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Abstract: Oligometastatic disease (OMD) has been proposed as an intermediate stage between localized and systemically metastasized disease. Early clinical trials support the hypothesis of improved survival by adding radical local therapy to standard systematic therapy for OMD. However, no biomarker for identification of truly oligometastatic patients is clinically available and therefore the diagnosis of OMD is only based on imaging findings. Limited numbers of metastases on imaging may represent very different clinical scenarios, which are associated with different prognosis and may require different treatment strategies. A comprehensive system for characterization and classification of OMD was developed by 19 international experts from the ESTRO & EORTC OligoCare project. A systematic review identified inclusion and exclusion criteria of prospective interventional OMD clinical trials and a Delphi process was designed and run until consensus was reached on a total of 17 OMD characterization factors. Five binary OMD characterization factors were identified for classification of OMD. A decision tree for OMD classification was established by consensus in a second Delphi process. Oligometastatic disease was agreed on as the overall umbrella term. A history of polymetastatic disease before diagnosis of OMD differentiates between induced OMD (prior history of polymetastatic disease) and genuine OMD (no prior history of polymetastatic disease). Genuine OMD is further subclassified into repeat OMD (prior history of OMD) and de-novo OMD (first time diagnosis of OMD). In de-novo OMD, synchronous and metachronous OMD are differentiated. Upper-level OMD states are further subdivided into oligorecurrence, oligoprogression and oligopersistence, which considerer whether OMD is diagnosed during a treatment-free interval or whilst receiving active

systemic therapy and whether any oligometastatic lesion is progressive on current imaging or not. This proposed OMD classification and nomenclature needs to be prospectively evaluated, which will be performed in the OligoCare study.

Characterization and classification of oligometastatic disease: an ESTRO and EORTC consensus recommendation

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Summary

Oligometastatic disease (OMD) has been proposed as an intermediate stage between localized and systemically metastasized disease. Early clinical trials support the hypothesis of improved survival by adding radical local therapy to standard systematic therapy for OMD. However, no biomarker for identification of truly oligometastatic patients is clinically available and therefore the diagnosis of OMD is only based on imaging findings. Limited numbers of metastases on imaging may represent very different clinical scenarios, which are associated with different prognosis and may require different treatment strategies. A comprehensive system for characterization and classification of OMD was developed by 19 international experts from the ESTRO & EORTC *OligoCare* project. A systematic review identified inclusion and exclusion criteria of prospective interventional OMD clinical trials and a Delphi process was designed and run until consensus was reached on a total of 17 OMD characterization factors. Five binary OMD characterization factors were identified for classification of OMD. A decision tree for OMD classification was established by consensus in a second Delphi process. Oligometastatic disease was agreed on as the overall umbrella term. A history of polymetastatic disease before diagnosis of OMD differentiates between induced OMD (prior history of polymetastatic disease) and genuine OMD (no prior history of polymetastatic disease). Genuine OMD is further subclassified into repeat OMD (prior history of OMD) and de-novo OMD (first time diagnosis of OMD). In de-novo OMD, synchronous and metachronous OMD are differentiated. Upper-level OMD states are further subdivided into oligorecurrence, oligoprogression and oligopersistence, which considerer whether OMD is diagnosed during a treatment-free interval or whilst receiving active systemic therapy and whether any oligometastatic lesion is progressive on current imaging or not. This proposed OMD classification and nomenclature needs to be prospectively evaluated, which will be performed in the *OligoCare* study.

Introduction

Hellman and Weichselbaum first proposed oligometastatic disease (OMD) as a distinct cancer stage between locally confined and systemically metastasized disease in 1995 [1]. Until today, three randomized trials have evaluated whether the addition of local metastases-directed therapy to standard-of-care systemic therapy improves outcome in OMD, as compared to systemic treatment alone: all three studies reported improved progression-free survival (PFS) [2] or overall survival (OS) [3,4]. Palma et al. described an OS benefit of metastases-directed stereotactic body radiotherapy (SBRT) in addition to standard-of-care for OMD patients with controlled primary malignancy in a tumor-agnostic trial of mostly breast, lung, colorectal and prostate cancer [5]. Ost et al. used a study design in oligometastatic prostate cancer where metastasis-directed SBRT was compared with surveillance; systemic therapy in the form of androgen deprivation was not a component of the initial treatment strategy but used only at disease progression [6]. In metastatic prostate cancer, local radiotherapy of the prostate was shown to improve OS in the situation of low metastatic burden but not in high metastatic burden, compared to androgen deprivation therapy only [7].

Conversely, less progress has been made in understanding and defining OMD based on biology, i.e. in recognizing patients with truly limited metastatic capacity, based on OMD-specific biomarkers [8]. A microRNA profile which differentiates oligo- and poly-metastatic lung disease has been reported [9,10] as well as an integrated molecular subtype for identifying a curable oligometastatic state in colorectal liver metastasis [11]. Dhondt et al. described a microRNA signature to identify oligometastatic prostate cancer [12]. However, external or independent validation of these biomarkers has been either unsuccessful or is still lacking.

The current lack of biomarkers has made imaging the most relevant diagnostic modality for defining OMD. Rapid advances in imaging that allow identification of small lesions aid in differentiating between oligo- and poly-metastatic disease, thereby excluding patients with more widespread disease from unnecessary local treatment. For example, Fluorodeoxyglucose positron emission tomography (FDG-PET) has been shown to improve the selection of patients with low tumor burden in non-small cell lung cancer (NSCLC) and colorectal cancer [13,14] who might benefit the most from radical local metastases-directed treatment. The EORTC has identified the crucial role of imaging to standardize and optimize the clinical diagnosis of OMD and has published expert recommendations [15,16]. Although

these recommendations are intended to assist in the design of clinical trials, ESMO clinical practice guidelines already refer to these imaging recommendations [17].

In today's clinical practice, imaging is therefore the primary diagnostic modality for OMD [18]. The current NSCLC ESMO guideline defines OMD as "limited number of distant metastases" [17]. There is still relevant uncertainty what "limited" actually means, but trial design and clinical practice today are usually rather consistent in limiting OMD to a maximum of three to five metastases [19]. Despite these improvements in imaging and some consensus on imaging-based definition of OMD, clinical outcome after treatment of OMD varies substantially: a systematic literature review in oligometastatic NSCLC reported a range of 5-year OS between 8.3% and 86% [20]. This is equivalent to the variation in OS between stage I and stage IV NSCLC.

The limitations of imaging, or more precisely its clinical interpretation, could substantially impact clinical outcome. In fact, Hellman and Weichselbaum already described in their landmark paper two very different clinical scenarios, both under the umbrella of "Oligometastases": (1) "Tumors early in the chain of progression with metastases limited in number and location" and (2) "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 tumor cells, the presence of drug-resistant cells, or the tumor foci being located in some pharmacologically privileged site" [1]. These two scenarios of OMD might present similar features on imaging but differ substantially from a clinical perspective, are most likely associated with very different outcome, and require different treatment strategies. There is consequently a need to better characterize and classify the different states of OMD.

This project aims to develop a consensus between a group of international experts in diagnosis and treatment of OMD from the EORTC and ESTRO *OligoCare* project on how to characterize OMD comprehensively. This characterization will then be used to develop and agree on an OMD classification system that covers all possible clinical situations resulting in imaging findings of a limited number of metastases and diagnosis of OMD. 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 OMD and be independent from the primary tumor type.

Methods

This project originates from the ESTRO & 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, tumor, staging, and treatment characteristics that impact OS of patients treated with metastases-directed radiotherapy for OMD. The inclusion criteria for this international prospective registry project are broad to reflect the diversity of daily clinical practice and to allow the identification of relevant prognostic and predictive factors. Patients are eligible irrespective of whether OMD is diagnosed synchronously or metachronously and irrespective of prior surgical, locally ablative radiotherapy and systemic treatments. Patients may have been treated previously for oligometastatic or non-oligometastatic disease.

All co-authors 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 OMD. All 19 participants contributed to all parts of the consensus definition process.

Factors for OMD characterization were defined in a two-step process, starting with a systematic literature review followed by a Delphi consensus process. It is the goal that these OMD characteristics will be assessed in all cancer patients treated with radical local treatment for OMD inside and outside of clinical trials and will form the basis for the prospective OligoCare registry trial, assessing real-world practice and outcome in this setting.

Systematic literature review

We followed PRISMA guidelines for this systematic literature review [21]. We searched PubMed and Embase for prospective clinical trials published about OMD. Two investigators (MG and DHS) independently searched the databases up to March 24th 2019. The search terms were: (oligometastasis OR oligometastatic OR oligometastases OR oligorecurrence OR oligorecurrent OR oligoprogression OR oligoprogressive OR oligopersistent OR oligopersistence) AND (randomised OR randomized OR prospective). We also reviewed the references of articles included in the final selection. To be eligible, trials needed to be prospective phase I - III studies AND be therapeutic interventional studies AND report outcome of OS or PFS or recurrence rates. 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 and the same

two reviewers independently extracted data from the studies. Data extracted were study inclusion and exclusion criteria, aiming to identify OMD characterization factors used in prospective clinical trials. General patient characteristics unrelated to OMD (e.g. age, sex) and comorbidity data were not extracted.

Consensus formation

A Delphi process was used to establish consensus about OMD characterization factors [22]. Surveys were circulated to all individual participants using the online survey tools SurveyMonkey and Google Forms. In round 1, the participants were provided with the results of systematic review (see Appendix for detailed description). The participants were asked to answer one open-ended question: to describe potential OMD characterization factors and classification factors which had not been identified in the systematic review (Step 1, Table S2). All responses were consolidated by two investigators (MG and DHS) and the consolidated list of OMD characteristics was circulated to all participants in the second round of the Delphi process in order to assess whether consolidation did introduce misinterpretations of individual responses (Step 2, Table S3). In the third round, all OMD characterization 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): the question for each item was: "should the OMD characterization factor be assessed in all cancer patients treated with radical local treatment for OMD inside and outside of clinical trials and form the basis for the CRFs of the prospective OligoCare registry trial, assessing real-world practice and outcome in this setting" (Step 3.1, Table S4). A threshold of ≥75% for agreement or disagreement was required for each item to reach consensus. All responses and comments were analyzed, items reaching consensus were recorded and were not included in the subsequent survey. Next, participants were asked to vote again on items that had not reached ≥75% agreement (Step 3.2, Table S5). Following this round, any item still lacking consensus was excluded from final recommendations. All items reaching consensus were aggregated to generate a consensus of OMD characterization factors. During this phase, only minor modifications to grammar and wording were accepted. No additions or removals of items were permitted.

The OMD classification system was developed in a three-step process. (1) Descriptive tumor and treatment characteristics, quantitative OMD characteristics and characteristics relating to individual metastases were excluded as potential OMD classification factors. The

remaining OMD characteristics were all addressing the process of OMD development and were formulated as binary yes/no questions. (2) Based on the binary questions, a decision tree was established. The decision tree started with imaging-based diagnosis of OMD and the hierarchical order aimed to minimize the number of branches and considered the temporal course of OMD development. (3) Nomenclatures of different oligometastatic states [1,23–28] were then applied to the decision tree and complemented for nodes, which remained unaddressed in the current literature.

The OMD classification system was assessed for consensus in a Delphi process (Step 4, Table S6): the participants were provided with the graphical overview of the classification system in form of a decision tree and each OMD state was scored by each participant on a five-point Likert scale (1 = strongly agree; 5 = strongly disagree). A threshold of ≥75% for agreement or disagreement was required for each item to reach consensus. In a second round, participants were provided the anonymous responses from the previous round. Following this round, any item still without consensus was excluded from final recommendations.

OMD characterization

Our database search retrieved 806 publications, from which we selected 68 potentially relevant articles after abstract screening. After full 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 OS or PFS of prospective interventional trials for OMD were analyzed (figure 1); study details are summarized in table S1 (appendix).

The full Delphi process is summarized in figure 2. Tables S2 and S3 summarize OMD-related study inclusion and exclusion criteria identified in the systematic literature review, which were potential candidates for OMD characterization factors. After four rounds of the Delphi consensus process, all ten OMD characteristics identified in the systematic review were agreed upon and seven additional OMD characteristics were added (table 1). Additionally, primary tumor characteristics were complemented by tumor mutational status and tumor marker status, and OMD staging was complemented by invasive staging procedures. The response rate of the 19 experts during the Delphi process was 89% at minimum during all rounds.

OMD classification

A comprehensive OMD classification system was established and reached consensus, where oligometastatic disease is the umbrella term for all states of limited metastatic disease, to stay within the tradition of the original publication of Hellman and Weichselbaum [1]. Differentiation is based on five OMD characterization factors which were identified as the basis for the OMD classification system and decision tree. This resulted in a total of eight branches and a total of nine distinct states of OMD. The full classification system is illustrated in figure 3 and each individual state of OMD is illustrated separately in figure 4

Question 1: Does the patient have a history of polymetastatic disease before current diagnosis of OMD? This question differentiates between ***genuine OMD*** (patients without a history of polymetastatic disease) and ***induced OMD*** (patients with a history of polymetastatic disease). In genuine OMD the absence of polymetastatic disease in the patient`s history indicates a limited metastatic capacity of cancer. Induced OMD has already been described by Hellman and Weichselbaum [1]: "the chemotherapy (or more in general systemic therapy) having failed to destroy (or control) those remaining (lesions) because of the number of tumor cells, the presence of drug-resistant cells, or the tumor foci being located in some pharmacologically privileged site". Induced OMD does therefore not indicate a possible limited metastatic capacity, as in genuine OMD, but a state of disease, which is the result of polymetastatic disease treated with systemic +/- local therapy.

Question 2: Does the patient have a history of OMD before current diagnosis of OMD? For patients with genuine OMD, this question differentiates between **de-novo OMD** (patients without prior diagnosis of OMD) and **repeat OMD** (patients with prior diagnosis of OMD). De-novo OMD is the classical state of OMD as initially described by Hellman and Weichselbaum [1]. In case OMD has previously been diagnosed in the patient's history, and disease has not become polymetastatic after failure of local and systemic treatment, repeat OMD may represent a favorable biology of limited metastatic capacity over a longer period of time. Polymetastatic disease is the most frequent failure pattern after treatment of OMD, but some studies report that repeat OMD is observed in 27-75% of OMD patients [29–31].

Question 3: Has OMD been first diagnosed >6 months after primary cancer diagnosis? For patients with de-novo OMD, this question differentiates between **synchronous OMD** (maximum 6 months interval between diagnosis of OMD and primary cancer diagnosis) and **metachronous OMD** (more than six months interval between diagnosis of OMD and primary

cancer diagnosis). There is no consensus about the interval between primary cancer diagnosis and development of OMD to differentiate between synchronous and metachronous disease [24]; however, diagnosis of OMD more than six months after diagnosis of the primary tumor has been a frequently used definition in the literature [32,33]. Whereas most studies report that synchronous de-novo OMD is associated with a more aggressive disease phenotype and a worse prognosis compared to metachronous de-novo OMD [34–36], this was not confirmed by all studies [37,38].

Question 4: Is the patient under active systemic therapy at the time of OMD diagnosis? For patients with metachronous OMD, repeat OMD and induced OMD, development of OMD in a treatment-free interval or during active systemic therapy should be differentiated. Diagnosis of metachronous OMD with the patient under active systemic therapy indicates **metachronous oligoprogression**. This state of OMD is more frequently expected in cancers with long-term systemic therapy at first diagnosis of cancer, e.g. androgen deprivation therapy (ADT) for high-risk prostate cancer, endocrine therapy for breast cancer or targeted therapy for driver-mutated NSCLC. Diagnosis of repeat OMD and induced OMD with the patient under active systemic therapy requires further sub-characterization by question five and is explained below. Diagnosis of metachronous, repeat and induced OMD with the patient not under active systemic therapy indicates **oligorecurrence**: cancer responded well to local and/or systemic treatment, which allowed a treatment-free interval, and disease recurred later as only a limited number of lesions.

Question 5: Are any oligometastatic lesions progressive on current imaging? For patients with repeat OMD and induced OMD under active systemic treatment, this question differentiates between **oligoprogression** (progressive disease on current imaging) and **oligopersistence** (stable disease or partial response on current imaging).

To the best of our knowledge, no data about incidence and prognosis of repeat oligoprogression and repeat oligopersistence is available. Induced oligoprogression is a well-recognized state of OMD: several studies have been conducted in oligoprogressive NSCLC patients, where systemic therapy achieved good response of polymetastatic disease but only few metastases progressed later on; local ablative treatment was combined with either continuation of systemic therapy [39–43] or switch to the next treatment line [44]. In patients with induced oligopersistence, only stable disease or partial response is achieved in the oligometastatic lesions, while a prolonged partial response or complete response is

observed in the remaining polymetastatic disease. Both randomized trials in oligometastatic NSCLC recruited patients with stage IV NSCLC after completing systemic therapy, irrespective of their tumor burden at primary diagnosis of NSCLC: the oligometastatic state was diagnosed at restaging after first-line therapy [2,4]. Consequently, heterogeneous patients could have been recruited into these trials: patients with chemotherapy- or targeted therapy resistant genuine OMD and patients with induced oligopersistence where systemic treatment of polymetastatic disease achieved complete response except for few resistant lesions.

Treatment strategies and goals

Traditionally, local treatment of metastatic disease, irrespective of oligometastatic or polymetastatic, was exclusively performed with palliative intent. The systemic treatment strategy was dependent on multiple 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, prior history of cancer treatment such as response to systemic treatment or disease-free interval, availability of current and future systemic therapy options, their efficacy and toxicity profile and patient preference.

Both treatment goals and treatment concepts have changed with the introduction of the concept of OMD. Considering the various states of OMD, it is obvious that the goals and strategies vary substantially. Within clinical trials, OS, PFS, avoidance of systemic therapy (ADT in oligometastatic prostate cancer) and quality of life are the most frequently defined endpoints [26,45]. Whereas local treatment always aims at eradication of all oligometastases, the combination strategy with systemic treatment depends on OMD state, the specific overall treatment goal and the factors mentioned above .

For all states of de-novo OMD and repeat OMD, radical treatment aims to achieve a status of freedom from disease; its translation into prolonged OS or cure will depend on the efficacy of local treatment and simultaneously on the absence of occult metastatic disease or its effective control by the addition of systemic therapy. Consequently, all but one [6] randomized trials in OMD currently published used standard systemic therapy as a backbone of the OMD treatment strategy [2–5]. The choice of the optimal systemic therapy is particularly unclear in metachronous oligoprogression, where OMD develops during active systemic therapy in the context of primary treatment; continuation of systemic therapy or switch to another drug are sensible options. Synchronous OMD adds another level of complexity as local treatment

to the locoregional primary tumor, 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 OMD and repeat OMD could be to prolong the time until systemic therapy is needed for polymetastatic disease and thereby maintain QoL of the patient. This strategy has been tested for oligometastatic prostate cancer where local metastases-directed therapy significantly prolonged the time until initiation of ADT [6].

Treatment goals and strategies are different in induced OMD. These patients have polymetastatic disease, which is converted into a state of induced OMD by partially effective systemic treatment. Local treatment for induced OMD therefore complements the systemic treatment and not vice versa as in genuine OMD. Consequently, based on currently available evidence, cure is not achieved in the majority of the 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 prior polymetastatic disease). Addition of systemic therapy could potentially enhance the effect of the local intervention. It is unknown 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. 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 by 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 switch 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 OMD classification system aims to define the oligometastatic state at one

timepoint in the patient's history. However, one patient can have multiple different states of OMD 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 [46], we propose a dynamic oligometastatic state model (figure 5). The three upper-level states are de-novo OMD, repeat OMD and induced OMD, where transition to a downstream state is unidirectional in the patient`s history. However, within repeat OMD and within induced OMD, patients can have dynamic transitions between oligorecurrent, oligoprogressive, and oligopersistent disease, depending on the response to local and systemic therapy. A registry study on oligometastatic NSCLC reported that 6·6% of all patients treated for oligometastatic NSCLC received more than one course of treatment, maximum four courses of SBRT [47]. Similarly complex and long histories of OMD with up to maximum four courses of radical local treatment have been reported for prostate cancer [30].

It needs to be noted that transition from one oligometastatic state to another is not necessarily associated with a worsening of the prognosis. A patient with multiple courses of treatment for repeat OMD most likely has a disease phenotype with truly limited metastatic capacity because no progression to polymetastases has developed [47]. Additionally, patients with induced OMD may have long-term survival when radical local treatment is combined with effective systemic treatment such as targeting drugs for NSCLC with driver mutations or immunotherapy for malignant melanoma.

In summary, we have established a system for comprehensive characterization of OMD, which is recommended as a minimum dataset for oligometastatic patients treated with radical local treatment within and outside clinical trials. An OMD classification system based on a decision tree of five binary OMD characterization factors has been developed and a dynamic oligometastatic state model has been proposed. These states of OMD will be prospectively tested in the OligoCare prospective cohort trial regarding their prognostic value and regarding their acceptance and compliance in routine practice.

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Figure Legends

Figure 1: Search strategy for the systematic review

Figure 2: Schematic overview over the Delphi process

Figure 3: Decision tree for classification of OMD

Q1: Does the patient have a history of polymetastatic disease before current diagnosis of OMD?

Q2: Does the patient have a history of OMD disease before current diagnosis of OMD?

Q3: Has OMD been first diagnosed > 6 months after primary cancer diagnosis?

Q4: Is the patient under active systemic therapy at the time of OMD diagnosis?

Q5: Are any oligometastatic lesions progressive on current imaging?

Figure 4: Illustration of the OMD classification system; consider that the primary tumor is assumed being controlled in repeat and induced OMD.

Figure 5: Oligometastatic state model

Table

Descriptive tumor, treatment and staging characteristics of OMD:
Primary tumor characteristics: primary tumor site; histology; TNM stage; mutational status *; tumormarker *;
History of cancer progression: time interval since first diagnosis; disease-free interval; treatment-free interval; *
History of treatment of primary tumor: modality of local treatment; radical or palliative intent; controlled primary tumor;
History of systemic therapy before diagnosis of OMD: types of systemic therapy; number of lines of systemic therapy; *
OMD staging: imaging modality; anatomical areas covered; invasive staging *;
Involved organs of oligometastatic disease
Quantitative characteristics of OMD
Maximum number of metastatic lesions
Maximum number of involved organs
Maximum number of lesions per organ *
Maximum size or volume of individual metastasis
Characteristics of OMD development
Are any oligometastatic lesions progressive on current imaging ?
Is OMD diagnosed within 6 months after diagnosis of the primary tumor (synchronous vs metachronous) ?
Does the patient have a history of polymetastatic disease before OMD diagnosis ?
Does the patient have a history of OMD before current diagnosis of OMD ? *
Is the patient under active systemic therapy at the time of OMD diagnosis ? *
Lesion-individual OMD characteristics
Is the oligometastatic lesion a newly developed metastatic lesion ? *
Is treatment of the oligometastatic lesion possible with radical intent ? *

Table 1: *OMD characteristics identified in the systematic literature review and confirmed in the Delphi process and OMD characteristics added in the Delphi process (*)*

Figure 1

CONSORT Diagram

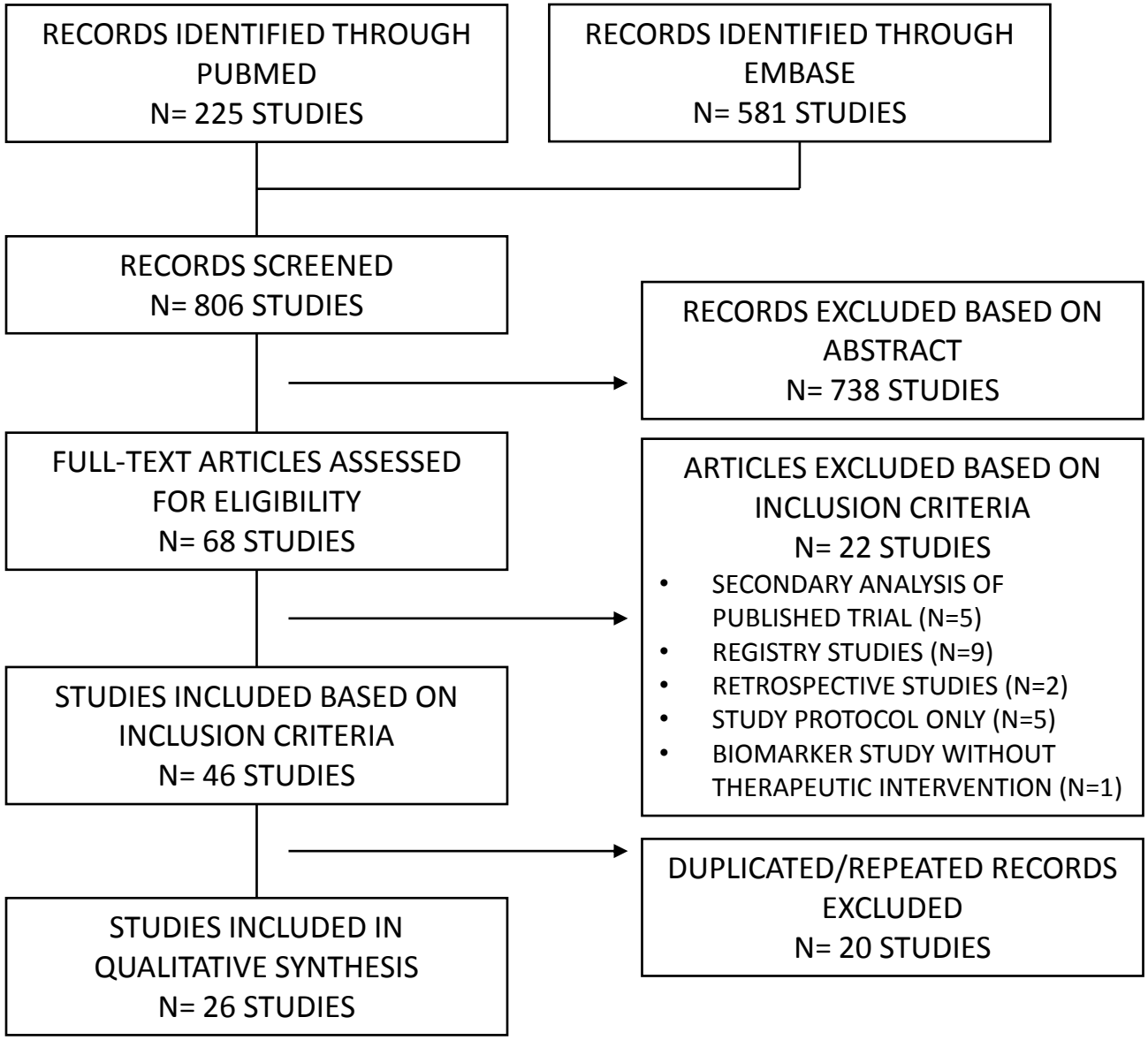


Figure 1: Search strategy for the systematic review

Figure 2

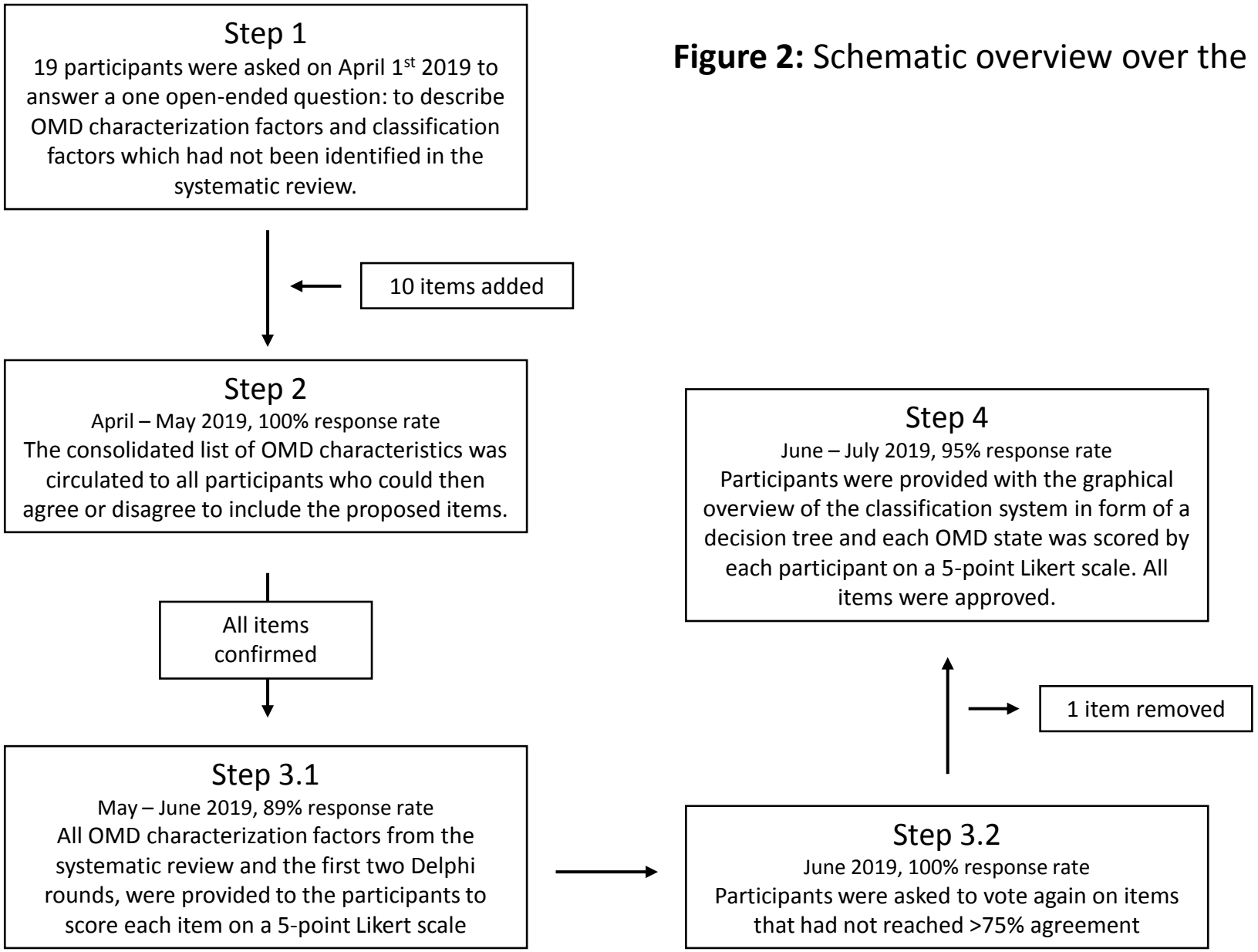


Figure 2: Schematic overview over the Delphi process

Figure 3

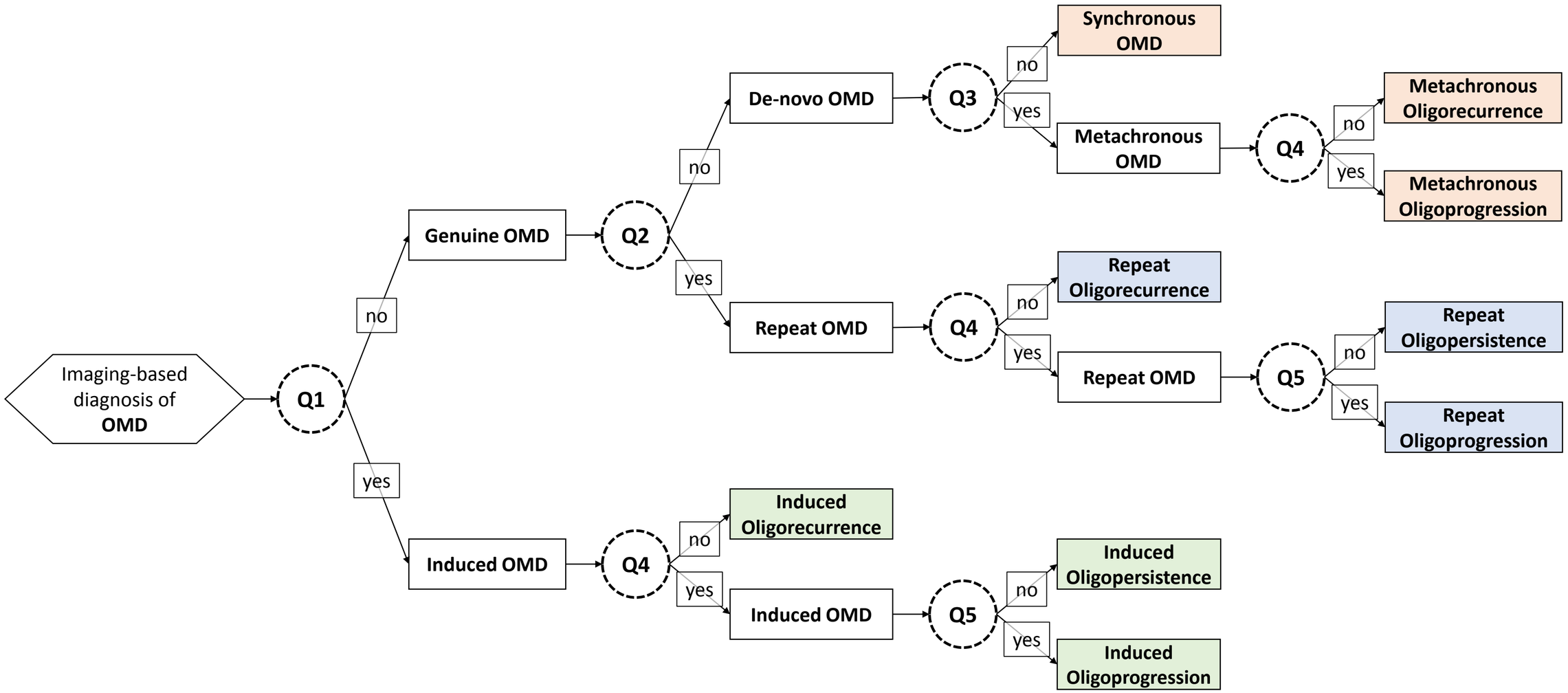
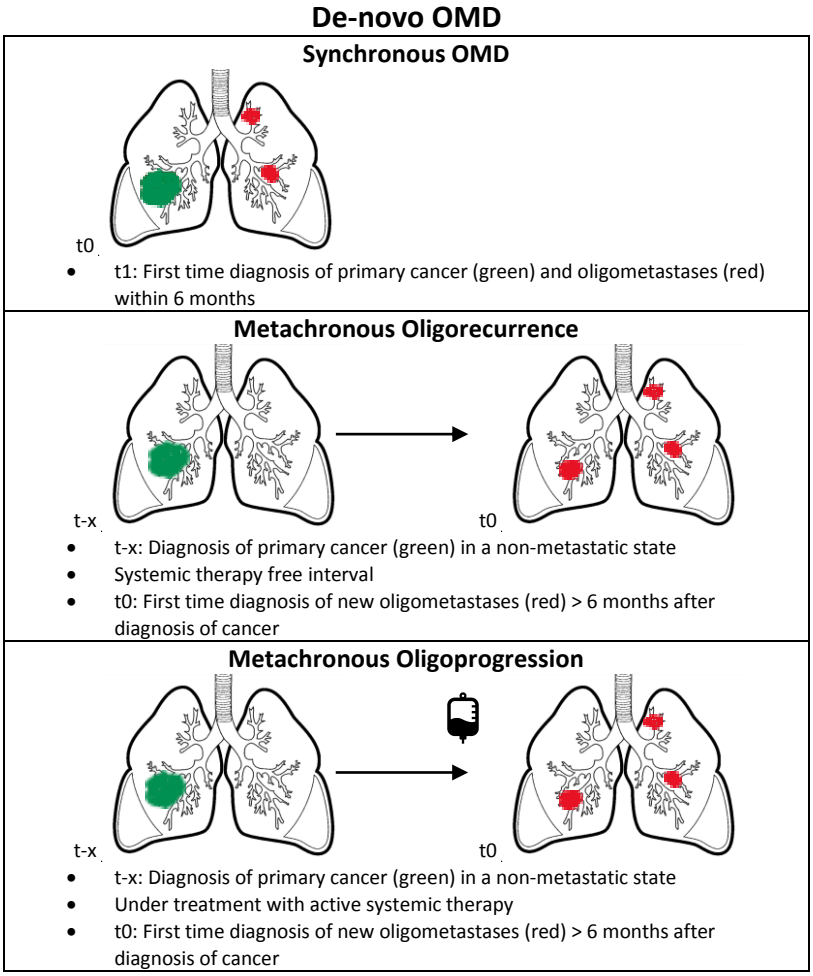


Figure 3: Decision tree for classification of OMD
Q1: Does the patient have a history of polymetastatic disease before current diagnosis of OMD?
Q2: Does the patient have a history of OMD disease before current diagnosis of OMD?
Q3: Has OMD been first diagnosed > 6 months after primary cancer diagnosis?
Q4: Is the patient under active systemic therapy at the time of OMD diagnosis?
Q5: Are any oligometastatic lesions progressive on current imaging?

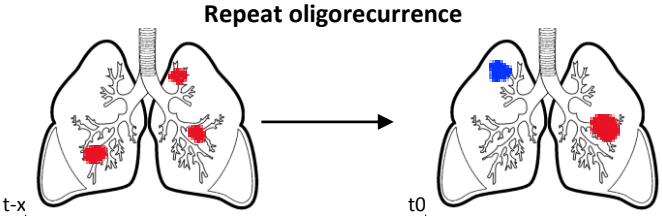
Figure 4

Figure 4: Illustration of the OMD classification system; consider that the primary tumor is assumed being controlled in repeat and induced OMD.



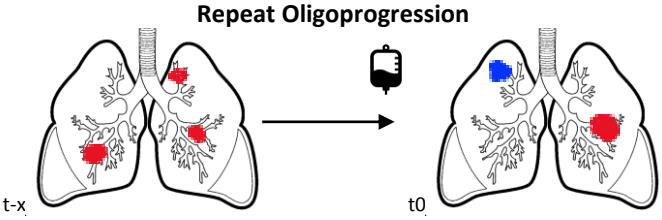
Repeat OMD

Repeat oligorecurrence



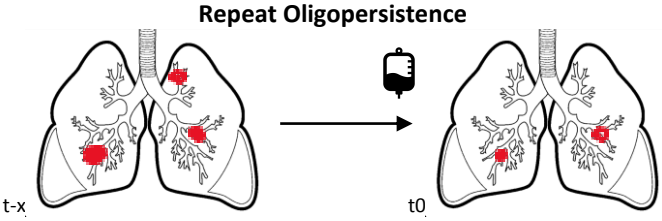
- t-x: Diagnosis of oligometastases followed by local and/or systemic treatment
- Systemic therapy free interval;
- t0: Diagnosis of new (blue) and/or (re-)growing (red) oligometastases

Repeat Oligoprogression



- t-x: Diagnosis of oligometastases followed by local and/or systemic treatment
- Under treatment with active systemic therapy;
- t0: Diagnosis of new (blue) and/or (re-)growing (red) oligometastases

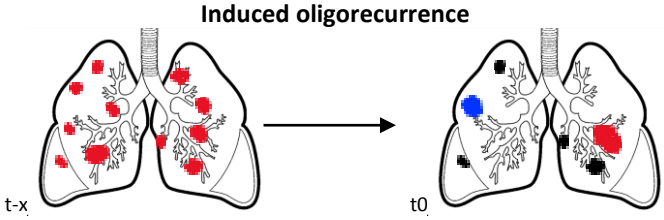
Repeat Oligopersistence



- t-x: Diagnosis of oligometastases followed by local and/or systemic treatment
- Under treatment with active systemic therapy;
- t0: Diagnosis of persistent non-progressive (red) oligometastases

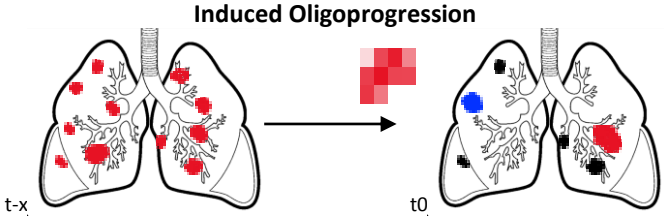
Induced OMD

Induced oligorecurrence



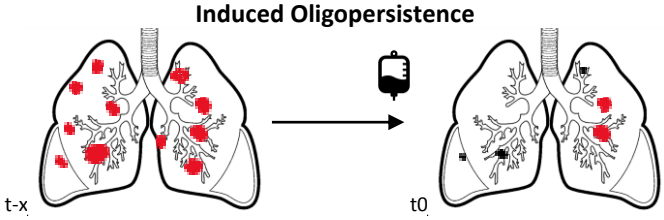
- t-x: Diagnosis of PMD followed by local and/or systemic treatment;
- Systemic therapy free interval;
- t0: Diagnosis of new (blue) and/or (re-)growing (red) oligometastases, possible residual non-progressive metastases (black)

Induced Oligoprogression



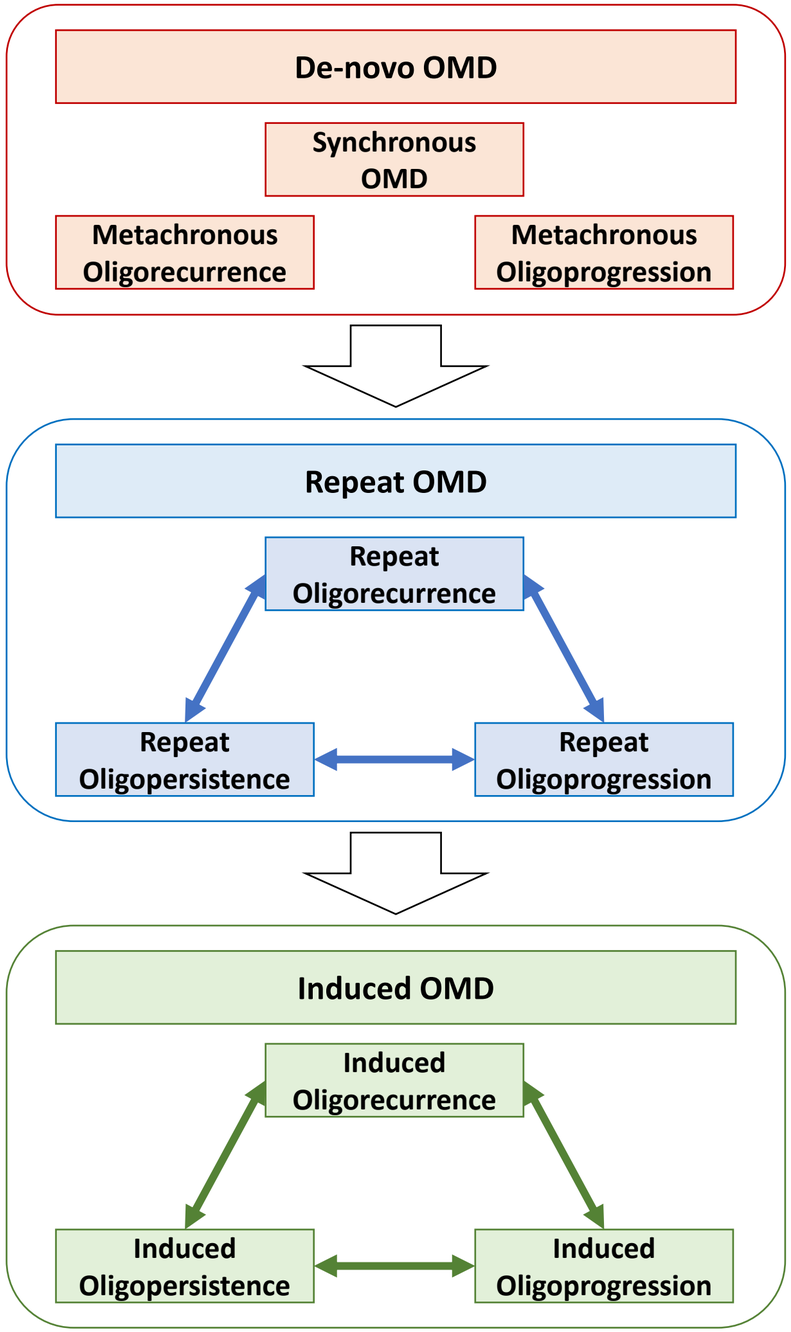
- t-x: Diagnosis of PMD followed by local and/or systemic treatment;
- Under treatment with active systemic therapy;
- t0: Diagnosis of new (blue) and/or (re-)growing (red) oligometastases, possible residual non-progressive metastases (black)

Induced Oligopersistence



- t-x: Diagnosis of PMD followed by local and/or systemic treatment;
- Under treatment with active systemic therapy;
- t0: Diagnosis of persistent non-progressive oligometastases (red), where response is worse compared to other residual metastases (black)

Figure 5: Oligometastatic state model



Necessary Additional Data

Click here to download Necessary Additional Data: ESTRO EORTC OMD classification - appendix.docx