediate relief can be treated with HDR-BT but only after other local ablative therapies or external beam radiation (EBRT) have been employed to shrink tumor size
Molassiotis, 2015 [15]	Systematic review (Cochrane) Cochrane, Medline, Embase, PsycINFO, AMED, CINAHL on June 9 2014	Interventions for cough in cancer (mostly with lung cancer)		8 studies of either brachytherapy, laser, or photodynamic therapy (RCTs and other trials with a comparison group)	Lack of credible evidence, most studies of low quality Brachytherapy seemed to improve cough in selected participants No new trials since previous version of review (although 2 ongoing without results yet)
Reveiz, 2012 [16]	Systematic review (Cochrane)	Palliative endobronchial brachytherapy vs EBRT or	953	RCTs only. 14 RTCs.	"The evidence did not provide conclusive results that EBB plus EBRT improved symptom relief over EBRT alone. We were not able to provide conclusive evidence to

	Cochrane, Medline, Embase until Jan 2012	other endobronchial interventions in advanced NSCLC		Included both low and high-dose-rate brachytherapy trials	recommend EBB with EBRT, EBB in preference to EBRT, chemotherapy or Nd:YAG laser. From heterogeneous information obtained from several small RCTs, we conclude that EBRT alone is more effective for palliation than EBB alone. For patients previously treated by EBRT who are symptomatic from recurrent endobronchial central obstruction, EBB may be considered in selected cases."

EBB, endobronchial brachytherapy; EBRT, external beam radiotherapy; HDR-BT, high-dose-rate (endobronchial) brachytherapy; Nd:YAG, neodymium-doped yttrium aluminum garnet ($Nd:Y_3Al_5O_{12}$) laser;

Table 4-3: Guidelines

Source	Organization	Topic	Relevant recommendations	Notes
Symptom Management/Palliative Care				
Molassiotis, 2017 [17]	American College of Chest Physicians (CHEST; known until ≈2014 as ACCP)	Symptomatic treatment of cough in patients with lung cancer	In adult patients with cough due to localized endobronchial disease for whom surgery, chemotherapy, or external beam radiation are not indicated, we suggest the use of endobronchial brachytherapy where such specialist facilities are available and in suitable patients (Grade 2C: weak recommendation, low/very-low quality evidence from observational studies, case series, or RCT with serious flaws) Evidence for brachytherapy comes from uncontrolled comparative trials (mostly prospective)	Based on 2015 Cochrane review plus uncontrolled studies, case studies, and clinical context
Simoff, 2013 [18]	American College of Chest Physicians (ACCP; rebranded as CHEST ≈ 2014)	Symptom management in lung cancer	In lung cancer patients with inoperable disease and symptomatic airway obstruction, therapeutic bronchoscopy employing mechanical debridement, brachytherapy, tumor ablation or airway stent placement is recommended for improvement in dyspnea, cough, hemoptysis and overall quality of life (QoL) (Grade 1C: strong recommendation [benefits clearly outweigh risk] based on low/very-low-quality evidence from observational studies, case series, or RCT with serious flaws)	Medline, Embase, Google Scholar, CINAHL, PsycINFO, Cochrane reviews, Web of Science back more than 10 years Replaces previous palliative care guideline (Kvale, 2007)
Alberta Health Services, 2016 [19]	Alberta Health Services	Palliative radiotherapy for superior vena cava obstruction, dyspnea, hemoptysis	EBB may be considered in patients with obstructing proximal airway tumours. A recent Cochrane review did not find conclusive evidence to support symptom relief or survival benefits associated with EBB plus EBRT over EBRT alone EBB may be used in the palliation of patients with NSCLC previously treated with EBRT who become obstructed due to recurrent or progressive disease. Other potential treatment options in this situation include PDT, endobronchial debulking, Nd:YAG laser, or stenting. There is no evidence to support delivery of immediate thoracic RT in patients with minimal to no symptoms secondary to incurable disease	PubMed Jan 2012-Sept 2014. Earlier data may be from original 2008 guideline and review in 2012

Source	Organization	Topic	Relevant recommendations	Notes
			EBB is an option for managing bleeding in patients who are not eligible for more aggressive treatment and/or after maximal EBRT	
Rodrigues, 2012 [20]	Third International Lung Cancer Consensus Workshop (2010 ASTRO meeting)	Palliative lung radiotherapy	There is no evidence to routinely recommend brachytherapy alone or in conjunction with other palliative maneuvers (XRT, chemotherapy, Nd:YAG laser) in the initial routine palliative management of lung cancer. EBB is a reasonable option in the palliative management of a patient with endobronchial obstruction who has previously received thoracic XRT or in the initial treatment of central obstructive endobronchial disease before definitive thoracic RT to open the airway.	PubMed search for other systematic reviews and guidelines, 1966-2010. Unclear whether search included trials, or these were only identified from other publications.
Rosenzweig, 2012, 2013 [21,22]	American College of Radiology (ACR)	Nonsurgical treatment for NSCLC: poor performance status or palliative intent	Endobronchial brachytherapy is useful for patients with symptomatic endobronchial tumours (obstructing endobronchial lesions)	Extensive analysis of current medical literature and application of established consensus methodology. Evidence is only nonrandomized, primarily retrospective reviews
Brachytherapy for lung cancer				
Van Limbergen, 2017 [23]	Groupe Européen de Curiethérapie-European Society for Radiotherapy & Oncology (GEC-ESTRO)	Handbook of brachytherapy: chapter on bronchus cancer	Brachytherapy plays an important role in the palliative treatment of obstructive disease, sometimes in conjunction with endobronchial laser therapy or stent implantation. Removal of endobronchial obstruction leads to quick improvement of clinical status and Quality of Life (QoL). Brachytherapy is one of the most efficient methods in overcoming difficulties in breathing that is caused by endobronchial obstruction in palliative treatment of tracheal and lung cancer. If obstruction is severe, endobronchial brachytherapy is usually preceded by endobronchial disobliteration techniques e.g. laser, cryocoagulation, electrocautery or endobronchial stenting	Comprehensive textbook; includes 16 trials on palliative HDR-BT and more details of use than in most reviews or guidelines. Table of adverse effects reported trial by trial (separate tables for hemoptysis and death)
Stewart, 2016 [24]	American Brachytherapy Society	Thoracic brachytherapy for lung cancer	Recommend the use of endobronchial brachytherapy for disease palliation in patients with central obstructing lesions, particularly in patients who have previously received external beam radiotherapy	Update of 1993 and 2001 based on literature review (no details reported) and clinical experience

Source	Organization	Topic	Relevant recommendations	Notes
			CT simulation recommended for endobronchial brachytherapy. CT planning with three-dimensional target definition recommended over point prescription for endobronchial brachytherapy. High dose rate or pulsed dose rate brachytherapy with the ability to optimize dose are recommended over low dose rate brachytherapy for endobronchial treatment.	
Du Rand, 2011 [25]	British Thoracic Society	Advanced diagnostic and flexible bronchoscopy in adults	Brachytherapy should not be used first-line in preference to EBRT for palliation of lung cancer (Grade C: based on well conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal) Brachytherapy should be considered for the palliation of hemoptysis or central airway obstruction in locally advanced central lung cancer (Grade D: based on non-analytic studies such as case reports or case series or expert opinion)	Medline, Embase, CINAHL, Cochrane until Sept 2010 Review due in 2017
Technical Issues				
Erickson, 2015, 2017 [26,27]	American College of Radiology (ACR) and the American Brachytherapy Society (ABS)	Practice parameter for performance of radionuclide-based HDR-BT(revised 2015)	HDR-BT also has a well-established role in the palliation of primary and recurrent endobronchial lesions	A literature search was performed and reviewed to identify published articles regarding practice parameters and technical standards in HDR-BT. Based on analysis of current literature, expert opinion, open forum commentary and formal consensus
Thomadsen, 2014 [28,29]	American Society for Radiation Oncology (ASTRO)	Safety, quality management, and practice guidelines for HDR-BT	This review considers the guidance documents that exist at this time and whether they adequately address the safety needs of the current state of practice This white paper recommends that practitioners become familiar with and follow existing guidance as appropriate.	Endorsed by the American Brachytherapy Society (ABS), American Association of Physicists in Medicine (AAPM), American Association of Medical Dosimetrists, and American Society of Radiologic Technologists. The document has also

Source	Organization	Topic	Relevant recommendations	Notes
				been reviewed and accepted by the American College of Radiology (ACR)'s Commission on Radiation Oncology.
Podder, 2014 [30]	American Association of Physicists in Medicine (AAPM) and Groupe Européen de Curiethérapie-European Society for Radiotherapy & Oncology (GEC-ESTRO)	Image-guided robotic brachytherapy	13 robotic systems have been developed for brachytherapy, differing according to features, functionalities, and automation. Only one has been commercialized and most have not been used clinically	
General Guidelines on Lung Cancer				
Ettinger, 2017 [31]	National Comprehensive Cancer Network (NCCN)	NSCLC	Endobronchial obstruction: any combination of laser/stent/other surgery; external-beam RT or brachytherapy; photodynamic therapy Severe hemoptysis: external-beam RT or brachytherapy; laser or photodynamic therapy or embolization; surgery	No details or further discussion of brachytherapy or how/when to choose it
Department of Health, 2017 [32]	Department of Health (Ireland)	Lung cancer: diagnosis, staging, treatment	In lung cancer patients with symptomatic (including breathlessness, hemoptysis and cough) malignant airway obstruction, any of the following therapeutic interventions may be considered: bronchoscopic debulking, tumour ablation modalities, airway stent placement and radiotherapy (external beam or brachytherapy). [Grade D: based on expert opinion, physiology, bench research; or with troubling inconsistent or inconclusive studies] [ablation may include electrocautery, cryotherapy, thermal laser ablation and photodynamic therapy]	Cochrane, Medline, Embase, CINAHL, PsycINFO Refers to NICE and UpToDate for this recommendation
Goeckenjan, 2011 [33]	German Respiratory Society and the	Prevention, diagnosis, therapy,	In patients without previous radiotherapy, the use of brachytherapy with palliative intention is appropriate in the individual cases for centrally stenosing tumors. If no radiotherapeutic preload is present, brachytherapy should be	Abridged version. Based on S3 guideline. Systematic literature review until 2006, then

Source	Organization	Topic	Relevant recommendations	Notes
	German Cancer Society	follow-up of lung cancer	combined with percutaneous radiotherapy (Grade B: moderate recommendation based on systematic review of cohort or case-control studies, or cohort study plus low quality RCT). In a tumor with stenosis of the central airways and radiotherapeutic preload endoluminal brachytherapy may be appropriate in certain cases (Grade C: weak recommendation based on case-series, poor quality cohort and case-control studies).	monitoring of publications until guideline finished (2010)

EBB, endobronchial brachytherapy; EBRT, external beam radiotherapy; HDR-BT, high-dose-rate (endobronchial) brachytherapy; Nd:YAG, neodymium-doped yttrium aluminum garnet ($Nd:Y_3Al_5O_{12}$) laser; pts, patients; NICE, National Institute for Health and Care Excellence (UK); n.s., not significant; OS, overall survival; QoL, quality of life

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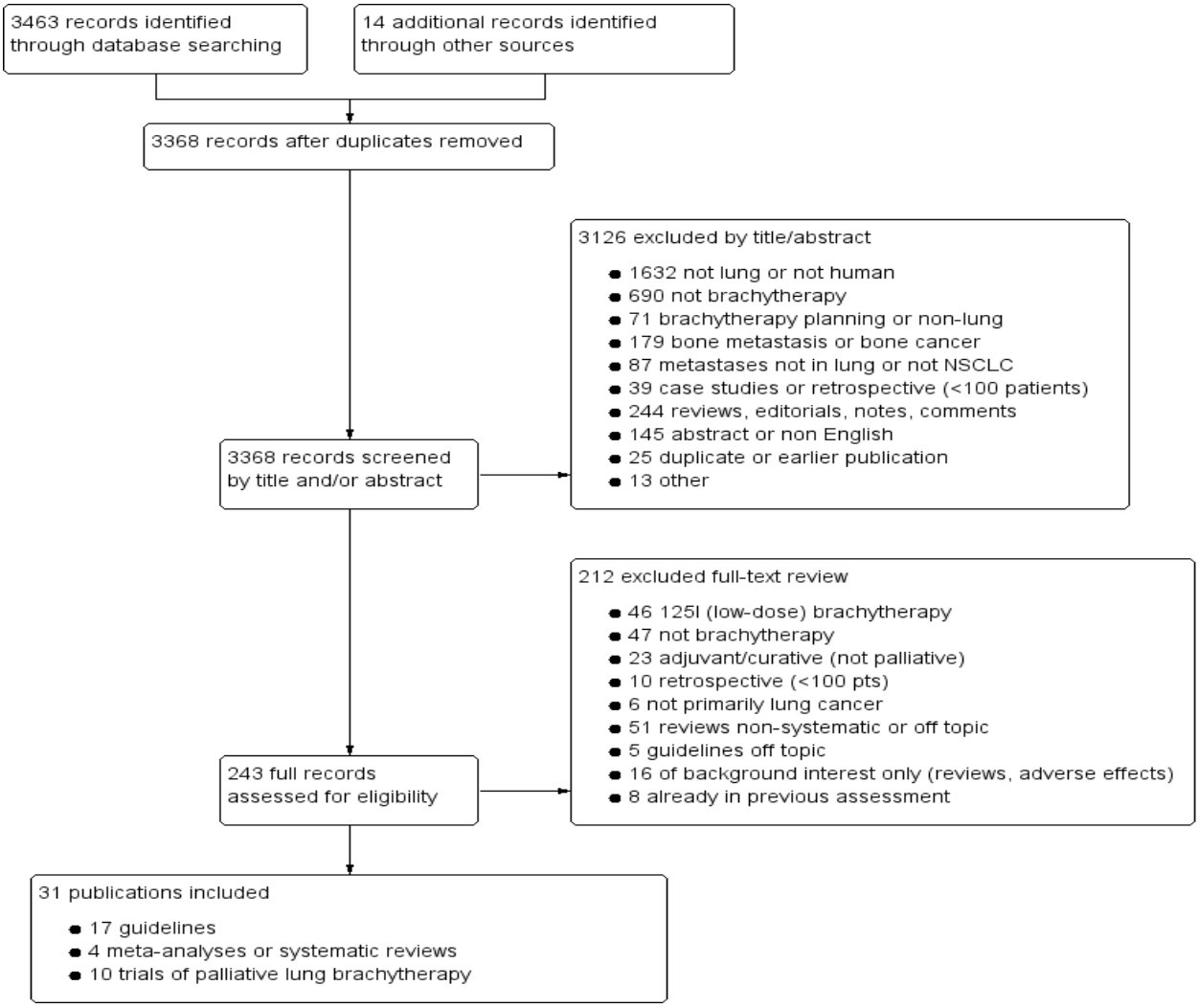
Appendix 4-1. Literature Search Strategy and Diagram of Results

Embase 1996 to 2017 September 12, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

1	exp Lung cancer/ or exp lung tumor/ or exp non small cell lung cancer/ or (non-small-cell lung or NSCLC).mp. or ((lung$ or pulmon: or bronchio:) and (cancer$ or carcinoma$ or adenocarcinoma or neoplasm$ or tumor$ or tumour$)).mp.	797457
2	limit 1 to yr="2005 -Current"	542842
3	2 and (Exp brachytherapy/ or (brachytherapy or HDREB or EBBT or HDREBBT or EBB or seed implant or ((internal or interstitial or endobronchial: or palliat:) adj2 (radiother: or radiation:))).mp)	4354
4	remove duplicates from 3	3463



Appendix 4-2. Reviewers and Members of the Expert Panel (Lung Cancer Disease Site Group)

Name	Affiliation	Declarations of Interest
REVIEWERS		
Yee Chung Ung Clinical Reviewer	Radiation Oncologist Odette Cancer Centre	Lead author of the original version of this guideline
Glenn Fletcher	Health Research Methodologist Program in Evidence-Based Care McMaster University	none
EXPERT PANEL		
Abdollah Behzadi	Surgeon Peel Regional Cancer Centre	none
Penny Bradbury	Medical Oncologist Queen's University	Received honouraria from Merck, Abbvie
Adrien Chan	Medical Oncologist Thunder Bay Regional Health Sciences Centre	none
Susanna Cheng	Medical Oncologist Odette Cancer Centre	none
Peter Ellis	Medical Oncologist Juravinski Cancer Centre	none
Medhat El-Mallah	Radiation Oncologist Lakeridge Health Corporation	none
Conrad Falkson	Radiation Oncologist Cancer Centre of Southeastern Ontario	Principal investigator on the OCOG Lung Brachytherapy trial Phase III study comparing the proportion of lung cancer patients with symptomatic and quality of life improvements receiving external beam radiation with or without high dose rate
Ron Feld	Medical Oncologist Princess Margaret Hospital	Retired from the University Health Network in July 2017
John Goffin	Medical Oncologist Juravinski Cancer Centre	none
Richard Gregg	Medical Oncologist Cancer Centre of Southeastern Ontario	none
Don Jones	Surgeon Peel Regional Cancer Centre	none
Jaro Kotalik	Bioethicist Centre for Health Care Ethics at Lakehead University	none
Swati Kulkarni	Medical Oncologist Windsor Regional Cancer Centre	none
Sara Kuruvilla	Medical Oncologist London Regional Cancer Program	none
Scott Laurie	Medical Oncologist	none

	The Ottawa Hospital Regional Cancer Centre	
Natasha Leighl	Medical Oncologist Princess Margaret Hospital	none
Robert MacRae	Radiation Oncologist The Ottawa Hospital Regional Cancer Centre	none
Richard Malthaner	Surgeon London Health Sciences Centre	none
Donna Maziak	Surgeon The Ottawa Hospital	none
Andrew Pearce	Radiation Oncologist Sudbury Regional Hospital	none
Kevin Ramchandar	Radiation Oncologist Thunder Bay Regional Health Sciences Centre	none
Andrew Robinson	Medical Oncologist Sudbury Regional Hospital	none
Alex Sun	Radiation Oncologist Princess Margaret Hospital	none
Anand Swaminath	Radiation Oncologist Juravinski Cancer Centre	none
Mojgan Taremi	Radiation Oncologist Southlake Regional Health Centre	none
Julius Toth	Surgeon Southlake Regional Health Centre	none
Kazuhiro Yasufuku	Surgeon Toronto General Hospital	none
Edward Yu	Radiation Oncologist London Regional Cancer Program	none
Robert Zeldin	Surgeon Toronto East General Hospital	none

Appendix 4-3. Definitions of Review Outcomes

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words "ARCHIVE."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.