ORIGINAL ARTICLE

Definition of Synchronous Oligometastatic Non–Small Cell Lung Cancer—A Consensus Report

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ABSTRACT

Introduction: Improved outcome has been shown in patients with synchronous oligometastatic (sOM) NSCLC when treated with radical intent. As a uniform definition of sOM NSCLC is lacking, we developed a definition and diagnostic criteria by a consensus process.

Methods: A pan-European multidisciplinary consensus group was established. Consensus questions were built on the basis of current controversies, and definitions were extracted from a survey, cases and a systematic review. This statement was formulated during a consensus meeting.

Results: It was determined that definition of sOM NSCLC is relevant when a radical treatment that may modify the disease course (leading to long-term disease control) is technically feasible for all tumor sites with acceptable toxicity. On the basis of the review, a maximum of five metastases and three organs was proposed. Mediastinal lymph node involvement was not counted as a metastatic site. Fludeoxyglucose F 18 positron emission tomography–computed tomography and brain imaging were considered mandatory. A dedicated liver magnetic resonance imaging scan was advised for a solitary liver metastasis, and thoracoscopy and biopsies of distant ipsilateral pleural sites were recommended for a solitary pleural metastasis. For mediastinal staging, fludeoxyglucose F 18 positron emission tomography–computed tomography was deemed the minimum requirement, with pathological confirmation recommended if this influences the treatment strategy. Biopsy of a solitary metastatic location was mandated unless the multidisciplinary team is of the opinion that the risks outweigh the benefits.

Conclusion: A multidisciplinary consensus statement on the definition and staging of sOM NSCLC has been formulated. This statement will help to standardize inclusion criteria in future clinical trials.

Keywords: Non–small cell lung cancer; Oligometastatic disease; Consensus definition; Staging

Introduction

There is a common belief that patients with metastatic NSCLC cannot be treated successfully with curative intent. However, for years patients presenting with a solitary brain or adrenal metastasis were pragmatically treated with local radical treatment (LRT), as retrospective series (and many anecdotes) demonstrated long-term overall survival (OS) in some of these patients.[1–4] Favorable outcomes of LRT in patients with NSCLC presenting with up to five metastatic sites were shown in several series, mainly retrospective, with a 5-year OS rate around 30%.[2,5]

The concept of a clinically significant state of oligometastasis was first described in 1995[6]: it was proposed that these patients have an intermediate state of metastatic potential and could potentially benefit from LRT. This concept was thought to be rare in metastatic disease; however, because of the implementation of more sensitive imaging methods (such as fludeoxyglucose F 18–positron emission tomography [^{18}F-FDG PET]) in daily practice, patients with synchronous oligometastatic disease (sOM) are being identified more frequently.[7] In the past few years the concept of treatment of sOM NSCLC with LRT has evolved. The continuing interest has been fueled by the increasing number of treatment strategies, with widespread introduction of minimally invasive surgery and stereotactic radiotherapy. sOM NSCLC was addressed as a special treatment entity in the 2016 and 2018 European Society of Medical Oncology guidelines[8,9] and in the National Comprehensive Cancer Network guideline.[10] In the last TNM classification (eighth edition), a new M subclassification was introduced; according to this subclassification, the category M1b[11] is used for patients with a solitary extrathoracic metastasis showing an improved survival compared with that of patients with multiple extrathoracic metastases (M1c), whereas the category M1a is used for patients with contralateral pulmonary nodule(s) without extrathoracic metastases.

After several prospective single-arm clinical studies,[12–14] two recent randomized phase II trials (with 49 and 29 randomized patients, respectively) showed improved progression-free survival (PFS) in patients with sOM NSCLC when treated with LRT versus with systemic treatment only.[15,16] In both trials non-progressing patients were randomized between LRT or observation after completing first-line chemotherapy. In the trial reported by Gomez et al., 48 patients were randomized and showed a significant difference in PFS of 4 versus 12 months. Recently, the OS data were presented; the data showed a median OS of 41.2 months for the LRT arm and 17 months for the control arm.[17] The second study was stopped early (after enrollment of 29 patients), as it met an early stringent stopping rule of improved local control (PFS 9.7 months for stereotactic ablative radiotherapy + maintenance chemotherapy versus 3.5 months in the maintenance chemotherapy–alone arm [$p = 0.01$]).[16]

Since these studies, sOM NSCLC has become established as a regular topic of debate at lung cancer conferences. However, different definitions and staging procedures have been used in the published clinical trials. A search on ClinicalTrials.gov (in December 2018) revealed that the ongoing clinical trials are all using varying and different definitions of sOM NSCLC and the staging procedures to categorize oligometastatic disease vary, as is also true for the recent published phase II studies (Table 1).[12,13,15,16]

As long-term survival may nowadays be achieved with innovative strategies, including targeted treatment and immunotherapy-based combinations, sOM NSCLC may represent an opportunity to develop curative-intent multimodal treatment. Uniformity in defining sOM NSCLC and an agreement on mandated staging of these patients is required to unify taxonomy. Importantly, such

Table 1. Definition and Staging Procedures Recommended in Recently Published and Ongoing Clinical Trials on Synchronous Oligometastatic NSCLC

Trial	Authors	Country	Trial No.	Phase	Definition of No. of Metastasis	Mandated ^{18}F-FDG PET	Mandated Brain Imaging
Concurrent and Nonconcurrent Chemoradiotherapy or Radiotherapy Alone for Patients with Oligometastatic Stage IV Non-Small Cell Lung Cancer (NSCLC)	De Ruysscher et al. (2012)[12]	The Netherlands	NCT 01282450	2	<5	Yes	Yes
Surgery and/or Radiation Therapy or Standard Therapy and/or Clinical Observation in Treating Patients with Previously Treated Stage IV Non-Small Cell Lung Cancer	Gomez et al. (2016)[15]	United States	NCT01725165	2	≤3[a] (LNs count as 1 metastatic site)	No[b]	No[b]
Phase II Study of Pembrolizumab after Curative Intent Treatment for Oligometastatic Non-Small Cell Lung Cancer	Bauml et al. (2018)[13]	United States	NCT02316002	2	NR	NR	NR
Maintenance Chemotherapy Versus Consolidative Stereotactic Body Radiation Therapy (SBRT) plus Maintenance Chemotherapy for Stage IV Non-Small Cell Lung Cancer (NSCLC): A Randomized Phase II Trial	Iyengar et al. (2018)[16]	United States	NCT02045446	2	≤6[c]	No[b]	NR
Stereotactic Ablative Radiotherapy for Oligometastatic NSCLC (SARON)	—	United Kingdom	NCT02417662	3	≤3	Yes	Yes
Local Nonsalvage Radiotherapy for Synchronous Oligometastatic Non-Small Cell Lung Cancer	—	People's Republic of China	NCT03119519	2	≤5	NR	NR
Phase Ib Study of Stereotactic Body Radiotherapy (SBRT) in Oligometastatic Non-Small Lung Cancer (NSCLC) With Dual Immune Checkpoint Inhibition	—	United States	NCT03275597	1b	≤6 Extracranial sites[d]	NR	NR
Radical Treatment of Synchronous Oligometastatic Non-Small Cell Lung Carcinoma	—	Mexico	NCT02805530	Single-arm	≤5	NR	NR
Stereotactic Body Radiation Therapy (SBRT) in Newly Diagnosed Advanced-Staged Lung Adenocarcinoma (Sindas)	—	People's Republic of China	NCT02893332	3	≤5 (inclusive primary site; lymph nodes are considered as a metastatic site)	NR	NR

Note: Search of ClinicalTrials.gov was performed on December 14, 2018, using search terms *oligometastatic* AND *lung cancer|recruiting studies*.
[a]After first-line systemic therapy.
[b]Positron emission tomography-computed tomography and/or brain magnetic resonance imaging were suggested but not mandated.
[c]Six active extracranial sites after no more than three sites in the liver or lung.
[d]A site may have multiple tumor lesions within it as long as the gross tumor volume of the site is 8 cm or less and can be covered in an acceptable stereotactic body radiation therapy field.
^{18}F-FDG PET, fludeoxyglucose F 18 positron emission tomography; NR, not reported on ClinicalTrials.gov; LN: lymph node.

agreement will help to standardize inclusion criteria in future clinical trials. Therefore, we aimed to develop a definition of sOM NSCLC by following a consensus process. In addition, a statement was made on the required optimal staging procedures.

Methods

The process to develop a consensus definition of sOM NSCLC was initiated by the European Organization of Research and Treatment of Cancer (EORTC) Lung Cancer Group (LCG) in October 2017. A multidisciplinary group of 35 European thoracic oncology experts (pulmonologists, medical oncologists, radiation oncologists, thoracic surgeons, and radiologists) from different societies (EORTC LCG, EORTC Radiotherapy Group, International Association for the Study of Lung Cancer, European Respiratory Society, European Society for Radiotherapy and Oncology, and European Society of Medical Oncology) and different European countries were invited to participate.

A meeting to define the statement was planned, and as a preparation for this meeting, a multistep process involving a systematic review was followed and a survey and real-life sOM SCLC cases were distributed (described in detail later). Results of this preparatory work were used to identify areas of consensus and areas for further discussion (Fig. 1). Consensus was defined as more than 75% agreement on a question in the context of the survey and during the meeting.

Survey

To obtain insight into the dilemmas around the definition and staging of sOM NSCLC, a questionnaire on the definition and staging of sOM NSCLC was developed by the EORTC LCG board members and sent around to the consensus group. Upon feedback from the consensus group, the online (Google form) survey was finalized (Supplementary Table 1). The online survey was distributed among all consensus group members and all EORTC LCG and EORTC Radiation Oncology Group members. National societies were asked to distribute the survey among their members.

The responses to this survey were used to build the questions that needed to be discussed during the consensus meeting. The results were also presented during the meeting and used in the discussion. The final results of the survey were presented at the 2018 World Conference on Lung Cancer (Toronto, Canada).[18]

Systematic Review

In parallel with the development and distribution of the survey, a systematic review of the definition and staging of sOM NSCLC used in publications between 1996 and 2017 was performed. The main selection

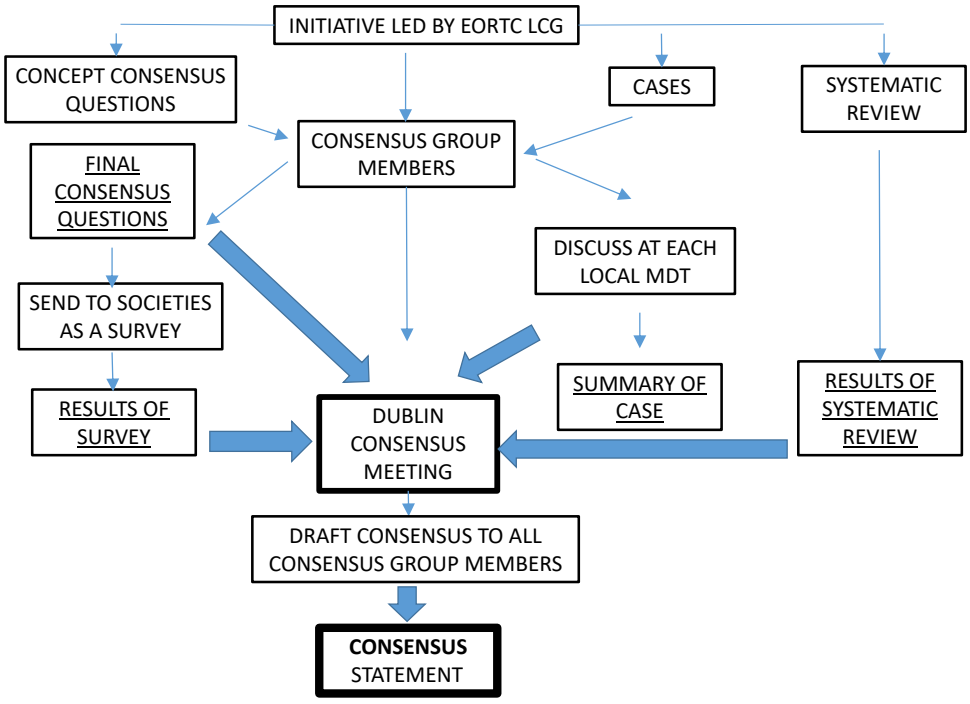

Figure 1. Multistep consensus process. EORTC LCG, European Organization of Research and Treatment of Cancer Lung Cancer Group; MDT, multidisciplinary team.

criteria were that sOM NSCLC be the subject and a definition of sOM be provided; for retrospective studies, at least 14 patients with sOM NSCLC had to be enrolled. Reviews were excluded.[19]

Cases

The cases of 10 real-life clinical patients with sOM NSCLC (all in good clinical condition, with no comorbidities, ^{18}FDG PET and brain magnetic resonance imaging [MRI] staging, and <5 metastases) were sent to 33 members of the consensus group. They were asked to determine, preferably by discussing the cases in their multidisciplinary team (MDT), whether a case was considered to be oligometastatic, and if so, what the proposed treatment should be. These cases were used in a previous survey, which was presented earlier.[20] The current responses were compared with the 2013 results. The final results of the survey were presented at 2018 World Conference on Lung Cancer in Toronto, Canada.[21]

Consensus Meeting

The consensus meeting took place in Dublin, Ireland, on January 23, 2018. Young investigator members of the EORTC LCG who were involved in the survey, cases, and review presented the results of the preparatory work and recorded the discussion. After a plenary presentation of the survey, case opinion results, literature review, and methodology to be used for the consensus process, the participants were split into two parallel discussion groups. In each discussion group, led by a senior chair, all questions had to be answered; young investigators recorded the discussion. In the last session of the meeting, the responses of both discussion groups were presented at the whole group and a consensus to each scenario was formulated and voted on. After the meeting, a draft consensus statement was circulated among the consensus group members, and the consensus was agreed on and finalized.

Results

Consensus Meeting Preparation

Survey. Between November 25, 2017, and January 18, 2018, a total of 423 physicians from 34 countries and 15 cancer societies (see the Supplementary Data) completed the survey. These results were presented at the consensus meeting (the survey was closed on February 29, 2018, with a total of 444 responders; how many physicians were invited is not known, as we did not collect those data). Most (>10%) of the respondents were from Belgium, Italy, the United Kingdom, and The Netherlands. The questions extracted from the survey that were discussed during the consensus meeting are presented in Table 2.[18]

Systematic Review. The first search identified 1125 potentially eligible abstracts; 73 of them fulfilled the full set of article selection criteria, and 21 of the articles were eligible for the systematic analysis. In total, 1215 patients with sOM NSCLC (18–198 patients per article) were included in these 21 articles. The number of metastasis allowed in the definition of sOM NSCLC varied between one and eight; more than five metastasis were allowed in only two out of 21 articles.[19]

Real-Life Cases. Of the 33 experts (from 24 centers), 26 replied; 62% discussed the cases in their MDT. One case

Table 2. Consensus Questions Discussed at the Dublin Meeting

Consensus Question No.	Consensus Question Content
Aim of treatment of sOM NSCLC	
1.1	Is it the aim of treatment of patients with OM NSCLC to achieve cure (to obtain long-term survival)?
Definition of sOM NSCLC	
2.1	Is it the aim of treatment of patients with OM NSCLC to achieve cure (to obtain long-term survival)?
2.2	For the definition of sOM NSCLC do you take into account whether you can treat all metastatic sites with radical intent?
2.3	For the definition of sOM NSCLC do you take into account the genomic background of the tumor?
2.4	How many metastasis are there at a maximum, regardless of number of organs?
2.5	Is number of organs involved important?
2.6	What is the maximum number of organs with metastasis (excluding primary) allowed in sOM NSCLC?
2.7	Would it be helpful to divide OM NSCLC into stages (i.e., OL1, OL2, OL3, and OL4)?
2.8	Are the specific organs involved with metastases important?
2.9	When considering specific organ involved important, which organs would you NOT involve in your definition of OM NSCLC?
2.10	Is pulmonary metastases considered as 1 site of metastasis?
2.11	Is mediastinal LN involvement allowed in the definition of OM NSCLC?
2.12	Is total tumor volume important?
Staging of sOM NSCLC	
3.1	Is PET-CT mandatory?
3.2	Is imaging of the brain mandatory?
3.3	Is staging of the mediastinum required?
3.4	Is pathological proof of metastatic disease (i.e., 1 or all metastatic sites) required?
3.5	When there is a solitary metastasis, is histological proof needed?

OL, oligo; OM, oligometastatic; sOM, synchronous oligometastatic; LN, lymph node; PET-CT, positron emission tomography–computed tomography.

had 100% consensus on the diagnosis of oligometastatic disease, and three cases had greater than 90% consensus. For the other cases, agreement ranged from 38% to 69%.[21]

Consensus Findings

Of the 35 invited thoracic oncology experts, 26 were present at the consensus meeting held in Dublin. Furthermore, four young investigator EORTC LCG members and the EORTC LCG clinical research physician were present. Findings from the meeting are presented in the following paragraphs (see Table 3).

Aim of Treatment of Oligometastatic NSCLC. Definition of sOM NSCLC is relevant when a radical treatment is technically feasible with acceptable toxicity, with all sites being amenable to a local treatment modality that may modify the course of the disease and may be considered as an opportunity for long-term disease control (see Table 3, consensus questions 1.1, 2.1, and 2.2).

The need for "modification of the disease course" was thought to be important, as it was noted that patients with sOM NSCLC might have a better prognosis than patients with more widespread disease, even without the addition of radical intent treatment. Hence, the addition of radical treatment should improve the outcome of patients with sOM disease irrespective of the pretreatment prognosis. The term *long-term disease control* was preferred over the term *cure*, as it was believed that patients could benefit from radical treatment resulting in prolonged disease control without gaining a cure. However, the participants debated whether toxicity should also be considered and discussed both in the MDT and with the patient. The term *technical feasibility* was added, as it was agreed that even with a limited number of metastatic sites, radical treatment may not always be feasible on account of the location of the metastasis or comorbidities of the patient. As the definition is not determined by the type of radical treatment (only by its feasibility), histologic subtype and genomic background are not taken into account in this definition.

Definition of Oligometastatic NSCLC. *Maximum Number of Metastases and Organs.* The maximum number of metastases and organs involved depends on the possibility of offering a radical intent treatment strategy. On the basis of the systematic review, a maximum of five metastases and three organs was agreed on. The presence of diffuse serosal metastases or bone marrow involvement excludes cases from this definition (see Table 3, consensus questions 2.4–2.6).

Table 3. Summary of Consensus Definition OF sOM NSCLC

Consensus Question	Statement
Aim of treatment sOM NSCLC	
1.1, 2.1, 2.2	Definition of sOM NSCLC is relevant when a radical treatment is technically feasible with acceptable toxicity, with all sites being amenable to local treatment modality that may modify the course of the disease and be considered as an opportunity for long-term disease control.
Defintion oF sOM NSCLC	
2.3	As the definition is not determined by the type of radical treatment (only by its feasibility), histologic type and genomic background are not taken into account in this definition.
2.4, 2.5, 2.6	The maximum number of metastases/organs involved depends on the possibility of offering a radical intent treatment strategy. On the basis of the systematic review, a maximum of 5 metastases and 3 organs is proposed. The presence of diffuse serosal metastases or bone marrow involvement excludes cases from this definition.
2.7, 2.12	Use of risk classification groups or total tumor volume is of interest, but there is a lack of data to formulate a statement.
2.8, 2.9	All organs, except diffuse serosal metastases (meningeal, pericardial, pleural, mesenteric), and bone marrow involvement are allowed, as these cannot be treated with radical intent.
2.10	Pulmonary metastases are counted as a metastatic site.
2.11	Mediastinal lymph nodes should not count as a metastatic site; mediastinal lymph nodes must be considered as regional disease. However, mediastinal lymph node involvement is of importance in determining whether radical local treatment of the primary may be applied.
Staging of sOM NSCLC	
3.1, 3.2	^{18}F-FDG PET-CT and brain imaging are mandatory. For brain imaging, MRI is preferred.
3.3	Mediastinal staging with ^{18}F-FDG PET-CT is needed, with pathological confirmation required if this influences treatment strategy.
3.4, 3.5	Pathological confirmation of $\geq$1 metastasis is required unless the MDT decides that the risk outweighs the benefit.
3.5	In addition to sections 3.2 and 3.3, for a solitary metastasis on ^{18}F-FDG PET imaging, in specific cases additional work-up is advised. When the liver is the only site of oligometastatic disease a dedicated MRI scan of the liver is advised, and if a solitary pleural metastasis is suspected on imaging, then thoracoscopy and dedicated biopsies of other ipsilateral pleural sites are recommended, as multifocal disease is often evidenced in this context during procedure.

sOM, synchronous oligometastatic. ^{18}F-FDG PET-CT, fludeoxyglucose F 18 positron emission tomography-computed tomography; MRI, magnetic resonance imaging; MDT, multidisciplinary team.

Despite extensive discussion, expert opinion significantly varied and no consensus was reached on the maximum number of metastasis or organs. Although there was agreement that the number of metastasis and organs involved is important, it was believed that there is a lack of data on the maximum number that should be included in a definition. The reason for the disagreement was the recognition of a lack of prospective data defining the maximum number of metastasis and organs that can be technically treated with radical intent and result in improved outcome (i.e., it was not clear whether radically treating 10 metastases results in improved outcome when radical treatment is technically feasible). In the survey conducted, a maximum of three metastases was the most frequent answer, but a maximum of five metastases was the most frequent definition found in the systematic review. To provide a workable definition, we combined the maximum number of metastases and organs with the aim of the treatment of sOM NSCLC and the results from the survey. We also discussed the fact that although a large number of metastasis (i.e., >5) can technically be treated radically, this is not in line with the term *oligo*, and therefore we do not consider this oligometastatic disease. There was a consensus opinion that prospective data collection and dedicated clinical trials are needed to refine the current definition.

Nature of Organs Involved. All organs are allowed, except diffuse serosal metastases (meningeal, pericardial, pleural, mesenteric) and bone marrow involvement, as these cannot be treated with radical intent (see Table 3, consensus questions 2.8 and 2.9).

Brain and adrenal metastases were not considered to be special sites, even though there are more data on sOM in these two organs. The group believed that there could be publication bias regarding data from these two sites and that more prospective data on influence of specific site on outcome are necessary.

Pulmonary Metastases. Pulmonary metastases are counted as a metastatic site (see Table 3, consensus question 2.10).

For pulmonary metastases, the eighth TNM classification should be followed. An M1a lesion counts as one metastatic site with regard to the definition of oligometastatic disease, Metastasis in the same lobe (T3) or in the same lung as the primary tumor (T4) should not be counted as a metastatic site, but it can influence the possibility of administering treatment with radical intent depending on the treatment modality or modalities planned.

Mediastinal involvement. Mediastinal lymph nodes should not count as a metastatic site; mediastinal lymph nodes must be considered as regional disease. However, mediastinal lymph node involvement is of importance in determining whether radical local treatment of the primary may be applied (see Table 3, consensus questions 2.11).

Given that in some trials mediastinal lymph nodes counted among the number of metastatic sites[15] and patients with N0 disease seem to have the best prognosis[2], whether mediastinal lymph node involvement should modify the metastatic sites count, provided it could be amenable to radical treatment, was discussed. Again, there was agreement that the criteria of the eight TNM classification should be followed. It was suggested that future clinical trials consider stratification according to N0 or N1 versus N2 or N3 status.

Data to Be Collected in Future Trials. Other definition-related questions were discussed (use of risk classification groups, total tumor volume (see Table 3, consensus questions 2.7 and 2.12), and there was consensus that these finding are of interest but there is a lack of data to formulate a statement. It was recommended that data should be collected in future trials and registries to evaluate the usefulness of risk classification groups and total tumor volume.

Staging. *Imaging work-up.* ^{18}F-FDG PET–computed tomography and brain imaging are mandatory. For brain imaging, MRI is preferred (see Table 3, consensus questions 3.1 and 3.2).

There was 100% agreement on these staging investigations, which was in keeping with the recently published EORTC recommendations.[22]

Mediastinal Staging. Mediastinal staging with ^{18}F-FDG PET–computed tomography is needed, with pathological confirmation required if this influences treatment strategy (see Table 3, consensus question 3.3).

There was extensive discussion as to whether mediastinal staging with endobronchial/esophageal ultrasound and/or mediastinoscopy should be performed to obtain the most reliable staging information (i.e., following the same principles as for early-stage disease).[23] However, for practical reasons it was agreed to request pathological confirmation only if it would influence the treatment strategy (e.g., whether to perform lobectomy, whether to include mediastinal lymph nodes in the radiation field).

Pathological Confirmation. Pathological confirmation of at least one metastasis is required unless the MDT

decides that the risk outweighs the benefit. (see Table 3, consensus questions 3.4 and 3.5).

This is especially important in the case of a solitary metastasis and if it may change the therapeutic strategy, including scenarios with mediastinal nodal involvement.

Solitary Metastasis. In addition to sections 3.2 and 3.3, for a solitary metastasis on ^{18}F-FDG PET, in specific cases additional work-up is advised. When the liver is the only site of oligometastatic disease, a dedicated MRI scan of the liver is advised, and if a solitary pleural metastasis is suspected on imaging, then thoracoscopy and dedicated biopsies of other ipsilateral pleural sites are recommended, as multifocal disease is often evidenced in this context during procedure (see Table 3, consensus question 3.5). Of note, pleural malignant effusion is not considered amenable to radical treatment to date.

Discussion

This is the first multidisciplinary formulated consensus statement on the definition and staging of sOM NSCLC. The work of the group includes results of a European survey, a systematic review, and real-life case discussions followed by a consensus meeting. This statement is needed to standardize inclusion criteria in future clinical trials, as well as to aid in prospective data collection, make results of the clinical trials comparable, and guide treatment discussion in MDT meetings. The aim of the working group was to be as inclusive as possible and avoid controversial extremes in order to settle on a clinically relevant consensus. Whereas there is no high-level evidence for a definition or staging of sOM NSCLC, we followed a rigorous multistep process to formulate this consensus. On the basis of the process that we followed and the extensive discussions with all the experts during the consensus meeting, we believe that this consensus statement will represent an opportunity, with endorsement of several societies involved in lung cancer treatment, to standardize the definitions, diagnosis, and assessment of oligometastatic disease. We acknowledge that although the definition of sOM NSCLC might change over time when more prospective data become available, this work provides a framework for such future research.

One of the important areas of disagreement in the survey and during the consensus meeting was the maximum number of metastases and organs allowed in the definition. Thanks to new treatment techniques, a large number of metastases can often be treated with radical intent. However, whether LRT improves outcome in these patients is not known. During the consensus meeting discussions, it was stated several times that the number of metastatic sites is not important if LRT is possible. This was also the position of only 16% of the survey responders, supporting the controversy.[18] However, the systematic review found that even if trials allowed up to five metastases, in reality the patients enrolled in these trials often had only one or two metastases. Although in the real-life cases only patients with up to four metastases were included, we think that this did not affect the outcome, as the restriction to a single or two metastases was also common in the provided answers to the real-life cases.[21] In the end, considering that oligo means "few" and with support from published data, we agreed that more than five metastases should not currently be allowed in the definition of oligometastatic disease. We believe that feasibility, safety, and amenability to radical treatment globally might still impose this constraint. To obtain more information, prospective registries should collect data on all patients treated with LRT to also evaluate outcome with LRT in patients with nonoligometastatic disease (e.g., EORTC/EORTC-RP-1822 E^2-RADIatE [OligoCare: A Pragmatic Observational Cohort Study to Evaluate Radical Radiotherapy for Oligo-metastatic Cancer Patients]) to define the optimal number of metastasis and metastatic sites suitable for LRT.

Although it is known that involvement of mediastinal lymph nodes has prognostic value in stage IV NSCLC with single-organ metastasis[24] and sOM NSCLC,[2] this was not taken into account in the eighth TNM classification.[25] We agreed that metastatic mediastinal lymph nodes should be allowed in the oligometastatic definition but not counted as a metastatic site and that ideally N categories should be used as an additional stratification factor, supporting MDT decisions, as we recognized that its involvement has prognostic significance.

The 5-year OS data from the two randomized phase II trials[15,16] are awaited, but the long-term OS data from the first single-arm phase II trial[12] are already available. In this trial, patients with sOM NSCLC at diagnosis (not after induction treatment) were treated with radical intent. The 5- and 6-year OS rates were disappointingly low, being only 7.7% and 5.1%, respectively.[26] With regard to the ongoing clinical trials, the randomized phase III SARON trial (NCT02417662) is designed to address the question as to whether LRT will improve OS in patients with sOM SCLC.[27] In this trial, patients with *EGFR*/ALK receptor tyrosine kinase (*ALK*)-negative NSCLC with sOM disease will be registered before treatment, and when no progression occurs after two cycles of chemotherapy, patients will be randomized between two additional cycles of chemotherapy with or without local ablative radiotherapy. In this trial, staging with ^{18}F-FDG PET and brain imaging is mandatory and a

maximum of three metastatic lesions is allowed. The primary outcome measure is OS. Patients are stratified according to presence versus absence of mediastinal lymph node metastasis (N0 or N1 versus N2 or N3), number of metastasis (one versus two or three), and presence versus absence of brain metastasis.

On the basis of our results, besides the number of metastases, number and type of organs with metastases, and involvement of mediastinal lymph nodes, other areas for future research are (1) the prognostic significance of total tumor volume and histological subtype and (2) the significance of dividing sOM NSCLC into risk groups (e.g., group 1, one metastasis in one organ; group 2, two or three metastases in one organ; and group 3, two or three metastasis in two organs). Ideally, ongoing registries and trials (e.g., EORTC OligoCare, SARON) should collect prospective data on these topics.

In addition to working toward an agreed-on definition of sOM NSCLC, clarifying the staging requirements is also essential. The EORTC Imaging Group published recently imaging recommendation for oligometastatic NSCLC to correctly identify these patients.[22] For lung cancer, an ^{18}F-FDG PET scan and a dedicated brain MRI scan are recommended, the same as proposed for stage III NSCLC.[28] During our consensus process, we also established the importance of adequate staging, as ^{18}F-FDG PET and brain imaging can upstage tumors and result in preventing unnecessary toxicity for patients with nonoligometastatic disease.

The major limitation of our work is the lack of evidence (as shown by the results of the systematic review and the variation in answers in the survey and real-life cases). In addition, this consensus definition represents the view of European lung cancer experts, which might not reflect the opinion of experts outside of Europe.

In conclusion, through a rigorous multistep process taking into account results of a systematic review, a European survey, and real case discussions, a multidisciplinary consensus statement on the definition and staging of sOM SCLC was formulated. This statement will help to harmonizing inclusion criteria in future 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.2019.07.025.

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