Guideline Endorsement 7-13-2 Version 2

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

Recommendations for Prophylactic Cranial Irradiation and Consolidative Radiation for Patients with Small Cell Lung Cancer: Endorsement of the 2019 National Institute for Health and Care Excellence Guidance

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This document describes the CCO-Lung Cancer Disease Site Group endorsement of the recommendations for prophylactic cranial irradiation and consolidative radiation for patients with small cell lung cancer from © NICE [2019] Lung cancer: diagnosis and management. The original publication is available at www.nice.org.uk/guidance/ng122.

An assessment conducted in December 2022 deferred the review of Guideline Endorsement 7-13-2. 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)

You can access the full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2396

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Section 1: Guideline Endorsement

ENDORSEMENT

The Lung Cancer Disease Site Group of Cancer Care Ontario (CCO) endorses the following clinical recommendations for prophylactic cranial irradiation and consolidative radiation for patients with small cell lung cancer (SCLC) found in the *Lung cancer: diagnosis and management* guideline, published by the National Institute for Health and Care Excellence (NICE) [1]. They are reprinted with the permission of NICE.[1]

RECOMMENDATIONS

Limited-stage disease SCLC

Offer prophylactic cranial irradiation at a dose of 25 Gy in 10 fractions to people with limited-stage disease SCLC and World Health Organization (WHO) performance status 0 to 2, if their disease has not progressed on first-line treatment.

Extensive-stage disease SCLC

Consider thoracic radiotherapy with prophylactic cranial irradiation for people with extensive-stage disease SCLC who have had a partial or complete response to chemotherapy within the thorax and at distant sites.

Consider prophylactic cranial irradiation at a dose of 25 Gy in 10 fractions for people with extensive-stage disease SCLC and WHO performance status 0 to 2, if their disease has responded to first-line treatment.

The Lung Cancer Disease Site Group of CCO also endorses the following recommendation to support research in order to develop better evidence in future to inform care decisions for prophylactic cranial irradiation for patients with SCLC.

Recommendation for Research

What is the effectiveness and cost effectiveness of prophylactic cranial irradiation compared with routine magnetic resonance imaging follow-up in people with SCLC without brain metastases?

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Section 2: Endorsement Methods Overview

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health (MOH). All work produced by the PEBC is editorially independent from the MOH.

BACKGROUND FOR GUIDELINE

In 2012, CCO's Lung Cancer Disease Site Group (DSG) determined the previous 2003 version of the PEBC guideline for prophylactic cranial irradiation (PCI) in small cell lung cancer (SCLC) needed to be updated because newer evidence would likely change the recommendations.

GUIDELINE ENDORSEMENT DEVELOPERS

This endorsement project was developed by the Prophylactic Cranial Irradiation for SCLC Guideline Development Group (GDG) (Appendix 1), which was convened at the request of the CCO's Lung Cancer DSG and the Thoracic Cancers Advisory Committee. The project was led by a small Working Group of the Prophylactic Cranial Irradiation for SCLC GDG, which was responsible for reviewing the evidence base and recommendations in the National Institute for Health and Care Excellence (NICE) *2019 Lung cancer: diagnosis and management* guideline [1] in detail and making an initial determination as to any necessary changes, drafting the first version of the endorsement document, and responding to comments received during the document review process. The Working Group members had expertise in radiation oncology, medical oncology, and health research methodology. Other members of the Prophylactic Cranial Irradiation for SCLC GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

ENDORSEMENT METHODS

The PEBC endorses guidelines using the process outlined in CCO's Guideline Endorsement Protocol [2]. This process includes selection of a guideline, assessment of the recommendations, drafting the endorsement document by the Working Group, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC assesses the quality of guidelines using the AGREE II tool [3]. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

Implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations may be provided along with the recommendations for information purposes.

Selection of Guidelines

As a first step in developing this document, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. Evidence-based guidelines with systematic reviews that addressed the research question, 'Is prophylactic cranial irradiation effective for patients with limited- or extensive-stage SCLC who have achieved any response to induction therapy (chemotherapy or chemoradiotherapy)?' were included. Guidelines older than three years (published before 2015) were excluded.

The following sources were searched for existing guidelines on October 15, 2018 with the search term lung cancer: National Institute for Health and Care Excellence Evidence Search, Canadian Partnership Against Cancer database, Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology, National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, and Cancer Council Australia – Cancer Guidelines Wiki. Four guidelines met the inclusion criteria [1,4-6]. At the time of the search, the NICE guideline was under development [1].

Assessment of Guidelines

Guidelines were considered for endorsement if the Working Group answered yes to the following questions:

1. Do you agree with the recommendations and think that no new evidence would change the recommendations?
2. Do you think the recommendations would be acceptable in Ontario?

All four guidelines met the criteria for endorsement [1,4-6]. The Working Group members chose to endorse the NICE 2019 guideline [1] because it was the most recent and detailed guideline that included the latest studies. The overall quality of the NICE guideline was assessed using the AGREE II tool [3] (Table 2-1). The pre-planned threshold for a high-quality guideline was a rigour of development score above 70% based on the AGREE II tool. Therefore, the Working Group members considered the NICE guideline to be of high quality because the rigour of development domain, which assesses the methodological quality of the guideline, was well above 70% (Table 2-1).

Table 2-1. Results of AGREE II Tool quality rating of the evidence-based guideline

Guideline	AGREE II Domain Scores					
	Scope and Purpose (%)	Stakeholder Involvement (%)	Rigour of Development (%)	Clarity and Presentation (%)	Applicability (%)	Editorial Independence (%)
NICE 2019 [1]	100	86	91	100	88	75

Abbreviations: NICE, National Institute for Health and Care Excellence

DESCRIPTION OF ENDORSED GUIDELINE

The NICE 2019 guideline covered a broad topic on the diagnosis and management of lung cancer and included recommendations on PCI for patients with SCLC [1]. NICE updated their previous 2011 version of this guideline in 2019. The recommendations for PCI for patients with extensive-stage SCLC were updated based on a review of the evidence from their systematic

review from March 2019 [1]. The recommendation for PCI for patients with limited-stage SCLC was endorsed from their previous version of this guideline developed in 2011. NICE's 2019 guideline was reviewed by stakeholders and their Guideline Executive.

ENDORSEMENT PROCESS

The Working Group held a meeting to review the recommendations from NICE to assess whether they agreed with the interpretation of the evidence with respect to the magnitude of the desirable and undesirable effects of PCI and took into account the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability, and feasibility of implementation according to GRADE's evidence-to-decision framework [7]. The evidence from NICE for each recommendation was summarized within this GRADE framework to help the Working Group consider the evidence used by the NICE group and to then make a judgement as to whether they agreed with the way NICE interpreted and used the evidence. The evidence from NICE and the judgements of the Working Group can be found in Appendices 2 and 3. Taking into consideration all of these factors within the GRADE framework, the Working Group members decided to endorse all of the recommendations from NICE without any modifications. They also agreed with NICE's recommendation for research to compare PCI with routine magnetic resonance imaging follow-up and endorse the need for further research in this area.

ENDORSEMENT REVIEW AND APPROVAL

Internal Review

For the endorsement document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP) with methodology expertise must unanimously approve the document. The Expert Panel and RAP may specify that approval is conditional, and that changes to the document are required. Results of this review are reported in Section 3.

External Review

Feedback on the approved draft endorsement document is obtained from content experts through Professional Consultation. Relevant care providers and other potential users of the endorsement document are contacted and asked to provide feedback on the recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners. Results of this review are reported in Section 3.

DISSEMINATION

The endorsement document will be published on the CCO website. The Professional Consultation of the External Review is intended to facilitate the dissemination of the endorsement document to Ontario practitioners. CCO-PEBC guidelines are routinely included in several international guideline databases including the Canadian Partnership Against Cancer Database, the Canadian Medical Association Infobase, NICE Evidence Search, and the Guidelines International Network Library.

UPDATING THE ENDORSEMENT

The Lung Cancer DSG will review the endorsement on an annual basis to ensure that it remains relevant and appropriate for use in Ontario.

ACKNOWLEDGEMENTS

The Prophylactic Cranial Irradiation for SCLC GDG would like to thank the following individuals for their assistance in developing this report:

- Fulvia Baldassarre for completing the AGREE II assessment of the NICE guideline
- Sheila McNair, Duvaraga Sivajohanathan, and Xiaomei Yao for reviewing draft versions of this endorsement
- Sara Miller for copyediting

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Section 3: Internal and External Review

INTERNAL REVIEW

The endorsement was evaluated by the GDG Expert Panel and the PEBC RAP (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 20 members of the GDG Expert Panel, 17 members voted, for a total of 85% response in July 2019. Of those who voted, 17 approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 3-1.

Table 3-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. This guideline is supposed to be about PCI, yet the recommendation for extensive-stage SCLC mentions thoracic radiotherapy. Is this a guideline for consolidation thoracic radiation for extensive-stage SCLC as well? If so, it should be titled as such, and if not, then shouldn't this phrase be removed (and included with the guidelines for thoracic radiotherapy in SCLC)?	We added consolidative radiation to the title.
2. The recommendation for limited-stage SCLC PCI has a clear dose (25 Gy in 10 fractions), while the recommendations for PCI for extensive-stage SCLC does not have any mention of dose. (I realize different doses may be used – 20 Gy/5 fractions, 25 Gy/10 fractions etc.), but for consistency should doses be at least mentioned?	The Working Group believed that 25 Gy in 10 fractions is probably the standard dose given to patients with extensive-stage SCLC. Therefore, for consistency, we have added 25 Gy in 10 fractions to the recommendation for patients with extensive-stage SCLC.
3. The recommendation about PCI in limited-stage SCLC is different to prior recommendations and the patient selection in the meta-analysis. It says any patient not progressing rather than patients with complete response (how they were selected in the trials). Is there any concern about this?	We have retained NICE's original wording. The PEBC acknowledges with this endorsement that actual practice does not strictly adhere to PCI study eligibility requiring response.

RAP Review and Approval

Two RAP members reviewed this document in July 2019. The RAP approved the document on July 16, 2019.

EXTERNAL REVIEW

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the endorsement document. Ninety radiation and medical oncologists in Ontario taken from the PEBC database were contacted by email to inform them of the survey. Sixteen (18%) responses were received. Eight oncologists stated that they did not have interest in this area or were unavailable to review this endorsement document at the time. The results of the feedback survey from eight people are summarized in Table 3-2.

Table 3-2. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	0	2 (25)	6 (75)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	0	0	1 (12.5)	7 (87.5)
3. I would recommend this guideline for use in practice.	0	0	0	1 (12.5)	7 (87.5)
4. What are the barriers or enablers to the implementation of this guideline report?	• As stated in the report, there are several limitations arising from the design of the referenced studies. Further comparative effectiveness analysis research would be needed to make more firm recommendations. At the current time, the stated strength of the recommendations is appropriate. Naturally, there will be practice variability arising from this. • What is in the guideline already reflects what is commonly done in Ontario. Access to this type of radiotherapy is available at all 14 sites.				

CONCLUSION

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

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Appendix 1: Affiliations and Conflict of Interest Declarations

In accordance with the PEBC Conflict of Interest Policy, the Members of the Prophylactic cranial irradiation for SCLC GDG Working Group, Expert Panel, and Report Approval Panel were asked to disclose potential conflicts of interest.

Name and Affiliation	Declarations of interest
Working Group	
Susanna Cheng Medical Oncologist Lung Cancer Disease Site Group	Received $500 or more in a single year to act on an advisory board and consultant for Roche, AstraZeneca, and Merck
Peter Ellis Medical Oncologist Lung Cancer Disease Site Group	None declared
John Goffin Medical Oncologist Lung Cancer Disease Site Group	• Received honorariums from Amgen (2014), Boehringer Ingelheim (2015), Bristol-Myers Squibb (2015), and Merck (2018) • Received conference travel support from AstraZeneca (2017) • Received a speaking fee from Amgen (2018)
Alexander Louie Radiation Oncologist Odette Cancer Centre - Sunnybrook Health Sciences Centre, Toronto, ON	• Received $500 or more in a single year to act on the speaker's bureau for Varian Medical Systems Inc. and as a consultant for AstraZeneca and RefleXion • Was the lead reviewer for the ASTRO small cell lung cancer Clinical Practice Guideline that is forthcoming
Robert MacRae Radiation Oncologist Lung Cancer Disease Site Group	None declared
Mojgan Taremi (Lead) Radiation Oncologist Lung Cancer Disease Site Group	None declared
Yee Ung Radiation Oncologist Lung Cancer Disease Site Group	None declared
Emily Vella Health Research Methodologist Program in Evidence-Based Care	None declared
Lung Cancer Disease Site Group 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
Conrad Falkson Radiation Oncologist Lung Cancer Disease Site Group	None declared
Ronald Feld Medical Oncologist Lung Cancer Disease Site Group	None declared

Richard Gregg Medical Oncologist Lung Cancer Disease Site Group	Received $500 or more in a single year to act in a consulting capacity for Merck
Donald Jones Surgeon Lung Cancer Disease Site Group	None declared
Swati Kulkarni Medical Oncologist Lung Cancer Disease Site Group	None declared
Sara Kuruvilla Medical Oncologist Lung Cancer Disease Site Group	None declared
Natasha Leighl Medical Oncologist Lung Cancer Disease Site Group	None declared
Richard Malthaner Surgeon Lung Cancer Disease Site Group	None declared
Donna Maziak Surgeon Lung Cancer Disease Site Group	None declared
Andrew Pearce Radiation Oncologist Lung Cancer Disease Site Group	None declared
Kevin Ramchandar Radiation Oncologist Lung Cancer Disease Site Group	None declared
Andrew Robinson Medical Oncologist Lung Cancer Disease Site Group	None declared
Alexander Sun Radiation Oncologist Lung Cancer Disease Site Group	None declared
Anand Swaminath Radiation Oncologist Lung Cancer Disease Site Group	• Received $500 or more in a single year to act in a consulting capacity for Astra Zeneca • Received $500 or more in a single year from an educational grant from Accuray
Kazuhiro Yasufuku Surgeon Lung Cancer Disease Site Group	None declared
Edward Yu Radiation Oncologist Lung Cancer Disease Site Group	None declared
Robert Zeldin Surgeon Lung Cancer Disease Site Group	None declared
Report Approval Panel	
Melissa Brouwers Professor and Director School of Epidemiology and Public Health Faculty of Medicine, University of Ottawa	None declared

Jonathan Sussman Scientific Director, Program in Evidence-Based Care Chair, Department of Oncology Juravinski Cancer Centre, Hamilton	None declared

Appendix 2: Questions for recommendation endorsement for patients with extensive-stage small cell lung cancer

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND				RECOMMEND →		NICE Evidence/Considerations PCI vs. no PCI in patients with ES-SCLC	PEBC Working Group discussion
Desirable effects	1a. How substantial are the desirable anticipated effects?	☐ Trivial	☑ Small	☐ Don't know	☐ Varies	☐ Moderate	☐ Large	Slotman 2007 [8] is relevant to UK practice and Takahashi 2017 [9] is not. In Slotman 2007 [8], the data favoured PCI for mortality, which is the most important outcome for people living with SCLC. In Slotman 2007 [8], the difference in survival duration was approximately 5.5 weeks between the PCI group and the observation group. The committee agreed that this represents a meaningful benefit for a person living with SCLC, particularly as the person's life expectancy is months rather than years at diagnosis. In the PCI group, fewer people experienced cancer progression and symptomatic brain metastases compared to the observation only group. Takahashi 2017 [9] could not differentiate for mortality. The committee agreed that interpreting this to mean that PCI is an unnecessary intervention in the UK would be misleading. This is because participants in both arms were followed up with brain MRIs at 3, 6, 9, 12, 18, and 24 months; participants found to have asymptomatic metastases were treated with chemotherapy and radiotherapy. The committee considered this follow-up regimen for adoption in the UK. However, this study was not designed to investigate the clinical effectiveness of the follow-up: both arms had it, and different follow-up regimens were also outside of the scope of the review. In addition, it is very unlikely that the thoroughness of this follow-up could be provided in the UK: there are approximately 9 times more MRI scanners in Japan compared to the UK.	The Working Group members believed there would be a small improvement in survival, although this does not take into account the Takahashi 2007 [9] findings that did not find a survival benefit. The Working Group members agreed that the Japanese study was not as directly applicable to Ontario because they believed the access to MRI follow-up in Japan is greater than it is in Ontario.

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND				RECOMMEND →		NICE Evidence/Considerations PCI vs. no PCI in patients with ES-SCLC	PEBC Working Group discussion
Undesirable effects	1b. How substantial are the undesirable anticipated effects?	☐ Large	☐ Moderate	☑ Don't know	☐ Varies	☐ Small	☐ Trivial	It is not possible to assess the effects of PCI on adverse events from Slotman 2007 [8] because the adverse event data were only collected from the PCI arm. The investigators wrote that some of the adverse events in the PCI arm were not from the PCI intervention but were from brain metastases that developed. Takahashi 2017 [9] may shed some light on the possible harms of PCI: Takahashi 2017 [9] found an increased risk ratio for all grades of nausea, vomiting, anorexia, malaise or dermatitis at 3 months for PCI compared to observation. However, these were mostly grade 1 and grade 2 adverse events. Consequently, the committee agreed that these adverse events would require no or minimal medical intervention. The data could not differentiate for any adverse event grade 3 or above. However, the study was not powered with a view to doing this.	The Working Group members agreed that the undesirable effects were not well documented. They believed the risk of grade 3 or above toxicities might be small, but this has not been measured adequately in the trials.

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND			RECOMMEND →	NICE Evidence/Considerations PCI vs. no PCI in patients with ES-SCLC	PEBC Working Group discussion
Certainty of evidence	1c. What is the overall certainty of this evidence?	☐ Very low	☐ Low	☐ No included studies	☑ Moderate ☐ High	The committee agreed that Takahashi 2017 [9] was not applicable for the UK. This is because the investigators followed up participants at 3, 6, 9, 12, 18, and 24 months using MRI brain imaging. Participants with asymptomatic brain metastases detected by MRI received radiotherapy and subsequent chemotherapy. Such MRI follow-up is not UK practice. This is because in Japan they have approximately 52 MRI scanners per million population compared to approximately 6 per million in the UK. Therefore, such rigorous follow-up and treatment would not be possible in the UK. Takahashi 2017 [9] had considerably more men compared to women (86% men) compared to Slotman 2007 [8] (55% men). The proportion of genders in Slotman 2007 [8] more closely reflects the UK. The committee acknowledged that Slotman 2007 [8] was a multi-centre study and there was heterogeneity of methods between centres. However, the committee agreed that Slotman 2007 [8] had greater applicability to people living in the UK compared to Takahashi 2017 [9] as the vast majority of the study centres were in Europe, almost one-half being in the UK.	The Working Group members agreed there was moderate certainty in the evidence, especially for the primary outcome of survival.
Values	1d. Is there important uncertainty about or variability in how much the target population value the outcomes?	☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☑ No important uncertainty or variability	The committee agreed that the outcome that matters most is mortality. This is because in the opinion of the committee, the life expectancy for someone with SCLC is generally so short that just a few months of extra life makes a difference. Secondary outcomes included adverse events, quality of life, number of people who dropped out, progression-free survival, and time to brain metastasis. With regards to adverse events, the committee agreed that adverse events grade 3 or above were more important than counting all adverse events (the total of grades 1 to 5). This is because according to the Common Terminology Criteria for Adverse Events, adverse events of grade 3 or above are generally considered to be 'medically significant'. For example, hospitalization is indicated.	The Working Group members agreed with the NICE committee that most patients would consider survival to be the most important outcome.

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND					RECOMMEND →		NICE Evidence/Considerations PCI vs. no PCI in patients with ES-SCLC	PEBC Working Group discussion
Balance of effects	2. What is the balance between the benefits and the harms?	☐ Benefits < Harms	☐ Benefits ≤ Harms	☐ Don't know	☐ Benefits = Harms	☐ Varies	☑ Benefits ≥ Harms	☐ Benefits > Harms	The committee agreed that "consider" is the appropriate strength for the recommendation on PCI. This is because there is a mix of evidence in the two main trials. The evidence showed that PCI improves survival versus best supportive care. PCI can adversely affect quality of life, and the survival benefits are limited. There is also some evidence from a study outside the UK that routine MRI follow-up may be more cost effective. The committee made a recommendation for further research, to provide evidence more relevant to the UK and to see if MRI could identify people who need whole-brain radiotherapy and so reduce the number of people having unnecessary treatment. The committee agreed that they could not make more specific recommendations about when PCI should be considered based on the data available. This is because the exclusion criteria in Slotman 2007 [8] discriminate on the basis of age, which is inappropriate.	The Working Group members agreed that the benefits are equal to or probably outweigh the harms, but they had some uncertainty about this. Therefore, they agreed with the NICE committee that the recommendation should not be strong and using the word "consider" was appropriate.
Equity	3. What would be the impact on health equity?	☐ Reduced	☑ Probably reduced	☐ Don't know	☐ Probably no impact	☐ Varies	☐ Probably increased	☐ Increased	The committee gave special consideration to people living in deprived areas regarding access to this treatment. This is because socioeconomic status was identified as a potential equality issue in the equity impact assessment. However, the committee agreed that no additional recommendations were necessary. The committee did not have any reason to believe that the interventions work better or worse in different groups.	The Working Group members believed there would be an issue with the access to imaging across Ontario. Some patients would have better access to receive MRI surveillance. They didn't think access to treatment would be as much of an issue in Ontario.

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND				RECOMMEND →		NICE Evidence/Considerations PCI vs. no PCI in patients with ES-SCLC	PEBC Working Group discussion
Acceptability	3. Is the option acceptable to key stakeholders (e.g., patients and providers)?	☐ No	☐ Probably no	☐ Don't know	☐ Varies	☐ Probably yes	☑ Yes	It is likely that the recommendation reflects current clinical practice.	The Working Group members agreed that the NICE recommendation reflects current clinical practice and would be acceptable to patients and providers.
Feasibility	5. Is the option feasible to implement?	☐ No	☐ Probably no	☐ Don't know	☐ Varies	☐ Probably yes	☑ Yes	The committee noted that the PCI and thoracic radiotherapy are both currently considered on a patient-by-patient basis on the balance of benefits and harms and they therefore thought that their recommendations would lead to a negligible difference in resource use.	The Working Group agreed that PCI is feasible to implement in Ontario.
Generalizable	4. Is this evidence generalizable to the entire target population?	☐ No	☐ Probably no	☐ Don't know	☑ Probably yes	☐ Yes		In the clinical experience of the committee, PCI is beneficial in a small and selected subgroup of people. The committee pointed out that both Slotman 2007 [8] and Takahashi 2017 [9] had exclusion criteria. These exclusion criteria included low performance status, life expectancy less than 3 months, age over 75 years, mental disorders, not being able to give informed consent, and not being able to comply with the protocol and follow-up schedule. While not explicitly listed in the recommendation, these exclusion criteria reflect current UK practice when considering PCI. They felt that clinicians would be able to select which people were likely to benefit from PCI on a case-by-case basis. The committee agreed that their recommendation should restrict consideration of PCI to people whose disease has responded to first-line treatment in order to reflect the inclusion criteria in Slotman 2007 [8] and Takahashi 2017 [9].	The Working Group members agreed that you cannot identify from the RCTs which subgroups of people would clearly benefit from PCI more than other patients. They agreed with the NICE committee that clinicians would be able to select which people were likely to benefit from PCI on a case-by-case basis and that the recommendation should restrict consideration of PCI to people whose disease has responded to first-line treatment.

Abbreviations: CAD, Canadian dollars; ES-SCLC, extensive-stage small cell lung cancer; MRI, magnetic resonance imaging; NICE, National Institute for Health and Care Excellence; PCI, prophylactic cranial irradiation; PEBC, Program in Evidence-Based Care; RCT, randomized controlled trial; UK, United Kingdom

Appendix 3: Questions for recommendation endorsement for patients with limited-stage small cell lung cancer

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND				RECOMMEND →		NICE Evidence/Considerations PCI vs. no PCI in patients with LS-SCLC	PEBC Working Group discussion
Desirable effects	1a. How substantial are the desirable anticipated effects?	☐ Trivial	☐ Small	☐ Don't know	☐ Varies	☑ Moderate	☐ Large	Cao et al. 2005 [10] in an RCT of low-moderate quality found that although the incidence of brain metastases were reduced in their sample of patients with LS-SCLC who received PCI relative to controls, there was no difference between the groups in terms of survival. Le Péchoux et al. 2009 [11] compared standard-dose PCI to high-dose PCI in patients with LS-SCLC in an RCT of moderate-high quality and found that the incidence of brain metastasis and extracranial metastasis as well as 2-year overall and disease-free survival did not differ significantly between the treatment groups. However, the 2-year incidence of relapse was lower and the incidence of brain metastasis as an isolated site of first failure was higher in the standard-dose PCI treatment group than in the high-dose treatment group.	The Working Group members believed the survival benefit in this population would be moderate.
Undesirable effects	1b. How substantial are the undesirable anticipated effects?	☐ Large	☐ Moderate	☐ Don't know	☐ Varies	☑ Small	☐ Trivial	Le Péchoux et al. 2009 [11] compared standard-dose PCI to high-dose PCI in patients with LS-SCLC in an RCT of moderate-high quality. The groups did not appear to differ in treatment-related adverse/toxic events.	The Working Group members believed the undesirable effects would be small for this population.
Certainty of evidence	1c. What is the overall certainty of this evidence?	☐ Very low	☐ Low	☐ No included studies	☑ Moderate	☐ High		Not reported	The Working Group members had moderate certainty in the evidence.

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND							RECOMMEND →	NICE Evidence/Considerations PCI vs. no PCI in patients with LS-SCLC	PEBC Working Group discussion
Values	1d. Is there important uncertainty about or variability in how much the target population value the outcomes?	☐ Important uncertainty or variability		☐ Possibly important uncertainty or variability		☐ Probably no important uncertainty or variability		☑ No important uncertainty or variability		Not reported	The Working Group members agreed that most patients would consider survival to be the most important outcome.
Balance of effects	2. What is the balance between the benefits and the harms?	☐ Benefits < Harms	☐ Benefits ≤ Harms	☐ Don't know	☐ Benefits = Harms	☐ Varies	☑ Benefits ≥ Harms	☐ Benefits > Harms		Not reported	The Working Group members judged that the benefits are at least equal to or outweigh the harms.
Equity	3. What would be the impact on health equity?	☐ Reduced	☑ Probably reduced	☐ Don't know	☐ Probably no impact	☐ Varies	☐ Probably increased	☐ Increased		Not reported	The Working Group members thought there would be an issue with the access to imaging across Ontario. Some patients would have better access to receive MRI surveillance.
Acceptability	3. Is the option acceptable to key stakeholders (e.g., patients and providers)?	☐ No	☐ Probably no	☐ Don't know	☐ Varies	☐ Probably yes	☑ Yes			Not reported	The Working Group members believed that the NICE recommendation reflects current clinical practice and would be acceptable to patients and providers.
Feasibility	5. Is the option feasible to implement?	☐ No	☐ Probably no	☐ Don't know	☐ Varies	☐ Probably yes	☑ Yes			The GDG considered this topic a low priority for health economic analysis.	The Working Group members agreed that the feasibility of PCI for this population has been well established.

Criteria	Questions	← NOT RECOMMEND JUDGEMENTS RECOMMEND →					NICE Evidence/Considerations PCI vs. no PCI in patients with LS-SCLC	PEBC Working Group discussion
Generalizable	4. Is this evidence generalizable to the entire target population?	☐ No	☐ Probably no	☐ Don't know	☐ Probably yes	☑ Yes	Not reported	The trials for PCI included patients with complete response, but current clinical practice extends giving PCI to patients with partial response.

Abbreviations: GDG, guideline development group; LS-SCLC, limited-stage small cell lung cancer; MRI, magnetic resonance imaging; NICE, National Institute for Health and Care Excellence; PCI, prophylactic cranial irradiation; PEBC, Program in Evidence-Based Care; RCT, randomized controlled trial