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Consensus

Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document

Yolande Lievens [a,*], Matthias Guckenberger [b], Daniel Gomez [c], Morten Hoyer [d], Puneeth Iyengar [e], Isabelle Kindts [f], Alejandra Méndez Romero [g], Daan Nevens [h], David Palma [i], Catherine Park [j], Umberto Ricardi [k], Marta Scorsetti [l], James Yu [m], Wendy A. Woodward [c]

[a] Department of Radiation Oncology, Ghent University Hospital, Ghent University, Belgium; [b] Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Switzerland; [c] Department of Radiation Oncology, UT MD Anderson Cancer Center, Houston, USA; [d] Danish Center for Particle Therapy, Aarhus University Hospital, Denmark; [e] Department of Radiation Oncology, UT Southwestern Medical Center, Dallas, USA; [f] Department of Radiotherapy, Cancer Centre, General Hospital Groeninge, Kortrijk, Belgium; [g] Department of Radiation Oncology, Erasmus MC University Medical Center, Rotterdam, The Netherlands; [h] Iridium Kankernetwerk, Radiation Oncology Department, Universiteit Antwerpen, Antwerp, Belgium; [i] London Health Sciences Centre, Canada; [j] Department of Radiation Oncology, UCSF Helen Diller Comprehensive Cancer Center, San Francisco, USA; [k] Department of Oncology, University of Turin; [l] Radiotherapy and Radiosurgery Dept, Humanitas Clinical and Research Hospital – IRCCS, Rozzano-Milan, Italy; [m] Yale School of Medicine, New Haven, USA

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ABSTRACT

Background: Recognizing the rapidly increasing interest and evidence in using metastasis-directed radiotherapy (MDRT) for oligometastatic disease (OMD), ESTRO and ASTRO convened a committee to establish consensus regarding definitions of OMD and define gaps in current evidence.
Methods: A systematic literature review focused on curative intent MDRT was performed in Medline, Embase and Cochrane. Subsequent consensus opinion, using a Delphi process, highlighted the current state of evidence and the limitations in the available literature.
Results: Available evidence regarding the use of MDRT for OMD mostly derives from retrospective, single-centre series, with significant heterogeneity in patient inclusion criteria, definition of OMD, and outcomes reported. Consensus was reached that OMD is largely independent of primary tumour, metastatic location and the presence or length of a disease-free interval, supporting both synchronous and metachronous OMD. In the absence of clinical data supporting a maximum number of metastases and organs to define OMD, and of validated molecular biomarkers, consensus supported the ability to deliver safe and clinically meaningful radiotherapy with curative intent to all metastatic sites as a minimum requirement for defining OMD in the context of radiotherapy. Systemic therapy induced OMD was identified as a distinct state of OMD. High-resolution imaging to assess and confirm OMD is crucial, including brain imaging when indicated. Minimum common endpoints such as progression-free and overall survival, local control, toxicity and quality-of-life should be reported; uncommon endpoints as deferral of systemic therapy and cost were endorsed.
Conclusion: While significant heterogeneity exists in the current OMD definitions in the literature, consensus was reached on multiple key questions. Based on available data, OMD can to date be defined as 1–5 metastatic lesions, a controlled primary tumor being optional, but where all metastatic sites must be safely treatable. Consistent definitions and reporting are warranted and encouraged in ongoing trials and reports generating further evidence to optimize patient benefits.
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Almost 25 years after the first description of an intermediate state between localised cancer and wide-spread metastatic disease, termed 'the oligometastatic state', the treatment of oligometastatic disease (OMD) with curative intent has been gaining increasing acceptance. Following surgical and radiotherapy evidence illustrating the potential for cure in OMD [1–4] and the advent of new radiotherapy technologies and techniques, the interest amongst radiation oncology (RO) professionals for treating OMD with curative intent has continuously been growing, even if some remain hesitant regarding wide-spread implementation until additional evidence across disease sites becomes available [5–8]. Although data from randomised phase II trials of stereotactic body

* Corresponding author at: Department of Radiation Oncology, Ghent University Hospital, C. Heymanslaan 10, BE-9000 Ghent, Belgium.
E-mail address: yolande.lievens@uzgent.be (Y. Lievens).

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radiotherapy (SBRT) are emerging for several primary tumour sites [9–13], there is not yet randomised phase III evidence on the efficacy of SBRT, or more generally, curative intent MDRT, for OMD. In addition, uncertainties remain regarding the exact definition of OMD [14,15], and reporting outcomes of patients with OMD is far from standardised, making cross-trial comparisons difficult.

Acknowledging the urgent need for standardisation within the RO community to advance science and clinical patient care in this important area, ESTRO (European Society for Radiotherapy and Oncology) and ASTRO (American Society for Radiation Oncology) launched a collaborative project to develop consensus on patient identification and treatment of OMD. The work was performed by a group of clinical experts from Europe and the US, mandated by the respective scientific councils and boards of both societies.

This consensus paper analyses the prevailing definitions of predominantly extra-cranial OMD and factors that may affect these definitions. Based on a systematic literature review and using a Delphi consensus process, agreement on statements pertaining to 6 different topics related to OMD (disease characteristics, disease burden, timing of OMD, relation to other treatments, endpoints and impact of technology) is presented, along with a critical discussion based on the evidence gathered in the review. Recommendations for improving future evidence generation and reporting are formulated.

Materials and methods

Literature review

A systematic literature review, following PRISMA principles [16], was performed in Medline, Embase and the Cochrane library. The initial search performed in September 2018 included all publications until that date, reporting outcome of patients with limited metastatic burden and treated with stereotactic radiotherapy. It is acknowledged that this scope excluded studies of non-stereotactic based curative intent MDRT which may also be of interest. To address limitations inherent to the rapid rate of new publications, we agreed *a priori* to repeat the systematic review for studies published between September 2018 and August 2019 to confirm robustness of the consensus findings over the timeframe of the process.

Retrospective and prospective series were included; reviews, surveys, letters and abstracts were excluded. Non-randomised reports including fewer than 50 patients treated with radiotherapy, studies solely focusing on brain metastases, not reporting clinical outcomes or solely covering non-English content were excluded (Appendix A).

Screening and initial eligibility were addressed by two authors (IK, DN), consulting others for disagreement resolution. All authors reviewed a proportion of the selected full papers for compliance with the inclusion criteria, and consistency of the data extraction was ascertained using predefined templates. Subsequently, the extracted evidence was analysed per topic: disease characteristics (AMR, DG, CP); maximum disease burden (DN, DP); timing of OMD development (MG, IK); relation of MDRT to other treatments (MH, MS, JY); relevant endpoints reported (PI, UR) and impact of technology on indication and outcome (YL, WW). The results were discussed amongst all authors and informed the Delphi process. Evidence retrieved in August 2019 was made available to support the final description.

Delphi survey

The Delphi consensus process (Appendix B) used methods previously described [17]. Consensus was defined *a priori* as $\geq$75% agreement on any statement. Three rounds of consensus-building were conducted using anonymous, online surveys (SurveyMonkey®). Prior to the first round, participants assembled a list of 16 key questions (KQs, Table 1) pertaining to SBRT for oligometastases and conform the 6 topics addressed in the systematic review.

Results

Literature review and Delphi process

The systematic literature review identified 7030 potential publications in the first search and 385 in the second search, which resulted, after screening and assessment, in 75 and 23 papers respectively. After excluding one interim report identified in the first round, published with final results in the second round, the number of publications amounted to 97 (for full list, see Appendix C). As illustrated in Fig. 1, there was a gap of more than 10 years between the initial publication of Hellmann and Weichselbaum and the publications fitting our search. The vast majority were retrospective reports, either single-centre (n = 50) or multicentre (n = 23). Six papers reported single-arm prospective cohorts; while studies reporting a phase I, II and phase II-randomised design accounted for 9, 5 and 4 publications, respectively.

There was large heterogeneity in study design: studies either reported on a variety of primary tumours or focused on specific tumour entities (e.g. prostate or lung) or metastatic sites (e.g. lymph nodes or lung metastases). The OMD definitions used across publications were equally variable (Table 2). The steps leading to the consensus statements are illustrated in Fig. 2.

Consensus statements and literature discussion

Table 1 lists the KQs and the consensus reached for each of them, below the different statements are organised in common concepts, commented by the experts and illustrated with the literature. The numbering follows that of the table.

Statements 1 and 2:

The concept of OMD is independent of primary tumour type and histology (Statement 1) and of the metastatic site(s) (Statement 2).

Although some papers focused on a specific primary tumour type, most frequently colorectal, prostate and lung [10,18–51], many diseases have been examined including unknown primary. Disease-specific histology has not been specified in many articles, adenocarcinoma was however frequently recorded.

There was broad agreement that prognosis can differ substantially based on the primary tumour, and that some tumour types are less likely to be oligometastatic (e.g., SCLC). However, is was agreed that the concept of an intermediate state of OMD with limited metastatic capacity is independent of the type of primary tumour [12].

Among reports focusing on site of metastases [52–78], lung, liver and lymph nodes are most widely studied. Patients with intracranial metastases are most commonly reported separately from extra-cranial OMD, but these patients should be included in future OMD studies.

There was agreement that prognosis may vary based on the metastatic site. However, apart from patients with diffuse disease such as malignant pleural effusions, leptomeningeal or peritoneal carcinomatosis, the concept of OMD is not considered to depend on the metastatic site.

Statement 3:

There are currently no validated biomarkers that differentiate between the oligometastatic and the polymetastatic state.

Table 1
Key questions per topic addressed in the Delphi process, with level of consensus obtained in the different Delphi rounds.

Key questions and consensus statements	Level of consensus	Delphi Round
Disease characteristics		
KQ 1: Is the concept of OMD depending on the type of primary tumour?		
No, the concept of OMD is not related to a specific primary	100% (11/11)	Delphi round 3
KQ 2: Is the concept of OMD depending on the site of metastasis?		
No, the concept of OMD is not dependent on the site of the metastasis	100% (10/10)	Delphi round 3
KQ 3: Are there any validated biomarkers that are indicative of an oligometastatic state?		
No, there are currently no validated biomarkers that differentiate between the oligometastatic and the polymetastatic state	100% (11/11)	Delphi round 1
KQ 4: Are there any minimum imaging requirements to define an oligometastatic state?		
Yes, diagnostic imaging should be performed using whichever modalities are adequate to image sites of common metastases and to detect small lesions for that histology.	91% (10/11)	Delphi round 2
CT scan of the chest/abdomen/pelvis and MRI of the brain or spine, if indicated, is recommended.	91% (10/11)	Delphi round 2
PET/CT is recommended	82% (9/11)	Delphi round 2
Maximum disease burden		
KQ 5: Is OMD defined by a maximum number of lesions and/or sites?		
No, the possibility to safely deliver curative intent metastasis-directed radiotherapy determines the maximum number	82% (9/11)	Delphi round 2
KQ 6: Is maximum disease burden defined by technically safe treatment with curative intent?		
Yes, but it is recognized that the ability to treat safely does not mean that one should treat.	90% (9/10)	Delphi round 3
Regardless of the number of metastases the patient should not be treated if not safe	100% (10/10)	Delphi round 3
Timing of OMD development		
KQ 7: Are there different types of OMD related to the time of diagnosis of primary tumour?		
Yes, there are different types of OMD, defined by the timing of OMD vs. primary tumour	91% (10/11)	Delphi round 1
KQ 8: Are there different types of OMD related to the onset of metastases?		
Yes, different states of systemic therapy induced OMD are reported in the literature	100% (11/11)	Delphi round 1
Relation of metastasis-directed radiotherapy to other treatments		
KQ 9: Should there be a disease-free interval after treatment of the primary tumour?		
No, a disease-free interval is not mandatory to define OMD	91% (10/11)	Delphi round 1
KQ 10: Should there be a treatment-free interval after systemic treatment of metastases?		
No, a treatment-free interval is not mandatory to define OMD	100% (11/11)	Delphi round 1
KQ 11: When is progression under systemic therapy considered oligo-metastatic?		
'Oligoprogression' should be defined differently than 'oligometastasis'.	90% (9/10)	Delphi round 3
There is no consensus whether or not the criteria for number of disease sites or locations should differ	50% (5/10)	Not reached
KQ 12: Are patients who had polymetastatic disease and have induced OMD after systemic therapy considered oligo-metastatic?		
Yes, patients with prior polymetastatic disease can become OM after successful systemic therapy	82% (9/11)	Delphi round 1
Endpoints		
KQ 13: Does the risk for toxicity of metastasis-directed radiotherapy impact the indications for treatment of OMD?	100% (11/11)	Delphi round 1
Yes, the risk of toxicity impacts treatment indications		
KQ 14: Which endpoints are important for OMD?		
Following endpoints are considered important:		
- overall survival	91% (10/11)	Delphi round 2
- disease-free or progression-free survival (including time to recurrence, progression or death)	100% (11/11)	Delphi round 2
- local control	91% (10/11)	Delphi round 2
- toxicity	100% (11/11)	Delphi round 2
- quality-of-life	82% (9/11)	Delphi round 3
- patient-reported outcomes	82% (9/11)	Delphi round 2
- cost	82% (9/11)	Delphi round 2
- delay or deferral of systemic treatment	82% (9/11)	Delphi round 2
- ability to stay on the same systemic treatment	80% (8/10)	Delphi round 3
Impact of technology on indication and outcome		
KQ 15: Does the availability of technology impact the indications for treatment of OMD?	82% (9/11)	Delphi round 1
Yes, although technology *per se* does not impact the indications, adequate technology and/or techniques (e.g. SBRT) are a minimum requirement to treat OMD		
KQ 16: Is there a minimum BED (α/β = 10) required to achieve local control of OMD?		
Yes, although likely there will be variation as the data emerge, the goal is control of the targeted metastasis, for which the data support a higher biologic equivalent dose (such as >100 Gy BED_{10})	90% (9/10)	Delphi round 2

Abbreviations:
KQ: Key question; OMD: oligometastatic disease; CT: computed tomography, MRI: magnetic resonance imaging, PET: positron-emission tomography; SBRT: sterotactic body radiotherapy; BED: biologically effective dose
Note: The order of the key questions and of the resulting statements presented here reflects the structure per topic used in the Delphi process. In the manuscript, the statements have been reorganised following their content and discussion.

The search for biomarkers indicative of OMD is an active research area, with preclinical and translational studies assessing blood-based biomarkers such as microRNA expression and circulating free DNA; tissue-based biomarkers such as mutational status and intratumoural heterogeneity; and radiomic parameters [79–82]. Ideally, integration of these categories of biomarkers into a multi-systems predictions model will lead to a more precise algorithm for defining OMD than the currently most often used number of metastatic lesions, and thus aid in assigning the appropriate treatment.

Statement 4:

Diagnostic imaging should be performed using whichever modalities are most adequate to image sites of common metastases and to detect small lesions for that histology.

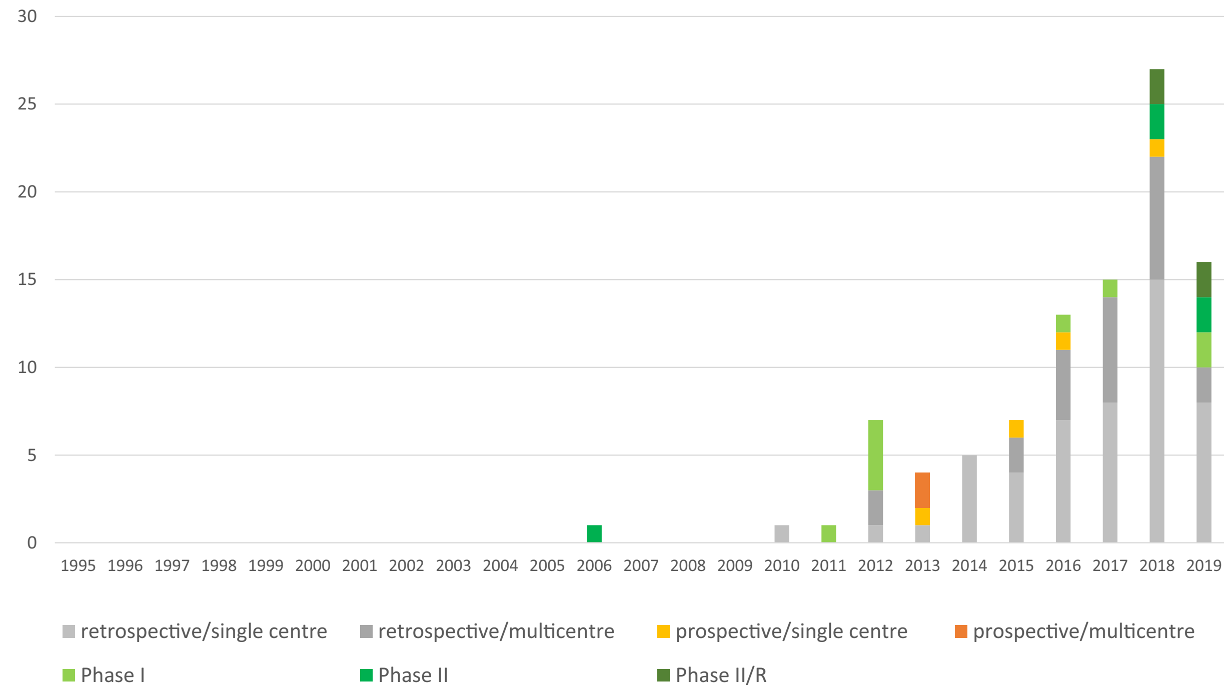

Fig. 1. Number of publications per year and per type, selected in both SLR searches, since the publication of Hellman and Weichselbaum in 1995 [6]. Note: Reports on interim results were not included.

Multi-modality diagnostic imaging was used for the evaluation of metastatic disease in most studies reviewed [47]. Although several studies did not specify modalities used in OMD workup [32,83], in areas of focused disease-site evaluations, highly specific imaging was utilized (e.g., contrast-enhanced biphasic liver CT for liver metastases [30], PSMA-PET for prostate OMD [37]).

While there was no consensus to recommend specific imaging modalities as a requirement for OMD workup, there was consensus to recommend PET/CT, contrast-enhanced chest/abdominal and pelvis CT scans, and/or MR brain or spine (when indicated) for diagnostic evaluation. Further, reflective of the future development of imaging technologies in certain areas, there was consensus to recommend any validated imaging modalities that adequately image sites of common metastasis and to detect small lesions.

Statements 5, 6, and 13:

The feasibility of safely delivering curative intent MDRT determines the maximum number of lesions and sites *that can be treated with radiotherapy** in OMD. The ability to safely treat all oligometastases with radiotherapy does not mean that one should treat every patient irrespective of other prognostic factors (Statement 5). Regardless of the number of metastases, the risks and benefits of MDRT should be balanced carefully in all oligometastatic patients (Statement 6). The risk of toxicity impacts treatment indications for OMD (Statement 13).

*Italicized text added after consensus was formed to provide needed clarification highlighted during the review process.

Reviewing the literature, 'up to 5' and 'up to 3' oligometastatic lesions are the most commonly-used quantitative definitions. Similar limits were sometimes placed on the maximum number of metastases per organ (Table 2). However, studies differ on whether the primary tumour is counted (for patients with synchronous oligometastases), on imaging modalities and their sensitivity used for patient staging, and whether regional lymph node targets are counted as individual targets or grouped together. Several papers have no maximum number of lesions defined, nor report median or range.

At present, there is no biological evidence supporting the maximal number of metastases, or the maximal lesion size, that can be treated to provide clinical benefit. In treatment planning, the upper limit of technically safe curative intent MDRT is not well-studied. No studies that met the review criteria attempted to determine the maximum lesion number or size. A maximum cut-off size of 5 cm is sometimes used, but larger lesions may be treatable depending on location and with careful attention to dose constraints, recognizing size is prognostic for control in multiple studies [26,27,41,83,84].

In the absence of sensitive and specific biomarkers, with number of metastatic lesions and organs commonly being used as surrogates for patient selection, the consensus obtained regarding maximum number of lesions that can be considered as OMD was that the maximum number must be limited by the ability to deliver safe, curative intent MDRT, which can vary on a case-by-case basis. This agrees with surgical strategies where technical resectability, not a fixed number of metastases, decides for or against a metastasis-directed treatment strategy. Similarly, the consensus also excludes patients who may have few lesions, but where the safety of delivering an adequate dose is questionable. Recognizing future technologies may increase the feasibility of targeting more widespread disease, there was also consensus that the technical ability to treat numerous lesions safely should not lead to expanded selection criteria off-protocol or without clinical data to support it.

While not formally concluded from the Delphi consensus process, to date, very little of the extra-cranial data reviewed includes more than 5 sites. For this reason, the authors agreed that 5 lesions should be considered an upper bound off-

Table 2
OMD definitions used across publications.

Oligometastatic disease (OMD)		
	Many refer to the original definition of Hellman and Weichselbaum [6]: An intermediate state between local and systemic disease, where radical local treatment of the primary cancer and all metastatic lesions might have a curative potential	[19,21,25,29,32,34,38,51,57,58,61,64,65,73–75,78,83,87,92,99,100,104–111]
+	*Outcome*	
	An intermediate state in which local or treated metastasis control may yield improved systemic control	[39,66]
+	*Disease burden*	
	Limited number of metastases: oligometastatic is defined as a small number of low volume metastases, 5 or less, 3 or less	[22,23,35,42,45,70,112–114]
	Limited number of sites/regions	[31,71]
	Single or limited number of organs	[115]
	Limited number of metastases and sites	[68,69]
	Limited number of distant metastatic regions (typically ≤5) that contain the primary tumor	[77]
+	*Disease type*	
	More indolent disease, tumors featuring limited metastatic capacity	[26,62,84,116]
	Specified for certain organ: limited pulmonary dissemination, limited number of nodal recurrences (in prostate cancer; typically, ≤3 or ≤5)	[11,44,55]
+	*Alternative hypotheses*	
	OMD represents the transition between localized and widespread systemic disease *OR* the clinical manifestation of detectable lesions in a setting of widespread occult disease	[117]
Synchronous OMD		
	OMD at the time of initial diagnosis, primary tumor and limited number of metastases detected simultaneously	[25,52]
+	*Disease load*	
	≤5 metastatic lesions with active primary lesions	[78]
Metachronous OMD, often used interchangeably with Oligo-Recurrence		
	Oligometastatic recurrence during the course of disease at least three months after the initial diagnosis ('metachronous'), as a state of metachronous limited recurrence	[25]
	Many refer to the original definition of Niibe and Hayakwa [85]: Metastases detected while the primary tumor is controlled and that can be treated with local therapy.	[52,71,89,104,115]
+	*Outcome*	
	Achieve control of metastatic sites	[104]
+	*Disease load*	
	One to several metastatic recurrences in one to several organs	[53]
	<5 new metastases in an otherwise well-controlled (primary) disease state	[39,78]
	A limited number of distant metastatic regions (typically ≤5) that contain the primary tumor	[77]
+	*Disease type*	
	After primary prostate cancer treatment: ≤3 metastases	[11]
Oligo-Progression		
	Few lesions progress on a background of widespread but stable metastatic disease	[83]
+	*Link with other therapies*	
	Progression occurs in a limited number of tumors/metastases while the majority of other metastases are responding or stable while on a systemic treatment strategy	[41,48,61]
	Progression occurs after a cytoreductive treatment	[67]
	Progression while other sites including the primary disease remain stable on systemic treatment or observation	[113]
	Resistant clones can result in isolated progression	[42]
+	*Disease load*	
	<5 enlarging metastases in an otherwise well-controlled disease state	[39]
	<5 sites of metastatic disease progression while other sites including primary remain stable on systemic treatment	[113]
	3–5 slowly progressive metastases	[36,48]
Oligo-Persistence		
	Persistent disease after systemic therapy	[67]
+	*Disease load*	
	<5 persistent lesions after systemic therapy	[39]

protocol, until further data emerges. Meanwhile, patient and treatment factors, as well as appropriateness of treatment (e.g., depending on performance status, pace of disease and likelihood of diffuse occult metastases) should be considered when taking decisions for individual patients. Importantly, treatment-related death [12,69,70,77,85] and other serious toxicities [59,60,65,72] are uncommon, but they have been reported. The utilization and benefits of MDRT for OMD must be determined by the therapeutic ratio of efficacy to toxicity. Normal tissue toxicity is dependent on the anatomic location of disease receiving therapy and should be measured with standard toxicity metrics.

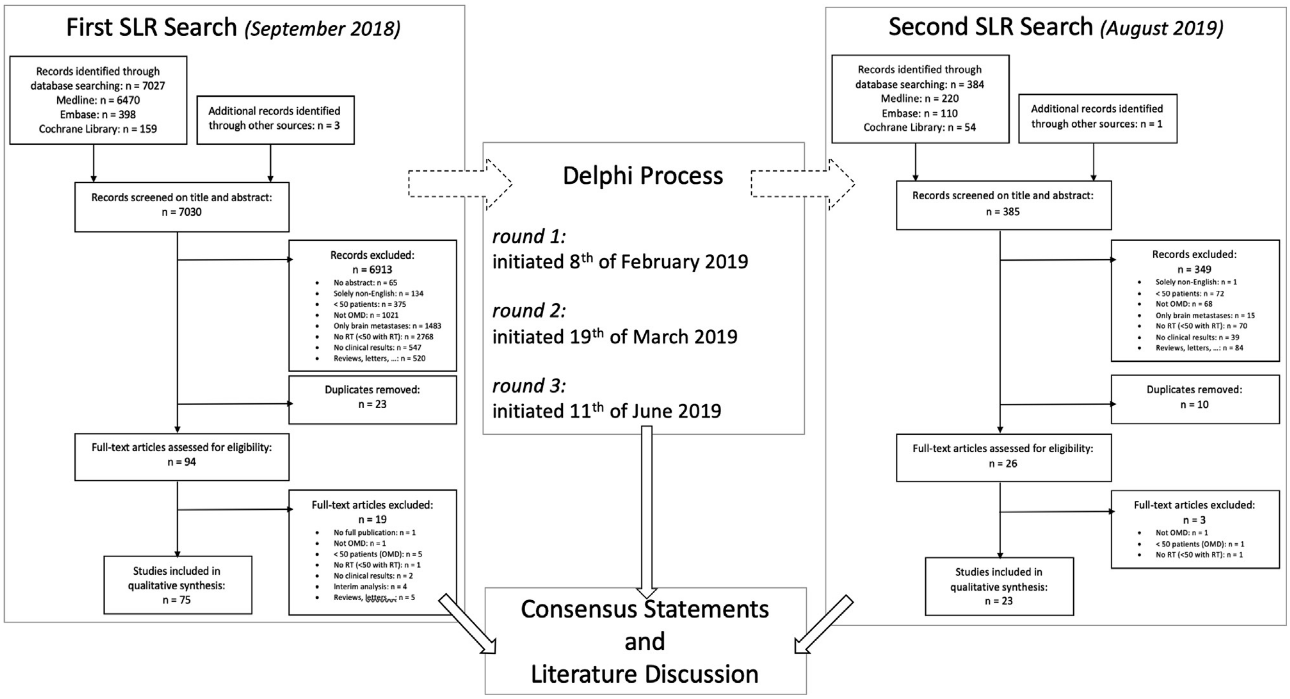

Fig. 2. Different steps and timing of the literature review and Delphi consensus. Note: Interim results were excluded within one SLR, but not across the SLR rounds. Abbreviations: SLR: systematic literature review; OMD: oligometastatic disease; RT: radiotherapy.

Statements 7 and 9:

OMD is differentiated into synchronous versus metachronous states, defined by the interval between primary cancer diagnosis and development of OMD (Statement 7). A disease-free interval (DFI) is not mandatory to define OMD (Statement 9).

The main categorization in the literature reviewed was synchronous versus metachronous (often referred to as oligorecurrent) OMD, typically differentiated by a time interval of 3–6 months between primary cancer diagnosis and development of OMD (Table 2). When reported, the primary tumour had frequently been treated with curative intent in metachronous OMD. A locoregionally controlled primary tumour is not a precondition but should be considered a prognostic parameter which is critical to report specifically. Some studies reported a better prognosis for metachronous OMD [28,86], but this was not consistently observed [25,74].

Though both synchronous and metachronous metastases are considered OMD, the prognosis, options for treatment and risk of occult disseminated metastases of these patients can differ, with the length of the DFI appearing to have a prognostic impact [46,69,87]. While concerns were raised about prognosis of metastases developing shortly after primary cancer treatment, uncertainty remains regarding the importance of the DFI, as data are lacking to support a consensus for minimum DFI in the definition of metachronous OMD.

Statements 8, 11 and 12:

Different states of systemic therapy induced OMD are reported in the literature, with inconsistent nomenclature and definitions (Statement 8). Patients with prior polymetastatic disease can become OM based on response to systemic therapy (Statement 12). There was no consensus on the criteria for a maximum number of metastases or organs for systemic therapy induced OMD (Statement 11).

There is growing but still limited evidence on the development of OMD after systemic therapy for polymetastatic disease. While it was agreed that originally polymetastatic disease that becomes OMD should be defined as ‘induced OMD’, concerns were raised on the difficulty in histopathologic confirmation of polymetastatic disease, and the potential importance of local tumour control. It was also cautioned that the treatment goal in induced OMD may not be improved survival as polymetastatic disease is generally considered ‘incurable’ for most malignancies but may be improved progression-free survival (PFS), quality-of-life (QoL) or local control (LC).

In the context of systemic therapy induced OMD, additional conceptual states of OMD are described in the literature e.g., oligoprogressive or oligopersistent disease. However, definitions of those terms varied in original research and in review articles (Table 2) [88–91]. Oligoprogression on systemic therapy is clearly a different clinical entity than OMD, with possibly worse prognosis compared to de novo or isolated metastatic disease [39,41,48,83,92], but with a treatment goal that may be more focused on keeping patients on a current line of systemic therapy, rather than ablation of the metastasis per se [93].

Statement 10:

A treatment-free interval (TFI) is not mandatory to define OMD.

Similar as for DFI, the heterogeneous reporting of TFI and disease at initial presentation is observed in the literature.

There was consensus that the relation of OMD states to the treatment status (during or after systemic therapy or after a minimum DFI or TFI) is of paramount importance to defining the relevant clinical scenario, but questions remain about these multiple clinical situations where OMD can arise as above, hence the multiple interpretations of 'TFI'. In some OMD states, TFI would have prognostic value (in the case of initially localized disease), in others it would ideally be minimized in a treatment course (in the case of initially polymetastatic disease). Complete reporting of primary presentation and subsequent systemic therapy is critical for future study.

Statement 14:

Overall survival (OS), disease-free survival (DFS) or PFS, LC, toxicity, QoL, patient-reported outcome measures, cost, delay or deferral of systemic therapy and ability to stay on the same line of systemic therapy are all considered important endpoints.

In the literature, efficacy of treatment for OMD is measured by various parameters, OS, PFS, LC and toxicity being most frequent. QoL and patient-reported outcome measures are infrequently identified based on our analysis of studies represented in this paper's literature review.
In the Delphi consensus, OS had the strongest support for being critical to showing benefit of MDRT for OMD, followed - in decreasing order - by PFS, LC, toxicity, QoL, patient-reported outcome measures, cost, delay or deferral of systemic therapy, and finally ability to stay on same systemic therapy without change.
While international criteria have been proposed for endpoints evaluating the benefit of oncology drugs (and support their reimbursement), it is acknowledged that other endpoints may also be important in the context of loco-regional oncology interventions [94–96] and that the most adequate endpoint may be dependent of the clinical situation.

Statements 15 and 16:

Although technology *per se* does not impact the indications, adequate technology and/or techniques (e.g., SBRT or hypofractionated image-guided radiotherapy) are a minimum requirement to treat OMD when pursuing curative intent (Statement 15). Although there is a broad variation in the delivered doses being reported, the goal is control of the targeted metastasis for which the current data support a higher biologic equivalent dose (BED, e.g., >100 Gy BED_{10}) (Statement 16), when it can be safely delivered.

The primary goal of delivering curative intent MDRT is to maximize tumour control while minimizing short and long-term effects of radiation. Therefore, every effort should be made to ensure precise delivery of radiotherapy using all available technological resources. More advanced technologies and/or techniques that facilitate smaller set-up margins, without compromising tumour coverage while limiting dose to normal tissues, have facilitated the increased interest in defining and treating OMD. Lack of motion management use [52,63], planning target volume size [23,63,84,97] and coverage [73,76] have been associated with lower tumour control. Overall however, detailed reporting of planning constraints and protocol deviations is minimal in the literature reviewed, highlighting an area in need of improvement.

While there are not sufficient literature data to address dose and BED by primary and in all relevant contexts, the convergence of existing data highlighting improved LC of the targeted metastasis with a minimum of 100 Gy BED_{10} makes this a goal when feasible until further evidence emerges [23,35,44,52,63,67,73,78,98]. It is noted however that in sites where normal tissue constraints make this infeasible near the bowel, great vessels or spinal cord, lower BEDs have been associated with control [99,100] and future studies may identify clinical scenarios where lower doses are adequate. Additionally, studies addressing systemic therapy induced OMD used lower radiation doses compared to studies addressing synchronous or metachronous OMD.

Discussion

Increasing enthusiasm for and technology to support safe radiation treatment of OMD has already led to a sharp increase in data in this field, and more trials are rapidly accruing to define the role of SBRT and other curative intent MDRT approaches in the context of the actual standards of care, of new systemic treatment strategies and compared to other local interventions. Meanwhile, this systematic literature review demonstrated substantial heterogeneity amongst the SBRT publications in terms of patients included, endpoints reported, and definitions used (Table 2). These findings guided the development of key unanswered questions, leading to consensus using the Delphi process. Key points, summarized in Table 1, emphasize there are not yet adequate biomarkers, including number of metastases, to conclude that primary tumour or metastatic site, response to therapy, or DFI limits preclude a potential oligometastatic state. It is clear many of these factors impact prognosis, however, explicitly describing the patient population studied and outcomes using consistent language is paramount to future progress.

In the absence of relevant biomarkers, the OMD state is currently defined based on imaging and clinical judgement. To homogenise diagnostic requirements, the EORTC (European Organisation for Research and Treatment of Cancer) Imaging Group has proposed minimal criteria for diagnostic imaging to define OMD [101]. To address the heterogeneity and uncertainties of OMD in its clinical implementation, ESTRO and EORTC have also jointly initiated OligoCare under the E2-RADIatE platform (EORTC-ESTRO RADiation InfrAstrucTure for Europe, NCT03818503). This international prospective registry trial aims to identify patient, tumour, staging, and treatment characteristics that impact OS of patients treated with radical radiotherapy for OMD. The inclusion criteria are broad to reflect the diversity of daily clinical practice and to allow the identification of relevant prognostic and predictive factors. In this frame, an OMD characterization system has been developed to classify distinct oligometastatic states and assign a consensus nomenclature [93]. The authors herein endorse the OligoCare classification consensus and encourage using this approach to unify definitions internationally.

The fast pace of clinical data emerging in this field limits the output of systematic literature review. Although randomised phase III evidence is lacking, recent randomised phase II trials have shown the potential of SBRT to improve survival of patients with OMD [9,10,12] and multiple randomized trials are expected in the next few years. A recent review reports 64 ongoing trials studying ablation of OMD, activated and accruing through February 2019 [102]. Over half were phase II (n = 35), however, 17 randomized controlled trials were noted. All are encouraged to build on these promising data by continuing to enrol in ongoing randomized trials. In addition, besides the further need for randomised data, it has been recognised that randomised evidence is difficult to generate and by itself insufficient to fully define the benefit of new radiotherapy indications, especially if set against the background of a continuously changing multidisciplinary environment, as is the case for MDRT for OMD [96,103]. This stresses the need for a blended approach to evidence generation, of real-world data – all or not collected in the context of a coverage with evidence programme –, together with randomised trials to further shed light on the benefit of curative intent radiotherapy, and of other local MDRT approaches such as surgery and radiofrequency ablation, used in the context of OMD.

In conclusion, considerably more data are needed to define the optimal patient selection for SBRT or otherwise curative intent MDRT for OMD. Synchronous and metachronous OMD are currently best defined as distinct disease states. Others such as oligorecurrence, -progression and -persistence are plausible scenarios where clinically evident disease may represent the true disease state as opposed to impending wide spread disease. Based on ongoing trials it is clear that further complexity will be added regarding the use of concurrent systemic therapy or immunotherapy [102]. It is therefore critical that authors and editors are explicit about inclusion criteria and definitions, endpoints and toxicity, while continuing to generate evidence on this complex and evolving clinical indication. Additional data are needed to determine the value of MDRT for selected cohorts of patients identified by key clinical features and/or extent and timing of OMD. Clinical judgement and individual patient factors remain key features of defining OMD. Future prospective studies should consider stratifying patients into different categories, e.g., such as will be performed in the context of the OligoCare trial. Meanwhile, based on the available evidence, indications for curative intent radiotherapy of OMD can be defined as 1 to 5 metastatic lesions, with a controlled primary tumor being optional, but where all metastatic sites must be safely treatable.

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Conflict of interest statement

The authors declare that they have no competing interests.

None of the authors has any financial and personal relationships with other people or organisations that could inappropriately influence (bias) of this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.04.003.

References

[1] Casiraghi M, De Pas T, Maisonneuve P, Brambilla D, Ciprandi B, Galetta D, et al. A 10-year single-center experience on 708 lung metastasectomies: the evidence of the "international registry of lung metastases". J Thorac Oncol 2011;6:1373–8.

[2] Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230:309–18 [discussion 18–21].

[3] Miller G, Biernacki P, Kemeny NE, Gonen M, Downey R, Jarnagin WR, et al. Outcomes after resection of synchronous or metachronous hepatic and pulmonary colorectal metastases. J Am Coll Surg 2007;205:231–8.

[4] Tree AC, Khoo VS, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA, et al. Stereotactic body radiotherapy for oligometastases. Lancet Oncol 2013;14:e28–37.

[5] Dingemans AC, Hendriks LEL, Berghmans T, Levy A, Hasan B, Faivre-Finn C, et al. Definition of synchronous oligo-metastatic non-small cell lung cancer – a consensus report. J Thorac Oncol 2019.

[6] Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13:8–10.

[7] Lewis D, Gardner E. "Do the trials": Caution urged in ASTRO Presidential Symposium on routine use of SABR as curative in metastatic cancer. 2019.

[8] Lewis SL, Porceddu S, Nakamura N, Palma DA, Lo SS, Hoskin P, et al. Definitive stereotactic body radiotherapy (SBRT) for extracranial oligometastases: an international survey of >1000 radiation oncologists. Am J Clin Oncol 2017;40:418–22.

[9] Gomez DR, Tang C, Zhang J, Blumenschein Jr GR, Hernandez M, Lee JJ, 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.

[10] Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. JAMA Oncol 2018;4:e173501.

[11] Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol 2018;36:446–53.

[12] Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, 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;393:2051–8.

[13] Ruers T, Van Coevorden F, Punt CJ, Pierie JE, Borel-Rinkes I, Ledermann JA, et al. Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. J Natl Cancer Inst 2017;109.

[14] Giaj-Levra N, Giaj-Levra M, Durieux V, Novello S, Besse B, Hasan B, et al. Defining synchronous oligometastatic non-small cell lung cancer: a systematic review. J Thorac Oncol 2019.

[15] Schanne DH, Heitmann J, Guckenberger M, Andratschke NHJ. Evolution of treatment strategies for oligometastatic NSCLC patients – A systematic review of the literature. Cancer Treat Rev 2019;80:101892.

[16] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

[17] Nguyen TK, Senan S, Bradley JD, Franks K, Giuliani M, Guckenberger M, et al. Optimal imaging surveillance after stereotactic ablative radiation therapy for early-stage non-small cell lung cancer: Findings of an International Delphi Consensus Study. Pract Radiat Oncol 2018;8:e71–8.

[18] Barata PC, Mendiratta P, Kotecha R, Gopalakrishnan D, Juloori A, Chao ST, et al. Effect of switching systemic treatment after stereotactic radiosurgery for oligoprogressive, metastatic renal cell carcinoma. Clin Genitourin Cancer 2018;16. 413–9 e1.

[19] Bowden P, See AW, Frydenberg M, Haxhimolla H, Costello AJ, Moon D, et al. Fractionated stereotactic body radiotherapy for up to five prostate cancer oligometastases: interim outcomes of a prospective clinical trial. Int J Cancer 2019.

[20] De Bleser E, Jereczek-Fossa BA, Pasquier D, Zilli T, Van As N, Siva S, et al. Metastasis-directed therapy in treating nodal oligorecurrent prostate cancer: a multi-institutional analysis comparing the outcome and toxicity of stereotactic body radiotherapy and elective nodal radiotherapy. Eur Urol 2019.

[21] De Rose F, Cozzi L, Navarria P, Ascolese AM, Clerici E, Infante M, et al. Clinical outcome of stereotactic ablative body radiotherapy for lung metastatic lesions in non-small cell lung cancer oligometastatic patients. Clin Oncol (R Coll Radiol) 2016;28:13–20.

[22] Decaestecker K, De Meerleer G, Lambert B, Delrue L, Fonteyne V, Claeys T, et al. Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence. Radiat Oncol 2014;9:135.

[23] Dell'Acqua V, Surgo A, Kraja F, Kobiela J, Zerella MA, Spychalski P, et al. Stereotactic radiation therapy in oligometastatic colorectal cancer: outcome of 102 patients and 150 lesions. Clin Exp Metastasis 2019;36:331–42.

[24] Didolkar MS, Fanous N, Elias EG, Moore RH. Metastatic carcinomas from occult primary tumors. A study of 254 patients. Ann Surg 1977;186:625–30.

[25] Fleckenstein J, Petroff A, Schafers HJ, Wehler T, Schope J, Rube C. Long-term outcomes in radically treated synchronous vs. metachronous oligometastatic non-small-cell lung cancer. BMC Cancer 2016;16:348.

[26] Franzese C, Comito T, Clerici E, Di Brina L, Tomatis S, Navarria P, et al. Liver metastases from colorectal cancer: propensity score-based comparison of stereotactic body radiation therapy vs. microwave ablation. J Cancer Res Clin Oncol 2018;144:1777–83.
[27] Franzese C, Comito T, Toska E, Tozzi A, Clerici E, De Rose F, et al. Predictive factors for survival of oligometastatic colorectal cancer treated with Stereotactic body radiation therapy. Radiother Oncol 2019;133:220–6.
[28] Franzese C, Franceschini D, Di Brina L, D'Agostino GR, Navarria P, Comito T, et al. Role of stereotactic body radiation therapy for the management of oligometastatic renal cell carcinoma. J Urol 2019;201:70–5.
[29] Franzese C, Zucali PA, Di Brina L, D'Agostino G, Navarria P, Franceschini D, et al. The efficacy of Stereotactic body radiation therapy and the impact of systemic treatments in oligometastatic patients from prostate cancer. Cancer Med 2018;7:4379–86.
[30] Gerum S, Heinz C, Belka C, Walter F, Paprottka P, De Toni EN, et al. Stereotactic body radiation therapy (SBRT) in patients with hepatocellular carcinoma and oligometastatic liver disease. Radiat Oncol 2018;13:100.
[31] Gomez DR, Blumenschein Jr GR, Lee JJ, Hernandez M, Ye R, Camidge DR, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol 2016;17:1672–82.
[32] Horner-Rieber J, Bernhardt D, Blanck O, Duma M, Eich HT, Gerum S, et al. Long-term follow-up and patterns of recurrence of patients with oligometastatic NSCLC treated with pulmonary SBRT. Clin Lung Cancer 2019.
[33] Hoyer M, Roed H, Traberg Hansen A, Ohlhuis L, Petersen J, Nellemann H, et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. Acta Oncol 2006;45:823–30.
[34] Hu F, Xu J, Zhang B, Li C, Nie W, Gu P, et al. Efficacy of local consolidative therapy for oligometastatic lung adenocarcinoma patients harboring epidermal growth factor receptor mutations. Clin Lung Cancer 2019;20:e81–90.
[35] Jingu K, Matsuo Y, Onishi H, Yamamoto T, Aoki M, Murakami Y, et al. Dose escalation improves outcome in stereotactic body radiotherapy for pulmonary oligometastases from colorectal cancer. Anticancer Res 2017;37:2709–13.
[36] Kinj R, Bondiau PY, Francois E, Gerard JP, Naghavi AO, Leysalle A, et al. Radiosensitivity of colon and rectal lung oligometastasis treated with stereotactic ablative radiotherapy. Clin Colorectal Cancer 2017;16:e211–20.
[37] Kneebone A, Hruby G, Ainsworth H, Byrne K, Brown C, Guo L, et al. Stereotactic body radiotherapy for oligometastatic prostate cancer detected via prostate-specific membrane antigen positron emission tomography. Eur Urol Oncol 2018;1:531–7.
[38] Kwint M, Walraven I, Burgers S, Hartemink K, Klomp H, Knegjens J, et al. Outcome of radical local treatment of non-small cell lung cancer patients with synchronous oligometastases. Lung Cancer 2017;112:134–9.
[39] Lazzari R, Ronchi S, Gandini S, Surgo A, Volpe S, Piperno G, et al. Stereotactic body radiation therapy for oligometastatic ovarian cancer: a step toward a drug holiday. Int J Radiat Oncol Biol Phys 2018;101:650–60.
[40] Lepinoy A, Silva YE, Martin E, Bertaut A, Quivrin M, Aubignac L, et al. Salvage extended field or involved field nodal irradiation in (18)F-fluorocholine PET/CT oligorecurrent nodal failures from prostate cancer. Eur J Nucl Med Mol Imaging 2019;46:40–8.
[41] Merino Lara T, Helou J, Poon I, Sahgal A, Chung HT, Chu W, et al. Multisite stereotactic body radiotherapy for metastatic non-small-cell lung cancer: delaying the need to start or change systemic therapy?. Lung Cancer 2018;124:219–26.
[42] Meyer E, Pasquier D, Bernadou G, Calais G, Maroun P, Bossi A, et al. Stereotactic radiation therapy in the strategy of treatment of metastatic renal cell carcinoma: a study of the Getug group. Eur J Cancer 2018;98:38–47.
[43] Mihai A, Mu Y, Armstrong J, Dunne M, Beriwal S, Rock L, et al. Patients with colorectal lung oligometastases (L-OMD) treated by dose adapted SABR at diagnosis of oligometastatic disease have better outcomes than patients previously treated for their metastatic disease. J Radiosurg SBRT 2017;5:43–53.
[44] Ost P, Jereczek-Fossa BA, As NV, Zilli T, Muacevic A, Olivier K, et al. Progression-free survival following stereotactic body radiotherapy for oligometastatic prostate cancer treatment-naive recurrence: a multi-institutional analysis. Eur Urol 2016;69:9–12.
[45] Ouyang W, Yu J, Nuerjiang S, Li Z, Wang D, Wang X, et al. Stereotactic body radiotherapy improves the survival of patients with oligometastatic non-small cell lung cancer. Cancer Med 2019;8:4605–14.
[46] Park HJ, Chang AR, Seo Y, Cho CK, Jang WI, Kim MS, et al. Stereotactic body radiotherapy for recurrent or oligometastatic uterine cervix cancer: a Cooperative Study of the Korean Radiation Oncology Group (KROG 14–11). Anticancer Res 2015;35:5103–10.
[47] Petty WJ, Urbanic JJ, Ahmed T, Hughes R, Levine B, Rusthoven K, et al. Long-term outcomes of a phase 2 trial of chemotherapy with consolidative radiation therapy for oligometastatic non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2018;102:527–35.
[48] Santini D, Ratta R, Pantano F, De Lisi D, Maruzzo M, Galli L, et al. Outcome of oligoprogressing metastatic renal cell carcinoma patients treated with locoregional therapy: a multicenter retrospective analysis. Oncotarget 2017;8:100708–16.
[49] Schick U, Jorcano S, Nouet P, Rouzaud M, Vees H, Zilli T, et al. Androgen deprivation and high-dose radiotherapy for oligometastatic prostate cancer patients with less than five regional and/or distant metastases. Acta Oncol 2013;52:1622–8.
[50] Tran S, Jorcano S, Falco T, Lamanna G, Miralbell R, Zilli T. Oligorecurrent nodal prostate cancer: long-term results of an elective nodal irradiation approach. Am J Clin Oncol 2018;41:960–2.
[51] Trovo M, Furlan C, Polesel J, Fiorica F, Arcangeli S, Giaj-Levra N, et al. Radical radiation therapy for oligometastatic breast cancer: results of a prospective phase II trial. Radiother Oncol 2018;126:177–80.
[52] Andratschke N, Alheid H, Allgauer M, Becker G, Blanck O, Boda-Heggemann J, et al. The SBRT database initiative of the German Society for Radiation Oncology (DEGRO): patterns of care and outcome analysis of stereotactic body radiotherapy (SBRT) for liver oligometastases in 474 patients with 623 metastases. BMC Cancer 2018;18:283.
[53] Aoki M, Hatayama Y, Kawaguchi H, Hirose K, Sato M, Akimoto H, et al. Stereotactic body radiotherapy for lung metastases as oligo-recurrence: a single institutional study. J Radiat Res 2016;57:55–61.
[54] Berber B, Ibarra R, Snyder L, Yao M, Fabien J, Milano MT, et al. Multicentre results of stereotactic body radiotherapy for secondary liver tumours. HPB (Oxford) 2013;15:851–7.
[55] Dohopolski MJ, Horne Z, Clump D, Burton SA, Heron DE. Stereotactic body radiation therapy for pulmonary oligometastases arising from non-lung primaries in patients without extrapulmonary disease. Cureus 2018;10:e2167.
[56] Fleming C, Rimner A, Foster A, Woo KM, Zhang Z, Wu AJ. Palliative efficacy and local control of conventional radiotherapy for lung metastases. Ann Palliat Med 2017;6:S21–7.
[57] Franceschini D, Cozzi L, De Rose F, Navarria P, Franzese C, Comito T, et al. Role of stereotactic body radiation therapy for lung metastases from radio-resistant primary tumours. J Cancer Res Clin Oncol 2017;143:1293–9.
[58] Franzese C, Cozzi L, Franceschini D, D'Agostino G, Comito T, De Rose F, et al. Role of stereotactic body radiation therapy with volumetric-modulated arcs and high-intensity photon beams for the treatment of abdomino-pelvic lymph-node metastases. Cancer Invest 2016;34:348–54.
[59] Frelinghuysen M, Schillemans W, Hol L, Verhoef C, Hoogeman M, Nuyttens JJ. Acute toxicity of the bowel after stereotactic robotic radiotherapy for abdominopelvic oligometastases. Acta Oncol 2018;57:480–4.
[60] Goodman BD, Mannina EM, Althouse SK, Maluccio MA, Cardenes HR. Long-term safety and efficacy of stereotactic body radiation therapy for hepatic oligometastases. Pract Radiat Oncol 2016;6:86–95.
[61] Helou J, Thibault I, Poon I, Chiang A, Jain S, Soliman H, et al. Stereotactic ablative radiation therapy for pulmonary metastases: histology, dose, and indication matter. Int J Radiat Oncol Biol Phys 2017;98:419–27.
[62] Jereczek-Fossa BA, Piperno G, Ronchi S, Catalano G, Fodor C, Cambria R, et al. Linac-based stereotactic body radiotherapy for oligometastatic patients with single abdominal lymph node recurrent cancer. Am J Clin Oncol 2014;37:227–33.
[63] Klement RJ, Guckenberger M, Alheid H, Allgauer M, Becker G, Blanck O, et al. Stereotactic body radiotherapy for oligo-metastatic liver disease – Influence of pre-treatment chemotherapy and histology on local tumor control. Radiother Oncol 2017;123:227–33.
[64] Klement RJ, Hoerner-Rieber J, Adebahr S, Andratschke N, Blanck O, Boda-Heggemann J, et al. Stereotactic body radiotherapy (SBRT) for multiple pulmonary oligometastases: analysis of number and timing of repeat SBRT as impact factors on treatment safety and efficacy. Radiother Oncol 2018;127:246–52.
[65] Lancia A, Ingrosso G, Carosi A, Di Murro L, Giudice E, Cicchetti S, et al. Oligometastatic cancer: stereotactic ablative radiotherapy for patients affected by isolated body metastasis. Acta Oncol 2017;56:1621–5.
[66] Loi M, Frelinghuysen M, Klass ND, Oomen-De Hoop E, Granton PV, Aerts J, et al. Locoregional control and survival after lymph node SBRT in oligometastatic disease. Clin Exp Metastasis 2018;35:625–33.
[67] Mazzola R, Fersino S, Ferrera G, Targher G, Figlia V, Triggiani L, et al. Stereotactic body radiotherapy for lung oligometastases impacts on systemic treatment-free survival: a cohort study. Med Oncol 2018;35:121.
[68] Navarria P, Ascolese AM, Tomatis S, Cozzi L, De Rose F, Mancosu P, et al. Stereotactic body radiotherapy (sbrt) in lung oligometastatic patients: role of local treatments. Radiat Oncol 2014;9:91.
[69] Oh D, Ahn YC, Seo JM, Shin EH, Park HC, Lim DH, et al. Potentially curative stereotactic body radiation therapy (SBRT) for single or oligometastasis to the lung. Acta Oncol 2012;51:596–602.
[70] Osti MF, Agolli L, Valeriani M, Reverberi C, Bracci S, Marinelli L, et al. 30 Gy single dose stereotactic body radiation therapy (SBRT): report on outcome in a large series of patients with lung oligometastatic disease. Lung Cancer 2018;122:165–70.
[71] Osti MF, Carnevale A, Valeriani M, De Sanctis V, Minniti G, Cortesi E, et al. Clinical outcomes of single dose stereotactic radiotherapy for lung metastases. Clin Lung Cancer 2013;14:699–703.
[72] Owen D, Laack NN, Mayo CS, Garces YI, Park SS, Bauer HJ, et al. Outcomes and toxicities of stereotactic body radiation therapy for non-spine bone oligometastases. Pract Radiat Oncol 2014;4:e143–9.
[73] Rieber J, Streblow J, Uhlmann L, Flentje M, Duma M, Ernst I, et al. Stereotactic body radiotherapy (SBRT) for medically inoperable lung metastases-A pooled analysis of the German working group "stereotactic radiotherapy". Lung Cancer 2016;97:51–8.
[74] Sharma A, Duijm M, Oomen-de Hoop E, Aerts JG, Verhoef C, Hoogeman M, et al. Survival and prognostic factors of pulmonary oligometastases treated with stereotactic body radiotherapy. Acta Oncol 2019;58:74–80.

[75] Siva S, Kirby K, Caine H, Pham D, Kron T, Te Marvelde L, et al. Comparison of single-fraction and multi-fraction stereotactic radiotherapy for patients with 18f-fluorodeoxyglucose positron emission tomography-staged pulmonary oligometastases. Clin Oncol (R Coll Radiol) 2015;27:353–61.
[76] Thibault I, Poon I, Yeung L, Erler D, Kim A, Keller B, et al. Predictive factors for local control in primary and metastatic lung tumours after four to five fraction stereotactic ablative body radiotherapy: a single institution's comprehensive experience. Clin Oncol (R Coll Radiol) 2014;26:713–9.
[77] Wang HH, Zaorsky NG, Meng MB, Zeng XL, Deng L, Song YC, et al. Stereotactic radiation therapy for oligometastases or oligorecurrence within mediastinal lymph nodes. Oncotarget 2016;7:18135–45.
[78] Yamashita H, Niibe Y, Yamamoto T, Katsui K, Jingu K, Kanazawa S, et al. Lung stereotactic radiotherapy for oligometastases: comparison of oligo-recurrence and sync-oligometastases. Jpn J Clin Oncol 2016;46:687–91.
[79] Dhondt B, De Bleser E, Claeys T, Buelens S, Lumen N, Vandesompele J, et al. Discovery and validation of a serum microRNA signature to characterize oligo- and polymetastatic prostate cancer: not ready for prime time. World J Urol 2018.
[80] Lussier YA, Khodarev NN, Regan K, Corbin K, Li H, Ganai S, et al. Oligo- and polymetastatic progression in lung metastasis(es) patients is associated with specific microRNAs. PLoS ONE 2012;7:e50141.
[81] Lussier YA, Xing HR, Salama JK, Khodarev NN, Huang Y, Zhang Q, et al. MicroRNA expression characterizes oligometastasis(es). PLoS ONE 2011;6:e28650.
[82] Pitroda SP, Khodarev NN, Huang L, Uppal A, Wightman SC, Ganai S, et al. Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. Nat Commun 2018;9:1793.
[83] Pembroke CA, Fortin B, Kopek N. Comparison of survival and prognostic factors in patients treated with stereotactic body radiotherapy for oligometastases or oligoprogression. Radiother Oncol 2018;127:493–500.
[84] Aujla KS, Katz AW, Singh DP, Okunieff P, Milano MT. Hypofractionated stereotactic radiotherapy for non-breast or prostate cancer oligometastases: a tail of survival beyond 10 years. Front Oncol 2019;9:111.
[85] Hoyer M, Roed H, Sengelov L, Traberg A, Ohlhuis L, Pedersen J, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. Radiother Oncol 2005;76:48–53.
[86] Fode MM, Hoyer M. Survival and prognostic factors in 321 patients treated with stereotactic body radiotherapy for oligo-metastases. Radiother Oncol 2015;114:155–60.
[87] Sutera P, Clump DA, Kalash R, D'Ambrosio D, Mihai A, Wang H, et al. Initial results of a multicenter phase 2 trial of stereotactic ablative radiation therapy for oligometastatic cancer. Int J Radiat Oncol Biol Phys 2019;103:116–22.
[88] Laurie SA, Banerji S, Blais N, Brule S, Cheema PK, Cheung P, et al. Canadian consensus: oligoprogressive, pseudoprogressive, and oligometastatic non-small-cell lung cancer. Curr Oncol 2019;26:e81–93.
[89] Niibe Y, Hayakawa K. Oligometastases and oligo-recurrence: the new era of cancer therapy. Jpn J Clin Oncol 2010;40:107–11.
[90] Palma DA, Salama JK, Lo SS, Senan S, Treasure T, Govindan R, et al. The oligometastatic state – separating truth from wishful thinking. Nat Rev Clin Oncol 2014;11:549–57.
[91] Reyes DK, Pienta KJ. The biology and treatment of oligometastatic cancer. Oncotarget 2015;6:8491–524.
[92] Triggiani L, Alongi F, Buglione M, Detti B, Santoni R, Bruni A, et al. Efficacy of stereotactic body radiotherapy in oligorecurrent and in oligoprogressive prostate cancer: new evidence from a multicentric study. Br J Cancer 2017;116:1520–5.
[93] Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, 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.
[94] Agency EM. Guideline on the evaluation of anticancer medicinal products in man. 2017
[95] FDA. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry. 2018.
[96] Lievens Y, Audisio R, Banks I, Collette L, Grau C, Oliver K, et al. Towards an evidence-informed value scale for surgical and radiation oncology: a multi-stakeholder perspective. Lancet Oncol 2019;20:e112–23.
[97] Erler D, Brotherston D, Sahgal A, Cheung P, Loblaw A, Chu W, et al. Local control and fracture risk following stereotactic body radiation therapy for non-spine bone metastases. Radiother Oncol 2018;127:304–9.
[98] Napieralska A, Miszczyk L, Stapor-Fudzinska M. CyberKnife stereotactic radiosurgery and stereotactic ablative radiation therapy of patients with prostate cancer bone metastases. Neoplasma 2016;63:304–12.
[99] Chang JH, Gandhidasan S, Finnigan R, Whalley D, Nair R, Herschtal A, et al. Stereotactic ablative body radiotherapy for the treatment of spinal oligometastases. Clin Oncol (R Coll Radiol) 2017;29:e119–25.
[100] Seo YS, Kim MS, Cho CK, Yoo HJ, Jang WI, Kim KB, et al. Stereotactic body radiotherapy for oligometastases confined to the para-aortic region: clinical outcomes and the significance of radiotherapy field and dose. Cancer Invest 2015;33:180–7.
[101] deSouza NM, Liu Y, Chiti A, Oprea-Lager D, Gebhart G, Van Beers BE, et al. Strategies and technical challenges for imaging oligometastatic disease: recommendations from the European Organisation for Research and Treatment of Cancer imaging group. Eur J Cancer 2018;91:153–63.
[102] Al-Shafa F, Arifin AJ, Rodrigues GB, Palma DA, Louie AV. A review of ongoing trials of stereotactic ablative radiotherapy for oligometastatic cancers: where will the evidence lead? Front Oncol 2019;9:543.
[103] Lievens Y. Access to innovative radiotherapy: how to make it happen from an economic perspective? Acta Oncol 2017;56:1353–8.
[104] Bhattacharya IS, Woolf DK, Hughes RJ, Shah N, Harrison M, Ostler PJ, et al. Stereotactic body radiotherapy (SBRT) in the management of extracranial oligometastatic (OM) disease. Br J Radiol. 2015;88(1048):20140712.
[105] Van den Begin R, Engels B, Collen C, de Vin T, Defauw A, Dubaere E, et al. The METABANK score: A clinical tool to predict survival after stereotactic radiotherapy for oligometastatic disease. Radiother Oncol. 2019;133:113–9.
[106] Lancia A, Ingrosse G, Carosi A, Bottero M, Cancelli A, Turturici I, et al. Oligometastatic cancer in elderly patients: the "blitzkrieg" radiotherapy approach. Aging Clin Exp Res. 2019;31:109–14.
[107] Milano MT, Katz AW, Zhang H, Okunieff P. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. Int J Radiat Oncol Biol Phys. 2011;83(3):878–86.
[108] Deodato F, Macchia G, Cilla S, Ianiro A, Sallustio G, Cammelli S, et al. Dose escalation in extracranial stereotactic ablative radiotherapy (DESTROY-1): A multi-arm Phase I trial. Br J Radiol. 2019;91: 20180422.
[109] Greco C, Zelefsky MJ, Lovelock M, Fuks Z, Hunt M, Rosenzweig K, et al. Predictors of local control aftersingle-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases. Int J Radiat Oncol Biol Phys. 2011;79(4):1151–7.
[110] Wong AC, Watson SP, Pitroda SP, Son CH, Das LC, Stack ME, et al. Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT). Cancer. 2016;122(14):2242–50.
[111] de Vin T, Engels B, Gevaert T, Storme G, De Ridder M. Stereotactic radiotherapy for oligometastatic cancer: a prognostic model for survival. Ann Oncol. 2014;25(2):467–71.
[112] Binkley MS, Trakul N, Jacobs LR, von Eyben R, Le QT, Maxim PG, et al. Colorectal Histology Is Associated With an Increased Risk of Local Failure in Lung Metastases Treated With Stereotactic Ablative Radiation Therapy. Int J Radiat Oncol Biol Phys. 2015;92(5):1044–52.
[113] Erler D, Brotherston D, Sagal A, Cheung P, Loblaw, Chu W, et al. Local control and fracture risk following stereotactic body radiation therapy for non-spine bone metastases. Radiother Oncol. 2018;127(2):304–9.
[114] Muldermans JL, Romak LB, Kwon ED, Park SS, Oliver KR. Stereotactic Body Radiation Therapy for Oligometastatic Prostate Cancer. Int J Radiat Oncol Biol Phys. 2016;95(2):696–702.
[115] Napieralska A, Miszczyk L, Stapor-Fudzinska M. Cyberknife stereotactic radiosurgery and stereotactic ablative radiation therapy of patients with prostate cancer bone metastases. Neoplasma 2016;63(2):304–12.
[116] Franceschini D, De Rose F, Franzese C, Comito T, Di Brina L, Radicioni G, et al. Predictive Factors for Response and Survival in a Cohort of Oligometastatic Patients Treated With Stereotactic Body Radiation Therapy. Int J Radiat Oncol Biol Phys. 2019;104(1):111–21.
[117] Kang J-K, Kim M-S, Kim JH, Yoo SY, Cho CK, Yang KM, et al. Oligometastases confined one organ from colorectal cancer treated by SBRT. Clin Exp Metastasis. 2010;27:273–8.