Clinical trial endpoints for metastases-directed therapy in oligometastatic cancer: a review and Delphi consensus on behalf of the EORTC–ESTRO OligoCare consortium

Joachim Widder, Guus M Bol, Inga-Malin Simek, Felix Ehret, Hoda Abdel-Aty, Selma Basic, David Chuter, Jacqueline Daly, Patricia Fairbrother, Donjeta Zeqa, Frank Aboubakar Nana, Verane Achard, Stefanie Corradini, Dora Correia, Dirk De Ruysscher, Anne-Marie C Dingemans, Corinne Faivre-Finn, Silke Gillessen, Marianne G Guren, Lizza Hendriks, Wolfgang G Kunz, Frederic E Lecouvet, Antonin Levy, Yolande Lievens, Fiona McDonald, Icro Meattini, Felix Oppong, Daniela Oprea-Lager, David Palma, Gitte Fredberg Persson, Jordi Remon, Miet Vandemaele, Hanneke W M van Laarhoven, Helena M Verkooijen, Luca Visani, Thomas Zilli, Piet Ost, Matthias Guckenberger

Oligometastatic cancer is characterised by a low volume of metastases to a small number of anatomical sites. However, evaluating the impact of metastases-directed therapies (MDTs) on overall survival or quality of life is often challenging. Current clinical trials use a wide range of primary endpoints that might not be validated or suited to MDT. To address this issue, we did a systematic review of international trial registries, alongside a Delphi consensus process involving 30 experts and five patient representatives. The aim was to identify preferred primary endpoints for MDT trials in oligometastatic disease, regardless of tumour type. Overall survival and progression-free survival were the most frequently used endpoints across the 121 comparative trials reviewed. Over four Delphi consensus rounds, overall survival had the highest level of agreement, although its limitations as a sole endpoint were emphasised. In addition to the widely used progression-free survival endpoint, polymetastatic progression-free survival and start-or-switch of systemic therapy-free survival also reached consensus, particularly for trials integrating systemic therapies. Both polymetastatic progression-free survival and systemic therapy-free survival permit repeat MDT without classifying it as treatment failure. Patient representatives highlighted the importance of time-to-deterioration of quality of life. This consensus supports overall survival as a primary endpoint and, in addition to progression-free survival, recommends polymetastatic progression-free survival and systemic therapy-free survival, especially in combination with systemic therapies. Adopting these endpoints will make MDT trials more relevant, comparable, and patient-centred, thereby empowering future clinical and policy decisions.

Lancet Oncol 2026; 27: e238–47

Department of Radiation Oncology, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria (Prof J Widder MD PhD, I-M Simek MD); **UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA** (G M Bol MD PhD); **Department of Medical Oncology, University Medical Center Utrecht, Utrecht, Netherlands** (G M Bol); **Charité–Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Radiation Oncology, Berlin, Germany** (F Ehret MD); **German Cancer Consortium (DKTK), partner site Berlin, a partnership between DKFZ and Charité–Universitätsmedizin Berlin, Germany** (F Ehret); **The Royal Marsden Foundation Trust and Institute of Cancer Research, London, UK** (H Abdel-Aty FRCR MD[Res], F McDonald FRCR MD[Res]); **Rovinj, Croatia** (S Basic); **ICPV (Independent Cancer Patients' Voice), London, UK** (D Chuter, P Fairbrother); **DiCE (Digestive Cancers Europe) Brussels, Belgium** (D Chuter); **EGM Cancer Support, Galway, Ireland** (J Daly); **Europa Donna Albania, Tirana, Albania** (D Zeqa MSc); **Europa Donna–The European Breast Cancer Coalition, Milan, Italy** (D Zeqa); **de Duve Institute, UCLouvain, Brussels, Belgium** (Prof F Aboubakar Nana); **Division of Pneumology** (Prof F Aboubakar Nana), **Cliniques Universitaires Saint-Luc, UCLouvain, Brussels, Belgium** (Prof F E Lecouvet MD PhD); **Radiotherapy Department, Institut Bergonié, Bordeaux, France** (V Achard MD PhD); **Faculty of Medicine**

Introduction

Oligometastatic disease is proposed as a cancer state between locally confined and widely disseminated metastatic cancer.[1] In 2020, it was characterised and classified to encompass the wide spectrum of oligometastatic disease manifestations.[2,3] Metastases-directed therapy (MDT; eg, stereotactic body radiotherapy [SBRT; used interchangeably with stereotactic ablative radiotherapy], surgery, or percutaneous tumour ablation) has been evaluated in prospective interventional clinical trials to define the roles of MDT across the spectrum of patients with oligometastatic disease.[2–12] Primary endpoints in clinical trials are methodological cornerstones to establish the success or failure of therapeutic interventions being investigated.[13] Recent advances in tumour biology suggest that comprehensive and serial administration of MDT to all visible lesions in oligometastatic disease over time can be beneficial, as MDT could suppress prometastatic signalling.[14] This perspective highlights the limitations of static one-time administration of MDT in a dynamic biological process and has clear implications for the selection of primary endpoints in oligometastatic disease clinical trials.

In life-threatening diseases such as cancer, overall survival and patients' experience of their quality of life (QOL)[15] are the most relevant outcome measures for interventions, irrespective of treatment modalities.[16,17] However, in multimodality treatment regimens, assessing the effect of each treatment component individually on overall survival or QOL might not always be feasible. Overall survival is influenced by variation in post-trial treatments and needs long follow-up times and large sample sizes. These requirements are particularly challenging with poor funding or when industry interest and support are lacking.[18] These considerations provide the rationale for incorporating additional endpoints in clinical trials, to more sensitively determine the efficacy of MDT.

Various response criteria have been defined to evaluate the potential benefit of different therapies by major bodies, such as the European Organisation for Research and Treatment of Cancer (EORTC),[19–21] WHO,[22] or the Response Assessment in Neuro-Oncology (RANO)[23] working group. The Response Evaluation Criteria in Solid Tumors (RECIST),[19] as defined by the EORTC, represent the most widely accepted framework for quantifying treatment response in clinical trials. Importantly, the RECIST working group defined progressive disease to be used as an event for the endpoint progression-free survival, and as a rational basis for discontinuing systemic therapy in metastatic disease.[19] Response criteria have been adjusted for immunotherapy,[21] for adjuvant therapy in breast cancer,[24] for brain tumours,[23] or for PET.[20] These adjustments accounted for the unique characteristics of the respective treatment modalities, conditions, or diagnostic

(Prof T Zilli MD), **University of Geneva, Geneva, Switzerland** (V Achard); **Department of Radiation Oncology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany** (Prof S Corradini MD); **Department of Radiation Oncology, Cantonal Hospital Aarau, Aarau, Switzerland** (D Correia MD); **Department of Radiation Oncology, Inselspital, Bern** (D Correia); **University Hospital, University of Bern, Switzerland** (D Correia); **Department of Radiation Oncology (Maastro Clinic)** (Prof D De Ruysscher MD PhD, I Meattini MD) **and Department of Pulmonary Diseases** (L Hendriks MD PhD), **GROW Research Institute for Oncology and Reproduction, Maastricht University Medical Center, Maastricht, Netherlands; Department of Pulmonary Medicine, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Netherlands** (Prof A-M C Dingemans MD PhD); **The Christie NHS Foundation Trust & The University of Manchester, UK** (C Faivre-Finn MD); **Oncology Institute of Southern Switzerland (IOSI), Ente Ospedaliero Cantonale (EOC), Bellinzona, Switzerland** (Prof S Gillessen MD); **Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland** (Prof S Gillessen); **Department of Oncology, Oslo University Hospital, Oslo, Norway** (Prof M G Guren MD PhD); **Institute of Clinical Medicine, University of Oslo, Oslo, Norway** (Prof M G Guren); **Department of Radiology, LMU University Hospital, LMU Munich, Munich, Germany** (Prof W G Kunz MD); **Department of Medical Imaging, Institut de Recherche Expérimentale et Clinique (IREC), Institut du Cancer Roi Albert II, Brussels, Belgium** (Prof F E Lecouvet); **Université Paris-Saclay, Gustave Roussy, Department of Radiation Oncology** (A Levy MD PhD) **and Department of Cancer Medicine** (J Remon MD PhD), **Villejuif, France; Radiation Oncology Department, Ghent University Hospital, Ghent, Belgium** (Prof Y Lievens MD PhD); **Radiation Oncology Department**

procedures, and were proposed to provide a common basis for conducting prospective clinical trials.

Generally, progressive disease is defined as the appearance of new metastases or existing metastases increasing in size, a determination that is often difficult in previously irradiated lesions. This assessment typically entails adjudicating systemic treatment failure due to tumour resistance. By contrast, although oligometastatic progression (or recurrence) constitutes a progression-free survival event, repeat MDT can often reach disease control again, even if locally recurrent, previously treated metastases require retreatment, making it questionable to define MDT failure at conventionally defined progressive disease. As MDT targets macroscopic metastases, the emergence of new lesions does not necessarily indicate treatment failure in the same way as it does for systemic therapy.[14] Nevertheless, progression-free survival remains a commonly used endpoint in clinical trials evaluating MDT for oligometastatic cancer, despite its restricted ability to fully reflect the distinct mechanism of action of MDT.

This Policy Review conducted by the EORTC–European Society for Radiotherapy and Oncology (ESTRO) OligoCare consortium aims to identify and define alternative clinical trial endpoints for MDT use in patients with oligometastatic disease. OligoCare is a multicentre, prospective observational cohort study investigating MDT in oligometastatic disease within the EORTC–ESTRO E²RADIatE framework (EORTC-1811), a study platform designed to harness real-world data on patients undergoing radiotherapy in emerging fields of oncology.[25] A panel of MDT experts with diverse backgrounds, including patient representatives, was convened to conduct a systematic review of the primary and secondary endpoints used in clinical trials evaluating MDT in oligometastatic disease, followed by a modified Delphi consensus process. The project aimed to establish consensus on primary endpoints that are applicable, irrespective of the primary tumour, and specific to clinical scenarios in comparative clinical trial designs involving MDT in oligometastatic disease.[2]

Methods

Composition of the panel and procedures

The principal investigators (PO, MG) of the EORTC–ESTRO E²RADIatE OligoCare project (NCT03818503) formed a project core group (JW, GMB, PO, MG), who convened a panel of MDT experts from the four EORTC disease groups suitable for inclusion in the OligoCare cohort study—ie, the breast, genitourinary, lung, and gastrointestinal tumour groups. In addition, the EORTC Imaging Group and its statistics department were included. The EORTC Patient Advocacy group invited four patient representatives (DC, JD, PF, DZ), one of whom (PF) was replaced by a fifth person (SB) for round four, for private reasons (appendix p 20). Elected members of the Young and Early Career Investigators Group of the Radiation Oncology Scientific Council (Y-ECI ROSC) conducted the systematic review before the Delphi consensus process (I-MS, HA-A, FE). The systematic review aimed to identify and define primary and secondary endpoints of clinical trials investigating MDT in oligometastatic disease that were registered in major clinical trial registries. A short list of clinical trial endpoints was established by qualitative synthesis. In the Delphi rounds to follow, candidate endpoints were stepwise adjusted based on panellists' voting and comments.

Review

Three investigators (I-MS, HA-A, FE) did a systematic review.[26] All prospective clinical trials on ablative treatments for oligometastases in solid tumours were retrieved. Oligometastatic disease was defined as no more than five metastases in no more than two organ systems.[27] The primary tumour must have been treated with curative intent, before or concurrently with treatment of oligometastatic disease. For the treatment of oligometastatic disease, surgical removal, stereotactic radiosurgery, SBRT, radiofrequency ablation, microwave ablation, microporation, or cryoablation of all metastases was deemed ablative. Combinations of treatments and the addition of systemic treatment options were allowed.

Delphi process

Before starting the consensus rounds, panellists received the results from the systematic review (April, 2024). The Delphi rounds were done online with Qualtrics and Google Forms, with every item queried for agreement (appendix pp 20–48), and allowing for free-text comments. Agreement rates of 75% or higher were regarded as consensus; lower rates were regarded as a lack of consensus and were re-queried once before they were excluded for the next round.

In round one (April to May, 2024), the short list of endpoints derived and adapted from the systematic review, together with detailed definitions of these endpoints, was queried. Panellists, including experts and patient representatives, were asked to agree ("yes", "no", or "I am uncertain") to the statement: "Endpoint [X] may be an appropriate primary endpoint in randomised clinical studies to assess the role of MDT in certain clinical scenarios". General comments, including additional endpoints, could also be proposed by panellists. After the distribution of the results of round one, including the panellists' comments and a video conference with the panel, in round two (September to October, 2024), the whole panel assessed the consolidated candidate endpoints from round one for their appropriateness as primary or secondary endpoints, or both. These assessments were done separately for five comparative clinical trial designs involving MDT with or without combinations with systemic therapies for oligometastatic disease, and for trials comparing two MDT modalities with each other (panel 1).

Panel 1: **Basic comparative clinical trial designs**

1 MDT versus observation (eg, STOMP and ORIOLE trials[9]: stereotactic body radiotherapy [SBRT] or observation for oligometastatic prostate cancer)
2 MDT versus systemic therapy (eg, CAIR07: hepatic artery radioembolisation or standard systemic therapy for colorectal liver metastases; NCT05092880)
3 MDT combined with systemic therapy versus systemic therapy alone (eg, SABR-COMET trial[6]: stereotactic ablative radiotherapy or systemic therapy for oligometastatic cancers; CURB trial[11]: SBRT added to systemic therapy in oligoprogressive breast or lung cancer)
4 MDT combined with systemic therapy versus MDT alone (eg, RAVENS trial[28]: SBRT with or without radium-223 for metastatic prostate cancer; RADIOSA trial[29]: SBRT with or without androgen deprivation therapy in hormone-sensitive prostate cancer)
5 MDT(a) versus MDT(b)—comparison of different MDT modalities (surgery, ablative radiotherapy, microwave ablation, thermal ablation, cryoablation, etc; eg, COLLISION trial[12]: surgery or thermoablation for colorectal liver metastases)

MDT=metastases-directed therapy.

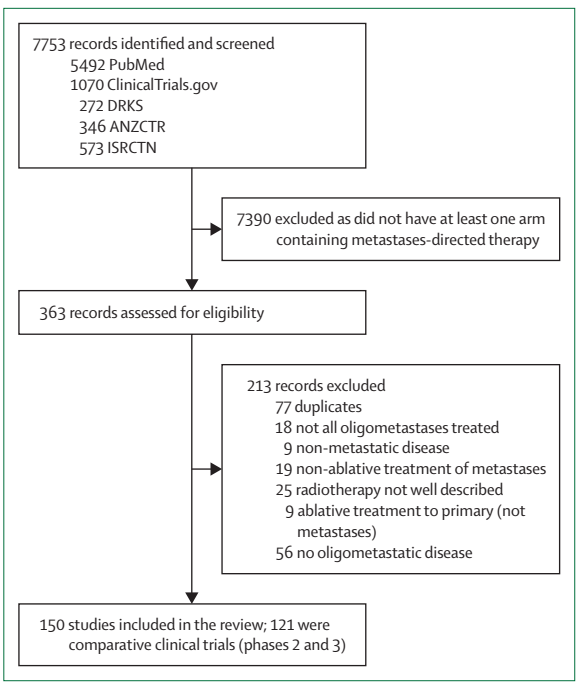


Figure 1: **Study selection**
DRKS=German Clinical Trials Register. ANZCTR=Australian New Zealand Clinical Trials Registry. ISRCTN=International Standard Randomized Controlled Trial Number.

The results from round two led to a further evaluation in round three among the MDT experts only, of the primary endpoints receiving the highest scores as primary endpoints (January to February, 2025). In addition, as panellists frequently commented on the potential appropriateness of endpoints as secondary rather than primary, the appropriateness of secondary endpoints was queried again in round three. Due to the function of secondary trial endpoints as informative and hypothesis-generating rather than as decisive, in terms of the success or failure of the tested treatments, the panel deselected candidate endpoints if they deemed them to be not useful even as secondary endpoints. Round four focused entirely on the patients' perspective. The primary endpoints that had reached consensus among MDT experts in round three were proposed to the patient representative panel via a video conference hosted by the project core group (May, 2025). Patient representatives discussed their perspectives on trial outcome measures and provided their assessment of candidate primary endpoints that had reached consensus from experts. The endpoint local control of lesions treated with MDT, and the trial design comparing different modalities of MDT, were not considered in this round, as these are more technical issues (appendix p 47).

The project report was subsequently submitted to the expert panel and patient representatives for comment and corrections (December, 2025), and all authors approved the final version of the manuscript.

Findings

The literature search done between Sept 7, 2023, and Feb 19, 2024, identified 7753 studies. 150 trials were included and analysed (figure 1; comparative phase 2 and 3 trials were analysed in more detail in the appendix pp 4–19).

All primary and secondary endpoints listed in the trial registries were collected and summarised (table, appendix pp 4–19). In comparative trials, progression-free survival was the most frequently used primary endpoint (in 66% of phase 2 trials and 42% of phase 3 trials), followed by overall survival (18% in phase 2 trials and 42% in phase 3 trials). Other endpoints such as adverse events, time to start or switch of systemic therapy, or feasibility were used relatively infrequently as primary endpoints.

The most frequently reported secondary endpoint was overall survival, observed in 66% of phase 2 trials and 50% of phase 3 trials. Additional commonly assessed secondary endpoints included QOL (50% in phase 2 and 3 trials) and adverse events, used in 39% of phase 2 trials and 67% of phase 3 trials (table).

Delphi rounds were done between April 26, 2024, and May 8, 2025. Overall, the panel consisted of 35 individuals, comprising 17 radiation oncologists, seven medical or pulmonary oncologists, four imaging specialists, two statisticians and epidemiology experts, and five patient representatives. One patient representative was replaced upon their request for round four, and

(M Vandemaele MD), **Department of Human Structure and Repair, Ghent University, Ghent, Belgium** (Prof Y Lievens, P Ost MD); **Radiation Oncology, Breast Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy** (I Meattini); **Department of Experimental and Clinical Biomedical Sciences "M Serio", University of Florence, Florence, Italy** (I Meattini); **European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium** (F Oppong MSc); **Department of Medical Imaging, Radboud University Medical Center, Nijmegen, Netherlands** (Prof D Oprea-Lager MD PhD); **Department of Oncology, Western University, London, ON, Canada** (Prof D Palma MD PhD); **Department of Oncology, Copenhagen University Hospital Herlev and Gentofte, Herlev, Denmark** (Prof G Fredberg Persson PhD); **Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark** (Prof G Fredberg Persson); **Amsterdam University Medical Center at the University of Amsterdam, Department of Medical Oncology, Amsterdam, Netherlands** (Prof H W M van Laarhoven MD PhD); **Cancer Center Amsterdam, Cancer Treatment and Quality of Life, Amsterdam, Netherlands** (Prof H W M van Laarhoven); **Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands** (Prof H M Verkooijen MD PhD); **Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands** (Prof H M Verkooijen); **Radiation Oncology, Breast Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy** (L Visani MD); **Department of Radiation Oncology, Oncology Institute of Southern Switzerland (IOSI), Ente Ospedaliero Cantonale, Bellinzona, Switzerland** (Prof T Zilli); **Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland** (Prof T Zilli);

	Patients (n [%]) in 109 phase 2 comparative trials	Patients (n [%]) in 12 phase 3 comparative trials
Primary or coprimary endpoint		
Progression-free survival	72 (66%)	5 (42%)
Overall survival	20 (18%)	5 (42%)
Adverse events	12 (11%)	0
Time to start or switch of systemic therapy	2 (2%)	1 (8%)
Feasibility	3 (3%)	0
Quality of life	1 (1%)	0
Local control	0	1 (8%)
Other	13 (12%)	1 (8%)
Secondary endpoint		
Overall survival	72 (66%)	6 (50%)
Quality of life	55 (50%)	6 (50%)
Adverse events	43 (39%)	8 (67%)
Local control	35 (32%)	3 (25%)
Progression-free survival	30 (28%)	5 (42%)
Time to start or switch of systemic therapy	27 (25%)	3 (25%)
Costs	5 (5%)	2 (17%)
Feasibility	4 (4%)	0
Multiple metastatic progression	3 (3%)	1 (8%)
Other	66 (61%)	9 (75%)

Table: **Frequency of endpoints used in phase 2 and phase 3 comparative clinical trials of metastasis-directed therapy in oligometastatic disease**

Panel 2: Endpoints for clinical trials and their corresponding events

Consensus during the Delphi process as primary endpoints

- Overall survival: death
- Progression-free survival: death or progression of disease (Response Evaluation Criteria in Solid Tumors, known as RECIST)
- Polymetastatic progression-free survival: death or polymetastatic progression of disease
- Start or switch of systemic therapy-free survival: death, or start of, or switch of systemic therapy
- Time to deterioration of quality of life: death or deterioration of patient-rated quality of life by a predefined margin

Not reaching consensus during the Delphi process as primary endpoints

- Local control: local recurrence or progression of lesions treated with MDT
- Progression-free interval: progression of disease
- Widespread progression-free survival: death or widespread progression of disease
- Time to failure of MDT strategy: death or progression of disease unamenable to MDT
- Time to switch of systemic therapy (ie, time to next treatment): switch of systemic therapy
- Time to deterioration of performance status: deterioration of physician-rated performance status by a predefined margin
- Time to symptomatic progression of disease: start of predefined symptoms due to progression of disease, rated by the physician

MDT=metastases-directed therapy.

Department of Radiation Oncology, Iridium Network, Antwerp, Belgium (P Ost); **Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Zurich, Switzerland** (Prof M Guckenberger MD)

Correspondence to: Prof Joachim Widder, Department of Radiation Oncology, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna 1090, Austria
joachim.widder@muv.ac.at

See Online for appendix

one expert panellist (a surgical oncologist) had declined further participation after round two, both for private reasons. Agreement rates for endpoints (synthesised based on the systematic review; panel 2, appendix pp 20–22) for all rounds and trial designs are shown in figure 2, with participation rates ranging between 89% and 100%.

Overall survival had the highest agreement rate (91%) in round one, but even panellists endorsing it gave some caveats and suggested that it should not be the only primary endpoint or rather that it be used as a secondary endpoint (figure 2A, appendix pp 22–48). In particular, a potential dilution of the effect of any trial intervention over a trajectory of consecutive treatments was mentioned as a concern. For five endpoints, consensus for primary endpoints was reached on particular trial designs when the 75% agreement rate among patient representatives for the QOL endpoint was included.

Progression-free survival reached consensus as a primary endpoint for trials comparing different MDT options, with slightly higher agreement rates than local control of locally treated metastatic lesions in rounds two and three, but remaining below consensus for other trial designs (figure 2A).

Polymetastatic progression-free survival, defined as progression beyond an oligometastatic state of disease (or death), reached consensus as a primary endpoint for trial designs investigating MDT in combination with systemic therapies. Clear criteria of polymetastatic as opposed to oligometastatic progression must be defined in detail in the study protocol (eg, demarcation, threshold size, threshold number of lesions), as long as no more general consensus is available on this issue.

Systemic therapy-free survival, defined as the start or switch of lines of systemic therapy (or death), was agreed upon as a primary endpoint for trials comparing systemic therapy alone versus MDT added to systemic therapy. Criteria and guidance for starting or switching systemic therapies need to be provided in the study protocol.

Local control of locally treated metastases was just below consensus as a primary endpoint for trials comparing different MDT options against each other, but scored high as a secondary endpoint (figure 2B).

Time to deterioration of QOL was below expert consensus as a primary endpoint in queried trial designs, but reached high endorsement rates as a secondary endpoint (>90%, figure 2B), and reached strong consensus as a primary endpoint from patient representatives. Clear threshold changes of QOL measures need to be provided in the study protocol.

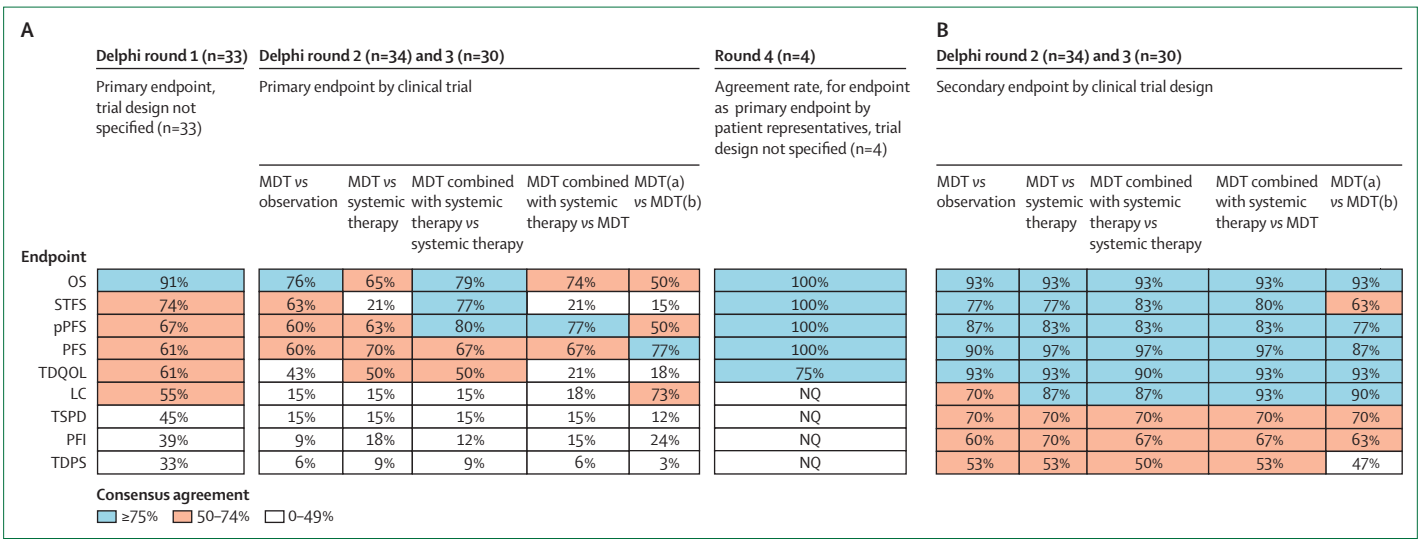


Figure 2: **Agreement rates on primary (A) and secondary (B) endpoints**
MDT(a) *vs* MDT(b) refers to different MDT modalities (surgery, ablative radiotherapy, microwave ablation, thermal ablation, cryoablation, etc). MDT=metastases-directed therapy. OS=overall survival. STFS=start or switch of systemic therapy-free survival. pPFS=polymetastatic progression-free survival. PFS=progression-free survival. TDQOL=time to deterioration of quality of life. LC=local control. NQ=not queried. TSPD=time to symptomatic progression of disease. PFI=progression-free interval. TDPS=time to deterioration of performance status.

There was no consensus regarding their use as primary endpoints for other queried endpoints (panel 2, figure 2A). Of note, physician-rated qualitative endpoints (time to deterioration of performance status, time to symptomatic progression of disease) and progression-free interval (same as progression-free survival, but death treated as a censoring event, rather than as an event) had the lowest overall agreement rates.

Discussion

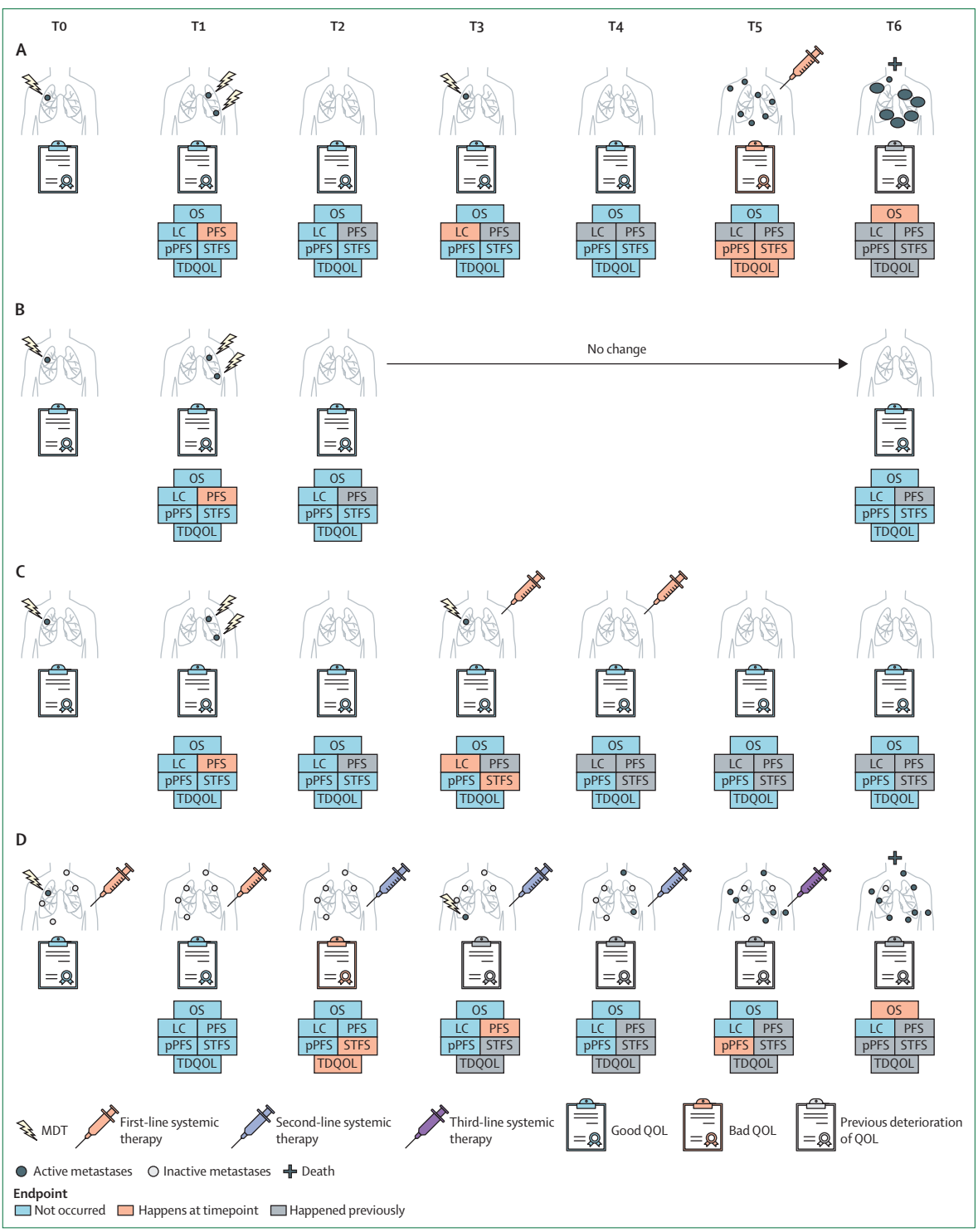
In this Policy Review, the systematic review identified substantial variability in primary endpoints among registered clinical trials exploring the role of MDT in patients with oligometastatic disease. As expected, progression-free survival and overall survival were the most common primary endpoints. In both phase 2 and phase 3 trials, overall survival, although universally recognised as the highest priority, was not the single most commonly selected primary endpoint. The following Delphi consensus process, involving multidisciplinary experts in MDT and including patient representatives within the ESTRO and EORTC frameworks, confirmed the importance of overall survival as a primary endpoint. In addition, consensus was reached on the appropriateness and relevance of polymetastatic progression-free survival and start or switch of systemic therapy-free survival as primary endpoints for clinical trials combining MDT with systemic therapy. For head-to-head comparative studies of different MDT modalities, progression-free survival was considered the most suitable primary endpoint. Patient advocates highlighted the importance of an endpoint measuring time to deterioration in QOL (figure 3). This consensus is expected to advance and standardise the field of clinical trial designs for patients with oligometastatic disease, given the substantial variability in endpoint choices identified in the systematic review of clinical trials involving MDT.

The need for alternative primary endpoints has been recognised previously. The OLIGO-DK protocol (NCT06356779) in Denmark, for example, uses time to failure of locally ablative therapy strategy as its main endpoint, to avoid prematurely calling an event in the study. In some published randomised phase 2 trials—particularly involving SBRT as MDT—progression-free survival was most common, with several also examining delay of systemic therapy.[4–12] The approaches towards repetition of MDT and its corresponding impact on endpoint coding varied across trials.[14]

The purpose of this Policy Review was to propose primary endpoints for clinical trials that would best measure the potential efficacy of MDT within a multidisciplinary approach for patients with oligometastatic disease. It did not aim to develop surrogate endpoints for overall survival.[30] Such endpoints would require thorough statistical analyses of multiple high-quality clinical trials within a defined clinical scenario and disease type rather than a consensus process. Ultimately, any clinically meaningful primary endpoint must show a correlation with improved survival accompanied by good patient-reported QOL. Since direct evaluation of how treatment impacts both QOL and overall survival is not always feasible in the assessment of multimodal oncological therapies—and in determining their optimal use—defining and rigorously testing alternative endpoints in clinical trials remains a priority.

In 2025, the US Food and Drug Administration issued new guidance on overall survival for cancer drug

trials.[31] The document emphasises the pivotal role of overall survival in clinical trials for regulatory approval of cancer drugs. Although it discusses important issues regarding crossover and post-protocol therapies,[32] which are also relevant for MDT clinical trials, the guidance is limited to cancer drugs and explicitly does not consider MDT, making it not directly applicable to MDT trials. In this respect, it mirrors the RECIST working group's non-consideration of MDT.[19] Here we specifically aimed to address the unique characteristics



of MDT particularly in the context of emerging cancer drugs, with respect to the selection of primary endpoints in clinical trials that should help to define the contribution—or lack of contribution—of MDT to improving the quality and duration of the lives of patients with cancer.

The differences in nature and mechanism of action between MDT and systemic therapy,[33] and the fact that oligometastatic disease is an intermediate cancer stage between advanced localised and systemic disease, formed the rationale for this Policy Review. MDT aims to ablate macroscopic lesions visible on imaging, leaving potential microscopic disease untreated, whereas systemic therapies aim to control both macroscopic and microscopic metastases. The traditional progression-free survival endpoint (as defined in RECIST,[19] PERCIST,[20] iRECIST,[21] and RANO[23]) was devised to evaluate systemic therapies, where progressive disease typically triggers discontinuation of a treatment line due to presumed drug resistance. This framework does not translate directly to MDT: new lesions have not yet been treated and might still be amenable to additional local interventions, whereas progression at previously treated sites can often be managed with repeat MDT, potentially with the same or different modality.[34,35] Consequently, progression as defined by RECIST, PERCIST, iRECIST, or RANO, which forms the basis for progression-free survival, might not justify adjudicating treatment failure when evaluating MDT. These considerations highlight the need for a more tailored approach. Figure 3 illustrates four potential courses of oligometastatic disease, emphasising how the choice of primary endpoints can affect time-to-event reporting. In cases of oligoprogression or oligorecurrence, progression-free survival is an early event, in which new metastases might be amenable to further MDT. In these cases, progression-free survival typically precedes polymetastatic progression-free survival and death, and a subgroup of patients might remain free from disease and treatment during further follow-up.

Several studies have suggested an added value of repeat SBRT for new or progressing lesions.[5,36] In the SAFRON II trial investigating fractionation for pulmonary oligometastases, at 3 years, the pooled rate of survival without any progression was 24%, whereas the pooled rate of survival without widespread progression was 39%: the difference was due to repeat SBRT for oligometastatic progressions.[36] A large retrospective study showed that progression-free survival was shorter, but widespread failure-free survival was similar after repeat versus single course SBRT for oligometastatic disease, whereas overall survival was longer in the repeat-SBRT cohort. This outcome could be due to immortal time bias, but a true beneficial effect of local treatment of oligometastases cannot be ruled out,[35] highlighting the need to conduct comparative prospective clinical trials encouraging repeat MDT.[37]

Use of MDT in oligometastatic disease as either an alternative or addition to systemic therapy further complicates endpoint selection. For example, MDT could be used to defer starting systemic therapy in treatment-naive patients or to allow continuation of use of effective systemic treatments in patients with mixed response patterns. For those with mixed response patterns, systemic therapy is continued beyond disease progression if progression is limited to oligoprogressive lesions amenable to MDT. The consensus process identified systemic therapy-free survival and polymetastatic progression-free survival as promising endpoints in these scenarios. Systemic therapy-free survival measures the time until a new systemic therapy is required, switched, or intensified. Although it accommodates additional factors, some of which are subjective, it might also be influenced by molecular pathology findings from metastatic tissue, adding complexity that can be challenging to regulate fully within a clinical trial protocol. By contrast, polymetastatic progression-free survival captures the time until progression beyond the oligometastatic state. Although clear criteria are needed to distinguish polymetastatic from oligometastatic progression or recurrence, this task can be defined in the designing of clinical trials.

Although the panel reached consensus on several MDT-specific endpoints, their feasibility in real-world clinical trials warrants careful consideration. Implementation of polymetastatic progression-free survival depends on consistent definitions of polymetastatic progression—such as the threshold number of new lesions—which might pose challenges across centres due to heterogeneous imaging protocols and reporting standards. Similarly, systemic therapy-free survival requires clearly predefined and uniformly applied criteria

Figure 3: **Exemplary illustration of endpoints when MDT is used**
(A) At baseline (T0), one metastasis is treated with MDT. At T1 (first follow-up), two new metastases triggering the PFS event receive MDT. At a follow-up encounter (T3), the lesion treated with MDT at baseline recurs (LC event) and is retreated with MDT. At T5, multiple metastases are detected (pPFS event); systemic therapy is started (STFS event), and quality of life deteriorates (TDQOL event). Death occurs at T6. (B) Same as (A), but after T1 (PFS event), no new lesions occur, no further treatment is given, and quality of life remains good. The patient is alive. (C) Same as (A), PFS-event occurs at T1, but at T3, the baseline lesion recurs locally (LC event) and receives repeat MDT. In addition, systemic therapy is started (STFS event), which continues at T4. It is stopped before T5, and no further event occurs. At T6, the patient is alive. (D) At baseline, one metastatic lesion grows under systemic therapy (oligoprogression) and receives MDT at baseline, while four pre-existing lesions are stable, and systemic therapy is continued. At T2, systemic therapy is switched (STFS event) due to intolerable side-effects (TDQOL event), but the pre-existing metastases are stable. At T3, one of the previously controlled lesions progresses (PFS event; oligoprogression) and is treated with MDT. At T4, two further metastases show progression (no event as PFS event has already occurred), but are not technically treatable by MDT. At T5, multiple new lesions are visible (pPFS event) and systemic therapy is switched again (no event as STFS had already occurred), and the patient dies at T6. LC=local control. MDT=metastases-directed therapy. OS=overall survival. PFS=progression-free survival. pPFS=polymetastatic-progression-free survival. QOL=quality of life. STFS=start or switch of systemic therapy-free survival. TDQOL=time to deterioration of quality of life.

Search strategy and selection criteria

PubMed (MEDLINE), ClinicalTrials.gov, the German Clinical Trials Register, the Australian New Zealand Clinical Trials Registry, and the International Standard Randomized Controlled Trial Number were searched to identify all clinical trials including metastasis-directed therapies (MDT) between Sept 7, 2023, and Feb 19, 2024. Search terms used were "oligometastatic", "limited metastatic disease", "limited metastasis", "stereotactic", "ablative therapy", "local therapy", "locoregional therapy", "body radiotherapy", "SABR", "SBRT", "SART", "SIRT", "radiosurgery", "surgery", "metastasectomy", "radiofrequency ablation", "microwave ablation", "microporation", "nano knife", and "cryoablation". Trials that did not have at least one arm containg MDT were excluded, as were duplicates, non-ablative tretaments of metastases, and therapies for conditions other than oligometastatic cancer. Only trials in English were considered.

for initiating or switching systemic therapy; in pragmatic trial settings, these decisions often incorporate clinical judgement and patient preference. Accurate assessment of local control also presents challenges, as post-MDT imaging interpretation can be difficult, particularly in organs such as the liver or after high-dose radiotherapy, when treatment-related changes might mimic progression. These operational complexities suggest that feasibility should be explicitly considered and solved when selecting primary endpoints for MDT trials. Further methodological work is needed to standardise imaging, harmonise reporting, and decision-making processes to ensure reproducibility across studies. Given that the OligoCare study investigates SBRT as the MDT modality, the panel was predominantly composed of European radiation oncologists, notably leading to limited surgical oncology perspectives.

Conclusions

Our systematic review and Delphi consensus highlighted the considerable heterogeneity of primary endpoints for MDT trials across the oligometastatic disease spectrum. Consensus was reached that, in addition to overall survival, polymetastatic progression-free survival and start or switch of systemic therapy-free survival should be endorsed as primary endpoints in trials combining MDT with systemic therapy. Ultimately, determining whether these endpoints can serve as surrogates for overall survival while maintaining good QOL will require thorough analysis, which is contingent upon their implementation in clinical trials. The rationale for proposing polymetastatic progression-free survival and start or switch of systemic therapy-free survival is their suitability for capturing outcomes following serial or repeat administration of MDT, a concept recently supported by emerging biological evidence.[14] No consensus was reached for clinical trials comparing MDT with observation or systemic therapy. However, endpoints with moderate agreement, such as polymetastatic progression-free survival, start or switch of systemic therapy-free survival, progression-free survival, and local control, might be considered depending on the specific treatment context. Patient representatives additionally reached consensus on incorporating patient-reported QOL as a key endpoint in clinical trials evaluating MDT in oligometastatic disease.

Contributors

Conceptualisation: JW, MG, GMB, I-MS, PO. Methodology: JW, MG, I-MS, GMB, PO, FE, HA-A. Project administration and supervision: JW, GMB, PO, MG. Validation: JW, I-MS, FE, HA-A, GMB, PO, MG. Writing the original draft: JW. Data provision, investigation, and providing guiding commentary during the Delphi project process, and review and editing of the writing: all authors.

Declaration of interests

All authors declaring conflicts of interest declare them outside the present work. JW reports research grants to their institution from Brainlab, Elekta, Philips, RaySearch, and Therapanacea. GMB reports institutional scientific grants from Bayer, Servier, Pierre Fabre, and Terumo. FE reports research funding from Deutsche Krebshilfe and Accuray; honoraria and travel support from Zap Surgical and Accuray; and committee or leadership roles including the jDEGRO Trial Group, the Radiosurgery Society, Resident Executive Board, EORTC Brain Tumour Group Steering Committee, European Association of Neuro-Oncology Guidelines Committee, ESTRO CNS Focus Group, DEGRO young Neurooncology Working Group Steering Committee, and EORTC Y-ECI ROSC Steering Committee. SB reports travel and accommodation support to attend EORTC patient days in 2025. DCh reports consulting fees from Medscape; payments for expert testimony from National Institute for Health and Care Research (NIHR) and National Institute for Health and Care Excellence; travel support from NIHR and World Cancer Research Fund Nutrition Initiative and Cancer Research UK conference; an honorarium from Health Data Research Alliance; and unpaid leadership roles with Independent Cancer Patients' Voice, Digestive Cancers Europe, Use MY data, and Oesophageal-Gastric Cancer Support UK. DZ reports honoraria from EORTC; travel and accommodation support from ESTRO, European Society For Medical Oncology (ESMO), and EORTC; a paid leadership role at Europa Donna Albania; an unpaid board membership at Europa Donna–The European Breast Cancer Coalition; and unpaid contributions to EORTC projects. FAN received a fellowship from the Fonds National de la Recherche Scientifique, Belgium, and travel support from Roche for ESMO 2025. VA reports honoraria from Janssen, Healthbook, Accord, Medtis, Astellas, and Viatris; and travel support from Bayer, Recordati, and e-hims. SC reports grants or contracts from Elekta, Brainlab, Viewray, and Siemens; honoraria and travel support from Elekta, Brainlab, and Siemens. DDR reports institutional research support and advisory roles from AstraZeneca, Bristol Myers Squibb (BMS), Beigene, Philips, Olink, Eli-Lilly, and Pfizer; and has no personal financial interests. A-MCD reports institutional grants from the Dutch Cancer Society, Hanarth Fonds, and Goergen Institute for Data Science; institutional consulting fees and honoraria from multiple pharmaceutical companies; advisory board roles for Roche, Lilly, and Boehringer Ingelheim; and unpaid leadership roles with EORTC. CF-F reports institutional grants, consulting fees, travel support, and advisory roles from AstraZeneca. SG reports institutional consulting fees from Ipsen and Avalere Health; institutional lecture honoraria from several organisations and companies; personal lecture honoraria from ESMO and Meister ConCept; travel support from Bayer, Intellisphere, Gilead, and Johnson & Johnson; has one patent (WO2009138392); served on several institutional data safety monitoring and advisory boards; had institutional leadership roles with Pfizer, Linkin Vax, and University of Applied Sciences and Arts of Southers Switzerland; had a guest engagement agreement with American Society of Clinical Oncology paid to her institution; and fulfilled unpaid consultancy roles for Unicancer, AstraZeneca, Pfizer, and Bayer. MGG reports research funding from the Health Region South-Eastern Norway and Norwegian Cancer Society;

unpaid roles on UK and Belgian trial committees (with institutional payment for SHAPERS); an unpaid leadership role in the Norwegian National Expert Group in Radiotherapy; and receipt of investigational products in clinical trials. LH reports institutional research funding and advisory board payments from multiple pharmaceutical companies, institutional payments for speaker engagements (some speaker and guideline committee payments were made directly to them), and serves as local principal investigator for clinical trials sponsored by several companies, with all payments to their institution. WGK reports consulting fees from BMS, mintMedical, Pfizer, Need, Boehringer Ingelheim, Falk Foundation, and AstraZeneca. FEL reports institutional research funding from GE Healthcare and paid advisory board participation for Novartis. AL reports institutional funding from Roche, AstraZeneca, Beigene, Pharmamar, and MSD. YL is promotor of the ESTRO-Value Based Radiation Oncology Chair at the University of Ghent, paid to the institution, and reports unpaid leadership roles at ESTRO and the Belgian Board of Oncology. FM reports consulting fees and honoraria from AstraZeneca. IM reports honoraria from Menarini StemLine, Eli Lilly, MSD, AstraZeneca, Daiichi Sankyo, Novartis, Pfizer, Gilead, TEcnologie MAteriali Sinergie, and Exact Sciences; participation on UK trial data monitoring boards; and committee roles with ESTRO and EORTC. DO-L reports personal honoraria and travel support from Ipsen, Astellas, Bayer, Novartis, Curium, and Telix. JR reports honoraria from Johnson & Johnson (to institution), Regeneron, Boehringer Ingelheim, and AstraZeneca; travel support from MSD and OSE Immunotherapeutics; and roles as Chair of EORTC Lung Cancer Group and editor for *Journal of Thoracic Oncology*, *Journal of Clinical Oncology Oncology Advances*, and *Lung Cancer*. HWMvL reports institutional research grants from Amgen, AstraZeneca, Auristone, BMS, Incyte, Merck, MyeloidTx, Oncolytic Replication Competent Agents, and Servier; institutional consulting fees and honoraria from Amphera, Astellas, Beigene, Daiichi, MyeloidTx, AstraZeneca, BMS, Benecke, Sankyo, JAAP publishing company, Medtalks, Novartis, Servier, and Travel Congress Management; and has a leadership role in ESMO. MV reports the Ghent University Value-Based Radiation Oncology chair, paid to the institution. HMV reports institutional grants or contracts from the Dutch Cancer Society, Horizon Europe, Elekta, and the Dutch Research Council; institutional support from Elekta for attending meetings or travel; personal honoraria from AstraZeneca, Daiichi Sankyo, Lilly, Menarini, Novartis, Gilead, and Pfizer for speaker educationals or webinars; and advisory board payments from AstraZeneca, Daiichi, Pfizer, and Exact Sciences. TZ reports a research grant from Varian, non-remunerated roles with ESTRO, International Society for RadioSurgery, Fond'action contre le cancer, European Multidisciplinary congress on Urologic Cancers, Groupe Francophone de Radiotherpie Urologique, and the Swiss Cancer Institute; institutional honoraria from Janssen, Amgen, Ferring, Debiopharm, Bayer, Astellas, Telix, Recordati, Ipsen, and Accord; and advisory roles for Groupe d'Etudes des Tumeurs Uro Genitales and Programmes d'Experimentations Academiques en Cancerologie de l'Europeenne. PO reports research funding to their institution from Bayer; and has received consulting fees from Janssen-Cilag, Bayer, Astellas Pharma, Telix Pharmaceuticals, Novartis, Astra Zeneca, Curium Pharma, and Recordati. MG reports research support to their institution from Siemens Healthineers –Varian and AstraZeneca; speaker honoraria from AstraZeneca; and advisory board roles for AstraZeneca and Johnson & Johnson. All other authors declare no competing interests.

References

1 Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol* 2011; **8:** 378–82.

2 Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol* 2020; **21:** e18–28.

3 Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. *Radiother Oncol* 2020; **148:** 157–66.

4 Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol* 2018; **4:** e173501.

5 Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non–small-cell lung cancer: long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol* 2019; **37:** 1558–65.

6 Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET Phase II randomized trial. *J Clin Oncol* 2020; **38:** 2830–38.

7 Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019; **393:** 2051–58.

8 Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. *JAMA Oncol* 2020; **6:** 650–59.

9 Deek MP, Van der Eecken K, Sutera P, et al. Long-term outcomes and genetic predictors of response to metastasis-directed therapy versus observation in oligometastatic prostate cancer: analysis of STOMP and ORIOLE trials. *J Clin Oncol* 2022; **40:** 3377–82.

10 Ruers T, Van Coevorden F, Punt CJA, et al, and the European Organisation for Research and Treatment of Cancer (EORTC), and the Gastro-Intestinal Tract Cancer Group, and the Arbeitsgruppe Lebermetastasen und tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO), and the National Cancer Research Institute Colorectal Clinical Study Group (NCRI CCSG). Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. *J Natl Cancer Inst* 2017; **109:** djx015.

11 Tsai CJ, Yang JT, Shaverdian N, et al, and the CURB Study Group. Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (Consolidative Use of Radiotherapy to Block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study. *Lancet* 2024; **403:** 171–82.

12 van der Lei S, Puijk RS, Dijkstra M, et al. Thermal ablation versus surgical resection of small-size colorectal liver metastases (COLLISION): an international, randomised, controlled, phase 3 non-inferiority trial. *Lancet Oncol* 2025; **26:** 187–99.

13 Tannock IF, Amir E, Booth CM, et al. Relevance of randomised controlled trials in oncology. *Lancet Oncol* 2016; **17:** e560–67.

14 Pitroda SP, Weichselbaum RR. Radiotherapy duality in metastatic disease-inhibiting seeding, unmasking dormancy. *JAMA Oncol* 2026; **12:** 24–25.

15 Pe M, Voltz-Girolt C, Bell J, et al. Using patient-reported outcomes and health-related quality of life data in regulatory decisions on cancer treatment: highlights from an EMA-EORTC workshop. *Lancet Oncol* 2025; **26:** 687–90.

16 Booth CM, Sengar M, Goodman A, et al. Common Sense Oncology: outcomes that matter. *Lancet Oncol* 2023; **24:** 833–35.

17 Sanford NN, Lievens Y, Aggarwal A, et al. Common Sense (Radiation) Oncology: redefining targets in radiotherapy. *Radiother Oncol* 2024; **193:** 110118.

18 Lawler M, Davies L, Oberst S, et al. European Groundshot—addressing Europe's cancer research challenges: a *Lancet Oncology* Commission. *Lancet Oncol* 2023; **24:** e11–56.

19 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

20 O JH, Lodge MA, Wahl RL. Practical percist: a simplified guide to PET response criteria in solid tumors 1.0. *Radiology* 2016; **280:** 576–84.

21 Seymour L, Bogaerts J, Perrone A, et al, and the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 2017; **18:** e143–52.

22 Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47:** 207–14.

23 Wen PY, van den Bent M, Youssef G, et al. RANO 2.0: update to the response assessment in neuro-oncology criteria for high- and low-grade gliomas in adults. *J Clin Oncol* 2023; **41:** 5187–99.

24 Tolaney SM, Garrett-Mayer E, White J, et al. Updated Standardized Definitions for Efficacy End Points (STEEP) in adjuvant breast cancer clinical trials: STEEP version 2.0. *J Clin Oncol* 2021; **39:** 2720–31.

25 EORTC. Cohorts. https://project.eortc.org/e2-radiate/cohorts/ (accessed March 24, 2026).

26 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev* 2021; **10:** 89.

27 Pasquier D, Bidaut L, Oprea-Lager DE, et al. Designing clinical trials based on modern imaging and metastasis-directed treatments in patients with oligometastatic breast cancer: a consensus recommendation from the EORTC Imaging and Breast Cancer Groups. *Lancet Oncol* 2023; **24:** e331–43.

28 Wang JH, Sherry AD, Bazyar S, et al. Outcomes of radium-223 and stereotactic ablative radiotherapy versus stereotactic ablative radiotherapy for oligometastatic prostate cancers: the RAVENS phase II randomized trial. *J Clin Oncol* 2025; **43:** 2059–68.

29 Marvaso G, Corrao G, Zaffaroni M, et al. ADT with SBRT versus SBRT alone for hormone-sensitive oligorecurrent prostate cancer (RADIOSA): a randomised, open-label, phase 2 clinical trial. *Lancet Oncol* 2025; **26:** 300–11.

30 Manyara AM, Ciani O, Taylor RS, and the SPIRIT-Surrogate and CONSORT-Surrogate Project team and Consensus Group. Transparent and complete reporting of surrogate endpoints in trials: the SPIRIT-Surrogate and CONSORT-Surrogate extensions. *Lancet* 2024; **404:** 322–24.

31 US FDA. Approaches to assessment of overall survival in oncology clinical trials. August, 2025. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/approaches-assessment-overall-survival-oncology-clinical-trials (accessed Oct 26, 2025).

32 Stevens SX, Teuwen L-A, Gyawali B. Overall survival assessment in cancer drug trials: a luxury or a necessity? *Lancet Oncol* 2025; **11:** 1402–04.

33 Widder J, Simek IM, Goldner GM, Heilemann G, Ubbels JF. Metastases-directed local therapies (MDT) beyond genuine oligometastatic disease (OMD): indications, endpoints and the role of imaging. *Clin Transl Radiat Oncol* 2024; **45:** 100729.

34 Hof J, Wertenbroek MWJLAE, Peeters PMJG, Widder J, Sieders E, de Jong KP. Outcomes after resection and/or radiofrequency ablation for recurrence after treatment of colorectal liver metastases. *Br J Surg* 2016; **103:** 1055–62.

35 Willmann J, Adilovic S, Vlaskou Badra E, et al. Repeat stereotactic body radiotherapy for oligometastatic disease. *Radiother Oncol* 2023; **184:** 109671.

36 Siva S, Sakyanun P, Mai T, et al. Long-term outcomes of TROG 13.01 SAFRON II randomized trial of single- versus multifraction stereotactic ablative body radiotherapy for pulmonary oligometastases. *J Clin Oncol* 2023; **41:** 3493–98.

37 Ruffolo LI, D'Angelica M. Rethinking surrogate endpoints in metastatic colorectal cancer: counting chickens only when they hatch. *J Gastrointest Oncol* 2025; **16:** 1763–67.