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Guideline Endorsement 7-24

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

An Endorsement of the ASTRO/ESTRO 2023 Guideline for the Treatment of Patients with Oligometastatic or Oligoprogressive Non-Small Cell Lung Cancer

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This document describes the OH (CCO)-Lung Cancer Disease Site Group endorsement of the 2023 Treatment of Oligometastatic Non-Small Cell Lung Cancer: An ASTRO/ESTRO Clinical Practice Guideline. The original publication is available at https://www.astro.org/patient-care-and-research/clinical-practice-statements/clinical-practice-guidelines/oligometastatic-nsclc.

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For information about the PEBC and the most current version of all reports, please visit the OH (CCO) website at https://www.cancercareontario.ca/en/guidelines-advice or contact the PEBC office at: Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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Table of Contents

An Endorsement of the ASTRO/ESTRO 2023 Guideline for the Treatment of Patients with Oligometastatic or Oligoprogressive Non-Small Cell Lung Cancer

Section 1: Guideline Endorsement

ENDORSEMENT

GUIDELINE OBJECTIVES

The objective of this guideline is to determine the most effective therapies for patients with oligometastatic or oligoprogressive non-small cell lung cancer (NSCLC).

TARGET POPULATION

The target population includes adult patients with oligometastatic or oligoprogressive NSCLC. Several terms were used throughout the American Society for Radiation Oncology/European Society for Radiotherapy & Oncology (ASTRO/ESTRO) 2023 guideline [1] when referencing the oligometastatic disease state: oligorecurrent, oligoprogressive, and oligopersistent. Oligorecurrence refers to the general growth of limited numbers (typically ≤5) of metastatic deposits in patients off systemic therapy. Patients are considered as having oligoprogressive disease if current imaging establishes progression of disease in a limited number (typically ≤5) of existing and/or new sites. For patients with oligometastases receiving active systemic treatment, patients are considered as having oligopersistent disease if current imaging establishes stable disease or partial response of the existing limited disease to therapy. Furthermore, synchronous oligometastatic disease refers to the occurrence of oligometastases de novo at the time of initial diagnosis of NSCLC. Although the presence of a disease-free interval differentiates metachronous from synchronous oligometastatic disease, there is no formal definition of the length of disease-free interval required, with intervals of both three and six months having been used in clinical trials. (ENDORSED WITH MODIFICATION – see below)

INTENDED USERS

The intended users include oncologists and thoracic surgeons involved in the treatment of patients with oligometastatic or oligoprogressive NSCLC.

RECOMMENDATIONS

The Oligometastatic NSCLC Guideline Development Group (GDG) of Ontario Health (Cancer Care Ontario) (OH [CCO]) endorses the recommendations of the ASTRO/ESTRO 2023 guideline, as modified by the endorsement process described in this document [1]. They are reprinted with the permission of ASTRO. A modified version of ASTRO's recommendation grading classification system can be found in Section 2 Table 2.1 [1]. Please see Section 2 Table 2.2 for the original ASTRO/ESTRO 2023 recommendations and any modifications to the recommendations or their scoring system made as well as the reasons for the modifications. Local therapy includes surgical excision, minimally invasive ablation (e.g., radiofrequency ablation), radiation therapy (including conventionally fractionated, stereotactic ablative radiation therapy, stereotactic body radiation therapy (SBRT), and stereotactic radiosurgery), and combinations. Systemic therapy includes targeted therapy, immunotherapy, chemotherapy, and combinations.

Recommendations about patient/disease characteristics for definitive systemic and local therapies (please also see Algorithm 1 on page 5)

1.1. For patients with oligometastatic NSCLC, treatment decisions should be made using a patient-centred multidisciplinary team approach. (strong recommendation, expert opinion) (ENDORSED)

1.2. For patients with oligometastatic NSCLC, if integration of definitive local therapy is indicated, it should only be in the context when it is technically feasible and clinically safe for all disease sites. (strong recommendation, low quality of evidence) (ENDORSED WITH MODIFICATION)

1.3. For patients with oligometastatic NSCLC, a discussion of definitive local therapy as a component of multimodality treatment approach may be considered irrespective of presence of activating driver mutations. (conditional recommendation, low quality of evidence) (ENDORSED WITH MODIFICATION)

1.4. For oligometastatic NSCLC, if definitive local therapy is being considered, it is recommended only for patients having up to five distant metastases, diagnosed with appropriate imaging. (strong recommendation, low quality of evidence) Implementation remark: Despite some prospective trials including patients with up to five extracranial metastases, most patients enrolled had one to two treated oligometastatic lesions, which should be factored into decision-making. (ENDORSED WITH MODIFICATION)

1.5. For patients with synchronous oligometastatic NSCLC, definitive local therapy to all cancer sites in addition to standard-of-care systemic therapy is conditionally recommended. (conditional recommendation, low quality of evidence) (ENDORSED WITH MODIFICATION)

1.6. For patients with metachronous oligorecurrent NSCLC, definitive local therapy to all oligorecurrent cancer sites in addition to standard-of-care systemic therapy is conditionally recommended. (conditional recommendation, low quality of evidence) (ENDORSED)

1.7. For patients with induced oligopersistent NSCLC, definitive local therapy to all persistent cancer sites in addition to continuing standard-of-care systemic therapy (if well tolerated) is conditionally recommended. (conditional recommendation, low quality of evidence) (ENDORSED WITH MODIFICATION)

1.8. For patients with induced oligoprogressive NSCLC receiving systemic therapy, definitive local therapy to all progressive cancer sites is conditionally recommended while continuing the current line of systemic therapy. (conditional recommendation, expert opinion) (ENDORSED)

Recommendations about local treatment modality selection criteria for oligometastatic NSCLC 2 (please also see Algorithm 2 on page 6)

2.1. For patients with oligometastatic NSCLC, a patient-centred multidisciplinary discussion of the most appropriate local treatment strategy of radiation therapy (RT) and/or surgery either alone or in combination are recommended. (strong recommendation, low quality of evidence) (ENDORSED WITH MODIFICATION)

2.2. For patients with oligometastatic NSCLC, RT and/or surgery are recommended as definitive local treatment modalities for the locoregional primary and all oligometastases. (conditional recommendation, low quality of evidence)
Implementation remark: Surgical approach and RT approach will depend on patient factors. (ENDORSED WITH MODIFICATION)

2.3. For patients with oligometastatic NSCLC, highly conformal RT approaches and minimally invasive techniques for surgery are recommended to minimize morbidity. (strong recommendation, low quality of evidence) (ENDORSED WITH MODIFICATION)

2.4. For patients with oligometastatic NSCLC, deciding between RT and surgery as the definitive local treatment modality should: (strong recommendation, expert opinion)
- Favour RT when multiple organ systems are being treated
- Favour RT when the clinical prioritization is to minimize breaks from systemic therapy (ENDORSED WITH MODIFICATION)

Recommendations about the sequencing and timing of treatment therapies for oligometastatic NSCLC

3.1. For patients with synchronous oligometastatic NSCLC, three or more months of systemic therapy is recommended prior to definitive local therapy. (conditional recommendation, low quality of evidence) (ENDORSED WITH MODIFICATION)

3.2. For patients with oligometastatic NSCLC, up-front definitive local treatment for *symptomatic* lesions should be prioritized. (strong recommendation, low quality of evidence)
Implementation remark: Symptomatic disease sites (e.g., bone metastases) may also be treated with up-front definitive local therapy. (ENDORSED WITH MODIFICATION)

3.3. For patients with synchronous oligometastatic NSCLC, the temporary pause of systemic therapy during definitive local therapy versus concomitant treatment should be discussed using a multidisciplinary team approach. (strong recommendation, expert opinion) (ENDORSED)

3.4. For patients with synchronous oligometastatic NSCLC, continuation on first-line systemic therapy is conditionally recommended after completion of definitive local therapy. (conditional recommendation, low quality of evidence) (ENDORSED WITH MODIFICATION)

Recommendations about RT dose-fractionation regimens, planning, and delivery techniques for oligometastatic NSCLC

4.1. For patients with oligometastatic NSCLC, appropriate staging with fluorodeoxyglucose F-18 positron emission tomography (PET)-computed tomography (CT), brain magnetic resonance imaging (MRI), and MRI in cases of suspect or proven spine or liver metastases are recommended. (strong recommendation, high quality of evidence)
Implementation remark: PET-CT scans are not yet approved outside of possibly the PET Access program in Ontario for patients with metastatic NSCLC, but they are recommended for patients with stage IV oligometastatic disease who are being considered for definitive therapy. (ENDORSED WITH MODIFICATION)

4.2. For patients with oligometastatic NSCLC, individual assessment of respiratory motion for targets in the lungs and upper abdomen using four-dimensional CT, fluoroscopy, or MR-cine with appropriate motion compensation is recommended. (strong recommendation, high quality of evidence) (ENDORSED)

4.3. For patients with oligometastatic NSCLC, highly conformal RT using inverse dose planning, appropriate motion management strategies and image-guided RT delivery are recommended. (strong recommendation, low quality of evidence) (ENDORSED WITH MODIFICATION)

4.4. For patients with oligometastatic NSCLC, a risk-adapted approach using stereotactic RT (preferred), hypofractionated RT, or alternatively definitive chemoradiation based on the location and burden of disease is recommended. (strong recommendation, high quality of evidence) (ENDORSED)

4.5. For patients with oligometastatic NSCLC, definitive local RT should use doses and fractionations which achieve durable local control. (strong recommendation, high quality of evidence)

Implementation remarks:

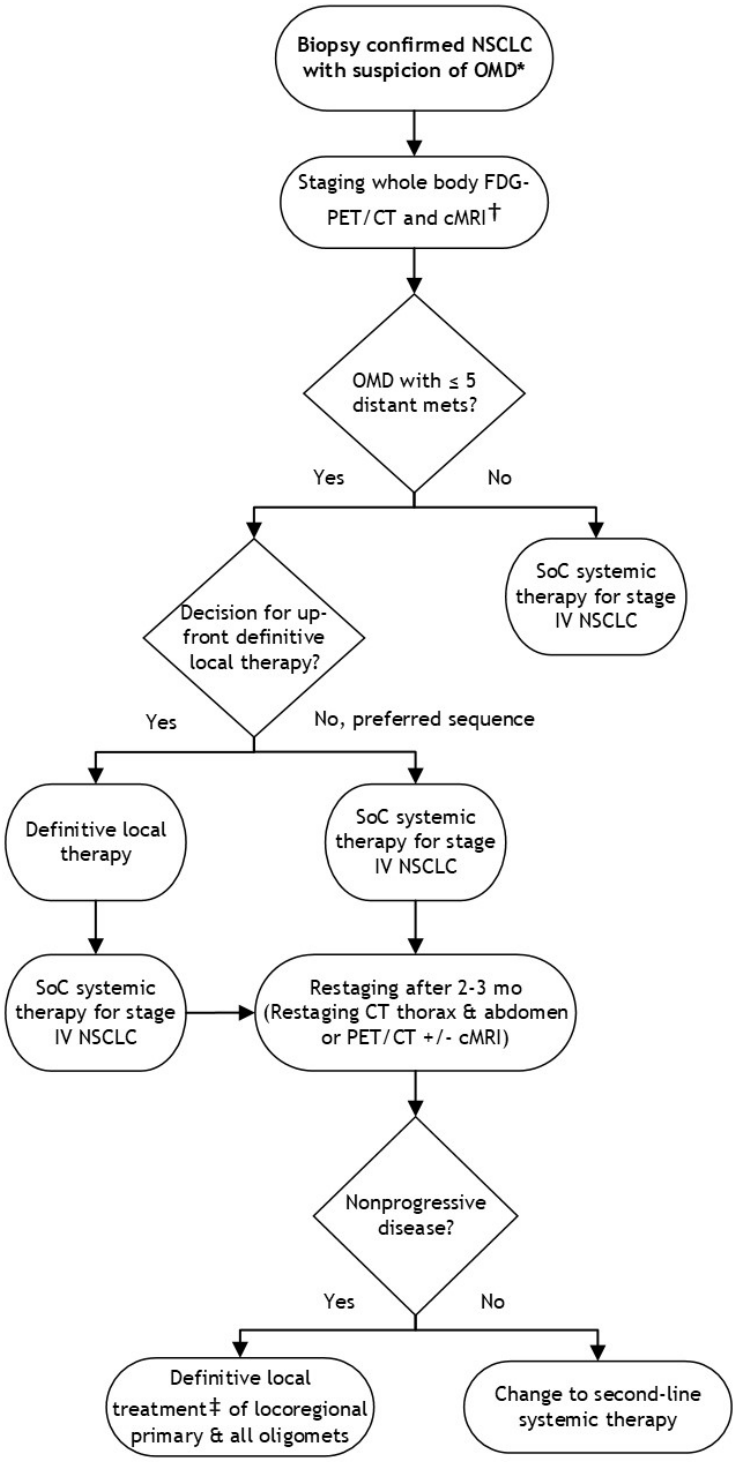
- Durable local control defined as minimum 85% local control at two years.
- Higher biologically effective dose (BED^{10}) (typically >75 Gy) with SBRT alone is associated with optimal local control.
- Lower BED^{10} (50-75 Gy range) is associated with acceptable local control, typically in the setting of combination systemic therapy and SBRT. (ENDORSED)

Recommendations about indications for additional local therapy on disease progression (after definitive local therapy approach)

5.1. In patients previously treated with definitive local therapy for oligometastatic NSCLC who subsequently develop repeat oligoprogression or recurrence, local therapy is conditionally recommended and should be discussed using a multidisciplinary team approach. (conditional recommendation, low quality of evidence) (ENDORSED WITH MODIFICATION)

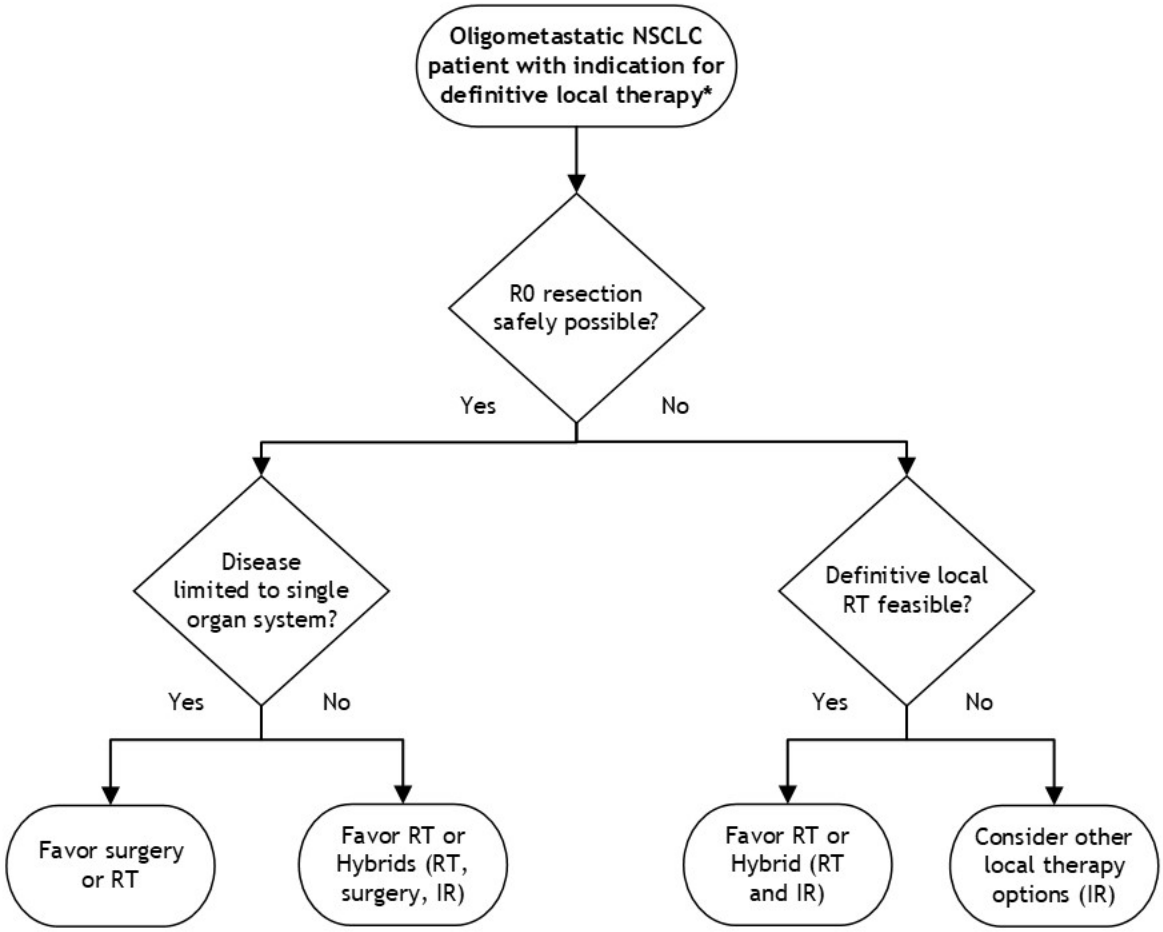
5.2. In patients previously treated with definitive local therapy for oligometastatic NSCLC who subsequently develop repeat oligoprogression or recurrence at sites previously treated with local therapy, re-treatment is conditionally recommended if systemic treatment options are limited, and local therapy can be delivered with toxicity acceptable to the multidisciplinary team and patient. (conditional recommendation, expert opinion) (ENDORSED)

Algorithm 1. Diagnosis and sequencing of local and systemic treatment for synchronous oligometastatic NSCLC. (ENDORSED WITH MODIFICATION)



Abbreviations: cMRI = cranial magnetic resonance imaging; CT = computed tomography; FDG PET = fluorodeoxyglucose F-18 positron emission tomography; mets = metastases; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; OMD = oligometastatic disease; SoC = standard of care. *Preferably biopsied OMD as well. †Additional imaging modalities that are reasonable to use in establishing an OMD state include contrast-enhanced chest and upper abdomen CT scan, MRI, bone scan, or PET-MRI. ‡Completion of definitive local treatment of all cancer sites if multimodality treatment was started with local treatment. cMRI†

Algorithm 2. Multidisciplinary decision-making process of definitive RT and surgery for oligometastatic NSCLC. (ENDORSED WITH MODIFICATION)



Abbreviations: IR = interventional radiology procedures; NSCLC = non-small cell lung cancer; RT = radiation therapy, which could include stereotactic body radiation therapy, intensity-modulated radiation therapy or radical RT. *Surgical approach and RT approach will depend on patient factors. Adequate tissue sampling should be performed prior to determining resectability.

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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, Ontario Health (Cancer Care Ontario). 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 OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

BACKGROUND FOR GUIDELINE

This was an important question for the clinical community and was brought forward by the OH (CCO) Thoracic Cancer Advisory Committee as well as the OH (CCO) Lung Cancer Disease Site Group. This was expected to be an increasingly common clinical problem, and so the production of clinical guidance on this topic was seen as a priority. There was no guidance available on the management of these patients and as such, the need was pressing to promote appropriate use of local therapies.

GUIDELINE ENDORSEMENT DEVELOPERS

This endorsement project was developed by the Oligometastatic NSCLC GDG (Appendix 1), which was convened at the request of the OH (CCO) Disease Pathway Management. The project was led by a small Working Group of the Oligometastatic NSCLC GDG, which was responsible for reviewing the evidence base and recommendations in the ASTRO/ESTRO 2023 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, surgical oncology, medical oncology, and health research methodology. Other members of the Oligometastatic NSCLC 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 OH (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 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.

DESCRIPTION OF ENDORSED GUIDELINE

The Working Group was aware of the ASTRO/ESTRO guideline published in 2023 on this topic [1]. The Working Group selected this guideline because the AGREE II rigour of development domain, which assesses the methodological quality of the guideline, was above 50% (rigour of development domain score: 86%) [3]. The ASTRO/ESTRO guideline was based on a systematic review that included five research questions:

1. What are the optimal patient/disease characteristics to select patients with oligometastatic NSCLC for definitive treatment combining systemic and local therapies?
2. What are the selection criteria for choice of local treatment modality in the management of patients with oligometastatic NSCLC?
3. What are the appropriate sequencing and timing of systemic therapy and definitive local therapies for patients with oligometastatic NSCLC?
4. What are the optimal dose-fractionation regimens, planning, and delivery technique of RT for patients with oligometastatic NSCLC?
5. After a definitive local therapy approach for oligometastatic NSCLC, what are the indications for additional local therapy upon disease progression?

Recommendations were developed by American and European experts in the fields of radiation, medical and surgical oncology, and a pulmonologist, a medical physicist, and a patient representative. A significant number of recommendations were based on low-quality evidence and/or expert opinion. The ASTRO recommendation grading classification system, which has been modified by the Working Group so that only randomized controlled trials can lead to high or moderate quality evidence, can be found in Table 2.1. The guideline was also endorsed by the Canadian Association of Radiation Oncology and the Royal Australian and New Zealand College of Radiologists.

ENDORSEMENT PROCESS

The Working Group reviewed each ASTRO/ESTRO 2023 [1] recommendation to determine whether it could be endorsed, endorsed with changes, or rejected. This determination was based on the agreement of the Working Group with the interpretation of the available evidence presented in the guideline, and whether the recommendation was applicable and acceptable to the Ontario context, whether it was feasible for implementation, and whether new evidence reported since the guideline was developed might change any of the recommendations. The Working Group held four meetings to assess each recommendation. The original ASTRO/ESTRO recommendations can be found in Table 2.2 as well as the reasons for any modifications to their recommendations.

Table 2.1 Modified ASTRO recommendation grading classification system [1]

ASTRO's recommendations are based on evaluation of multiple factors including the QoE, and panel consensus, which, among other considerations, inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.			
Strength of Recommendation	**Definition**	**Overall QoE Grade**	**Recommendation Wording**
Strong	•Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. •All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/Should"
Conditional	•Benefits are finely balanced with risks and burden or appreciable uncertainty exists about the magnitude of benefits and risks. •Most informed people would choose the recommended course of action, but a substantial number would not. •A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"
Overall QoE Grade	**Type/Quality of Study**	**Evidence Interpretation**	
High	•2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.	
Moderate	•1 well-conducted and highly generalizable RCT or a meta-analysis of such trials OR •2 or more RCTs with some weaknesses of procedure or generalizability	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.	
Low	•1 RCT with some weaknesses of procedure or generalizability OR •1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes OR •2 or more strong observational studies with consistent findings OR •2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.	

Expert Opinion*	•Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

* A lower quality of evidence, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

ASTRO's methodology allows for use of implementation remarks meant to convey clinically practical information that may enhance the interpreta- tion and application of the recommendation. Although each recommendation is graded according to recommendation strength and QoE, these grades should not be assumed to extend to the implementation remarks.

Table 2.2 Reasons for any modifications to the ASTRO/ESTRO guideline

Candidate Recommendation from ASTRO/ESTRO 2023 (strength of recommendation, quality of evidence)	Interpretation/ Justification Comments	Ontario Context Comments	New evidence likely to change recommendation?	Assessment? (Endorse /Endorse with Changes/Reject)
Definitions: Several terms are used throughout the guideline when referencing the oligometastatic disease state: oligorecurrent, oligoprogressive, and oligopersistent. Oligorecurrence refers to the general growth of limited numbers of metastatic deposits in patients off systemic therapy. For patients with oligometastases receiving active systemic treatment, they are considered as having oligoprogressive disease if current imaging establishes progression of disease in a limited number of existing and/or new sites and oligopersistent disease if current imaging establishes stable disease or partial response of the existing limited disease to therapy. Furthermore, synchronous oligometastatic disease refers to the occurrence of oligometastases de novo at the time of initial diagnosis of NSCLC. Although the presence of a disease-free interval differentiates metachronous from synchronous oligometastatic disease, there is no formal definition of the length of disease-free interval required, with intervals of both three and six months having been used in clinical trials.	None	Patients with oligoprogression do not always begin with oligometastases.	No	Changed to: Patients are considered as having oligoprogressive disease if current imaging establishes progression of disease in a limited number (typically ≤5) of existing and/or new sites.
ASTRO recommendation grading classification system	Not applicable	Not applicable	Not applicable	The Working Group believed only RCTs should lead to high or moderate quality evidence. Therefore, 2 or more strong observational studies with consistent findings was moved to low quality of evidence.
Patient/disease characteristics for definitive systemic and local therapies				

Candidate Recommendation from ASTRO/ESTRO 2023 (strength of recommendation, quality of evidence)	Interpretation/ Justification Comments	Ontario Context Comments	New evidence likely to change recommendation?	Assessment? (Endorse /Endorse with Changes/Reject)
1. For patients with oligometastatic NSCLC, treatment decisions should be made using a patient-centered multidisciplinary team approach. (strong, expert opinion)	None	None	No	1.1 Endorse
2. For patients with oligometastatic NSCLC, the integration of definitive local therapy is only recommended if technically feasible and clinically safe for all disease sites. (strong, moderate)	None	None	No	1.2 • Reworded for clarity: For patients with oligometastatic NSCLC, if integration of definitive local therapy is indicated, it should only be in the context when it is technically feasible and clinically safe for all disease sites. • Quality of evidence was changed from moderate to low because it was based on observational studies.
3. For patients with oligometastatic NSCLC, a discussion of definitive local therapy as a component of multimodality treatment approach is recommended irrespective of presence of activating driver mutations. (strong, moderate)	None	None	A new NRG-LU002 abstract [4] suggested limited benefits of local consolidative therapy when added to systemic therapy as maintenance in the management of oligometastatic NSCLC.	1.3 Endorse with changes: • For patients with oligometastatic NSCLC, a discussion of definitive local therapy as a component of multimodality treatment approach may be considered irrespective of presence of activating driver mutations. (conditional, low) • Quality of evidence was changed from moderate to low because it was based on observational studies.

Candidate Recommendation from ASTRO/ESTRO 2023 (strength of recommendation, quality of evidence)	Interpretation/ Justification Comments	Ontario Context Comments	New evidence likely to change recommendation?	Assessment? (Endorse /Endorse with Changes/Reject)
4. For oligometastatic NSCLC, definitive local therapy is recommended only for patients having up to 5 distant metastases, diagnosed with appropriate imaging. (strong, moderate) Implementation remark: Despite some prospective trials including patients with up to 5 extracranial metastases, most patients enrolled had 1-2 treated oligometastatic lesions, which should be factored into decision-making.	None	None	No	1.4 • Reworded for clarity: For oligometastatic NSCLC, if definitive local therapy is being considered, it is recommended only for patients having up to 5 distant metastases, diagnosed with appropriate imaging. • Quality of evidence was changed from moderate to low because it was based on observational studies.
5. For patients with synchronous oligometastatic NSCLC, definitive local therapy to all cancer sites in addition to standard of care systemic therapy is conditionally recommended. (conditional, moderate)	None	None	No	1.5 Quality of evidence was changed from moderate to low because it was based on observational studies.
6. For patients with metachronous oligorecurrent NSCLC, definitive local therapy to all oligorecurrent cancer sites in addition to standard of care systemic therapy is conditionally recommended. (conditional, low)	None	None	No	1.6 Endorse
7. For patients with induced oligopersistent NSCLC, definitive local therapy to all persistent cancer sites in addition to standard of care systemic therapy is conditionally recommended. (conditional, low)	None	None	No	1.7 Reworded for clarity: 1.7. For patients with induced oligopersistent NSCLC, definitive local therapy to all persistent cancer sites in addition to continuing standard-of-care systemic therapy (if well tolerated) is conditionally recommended.

Candidate Recommendation from ASTRO/ESTRO 2023 (strength of recommendation, quality of evidence)	Interpretation/ Justification Comments	Ontario Context Comments	New evidence likely to change recommendation?	Assessment? (Endorse /Endorse with Changes/Reject)
8. For patients with induced oligoprogressive NSCLC receiving systemic therapy, definitive local therapy to all progressive cancer sites is conditionally recommended while continuing the current line of systemic therapy. (conditional, expert opinion)	None	None	No	1.8 Endorse
Figure 1 algorithm	None	Oligometastatic disease should preferably be biopsied as well. PET/CT may be used for restaging in Ontario.	No	Endorse with changes - Added *Preferably biopsied oligometastatic disease as well. Restaging after 2-3 mo (Restaging CT thorax & abdomen or PET/CT +/- cMRI)
Local treatment modality selection criteria for oligometastatic NSCLC				
1. For patients with oligometastatic NSCLC, a patient-centered multidisciplinary discussion of the most appropriate local treatment strategy of RT and/or surgery either alone or in combination are recommended. (strong, moderate)	None	None	No	2.1 Quality of evidence was changed from moderate to low because it was based on observational studies.

Candidate Recommendation from ASTRO/ESTRO 2023 (strength of recommendation, quality of evidence)	Interpretation/ Justification Comments	Ontario Context Comments	New evidence likely to change recommendation?	Assessment? (Endorse /Endorse with Changes/Reject)
2. For patients with oligometastatic NSCLC, RT and/or surgery are recommended as definitive local treatment modalities for the locoregional primary and all oligometastases. (strong, moderate - The quality of evidence for RT and surgery as definitive local therapy differs, with implications for multidisciplinary decision-making as described in the narrative text.)	None	Surgical approach and RT approach will depend on patient factors.	No	2.2 Endorse with changes – • Remove - The quality of evidence for RT and surgery as definitive local therapy differs, with implications for multidisciplinary decision-making as described in the narrative text. • Add - Implementation remark: Surgical approach and RT approach will depend on patient factors. • Quality of evidence was changed from moderate to low because it was based on observational studies. • The strength of the recommendation was changed from strong to conditional because the evidence was considered low.
3. For patients with oligometastatic NSCLC, highly conformal RT approaches and minimally invasive techniques for surgery are recommended to minimize morbidity. (strong, moderate)	None	None	No	2.3 Quality of evidence was changed from moderate to low because it was based on observational studies.

Candidate Recommendation from ASTRO/ESTRO 2023 (strength of recommendation, quality of evidence)	Interpretation/ Justification Comments	Ontario Context Comments	New evidence likely to change recommendation?	Assessment? (Endorse /Endorse with Changes/Reject)
4. For patients with oligometastatic NSCLC, deciding between RT and surgery as the definitive local treatment modality should: (strong, expert opinion) • Favor RT when multiple organ systems are being treated • Favor RT when the clinical prioritization is to minimize breaks from systemic therapy • Favor surgery when large tissue sampling is needed for molecular testing, to guide systemic therapy.	None	Molecular testing does not always require large tissue sampling. There may be cases when surgical tissue sampling is performed but RT is still favoured.	No	2.4 Endorse with changes – Remove - Favour surgery when large tissue sampling is needed for molecular testing, to guide systemic therapy
Figure 2 algorithm	None	• Tissue sampling is done prior to determining resectability. • Feasibility of minimally invasive surgery is not a prerequisite to favour RT. Patients can also receive an open approach. • Hydrid options are also considered. • Breaking from systemic therapy is not the only consideration to favour surgery vs. RT.	No	Endorse with changes – • Remove 'Minimally invasive surgery feasible?' • Add Hybrid options in two places in the figure. • Remove 'tissue sampling needed?' and add 'Adequate tissue sampling should be performed prior to determining resectability?' to the figure caption. • Add to figure caption that RT could include SBRT, IMRT or radical RT • Remove "Patient can break from systemic therapy for surgical recovery?"

Candidate Recommendation from ASTRO/ESTRO 2023 (strength of recommendation, quality of evidence)	Interpretation/ Justification Comments	Ontario Context Comments	New evidence likely to change recommendation?	Assessment? (Endorse /Endorse with Changes/Reject)
Sequencing and timing of treatment therapies for oligometastatic NSCLC				
1. For patients with synchronous oligometastatic NSCLC, ≥3 months of systemic therapy is recommended prior to definitive local therapy. (strong, moderate)	None	None	No	3.1 • Quality of evidence was changed from moderate to low because it was based on observational studies. • The strength of the recommendation was changed from strong to conditional because the evidence was considered low.

Candidate Recommendation from ASTRO/ESTRO 2023 (strength of recommendation, quality of evidence)	Interpretation/ Justification Comments	Ontario Context Comments	New evidence likely to change recommendation?	Assessment? (Endorse /Endorse with Changes/Reject)
2. For patients with oligometastatic NSCLC, up-front definitive local treatment for *symptomatic* lesions should be prioritized. (strong, low) Implementation remark: Symptomatic disease sites (e.g., brain metastases) are treated with up-front definitive local therapy.	None	• Asymptomatic patients with brain metastases would also be treated with up-front definite local therapy. Another example was chosen where up-front definitive local therapy would be preferred mainly for symptomatic patients. • There are cases where systemic therapy may be highly effective and provide rapid symptomatic relief.	No	3.2 Endorse with changes - • Change example to bone metastases • Symptomatic disease sites (e.g., brain metastases) may also be treated with up-front definitive local therapy.
3. For patients with synchronous oligometastatic NSCLC, the temporary pause of systemic therapy during definitive local therapy versus concomitant treatment should be discussed using a multidisciplinary team approach. (strong, expert opinion)	None	None	No	3.3 Endorse

Candidate Recommendation from ASTRO/ESTRO 2023 (strength of recommendation, quality of evidence)	Interpretation/ Justification Comments	Ontario Context Comments	New evidence likely to change recommendation?	Assessment? (Endorse /Endorse with Changes/Reject)
4. For patients with synchronous oligometastatic NSCLC, maintenance systemic therapy is conditionally recommended after completion of definitive local therapy. (conditional, low)	None	None	No	3.4 Reworded for clarity: For patients with synchronous oligometastatic NSCLC, continuation on first-line systemic therapy is conditionally recommended after completion of definitive local therapy.
RT dose-fractionation regimens, planning, and delivery techniques for oligometastatic NSCLC				

Candidate Recommendation from ASTRO/ESTRO 2023 (strength of recommendation, quality of evidence)	Interpretation/ Justification Comments	Ontario Context Comments	New evidence likely to change recommendation?	Assessment? (Endorse /Endorse with Changes/Reject)
1. For patients with oligometastatic NSCLC, appropriate staging with FDG PET, cranial MRI, and MRI in cases of suspect or proven spine or liver metastases are recommended. (strong, high)	None	• Cranial MRI is typically referred to as brain MRI. • FDG PET-CT is typically used in Ontario. • PET-CT scans are not approved outside of possibly the PET Access program in Ontario for patients with metastatic NSCLC, but they are recommended for patients with stage IV oligometastatic disease who are being considered for definitive therapy.	No	4.1 Endorse with changes - • Change cranial MRI to brain MRI • Change FDG PET to FDG PET-CT • Add implementation remark: PET-CT scans are not yet approved outside of possibly the PET Access program in Ontario for patients with metastatic NSCLC, but they are recommended for patients with stage IV oligometastatic disease who are being considered for definitive therapy.
2. For patients with oligometastatic NSCLC, individual assessment of respiratory motion for targets in the lungs and upper abdomen using 4-D CT, fluoroscopy, or MR-cine with appropriate motion compensation is recommended. (strong, high)	None	None	No	4.2 Endorse

Candidate Recommendation from ASTRO/ESTRO 2023 (strength of recommendation, quality of evidence)	Interpretation/ Justification Comments	Ontario Context Comments	New evidence likely to change recommendation?	Assessment? (Endorse /Endorse with Changes/Reject)
3. For patients with oligometastatic NSCLC, highly conformal RT using inverse dose planning, appropriate motion management strategies and image-guided RT delivery are recommended. (strong, moderate)	None	None	No	4.3 Quality of evidence was changed from moderate to low because it was based on observational studies.
4. For patients with oligometastatic NSCLC, a risk adapted approach using stereotactic RT (preferred), hypofractionated RT, or alternatively definitive chemoradiation based on the location and burden of disease is recommended. (strong, high)	None	None	No	4.4 Endorse
5. For patients with oligometastatic NSCLC, definitive local RT should use doses and fractionations which achieve durable local control. (strong, high) Implementation remarks: • Durable local control defined as minimum 85% local control at 2 years. • Higher BED[10] (typically >75 Gy) with SBRT alone is associated with optimal local control. • Lower BED[10] (50-75 Gy range) is associated with acceptable local control, typically in the setting of combination systemic therapy and SBRT.	None	None	No	4.5 Endorse
Indications for additional local therapy on disease progression (after definitive local therapy approach)				
1. In patients previously treated with definitive local therapy for oligometastatic NSCLC who subsequently develop widespread disease progression or recurrence, systemic therapy is recommended as the preferred treatment option. (strong, expert opinion)	None	None	No	Rejected because this is not about our target population. These patients could be considered for palliative care.

Candidate Recommendation from ASTRO/ESTRO 2023 (strength of recommendation, quality of evidence)	Interpretation/ Justification Comments	Ontario Context Comments	New evidence likely to change recommendation?	Assessment? (Endorse /Endorse with Changes/Reject)
2. In patients previously treated with definitive local therapy for oligometastatic NSCLC who subsequently develop repeat oligoprogression or recurrence, additional local therapy should be discussed using a multidisciplinary team approach. (strong, expert opinion)	None	None	No	5.1 Endorse with changes – combine 2 and 3 (please see below).
3. In patients previously treated with definitive local therapy for oligometastatic NSCLC who subsequently develop repeat oligoprogression or recurrence, local therapy is conditionally recommended. (conditional, low)	None	2 and 3 are recommending the same thing and therefore have been combined.	No	5.1 Endorse with changes - combine 2 and 3 "In patients previously treated with definitive local therapy for oligometastatic NSCLC who subsequently develop repeat oligoprogression or recurrence, local therapy is conditionally recommended and should be discussed using a multidisciplinary team approach. (conditional, low)"
4. In patients previously treated with definitive local therapy for oligometastatic NSCLC who subsequently develop repeat oligoprogression or recurrence at sites previously treated with local therapy, re-treatment is conditionally recommended if systemic treatment options are limited, and local therapy can be delivered with toxicity acceptable to the multidisciplinary team and patient. (conditional, expert opinion)	None	None	No	5.2 Endorse

Abbreviations: ASTRO = American Society for Radiation Oncology; CT = computed tomography; ESTRO = European Society for Radiotherapy & Oncology; FDG = fludeoxyglucose-18; IMRT = intensity-modulated radiation therapy; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PET = positron emission tomography; RCT = randomized controlled trial; RT = radiation therapy; SBRT = stereotactic body radiation therapy

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 they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. The Expert Panel may specify that approval is conditional, and that changes to the document are required.

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.

DISSEMINATION AND IMPLEMENTATION

The endorsement document will be published on the OH (CCO) website. The Professional Consultation of the External Review is intended to facilitate the dissemination of the endorsement document to Ontario practitioners. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

UPDATING THE ENDORSEMENT

The PEBC in collaboration with OH (CCO)'s Lung Cancer Disease Site Group will review the endorsement on an annual basis to ensure that it remains relevant and appropriate for use in Ontario.

ACKNOWLEDGEMENTS

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- Sheila McNair, Norma Varela, Xiaomei Yao
- Sara Miller for copyediting

An Endorsement of the ASTRO/ESTRO 2023 Guideline for the Treatment of Patients with Oligometastatic or Oligoprogressive Non-Small Cell Lung Cancer

Section 3: Internal and External Review

INTERNAL REVIEW

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

Expert Panel Review and Approval

Of the 19 members of the GDG Expert Panel, 17 (89%) members voted in September 2024. Of those who voted, 17 (100%) approved the document. 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. Under section 3.1 sequencing and timing of therapies, it states that 3 or more months of systemic therapy is recommended prior to definitive local therapy. 1.5 says that definitive local therapy to all sites in addition to standard therapy is recommended. These two are slightly at odds with each other as 1.5 suggests upfront chemoradiation to chest.	The Working Group added the local therapy definition from ASTRO/ESTRO guideline - "Local therapy includes surgical excision, minimally invasive ablation (e.g., radiofrequency ablation), and radiation therapy (including conventionally fractionated, SBRT, stereotactic body radiation therapy, and stereotactic radiosurgery)."
2. 3.4 states that maintenance systemic therapy is recommended. If someone has synchronous oligometastatic disease, then the maintenance systemic therapy would be consolidation durvalumab. CCO will not fund durvalumab in this setting as they state the patient has metastatic disease and it is indicated/funded in stage III disease. I think the biggest challenge relates to patients presenting with synchronous oligometastatic disease. Treatment of the chest is the biggest challenge we have in our multidisciplinary cancer conferences. The bulk of mediastinal nodal disease is a known prognostic factor, but this is not really captured. The recommendations do not capture any of this nuance and I think a little more guidance would be beneficial.	The Working Group agreed that mediastinal node positivity is a complicated situation. They didn't think the ASTRO/ESTRO guideline was recommending "Standard of care systemic therapy in the setting of mediastinal node positivity and distant oligometastatic disease, is concurrent chemotherapy/consolidation durvalumab, (if driver mutation negative), or that if it's a "T3N0M1" resected situation that the standard of care would be 4 cycles of platinum "pseudoadjuvant" followed by osimertinib. It does not speak to "standard of care systemic therapy" for early-stage disease vs. stage IV disease. In the text of the ASTRO/ESTRO guideline, they address the issue of mediastinal node positivity, and state something along the lines of "treat for 3 months with systemic therapy, and then give definitive local treatment to local disease including nodes". This approach could include hypofractionated radiation to the nodes, or possibly chemoradiation.
3. Algorithm 1 recommends a repeat PET-CT after two to three months. These are patients with metastatic disease who are not	The Working Group added an implementation remark to 4.1: PET-CT scans are not approved outside of possibly the PET Access program in Ontario for

eligible for PET-CT. This has funding implications. Is this being addressed?	patients with metastatic NSCLC, but they are recommended for patients with stage IV oligometastatic disease

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. All healthcare professionals with an interest in lung cancer in the PEBC database as well as the following organizations: Canadian Society of Surgical Oncology, Canadian Association of Thoracic Surgeons, Canadian Partnership Against Cancer, and Canadian Association for Interventional Radiology were contacted by email to inform them of the survey. Responses of the survey were received from 13/98 (13%) people who practice in Ontario and 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	2 (15)	6 (46)	5 (38)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	0	3 (23)	2 (15)	8 (62)
3. I would recommend this guideline for use in practice.	0	1 (8)	0	4 (31)	8 (62)
4. What are the barriers or enablers to the implementation of this guideline report?	• Prompt dissemination of this guideline to healthcare professionals is needed. • Lack of regular discussion of oligometastatic NSCLC patients in multidisciplinary cancer conference rounds • Lack of access to operating room time for surgeons (diffuse problem), access to radiotherapy for specialized treatment like this (sporadic, in some centres of Ontario), and systemic therapies. • Repeat PET for these patients is difficult to obtain in many parts of Ontario, i.e. for restaging to help define the oligometastatic state. • Increased funding for molecular testing is essential to ensure all patients can access comprehensive diagnostic tools.				

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.

References

1. Iyengar P, All S, Berry MF, Boike TP, Bradfield L, Dingemans AC, et al. Treatment of Oligometastatic Non-Small Cell Lung Cancer: An ASTRO/ESTRO Clinical Practice Guideline. Pract Radiat Oncol. 2023;13(5):393-412.
2. OH (CCO) Guideline Endorsement Protocol available at: https://pebctoolkit.mcmaster.ca/doku.php?id=projectdev:cco_endorsement_protocol.
3. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. J Clin Epidemiol. 2010;63(12):1308-11.
4. Iyengar P, Hu C, Gomez DR, Timmerman RD, II CBS, Robinson CG, et al. NRG-LU002: Randomized phase II/III trial of maintenance systemic therapy versus local consolidative therapy (LCT) plus maintenance systemic therapy for limited metastatic non-small cell lung cancer (NSCLC). J Clin Oncol. 2024;42(16_suppl):8506-.

Appendix 1: Affiliations and Conflict of Interest Declarations

Name and Affiliation	Declarations of interest
Working Group	
Adrien Chan Medical Oncologist Lung Cancer Disease Site Group	Currently owns a relevant medical professional corporation.
Donna Maziak Surgeon Lung Cancer Disease Site Group	None declared.
Rahul Nayak Surgeon 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	Received $500 or more in a single year in a consulting capacity for Merck SD, BMS, AstraZeneca, Eisai.
Yee Ung Radiation Oncologist Lung Cancer Disease Site Group	None declared.
Emily Vella Health Research Methodologist Program in Evidence-Based Care	None declared.
Expert Panel	
Abdollah Behzadi Surgeon Lung Cancer Disease Site Group	None declared.
Peter Ellis Medical Oncologist Lung Cancer Disease Site Group	Honoraria for advisory boards from AstraZeneca, Jannsen, Novartis, and Roche. Honoraria for speaking from AstraZeneca, Eli Lilly, Merck, Pfizer, and Sanofi.
Medhat El-Mallah Radiation Oncologist Lung Cancer Disease Site Group	None declared.
Michela Febbraro Medical Oncologist Lung Cancer Disease Site Group	None declared.
Andrew Giles Surgeon Lung Cancer Disease Site Group	Advisory board member for BMS, AZ, and Merck.
Swati Kulkarni Medical Oncologist Lung Cancer Disease Site Group	None declared.
Sara Kuruvilla Medical Oncologist Lung Cancer Disease Site Group	Received financial or material support and acted in a consulting capacity for AstraZeneca, Regeneron, and Sanofi.

Natasha Leighl Medical Oncologist Lung Cancer Disease Site Group	Received research funding or materials from: AZ, BMS, Lilly, Janssen, MSD, Pfizer, Guardant Health, Neogenomics, Roche, EMD Serono, Bayer, and Takeda.
Robert MacRae Radiation Oncologist Lung Cancer Disease Site Group	The treatment of oligometastatic disease forms a significant part of radiation oncology practice.
Ambika Parmar Medical Oncologist Lung Cancer Disease Site Group	None declared.
Andrew Pearce Radiation Oncologist Lung Cancer Disease Site Group	None declared.
Lacey Pitre Medical Oncologist Lung Cancer Disease Site Group	Merck Oncology – Speaker honoraria January 2021 Astra Zeneca – Speaker honoraria April 2021 Astra Zeneca – Rounds moderating January 2022 Astra Zeneca – Rounds moderating January 2023 Novartis - Rounds moderating July 2023 Pfizer - Equity Grant - $100,000. Project examines Equitable access to Clinical trials in Canada.
Alexander Sun Radiation Oncologist Lung Cancer Disease Site Group	None declared.
Simon Sun Surgeon Lung Cancer Disease Site Group	None declared.
Anand Swaminath Radiation Oncologist Lung Cancer Disease Site Group	Spouse is employed at Roche. Advisory board member for AstraZeneca. Received grants or research support from Roche, AstraZeneca, and BMS.
Julius Toth Surgeon Lung Cancer Disease Site Group	None declared.
Paul Wheatley-Price Medical Oncologist Lung Cancer Disease Site Group	Attended advisory boards or received speaker honoraria from the following companies in the last five years: Astra Zeneca, Pfizer, Amgen, Janssen, BMS, Merck, Daiichi Sankyo, Roche, SteriMax, Abbvie, Lilly, Novartis, Sanofi, Guardant, Jazz Pharmaceuticals, EMD Serono, Bayer, Takeda. Received research grants from Roche, Pfizer, Merck and BMS.
Kazuhiro Yasufuku Surgeon Lung Cancer Disease Site Group	None declared.
Edward Yu Radiation Oncologist Lung Cancer Disease Site Group	None declared.