

# Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation

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# Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation

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Oligometastatic disease has been proposed as an intermediate state between localised and systemically metastasised disease. In the absence of randomised phase 3 trials, early clinical studies show improved survival when radical local therapy is added to standard systemic therapy for oligometastatic disease. However, since no biomarker for the identification of patients with true oligometastatic disease is clinically available, the diagnosis of oligometastatic disease is based solely on imaging findings. A small number of metastases on imaging could represent different clinical scenarios, which are associated with different prognoses and might require different treatment strategies. 20 international experts including 19 members of the European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer OligoCare project developed a comprehensive system for characterisation and classification of oligometastatic disease. We first did a systematic review of the literature to identify inclusion and exclusion criteria of prospective interventional oligometastatic disease clinical trials. Next, we used a Delphi consensus process to select a total of 17 oligometastatic disease characterisation factors that should be assessed in all patients treated with radical local therapy for oligometastatic disease, both within and outside of clinical trials. Using a second round of the Delphi method, we established a decision tree for oligometastatic disease classification together with a nomenclature. We agreed oligometastatic disease as the overall umbrella term. A history of polymetastatic disease before diagnosis of oligometastatic disease was used as the criterion to differentiate between induced oligometastatic disease (previous history of polymetastatic disease) and genuine oligometastatic disease (no history of polymetastatic disease). We further subclassified genuine oligometastatic disease into repeat oligometastatic disease (previous history of oligometastatic disease) and de-novo oligometastatic disease (first time diagnosis of oligometastatic disease). In de-novo oligometastatic disease, we differentiated between synchronous and metachronous oligometastatic disease. We did a final subclassification into oligorecurrence, oligoprogression, and oligopersistence, considering whether oligometastatic disease is diagnosed during a treatment-free interval or during active systemic therapy and whether or not an oligometastatic lesion is progressing on current imaging. This oligometastatic disease classification and nomenclature needs to be prospectively evaluated by the OligoCare study.

## Introduction

Hellman and Weichselbaum<sup>1</sup> first proposed oligometastatic disease as a distinct cancer state between locally confined and systemically metastasised disease in 1995. In such patients with limited metastatic disease, the value of integrating local metastases-directed therapy into the treatment framework has been investigated in five randomised phase 2 studies. Three of these studies<sup>2-4</sup> have assessed whether or not the addition of metastases-directed local therapy to standard-of-care systemic therapy improves outcome in oligometastatic disease, as compared with systemic treatment alone. All three studies reported improved progression-free survival<sup>2</sup> or overall survival<sup>3,4</sup> with the addition of metastases-directed local therapy. Palma and colleagues<sup>5</sup> described an overall survival benefit of metastases-directed stereotactic body radiotherapy in addition to standard of care for patients with oligometastatic disease with controlled primary malignancy in a tumour-agnostic trial that mostly involved patients with breast, lung, colorectal, and prostate cancer. Ost and colleagues<sup>6</sup> did a study in

patients with oligorecurrent prostate cancer, in which metastases-directed stereotactic body radiotherapy was compared with surveillance; systemic therapy in the form of androgen deprivation was not a component of the initial treatment strategy but was used only at disease progression. Androgen deprivation therapy-free survival was longer with metastasis-directed therapy than with surveillance alone. In another prostate cancer study, the randomised phase 3 STAMPEDE trial, the investigators addressed the hypothesis that local treatment of the primary tumour alone, without metastases-directed therapy, affects outcome in metastatic disease. Local radiotherapy of the prostate was shown to improve overall survival in patients with a low metastatic burden, but not in those with a high metastatic burden, compared with androgen deprivation therapy only.<sup>7</sup>

Conversely, less progress has been made in understanding and defining oligometastatic disease based on tumour biology (ie, in recognising patients with truly limited metastatic capacity by oligometastatic disease-specific biomarkers).<sup>8</sup> MicroRNA profiles, which

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correlate with progression or differentiate oligometastatic and polymetastatic lung disease, have been reported<sup>9,10</sup> as has an integrated molecular subtype for identifying a curable oligometastatic state in colorectal liver metastasis.<sup>11</sup> Dhondt and colleagues<sup>12</sup> described a microRNA signature to identify oligometastatic prostate cancer. However, external or independent validation of these biomarkers has been either unsuccessful or is still absent.

The current scarcity of biomarkers has made imaging the most relevant diagnostic method for defining oligometastatic disease.<sup>13</sup> Rapid advances in imaging that allow identification of small metastases help to differentiate between oligometastatic and polymetastatic disease, thereby excluding patients with more widespread disease from unnecessary local treatment. For example, fluorodeoxyglucose PET has been shown to improve the selection of patients with a low tumour burden in non-small-cell lung cancer and colorectal cancer<sup>14,15</sup> who might benefit the most from radical local metastases-directed treatment. The European Organisation for Research and Treatment of Cancer (EORTC) has identified the crucial role of imaging to standardise and optimise the clinical diagnosis of oligometastatic disease and has published expert recommendations.<sup>16,17</sup> Although these recommendations are intended to assist in the design of clinical trials, European Society for Medical Oncology (ESMO) clinical practice guidelines already refer to these imaging recommendations.<sup>18</sup> Uncertainty remains with regards to the exact meaning of limited metastases; however, trial design and clinical practice today are rather consistent in limiting oligometastatic disease to a maximum of three to five metastases.<sup>19</sup> Despite these improvements in imaging and some consensus on imaging-based definition of oligometastatic disease, clinical outcome after treatment of oligometastatic disease varies substantially: a systematic literature review in oligometastatic non-small-cell lung cancer reported that 5-year overall survival ranges between 86% and 8.3%.<sup>20</sup> This range is equivalent to the variation in overall survival between stage I and stage IV non-small-cell lung cancer.<sup>21</sup> Several studies have proposed prognostic scoring systems or nomograms to achieve more accurate overall survival prediction and patient selection;<sup>22–25</sup> however, all these studies are based on retrospective cohorts with potential bias in patient selection and none have been prospectively validated.

The limitations of imaging, or more precisely its clinical interpretation, could substantially affect clinical outcomes. In fact, Hellman and Weichselbaum<sup>1</sup> described in their landmark paper two very different clinical scenarios, both under the umbrella of oligometastases: “tumors early in the chain of progression with metastases limited in number and location” and “another group of patients with oligometastases who had widespread metastases that were mostly eradicated by systemic agents, the

chemotherapy having failed to destroy those remaining because of the number of tumour cells, the presence of drug-resistant cells, or the tumour foci being located in some pharmacologically privileged site”. These two scenarios of oligometastatic disease, which might present with similar features on imaging but differ substantially from a clinical perspective, are most likely associated with very different outcome and require different treatment strategies. Consequently, better characterisation and classification of the different states of oligometastatic disease is needed.

We have convened a group of international experts in diagnosis and treatment of oligometastatic disease from the EORTC and European Society for Radiotherapy and Oncology (ESTRO) OligoCare project and initiated this consensus process on characterisation and classification of oligometastatic disease. We aimed to establish a comprehensive system of oligometastatic disease characterisation factors, which should be assessed in all patients treated with radical local treatment for oligometastatic disease both inside and outside of clinical trials. These oligometastatic disease characterisation factors were the basis to develop and agree on an oligometastatic disease classification system and nomenclature that cover all possible clinical situations of imaging findings with few metastases. The classification system should be unambiguous, based on established prognostic patient and disease characteristics, and not require additional diagnostic testing. The classification system should also reflect fundamental biological and clinical processes underlying the development of oligometastatic disease and should be independent from the primary tumour type.

## Methods

### Data collection

This project originates from the ESTRO and EORTC OligoCare registry project (EORTC 1822, first cohort of the joint EORTC–ESTRO RADIation InfrAstrucTure for Europe—E2-RADIatE, EORTC 1811, NCT03818503) which aims to identify patient, tumour, staging, and treatment characteristics that affect overall survival of patients treated with metastases-directed radiotherapy for oligometastatic disease. The inclusion criteria for this project are broad to represent the diversity of daily clinical practice and to allow the identification of relevant prognostic and predictive factors. Patients are eligible irrespective of whether oligometastatic disease is diagnosed synchronously or metachronously and regardless of previous surgical, locally ablative therapy, and systemic treatments. Included patients can have been treated previously for oligometastatic or non-oligometastatic disease.

We defined factors for oligometastatic disease characterisation in a two-step process, starting with a systematic literature review followed by a Delphi consensus process. All coauthors of this manuscript

(except DHS) are members of the OligoCare project and represent ESTRO or EORTC as experts in clinical trial design, diagnosis, and treatment of oligometastatic disease. All 19 members of the OligoCare project contributed to all parts of the Delphi consensus definition process.

### Search strategy and selection criteria

We followed PRISMA guidelines for this systematic literature review.<sup>26</sup> PubMed and Embase were searched for prospective clinical trials on oligometastatic disease published in English. Two investigators (MG and DHS) independently searched the databases up to March 24, 2019. The search terms were: ([“oligometastasis” OR “oligometastatic” OR “oligometastases” OR “oligo-recurrence” OR “oligorecurrent” OR “oligoprogression” OR “oligoproggressive” OR “oligopersistent” OR “oligo-persistence”] AND [“randomised” OR “randomized” OR “prospective”]). We also reviewed the references of articles included in the final selection. To be eligible, trials had to be prospective phase 1–3 studies (to reduce bias), be therapeutic interventional studies, and report outcome of overall survival or progression-free survival, or disease recurrence. Studies reporting quality of life only or studies limited to brain metastases were excluded. Two investigators (MG and DHS) independently reviewed the list of retrieved articles and selected potentially relevant articles. The same two investigators independently extracted study inclusion and exclusion criteria data from all selected studies. We did not extract general patient characteristics unrelated to oligometastatic disease (eg, age, sex, or performance status) or comorbidity data. We considered these study inclusion and exclusion criteria as factors for oligometastatic disease characterisation and included them into the Delphi process for consensus definition.

### Consensus formation

We used a Delphi process to establish consensus about oligometastatic disease characterisation factors.<sup>27</sup> We circulated surveys to all individual participants using the online survey tools SurveyMonkey and Google Forms. In round one, the participants were provided with the results of the systematic review. The participants were asked to answer one open-ended question: to describe potential oligometastatic disease characterisation factors and classification factors that had not been identified in the systematic review. We assumed that simultaneous or secondary primaries or non-malignant lesions had been excluded by clinical judgment, repeated or multi-method imaging, or biopsy confirmation. Two investigators (MG and DHS) consolidated all the participants' responses into a list of oligometastatic disease characteristics that was circulated to all participants in the second round of the Delphi process to assess whether or not consolidation did introduce misinterpretations of individual responses. In the third round, all

oligometastatic disease characterisation factors, extracted from the systematic review and from the first two Delphi rounds, were provided to the participants to score each item on a 5-point Likert scale (1=strongly agree; 5=strongly disagree); for each item, we asked: “should the oligometastatic disease characterisation factor be assessed in all patients treated with radical local treatment for oligometastatic disease inside and outside of clinical trials and form the basis for the case report forms of the prospective OligoCare registry trial, assessing real-world practice and outcome in this setting?”. A threshold of 75% or more for agreement or disagreement was required for each item to reach consensus. We analysed all responses and comments, recorded items reaching consensus and did not include these in the subsequent survey. Next, we asked the participants to vote again on items that had not reached 75% or more agreement. Following this round, we excluded from the final recommendations any item that still did not have consensus. We generated a consensus of oligometastatic disease characterisation factors by combining all items that reached consensus. During this phase, only minor modifications to grammar and wording were accepted. No additions or removals of items were permitted.

We developed the oligometastatic disease classification system in a three-step process. First, descriptive tumour and treatment characteristics, quantitative oligometastatic disease characteristics, and characteristics relating to individual metastases were excluded as potential oligometastatic disease classification factors. The remaining oligometastatic disease characteristics were all addressing the process of oligometastatic disease development and were formulated as binary yes or no questions. Second, a decision tree was established on the basis of binary questions. The decision tree started with imaging-based diagnosis of oligometastatic disease and the hierarchical order aimed to minimise the number of branches and considered the temporal course of oligometastatic disease development. Lastly, nomenclatures of previously proposed oligometastatic states<sup>1,28–33</sup> were applied to the decision tree and complemented two of the oligometastatic disease states, which remained unaddressed in the literature.

We assessed the oligometastatic disease classification system for consensus in a Delphi process: we provided the participants with the graphical overview of the classification system in form of a decision tree and each participant scored each oligometastatic disease state on a five-point Likert scale (1=strongly agree; 5=strongly disagree). We set a threshold of 75% or more for agreement or disagreement for each item to reach consensus. In a second round, we provided the participants with the anonymous responses from the previous round. Following this round, any item still without consensus was excluded from final recommendations.

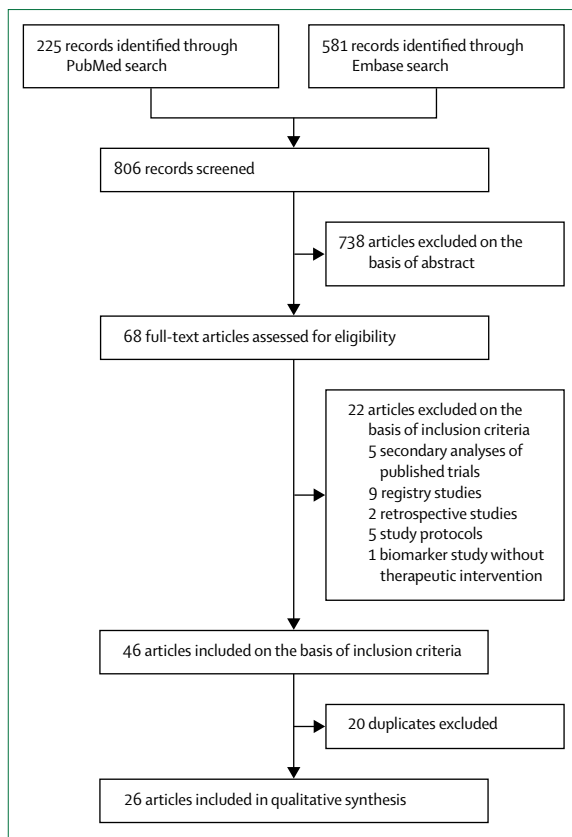


Figure 1: Flowchart of article selection process

## Findings

### Oligometastatic disease characterisation

The systematic review retrieved 806 publications, from which we selected 68 potentially relevant articles after abstract screening. After full-text article review, 46 manuscripts fulfilled the inclusion criteria, and after exclusion of 20 duplicate records or repeated publications of identical clinical trials, 26 studies reporting overall survival or progression-free survival of prospective interventional trials for oligometastatic disease were analysed (figure 1). We identified a total of ten oligometastatic disease-related study inclusion and exclusion criteria in these 26 prospective trials, which were potential candidates for oligometastatic disease characterisation factors (appendix pp 2–3).

See Online for appendix

In the first two rounds of the Delphi process (figure 2, appendix pp 4–5), we collected eight additional candidates for oligometastatic disease characterisation and combined invasive staging with imaging-based staging arriving at a total of 18 characteristics, which were scored independently in rounds 3·1 and 3·2 of the Delphi process (figure 2, appendix pp 6–11). After this Delphi consensus process, we agreed upon all ten oligometastatic disease characteristics identified in the systematic review and added seven additional characteristics to the final list of 17 oligometastatic disease characteristics (panel). The

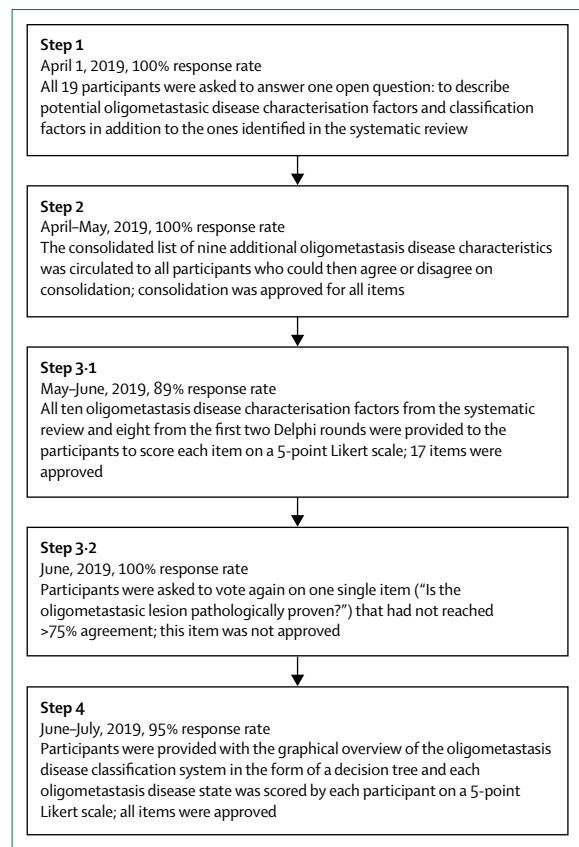


Figure 2: Schematic overview of the Delphi process

response rate of the 19 experts during the Delphi process was at least 89% for all rounds of the process (figure 2).

### Oligometastatic disease characterisation classification

We established and agreed the oligometastatic disease classification system on the basis of the previously agreed characterisation system. After discussion, 17 (94%) of 18 participants agreed (either strongly agreed or agreed) on oligometastatic disease as the umbrella term for all states of limited metastatic disease, staying within the tradition of the original publication of Hellman and Weichselbaum.<sup>1</sup> Differentiation is based on five characterisation factors which we identified as the basis for the oligometastatic disease classification system and decision tree comprising of a total of eight branches and a total of nine distinct states of oligometastatic disease (figure 3 and figure 4).

#### Question 1: Does the patient have a history of polymetastatic disease before current diagnosis of oligometastatic disease?

This question differentiates between genuine oligometastatic disease (patients without a history of polymetastatic disease) and induced oligometastatic disease (patients with a history of polymetastatic disease). In genuine oligometastatic disease, the absence of polymetastatic disease in the patient's history indicates a

low metastatic capacity of cancer. Induced oligometastatic disease has already been described by Hellman and Weichselbaum:<sup>1</sup> “the chemotherapy (or more in general systemic therapy) having failed to destroy (or control) those remaining (metastases) because of the number of tumour cells, the presence of drug-resistant cells, or the tumour foci being located in some pharmacologically privileged site”. Induced oligometastatic disease does therefore not indicate a possible low metastatic capacity, as is the case in genuine oligometastatic disease, but rather a state of disease, which is the result of polymetastatic disease treated with systemic therapy with or without local therapy.

### Question 2: Does the patient have a history of oligometastatic disease before the current diagnosis of oligometastatic disease?

For patients with genuine oligometastatic disease, this question differentiates between de-novo oligometastatic disease (patients without a previous diagnosis of oligometastatic disease) and repeat oligometastatic disease (patients with a previous diagnosis of oligometastatic disease). De-novo oligometastatic disease is the classic state of the disease as initially described by Hellman and Weichselbaum.<sup>1</sup> For patients with a previous diagnosis of oligometastatic disease, who have not progressed to polymetastatic disease after failure to local and systemic treatment, repeat oligometastatic disease might represent a cancer with favourable biology of low metastatic capacity over a long period of time. Polymetastatic disease is the most frequent failure pattern after treatment of oligometastatic disease, but some studies report that repeat oligometastatic disease is observed in 27–75%.<sup>34–36</sup>

### Question 3: Has oligometastatic disease been first diagnosed more than 6 months after the primary cancer diagnosis?

For patients with de-novo oligometastatic disease, this question differentiates between synchronous oligometastatic disease (maximum 6 months interval between diagnosis of oligometastatic disease and primary cancer diagnosis) and metachronous oligometastatic disease (more than 6 months interval between diagnosis of oligometastatic disease and primary cancer diagnosis). No consensus exists in the literature about the interval between primary cancer diagnosis and the development of oligometastatic disease to differentiate between synchronous and metachronous disease;<sup>29</sup> however, diagnosis of oligometastatic disease more than 6 months after diagnosis of the primary tumour has been a frequently used definition for metachronous instead of synchronous oligometastatic disease.<sup>37,38</sup> Although most studies report that synchronous oligometastatic disease is associated with a more aggressive disease phenotype and a worse prognosis than metachronous oligometastatic disease,<sup>22,39,40</sup> these predictions were not confirmed by all studies.<sup>41,42</sup>

#### Panel: Characteristics of oligometastatic disease

##### Descriptive tumour characteristics

- Primary tumour characteristics: primary tumour site, histology, stage according to TNM Classification of Malignant Tumours, mutational status, tumour marker
- History of cancer progression: time interval since first diagnosis, disease-free interval, treatment-free interval
- History of treatment of primary tumour: method of local treatment, radical or palliative intent, controlled primary tumour
- History of systemic therapy before diagnosis of oligometastatic disease: types of systemic therapy, number of lines of systemic therapy
- Oligometastatic disease staging: imaging method, anatomical areas covered, invasive staging
- Involved organs of oligometastatic disease

##### Quantitative characteristics

- Number of metastatic lesions
- Number of involved organs
- Number of lesions per organ
- Maximum size or volume of individual metastasis

##### Developmental characteristics

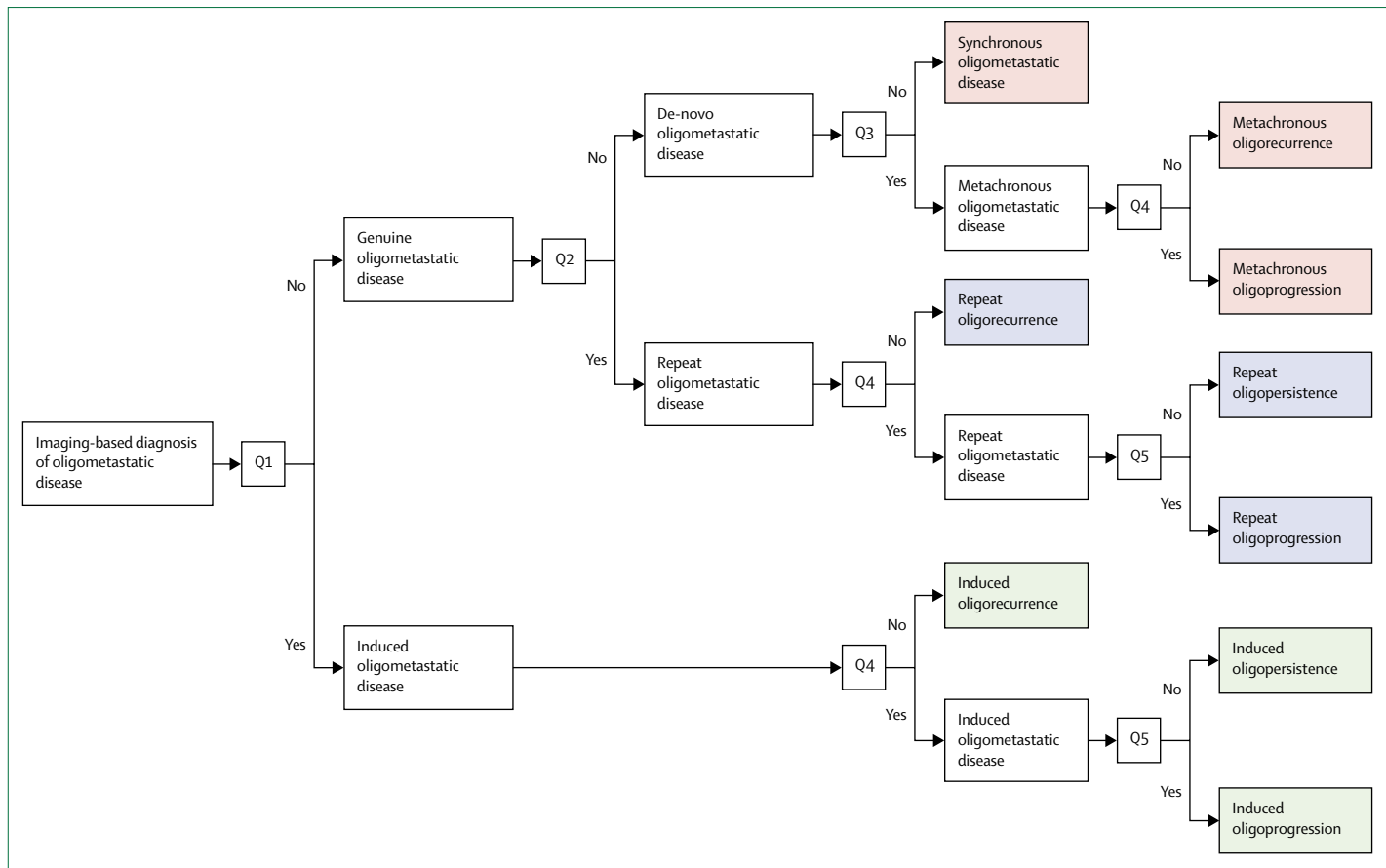
- Does the patient have a history of polymetastatic disease before oligometastatic disease diagnosis?
- Does the patient have a history of oligometastatic disease before current diagnosis?
- Is oligometastatic disease diagnosed within 6 months after diagnosis of the primary tumour?
- Is the patient under active systemic therapy at the time of oligometastatic disease diagnosis?
- Are any oligometastatic lesions progressive on current imaging?

##### Metastases-specific characteristics

- Is the oligometastatic lesion a newly developed metastatic lesion?
- Is treatment of the oligometastatic lesion possible with radical intent?

### Question 4: Is the patient under active systemic therapy at the time of oligometastatic disease diagnosis?

For patients with metachronous oligometastatic disease, repeat oligometastatic disease, and induced oligometastatic disease, development of oligometastatic disease in a treatment-free interval or during active systemic therapy is differentiated. Diagnosis of metachronous oligometastatic disease with the patient under active systemic therapy indicates metachronous oligoprogression. This state of oligometastatic disease is more frequently expected in those cancers that are treated with long-term systemic therapy at primary diagnosis (eg, androgen deprivation therapy for high-risk prostate cancer, endocrine therapy for breast cancer, or targeted therapy for driver-mutated non-small-cell lung cancer). The finding of repeat



**Figure 3: Decision tree for classification of oligometastatic disease**

The decision tree starts with oligometastatic disease as umbrella term. Questions 1 and 2 differentiate between the upper-level oligometastatic states of de-novo (red), repeat (blue) and induced oligometastatic disease (green). Question 3 differentiates de-novo oligometastatic disease into synchronous and metachronous oligometastatic disease. Questions 4 and 5 subclassify into oligorecurrence, oligoprogession, and oligopersistence. Q1: Does the patient have a history of polymetastatic disease before current diagnosis of oligometastatic disease? Q2: Does the patient have a history of oligometastatic disease before current diagnosis of oligometastatic disease? Q3: Has oligometastatic disease been first diagnosed more than 6 months after the primary cancer diagnosis? Q4: Is the patient under active systemic therapy at the time of oligometastatic disease diagnosis? Q5: Are any oligometastatic lesions progressive on current imaging?

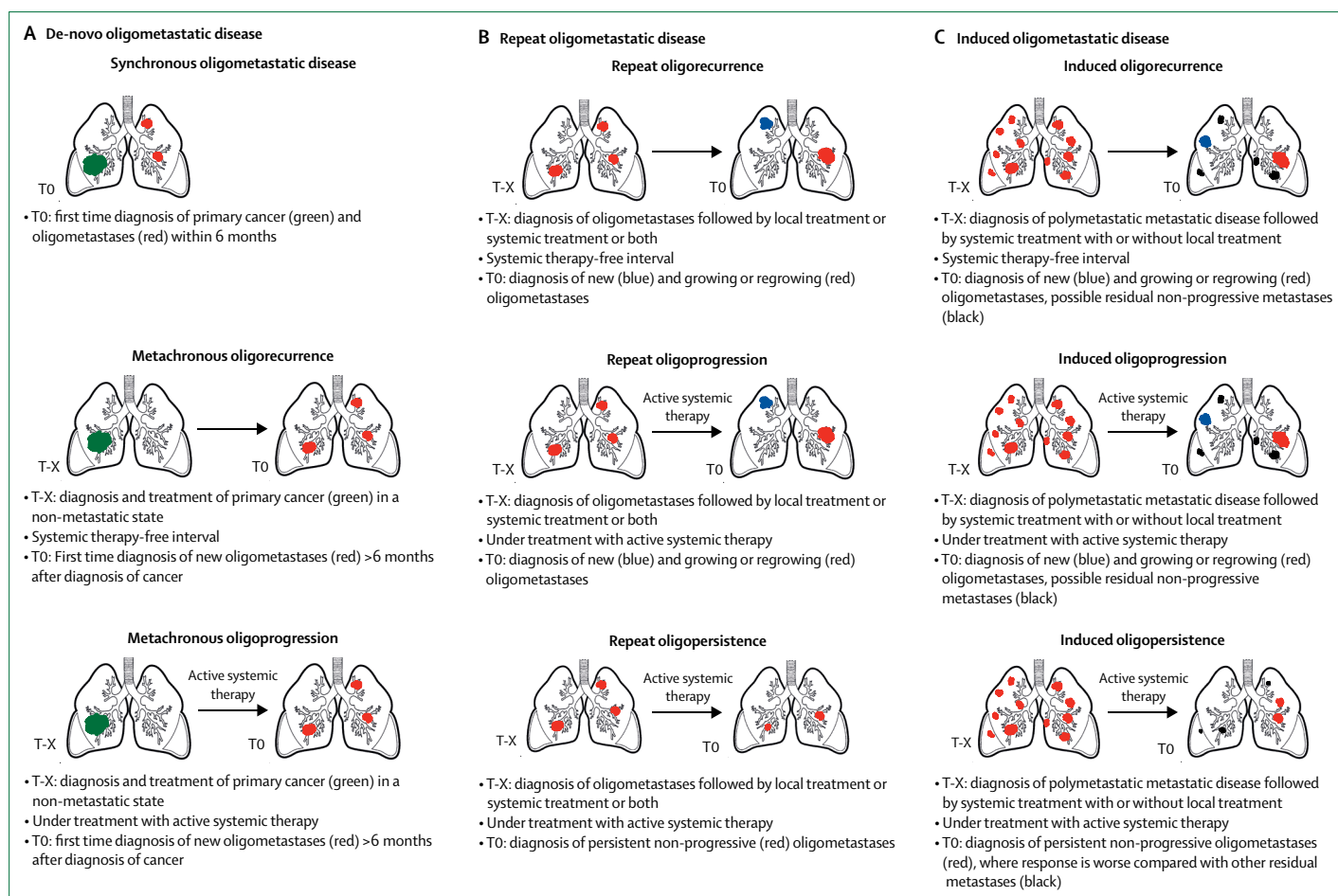
oligometastatic disease and induced oligometastatic disease with the patient under active systemic therapy requires further sub-classification by question five and is explained below. Metachronous, repeat, and induced oligometastatic disease in patients not under active systemic therapy indicates oligorecurrence: the cancer responded well to local treatment, systemic treatment, or both, which allowed a treatment-free interval, and disease recurred later presenting as only a small number. The term oligo refers to the small number of growing or newly developed metastases; patients with induced oligorecurrence might have additional stable metastases, and the value of treating these stable metastases is currently unclear.

**Question 5: Are any oligometastatic lesions progressive on current imaging?**

For patients with repeat oligometastatic disease and induced oligometastatic disease under active systemic treatment, this question differentiates between

oligoprogession (progressive disease on current imaging) and oligopersistence (stable disease or partial response on current imaging). The term oligo refers to a few growing or newly developed metastases (oligoprogession) or a few persistent metastases (oligopersistence). Patients with induced oligoprogession or induced oligopersistence might have additional metastases, which are controlled by or respond to systemic therapy; the value of treating these nonprogressive and nonpersistent metastases locally is currently unclear.

To the best of our knowledge, no data about the incidence and prognosis of repeat oligoprogession and repeat oligopersistence are available. Induced oligoprogession is a well-recognised state of oligometastatic disease: several studies have been done in patients with oligoprogessive non-small-cell lung cancer, in whom systemic therapy achieved good responses of polymetastatic disease but only a few metastases developed resistance and progressed later on; local ablative



**Figure 4: Illustration of the oligometastatic disease classification system**

(A) De-novo oligometastatic disease. (B) Induced oligometastatic disease. (C) Repeat oligometastatic disease. In repeat and induced oligometastatic disease the primary tumour is assumed to be controlled by ongoing or previous treatment. Oligometastases are confirmed by imaging or biopsy to exclude simultaneous or secondary primary tumours. T0=at this current point of time. T-x=any previous point in time.

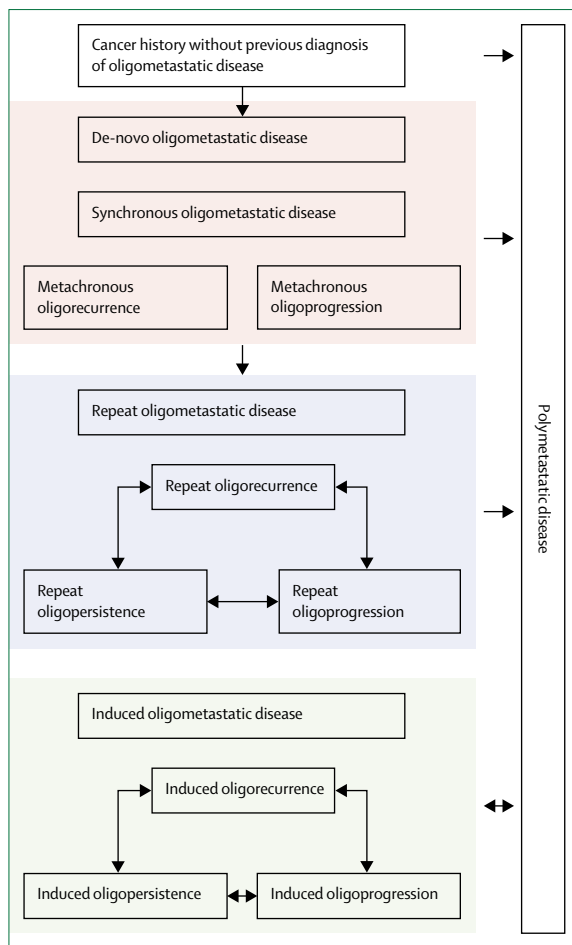
treatment was combined with either continuation of systemic therapy<sup>43–47</sup> or switch to the next treatment line.<sup>48</sup> In patients with induced oligopersistence, only stable disease or partial response is achieved in a few metastases, whereas a prolonged partial response or complete response is observed in the remaining polymetastatic disease. Both randomised trials in oligometastatic non-small-cell lung cancer enrolled patients with stage IV non-small-cell lung cancer after completing systemic therapy, irrespective of their tumour burden at their primary cancer diagnosis; the oligometastatic state was defined at the time of restaging after first-line therapy.<sup>2,4</sup> Consequently, heterogeneous patients could have been recruited into these trials: ie, a mixture of patients with chemotherapy-resistant or targeted therapy-resistant genuine oligometastatic disease and patients with induced oligopersistence, in whom systemic treatment of polymetastatic disease achieved a complete response except for a few resistant metastases.

## Treatment strategies and goals

Traditionally, local treatment for metastatic disease, irrespective of oligometastatic or polymetastatic state, was exclusively done with palliative intent. The systemic treatment strategy was dependent on several factors, including patient characteristics such as age and comorbidities; primary cancer type and molecular disease features; pattern, volume, and kinetics of disease progression; presence of symptoms; previous history of cancer treatment such as response to systemic treatment or disease-free interval; availability of current and future systemic therapy options, and their efficacy and toxicity profile; and patient's preference.

Both treatment goals and treatment strategies have changed with the introduction of the concept of oligometastatic disease. In clinical trials, overall survival, progression-free survival, avoidance of systemic therapy (eg, androgen-deprivation therapy in oligometastatic prostate cancer), and quality of life are the most frequently defined endpoints.<sup>31,49</sup> Whereas local treatment





**Figure 5: Dynamic oligometastatic state model**  
 The model illustrates pathways for developing multiple and different states of oligometastatic disease throughout a patient's disease history. Patients might have de-novo oligometastatic disease or develop induced oligometastatic disease via polymetastatic disease as first-time diagnosis of oligometastatic disease. Repeat oligometastatic disease might develop as a degree of failure after treatment of de-novo oligometastatic disease; induced oligometastatic disease might develop after systemic failure following treatment of de-novo and repeat oligometastatic disease. Patients with repeat oligometastatic disease and induced oligometastatic disease might have dynamic transitions between oligorecurrent, oligoprogressive, and oligopersistent disease, depending on the response to local and systemic therapy.

aims to eradicate all oligometastases and the potentially uncontrolled primary tumour, the choice of the optimal combination strategy with systemic treatment depends on the oligometastatic disease state, the specific treatment goal, and the factors mentioned.

For all states of de-novo oligometastatic disease and repeat oligometastatic disease, radical treatment aims to achieve a status of freedom from disease. Translation of such status into prolonged overall survival or cure will depend on the efficacy of local treatment and on the absence or effective control of occult metastatic disease by the addition of systemic therapy. Consequently, all but one<sup>6</sup> randomised trials in oligometastatic disease published so far used standard systemic therapy as a

backbone of the oligometastatic disease treatment strategy.<sup>2-5</sup> The choice of the optimal systemic therapy is especially unclear in metachronous oligoprogression, in which oligometastatic disease develops during active systemic therapy in the context of primary treatment, and continuation of systemic therapy or switching to another drug are sensible options. Synchronous oligometastatic disease adds another level of complexity because local treatment to the locoregional primary tumour, local treatment of all oligometastases, and systemic treatment all need to be combined into one treatment strategy. However, another goal of the local intervention in de-novo oligometastatic disease and repeat oligometastatic disease could be to prolong the time until systemic therapy is needed for polymetastatic disease and thereby maintain the patient's quality of life. This strategy has been tested for oligorecurrent prostate cancer, for which local metastases-directed therapy considerably prolonged the time until initiation of androgen deprivation therapy.<sup>6</sup>

Treatment goals and strategies are different in induced oligometastatic disease. These patients have polymetastatic disease, which is converted into a state of induced oligometastatic disease by partially effective systemic treatment. Local treatment for induced oligometastatic disease therefore complements the systemic treatment and not vice versa as is the case in genuine oligometastatic disease. Consequently, based on currently available evidence, cure is not achieved in most patients.

For patients with induced oligorecurrence, radical local treatment aims to restore a status of stable disease (in case of stable residual polymetastatic disease) or a status of complete response (in case of complete response of previous polymetastatic disease). The addition of systemic therapy could potentially enhance the effect of the local intervention. Whether systemic therapy is best performed as re-challenge with the previous line of treatment—which achieved stable disease or complete response and a systemic therapy-free interval thereafter—or switch to the next line of treatment is unknown. Another goal of the local intervention could be to prolong the systemic therapy-free interval.

For patients with induced oligoprogression, radical local treatment aims to restore a status of overall sensitivity to systemic therapy through eradication of oligometastases with resistance to the current line of systemic therapy. For patients with induced oligopersistence, the goal of radical local treatment is to achieve an overall deeper response to systemic therapy by eradication of oligometastases with reduced sensitivity to the current line of systemic therapy. In both induced oligoprogression and induced oligopersistence, continuation of the current systemic therapy or switching to the next line of systemic therapy are possible options. The decision depends on the previous depth and duration of response, the volume and kinetics of progressive disease, associated symptoms, tolerability of the current and next

line of systemic treatments, and likely efficacy of the next line of systemic treatment.

### Dynamic oligometastatic state model

The proposed oligometastatic disease classification system defines the oligometastatic state at one timepoint in the patient's history. However, one patient might develop several and different states of oligometastatic disease throughout the course of disease, resulting in multiple courses of radical local and systemic treatment. Similar to the clinical states model proposed for prostate cancer,<sup>50</sup> we therefore propose a dynamic oligometastatic state model (figure 5). First-time diagnosis of oligometastatic disease might occur as de-novo oligometastatic disease or as induced oligometastatic disease after systemic therapy of polymetastatic disease. Repeat oligometastatic disease might be the consequence of failure after treatment of de-novo oligometastatic disease, with failure being again limited to a few metastases. Following local ablative therapy with or without systemic therapy of de-novo or repeat oligometastatic disease, cancer might progress into polymetastatic disease. This situation will trigger initiation of systemic therapy, which might result in induced oligometastatic disease. Within repeat oligometastatic disease and within induced oligometastatic disease, patients can have dynamic transitions between oligorecurrent, oligoprogressive, and oligopersistent disease, depending on the response to local and systemic therapy.

For the three upper-level states of de-novo oligometastatic disease, repeat oligometastatic disease and induced oligometastatic disease, transition to any downstream state is possible, which is then unidirectional in the patient's history. Notwithstanding, transition from one oligometastatic state to another is not necessarily associated with a worsening of the prognosis. A patient with several courses of treatment for repeat oligometastatic disease most likely has a disease phenotype with truly limited metastatic capacity because no progression to polymetastases has developed.<sup>51</sup> Additionally, patients with induced oligometastatic disease might have long-term survival when radical local treatment is combined with effective systemic treatment, such as targeting drugs for non-small-cell lung cancer with driver mutations or immunotherapy for malignant melanoma.

Clinical data support this dynamic oligometastatic state model with several sequential courses of radical local therapy for oligometastatic disease. A registry study on oligometastatic non-small-cell lung cancer reported that 6.6% of all patients treated for oligometastatic non-small-cell lung cancer received more than one course of treatment and a maximum of four courses of metastases-directed stereotactic body radiotherapy.<sup>51</sup> Similarly, complex and long histories of oligometastatic disease, with up to maximum of four courses of radical local treatment, have been reported for prostate cancer.<sup>35</sup> A patient case example with multiple course of

metastases-directed therapy for different states of oligometastatic disease is given in the appendix p15.

### Implementation

The proposed oligometastatic disease characteristics should be assessed in all patients with cancer treated with radical local treatment for oligometastatic disease, although use of the classification as a definitive decision-making tool remains to be established. These characteristics should enable harmonisation of reporting of patients treated for oligometastatic disease and therefore allow outcome analyses of improved quality. In the context of clinical trials, the harmonised oligometastatic disease characterisation system will contribute to a better understanding and interpretation of study results and facilitate cross-study comparisons, as well as meta-analyses and systematic reviews. Acceptance and implementation of oligometastatic disease-related clinical trials into clinical practice will be facilitated by a clear and unambiguous classification system and nomenclature.

### Conclusions

In summary, we have established a system for comprehensive characterisation of oligometastatic disease, which should be assessed in all patients with oligometastatic disease treated with radical local therapy within and outside of clinical trials. We have developed an oligometastatic disease classification system on the basis of a decision tree of five binary disease characterisation factors and we have proposed a dynamic oligometastatic state model. We envisage to test these states of oligometastatic disease in the OligoCare prospective cohort trial (NCT03818503) to assess their prognostic value and their acceptance and compliance in routine practice.

#### Contributors

MG, YL, and PO designed the project. MG, YL, PO, and DHS collected data and did the literature review. MG, YL, PO, and DHS analysed the data. All authors contributed to the interpretation of data and writing and approval of the manuscript.

#### Declaration of interests

MG reports grants from Varian and an advisory board role at AstraZeneca, outside the submitted work. YL reports personal fees from AstraZeneca and RaySearch, outside the submitted work. AD reports grants and personal fees from Varian Medical Systems and personal fees from Medical Data Works and Roche, outside the submitted work. AMCD reports grants and personal fees from BMS and personal fees from Roche, MSD, Eli Lilly, Takeda, Pfizer, and Boehringer Ingelheim, outside the submitted work. AMR reports grant from Varian Medical Systems, outside the submitted work. BT reports personal fees from Amgen, Janssen, Sanofi-Genzyme, and Myovant, and grants and personal fees from Astellas, Bayer, and Ferring, outside the submitted work. DV reports grants from RaySearch Laboratories, Sun Nuclear Corporation, and Sordina IORT Technologies, outside the submitted work. PO reports grants from Ferring, Merck, and Varian, and consultancy and advisory board roles at Janssen, Bayer, and Sanofi, outside the submitted work. The other authors declare no competing interests.

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