Defining Synchronous Oligometastatic Non-Small Cell Lung Cancer

REVIEW ARTICLE

Defining Synchronous Oligometastatic Non–Small Cell Lung Cancer: A Systematic Review

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ABSTRACT

Introduction: Synchronous oligometastatic (sOM) disease is an oncological concept characterized by a limited cancer burden. Patients with oligometastasis could potentially benefit from local radical treatments. Despite the fact that the sOM condition is well recognized, a universal definition, including a specific definition for NSCLC, is not yet available. The aim of this systematic review was to summarize the definitions of and staging requirements for use of the term *synchronous oligometastatic* in the context of NSCLC.

Methods: The key issue was formulated in one research question according to the population, intervention, comparator, and outcomes strategy. The question was introduced in MEDLINE (OvidSP). All articles dealing with sOM NSCLC and providing a definition of synchronous oligometastasis in NSCLC were selected and analyzed.

Results: A total of 21 eligible articles focusing on sOM NSCLC were retrieved and analyzed. In 17 studies (81%), patients had to be staged with magnetic resonance imaging or computed tomography of the brain, thoracic and abdominal computed tomography, and positron emission tomography. The total number of metastases allowed in the definitions ranged from one to eight, but in 38.1% of studies the maximum number was 5. Most of the publications did not define the number of involved organs or the maximum number of metastases per organ. For mediastinal lymph

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node involvement, only five articles (27.8%) counted this as a metastatic site.

Conclusions: No uniform definition of sOM NSCLC could be retrieved by this systematic review. However, extended staging was mandated in most of the studies. An accepted oncological definition of synchronous oligometastasis is essential for patient selection to define prospective clinical trials.

Keywords: NSCLC; Oligometastatic disease definition; Synchronous; Systematic review

Introduction

Approximately half of all patients with NSCLC present with metastatic disease, with a median overall survival (OS) of 12 months.[1] However, metastatic NSCLC is a heterogeneous status, characterized by different clinical presentations and prognoses according to anatomical site and number of metastases. In 1995, Hellman and Weichselbaum defined oligometastatic disease[2] as a state of limited systemic metastatic burden in which eradication of oligometastases with local radical therapies (i.e., surgery and radiotherapy) could be curative in selected patients.[3]

Currently, no single, uniform, and reliable definition of synchronous oligometastatic (sOM) disease in NSCLC exists. In the European Society for Medical Oncology guidelines a paragraph is dedicated on oligometastatic disease, without a clear definition of this status, reporting that many clinical trials investigating local treatment of oligometastatic disease have limited inclusion to patients with no more than five metastases, but the vast majority of the trials have included patients with no more than three metastases.[1] In the National Comprehensive Cancer Network guidelines patients with oligometastasis are defined as those with isolated or limited metastatic disease.[4]

A uniform definition is of importance as new effective local ablative therapies are developed. Their integration in therapeutic algorithms for sOM NSCLC has been tested in different prospective clinical trials.[5,6]

In an attempt to provide a definition of sOM NSCLC, the European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer Group (LCG) developed a consensus definition based on clinical cases of sOM disease, a European survey on sOM disease, and a systematic review of the currently requested staging methods and definitions of the term *synchronous oligometastatic* used in clinical trials.[7–9] Here we report the results of the systematic review.

Materials and Methods

The key issue was formulated in one question according to the population, intervention, comparator, and outcomes criteria (population, intervention, control, and outcomes). The standard reporting guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [http://www.prisma-statement.org/]) has been used for this systematic review. The research question was concentrated strictly on the clinical definition of sOM NSCLC. The research equation composed of Medical Subject Headings

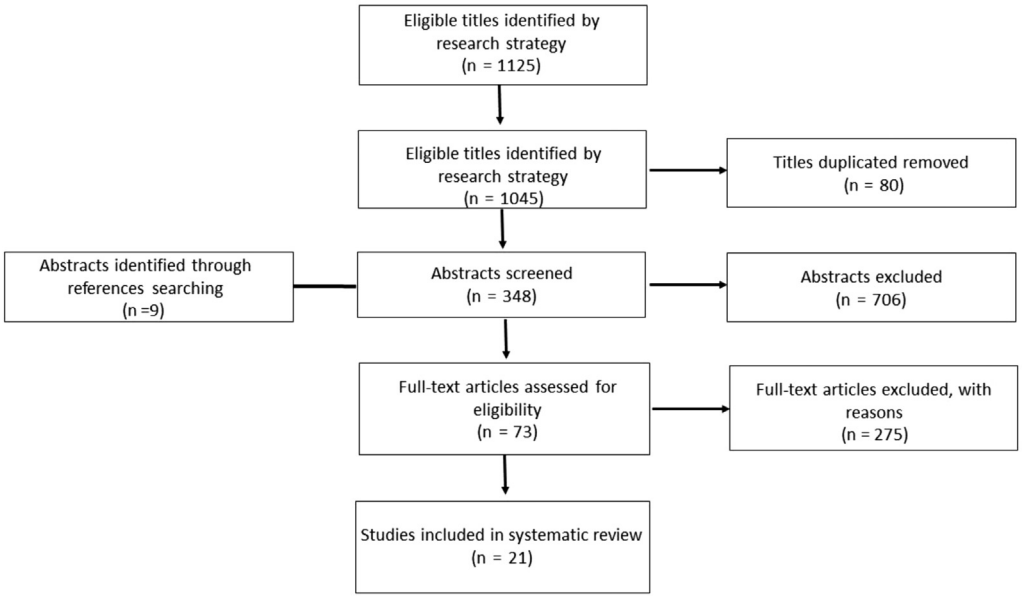

Figure 1. Search flowchart.

Table 1. Studies Selected, Population, and Intervention in Synchronous Oligometastatic NSCLC (PICO Criteria)

	Population				Intervention					
Authors/Year	Type of Study	Single-Center/ Multicenter	Patients, n	TNM Edition	Work-up	PET-CT	Brain MRI	Brain CT	Mediastinal Staging	Pathological Proof of Malignancy
Downey et al. (2002)[27]	NRT	Single	23	Fifth	Complete	No	Yes	NA	EBUS	All sites
Khan et al. (2006)[12]	RS	Single	23	NA	Partial[a]	Yes	NA	NA	PET-CT	NA
Inoue et al. (2010)[22]	RS	Single	25	NA	Complete	No	No	NA	PET-CT	No
Cheruvu et al. (2011)[23]	RS	Single	38	Seventh	Complete	Yes	Yes	NA	PET-CT	NA
Collaud et al. (2012)[24]	RS	Single	29	Sixth	Complete	Yes	Yes	NA	EBUS	NA
Congedo et al. (2012)[25]	RS	Single	53	Fifth	Complete	Yes	No	Yes	EBUS	NA
De Ruysscher et al. (2012)[26]	NRT	Single	40	Sixth	Complete	Yes	Yes	NA	PET-CT	≥1 site
Lopez Guerra et al. (2012)[13]	RS	Single	78	Sixth	Incomplete	NA	NA	NA	NA	NA
Griffioen et al. (2013)[28]	RS	Multicenter	61	Fifth-seventh	Complete	Yes	Yes	NA	PET-CT	NA
Nieder et al. (2014)[14]	RS	Multicenter	23	Seventh	Complete	Yes	Yes	Yes	PET-CT	NA
Parikh et al. (2014)[15]	C	Single	186	Seventh	Complete	Yes	Yes	No	PET-CT	NA
Sheu et al. (2014)[18]	DB	Single	90	Seventh	Incomplete	NA	NA	NA	NA	No
Plones et al. (2015)[16]	RS	Single	56	Sixth	Complete	Yes	Yes	Yes	EBUS	NA
Su et al. (2015)[20]	NRT	Multicenter	198	Sixth	Complete	Yes	Yes	Yes	PET-CT	NA
Xanthopoulos et al. (2015)[21]	DB	Single	29	Seventh	Complete	Yes	NA	No	PET-CT	NA
Fleckenstein et al. (2016)[29]	DB	Single	39	Fifth-seventh	Complete	Yes	NA	NA	NA	NA
Gomez et al. (2016)[6]	RT	Multicenter	49	Seventh	Complete	Yes	Yes	NA	PET-CT	NA
Johnson et al. (2016)[11]	DB	Single	37	Fifth-seventh	Complete	Yes	Yes	Yes	EBUS	No
Sakai et al. (2016)[17]	RS	Single	18	Seventh	Complete	Yes	Yes	Yes	PET-CT	NA
Su et al. (2016)[20]	NRT	Single	91	Sixth	Complete	Yes	Yes	Yes	PET-CT	NA
Iyengar et al. (2018)[5]	RT	Single	29	NA	Complete[b]	Yes	Yes	Yes	PET-CT	≥1 site

[a]PET (or thorax + abdomen CT and bone scan) without brain MRI/CT.
[b]Brain MRI/CT + PET (or thorax + abdomen CT and bone scan).
PICO, population, intervention, comparator, and outcomes; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; NRT, no randomized trial; EBUS, endobronchial ultrasound; NA, not available, RS, retrospective series; C, cohort; DB, database.

descriptors and free text keywords, as reported in Supplement Table 1, was launched in MEDLINE (OvidSP) in October 2017.

A time cutoff of January 1, 1996, has been used to identify publications with patients staged according to the fifth and later TNM classifications.[10] Titles and abstracts were screened independently by two authors (M. G. L. and N. G. L.) and reviewed by two other authors (A. M. D. and T. B.) to determine potentially relevant articles for the systematic review. The selection process

Table 2. Outcomes in NSCLC Synchronous Oligometastatic (PICO criteria)

	Outcomes									
Authors/Year	Organs with ≥1 Mts, n	Mts, n	Mts per organ, n	N status as organ/N level	Prognostic Factor Analysis	Primary Outcome	Multivariate Analysis and OS	Metastatic Site Excluded	Mutational Analyses /Impact on Outcomes	Curative Intent
Downey et al. (2002)[27]	1	1	1	No	No	Other	—	No	No	NA
Khan et al. (2006)[12]	NA	2	ND	Yes/N3	No	OS	None	No	No	Yes
Inoue et al. (2010)[22]	2	5	ND	No	Yes	OS/PFS/ Other	None	No	No	Yes
Cheruvu et al. (2011)[23]	NA	8	ND	Yes/N3	Yes	OS	GTV	No	No	Yes
Collaud et al. (2012)[24]	1	1	1	No	Yes	OS	None	No	Yes (*EGFR*)/ No	Yes
Congedo et al. (2012)[25]	2	2	2	No	Yes	OS	Weight loss, PET-CT, surgical resection	No	No	NA
De Ruysscher et al. (2012)[26]	NA	5	ND	No	No	OS	None	Pleural or pericardial effusion	Yes (*EGFR*)/ NA	Yes
Lopez Guerra et al. (2012)[13]	NA	4	ND	No	Yes	OS	Radiation dose, PS, tumor volume	No	No	Yes
Griffioen et al. (2013)[28]	NA	3	ND	No	Yes	OS/PFS/ Other	None	No	No	Yes
Nieder et al. (2014)[14]	1	3	3	No	Yes	OS	None	No	No	Yes
Parikh et al. (2014)[15]	NA	5	ND	Yes/N3	Yes	OS	PS, N status, number of organs,	No	Yes (*EGFR*)/ Yes	Yes
Sheu et al. (2014)[18]	NA	3	ND	NA	Yes	OS/PFS	Sex, PS, local therapy	No	No	Yes
Plones et al. (2015)[16]	NA	5	ND	No	Yes	OS	Bone mts	No	No	Yes
Su et al. (2015)[20]	3	NA	≤2 liver Mts	No	Yes	OS	Radiation dose (>63 Gy), tumor volume, PS	No	Yes (*EGFR*)/ No	Yes
Xanthopoulos et al. (2015)[21]	NA	4	ND	No	Yes	OS	Radiotherapy, female, number of metastatic organs	No	No	Yes
Gomez et al. (2016)[6]	NA	3	ND	Yes/N3	No	PFS	—	No	Yes (*EGFR*/ *ALK*) /Yes	Yes
Fleckenstein et al. (2016)[29]	NA	5	3 for brain Mts	NA	Yes	OS/PFS	None	No	No	Yes
Johnson et al. (2016)[11]	2	5	<5	No	No	OS	None	No	No	Yes

(continued)

Table 2. Continued

Authors/Year	Outcomes									
	Organs with ≥1 Mts, n	Mts, n	Mts per organ, n	N status as organ/N level	Prognostic Factor Analysis	Primary Outcome	Multivariate Analysis and OS	Metastatic Site Excluded	Mutational Analyses /Impact on Outcomes	Curative Intent
Sakai et al. (2016)[17]	2	5	5	No	No	OS	None	No	Yes (*EGFR*)/ Yes	Yes
Su et al. (2016)[20]	NA	4	ND	NA	Yes	OS	Radiation dose, tumor volume	No	No	Yes
Iyengar et al. (2018)[5]	NA	5	5 (≤3 lung or liver)	Yes/No	No	PFS	–	Uncontrolled brain Mts	No	Yes

Mts, metastasis; N, node; OS, overall survival; NA, not available; ND, not determined; PFS, progression-free survival; GTV, gross tumor volume; PET, positron emission tomography; CT, computed tomography; PS, performance status; *ALK*, ALK receptor tyrosine kinase gene.

was divided into two parts: selection of abstracts and selection of full articles.

Abstracts were selected if they (1) focused only on lung cancers (NSCLC or SCLC), (2) dealt with sOM tumors, whatever the definition used by the authors, (3) provided a definition of oligometastatic status, (4) were a retrospective or prospective study, and (5) in the case of retrospective studies, the number of patients was at least 14 (adapted from the statistical Simon's design).

Full articles were evaluated according to the previous criteria, and contributions in French, English, Dutch, and Italian were accepted.

Series focusing on a specific single metastatic organ (e.g., brain only or adrenal gland only) were excluded, as the focus of the review was oligometastasis instead of solitary metastasis. Also, systematic reviews, meta-analysis, and editorials were not included.

Additional publications were identified through examination of references cited in the eligible publications and were added if they also fulfilled the selection criteria. Disagreements were resolved by consensus.

The following variables were extracted from the publications for the definition of the sOM NSCLC: (1) number of metastases, (2) number of organs with at least one metastasis, (3) number of metastases per organ, (4) lymph node status, and (5) metastatic sites that were excluded.

Additional data describing the population, intervention, and outcomes were also extracted: (1) type of study; (2) single-center or multicenter experience; (3) number of patients enrolled; (4) staging system; (5) radiological assessment (thoracic, mediastinal, cranial, and extracranial metastatic staging); (6) pathological proof of malignancy; (7) primary outcome; and (8) curative therapeutic intent.

Results

The search strategy and potentially eligible abstracts are shown in Supplement Table 2. A total of 1125 potentially eligible titles were identified and 80 duplicates were removed. Among 1045 titles, 348 respected the abstract selection criteria and another nine articles were added by reviewing the references from the included articles. A total of 73 articles fulfilled the publication selection criteria, and among them we selected those that were focused on the sOM condition (i.e., articles focusing only on oligoprogression and oligorecurrence were excluded). We accepted articles if they evaluated both sOM disease (the main issue of the systematic review) and oligoprogression/recurrence. A total of 21 articles were eligible for this systematic analysis,[5,6,11–28] as reported in Figure 1.

Table 3. Summary of Variables

Variables	Publications (%) (N = 21)
Type of study, n (%)	
Retrospective series	10 (47.6%)
Prospective nonrandomized study	4 (19%)
Randomized study	2 (9.6%)
Cohort	1 (4.8%)
Database/registry	4 (19%)
Other	0
Single center	17 (81%)
Multicentric	4 (19%)
Total patients (in all the studies combined)	1215 (range 18-198)
Median no. of patients	39
Staging system, n, (%)	
Fifth or sixth	8 (38.1%)
Sixth and seventh	3 (14.3%)
Seventh	7 (33.3%)
Eighth	0
Not available	3 (14.3%)
Work-up, n (%)	
Brain MRI/CT + PET (or thoracic + abdominal CT and bone scan), (%)	17 (81%)
PET (or thoracic + abdominal CT and bone scan) w/o MRI/CT	1 (4.8%)
Incomplete work-up	3 (14.2%)
PET-CT, n (%)	
No	2 (9.5%)
Yes	17 (81%)
Not reported	2 (9.5%)
Brain MRI, n (%)	
No	2 (9.5%)
Yes	13 (61.9%)
Not reported	6 (28.6%)
Brain CT, n (%)	
No	2 (9.5%)
Yes	7 (33.4%)
Not reported	12 (57.1%)
Mediastinal staging, n, (%)	
PET	13 (62%)
CT only	0 (0%)
EBUS or EUS or mediastinoscopy	5 (23.8%)
Not reported/not assessed	3 (14.2%)
Organs with at ≥1 metastasis, n, (%)	
1	3 (14.3%)
2	4 (19%)
3	1 (4.8%)
Any	5 (23.8%)
NA	8 (38.1%)
Mediastinal lymph nodes are counted as an organ, n, (%)	
No	12 (51.1%)
Yes	6 (28.6%)
Not define	3 (14.3%)
Volume is considered to be an issue, n, (%)	
No	8 (38.1%)
Yes	5 (23.8%)
Not assessed	8 (38.1%)
Primary outcome measure, n (%)	
OS	14 (66.7%)
PFS	2 (9.5%)
Response	0 (0%)
QoL	0 (0%)
Other/multiple	5 (23.8%)
Pathological proof of metastasis, n (%)	
No	3 (14.3%)
Systematic for all sites	1 (4.8%)
Systematic for ≥1 site	2 (9.5%)
Not reported	15 (71.4%)
Curative therapeutic intent, n (%)	
No	1 (4.8%)
Yes	18 (85.7%)
Not reported	2 (9.5%)
Mutational status is considered, n, (%)	
No	15 (71.4%)
Yes	6 (28.6%)
Mutational status analyzed, n	
EGFR	4
ALK	0
Combination (*EGFR*/*ALK*)	2

MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography; EBUS, endobronchial ultrasound; endoscopic ultrasound, NA, not available; OS, overall survival; PFS, progression-free survival; QoL, quality of life; *ALK*, ALK receptor tyrosine kinase gene.

Population

The main studies' characteristics are reported in Table 1[5,6,11–18,20–26,28] Most of the published data were retrospective (n = 14 [66.6%]) and from a single center (n = 17 [81%]). The total number of patients with sOM NSCLC described in the 21 studies was 1215 (range 18–198), with a median number of 39.

Mandated Staging

In most of the studies (n = 17 [81%]), staging with thoracic and abdominal computed tomography (CT) scan, positron emission tomography with fludeoxyglucose F 18 integrated with CT (^{18}F-FDG PET/CT), and brain magnetic resonance imaging (MRI) or CT was mandated. In particular, in 16 studies baseline brain imaging was mandated and baseline brain MRI was preferred in 14 articles (66.7%). Mediastinal staging was predominantly clinical (n = 13 [62%]) with ^{18}F-FDG PET/CT, with only five articles (23.8%) mandating a pathological mediastinal staging by endobronchial ultrasound. A pathological proof of metastases was not requested in three articles (14.3%) but was mandated for all sites in one study (4.8%) and for at least one metastatic site in two studies (9.5%). In most studies (n = 15 [71.4%]) this information was not available (Table 1).

Outcomes

The main information about the applied definitions of sOM NSCLC is reported in Table 2.[5,6,11–18,20–29] The total number of metastases used in the definition of sOM disease ranged from one to eight, and in eight studies (38.1%) the maximum number of metastases allowed was 5. In most of the series (n = 13 [61.9%]), we did not find any limitation or restriction about the number of organs involved with at least one metastasis; otherwise, when defined, the maximum number of allowed metastatic organs was 3 in one article (4.8%), 2 in four articles (19%), and 1 in three articles(14.3%).

The maximum number of metastases per organ was not defined in 12 articles (51.1%), and in three (14.3%) a partial definition was given (e.g., no more than two liver metastases, no more than three metastases for the brain, fewer than five in a single organ other than lung). When a maximum number of metastases per organ was defined, it ranged from one to five (six articles [28.6%]).

We checked whether mediastinal lymph nodes involvement was counted as a separate metastatic site. This was not specified in three studies (14.3%), in 13 studies (61.9%) lymph node involvement was not counted in the number of metastatic organs allowed, and in only five studies (23.8%) were mediastinal lymph nodes effectively counted as a metastatic site. In one article, all lymph nodal sites were considered to be metastatic sites, whereas in four articles only the N3 stations were counted as a metastatic site.

Of the 21 studies, 19 did not exclude any specific metastatic site, whereas in two articles uncontrolled brain, gastrointestinal, and skin metastases or pleural/pericardial metastases were not allowed.

OS was the primary outcome in most of the published articles (n = 18 [85.7%]), whereas in two articles (9.5%) it was progression free-survival (PFS). In four articles both OS and PFS were considered to be coprimary end points. In 18 articles (85.7%) the authors declared that the treatment of oligometastatic disease had a curative intent. All of the variables have been summarized in Table 2.

Discussion

Despite the fact that the sOM status is currently recognized in NSCLC, a uniform definition is not available and several issues are still open. Hence, we have performed a systematic review of the literature to offer scientific support on the published definitions of sOM NSCLC and to support the EORTC LCG consensus.[8] On the basis of this systematic review, it emerges that a single clinical definition of sOM NSCLC does not exist; of the numerous retrieved publications on sOM disease, only a minority provided a clear definition (Table 3).

Although there is no clear definition of sOM disease, in most of the articles a complete radiological staging using brain MRI and ^{18}F-FDG PET/CT was mandated. This is in line with the general consensus in scientific societies such as the European Society for Medical Oncology, National Comprehensive Cancer Network, and EORTC.[1,4,30] Complete radiological staging remains important for the definition of sOM disease, but also the outcome of radical treatment of patients with sOM disease, as stage migration is a well-known phenomenon when introducing more sensitive diagnostic techniques as ^{18}F-FDG-PET/CT and brain MRI. Potentially, this could be useful in better patient selection and, consequently, improvement in clinical outcomes.

Furthermore, ^{18}F-FDG PET/CT was the main method required to stage both systemic disease and mediastinal lymph node status. On the other hand, it is unclear whether pathological proof of mediastinal lymph node involvement in the metastatic process is necessary in addition to the metabolic and morphologic assessment, probably because of excellent sensitivity and specificity of ^{18}F-FDG PET/CT. A recent systematic review reported that ^{18}F-FDG PET/CT is associated with a sensitivity and specificity in the identification of lymph node involvement with a value between 79% and 85% and between 87% and 92%, respectively.[31]

In most articles, the authors did not report on the histopathologic proof of malignancy of the metastatic site. Apparently, mediastinal lymph node involvement is not uniformly considered relevant in the definition of sOM NSCLC or in the selection of patients eligible for combined local and systemic treatments. It is also uncertain whether involved mediastinal lymph nodes should be counted as a separate metastatic site. According to the TNM classification,[10] mediastinal lymph nodes are considered locally advanced but not metastatic. However, from the available literature it is known that mediastinal lymph node involvement negatively affects the outcome of patients with sOM disease.[10] In most of the studies included in this systematic review, mediastinal lymph node involvement was not counted as a separate metastatic anatomical site. Future prospective trials should establish or evaluate whether radical treatment of sOM NSCLC with mediastinal lymph node involvement is recommended and which levels (N1–N3) have an impact on outcomes of these patients.

Additionally, in all the included articles, we could not identify any specific metastatic site that was uniformly excluded from a radical combined oncological approach. This could be a selection bias, as some clinical presentations (e.g., leptomeningeal dissemination, lung lymphangitis) are associated with poor clinical outcomes and those patients have not been considered in the selected, mostly retrospective, studies for this

review because they are generally not included in trials involving sOM disease.

The level of evidence and the potential biases of the retrieved publications can limit the information provided by this review. The majority of the studies were retrospective single-center series, and outside of the maximum number of metastases, other information such as the number of organs with at least one metastasis, the maximal number of metastases per organ was a selection criteria in only a limited number of publications. Even for the maximal number of metastases, which was defined in all studies, no clear cutoff could be found; however, most of the studies did not allow more than five metastases. From the published papers we cannot deduce whether these data were missing or the authors had not considered them fundamental for their research.

Conclusions

Synchronous oligometastatic NSCLC refers to NSCLC in which the combination of systemic and local ablative treatments may influence tumor behavior. Although many studies have been published on this subject, the evidence from this systematic review suggests that a uniform and reliable definition of sOM disease does not exist. However, mandated diagnostic staging was very stringent with ^{18}F-FDG PET/CT and imaging of the brain. Nevertheless, some consensus emerged in the cutoff defining the maximal number of metastases and the staging work-up.

The results of this systematic review served as a scientific basis for the consensus meeting on the definition of sOM disease, as initiated by the EORTC LCG, to propose a collective multidisciplinary definition of sOM NSCLC for use in prospective clinical trials.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.05.037.

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