Definition of synchronous oligo-metastatic non-small cell lung cancer - a consensus report

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Title page

Definition of synchronous oligo-metastatic non-small cell lung cancer – a consensus report

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Abstract

Introduction:

Improved outcome has been shown in patients with synchronous oligometastatic non-small cell lung cancer (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 based on current controversies, and definitions extracted from a survey, cases and a systematic review. This statement was formulated during a consensus meeting.

Results:

Defining sOM-NSCLC

Definition of sOM-NSCLC is relevant when a radical treatment is technically feasible for all tumor sites with acceptable toxicity, that may modify the disease course leading to long-term disease control. Based on the review, a maximum of 5 metastasesand 3 organs is proposed. Mediastinal lymph node involvement is not counted as a metastatic site.

Staging of sOM-NSCLC

A ^{18}fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET-CT) and brain imaging were considered mandatory. A dedicated liver MRI is advised for a solitary liver metastasis, and thoracoscopy and biopsies of distant ipsilateral pleural sites for a solitary pleural metastasis. For mediastinal staging, a ^{18}FDG-PET-CT is the minimum requirement, with pathological confirmation recommended if this influences the treatment strategy. Biopsy of a solitary metastatic location is 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 standardise 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 non-small cell lung cancer (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]. Favourable outcomes of LRT in NSCLC patients presenting with up to 5 metastatic sites were shown in several series, mainly retrospective, with 5-year OS 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, due to the implementation of more sensitive imaging methods (as ^{18}fluorodeoxyglucose-positron emission tomography [^{18}F-FDG-PET]) in daily practice, patients with synchronous oligometastatic disease (sOM) are more frequently identified [7]. In the last few years the concept of treatment of sOM-NSCLC with LRT has evolved. The continuing interest is fuelled 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 (ESMO) guidelines [8, 9] and in the National Comprehensive Cancer Network (NCCN) guideline[10]. In the last tumor-node-metastasis (TNM) classification (8th edition) a new M-subclassification was introduced for patients with a solitary extrathoracic metastasis, M1b [11], showing an improved survival compared to multiple extrathoracic metastases, M1c. However, patients with contralateral pulmonary nodule/s without extrathoracic metastases are classified as M1a.

Following 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 compared to systemic treatment only [15, 16]. In both trials non-progressing patients were randomized between LRT or observation after completing first-line chemotherapy. In the Gomez trial, 48 patients were randomised and showed a significant difference in PFS of 4 versus 12 months. Recently the OS data were presented showing 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 enrolment 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 (December 2018) revealed that the ongoing clinical trials are all using varying and different definitions of sOM-NSCLC and the staging procedures to categorise OM vary, this is also true for the recent published phase II studie (Table 1)[12, 13, 15, 16] .

As long-term survival may be achieved nowadays 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 of sOM-NSCLC and an agreement on mandated staging of these patients is required in order to unify taxonomy. Importantly such agreement will help to standardise inclusion criteria in future clinical trials. Therefore, we aimed to develop a definition of sOM- NSCLC 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 Organisation 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, radiologists) from different societies (EORTC-LCG and radiotherapy group, International Association for the Study of Lung Cancer (IASLC), European Respiratory Society (ERS), European Society for Radiotherapy & Oncology (ESTRO), ESMO) and different European countries were invited to participate.

A meeting to define the statement was planned and, as a preparation for this meeting, a multi-step process was followed involving a systematic review, a survey and real-life sOM-

NSCLC cases were distributed (described in detail below). Results of this preparatory work were used to identify areas of consensus and areas for further discussion (figure 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 of the consensus group, the online (Google form) survey was finalized (table S1). The online survey was distributed among all consensus group members and all LCG and radiation oncology group members of the EORTC. National societies were asked to distribute the survey among their member.

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 were used in the discussion. The final results of the survey were presented at World Conference for Lung Cancer (WCLC) Toronto 2018[18].

Systematic review: In parallel with the development and distribution of the survey, a systematic review was performed on the definition and staging of sOM-NSCLC used in publications between 1996-2017. The main selection criteria were: subject sOM-NSCLC, providing a definition of sOM, for retrospective studies at least 14 patients with sOM-NSCLC had to be enrolled; reviews were excluded[19].

Cases: Ten real life clinical cases of patients with sOM-NSCLC (all in good clinical condition, with no comorbidities, ^{18}FDG-PET and brain MRI staged and < 5 metastases), were sent to 33 members of the consensus group. They were asked, 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 has been presented earlier[20]. The current responses were compared with the 2013 results. The final results of the survey were presented at World Lung Cancer Conference (WCLC) Toronto 2018[21].

Consensus meeting: The consensus meeting took place in Dublin on January 23th 2018. Young Investigator members of the EORTC-LCG, who were involved in the survey, cases and

the 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 the 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, and 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. After the meeting, a draft consensus statement was circulated among the consensus group members, and the consensus was agreed and finalised.

Results

Consensus meeting preparation

Survey: Between 25-Nov-2017 and 18-Jan-2018, 423 physicians from 34 countries and 15 cancer societies (see supplementary data) completed the survey, these results were presented at the consensus meeting (the survey was closed 19-Febr-2018, with a total of 444 responders, it is not known how many physicians were invited as we did not collect this data). The majority (> 10%) of responders were from Belgium, Italy, United Kingdom and the Netherlands respectively. 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 those fulfilled the full paper selection criteria of which 21 papers were eligible for the systematic analysis In total 1215 (range 18-198) patients with sOM-NSCLC were included in these 21 papers. The number of metastasis allowed in the definition of sOM-NSCLC varied between 1 and 8, more than 5 metastasis was allowed in only 2 out of 21 papers[19].

Real-life cases: 26/33 experts (24 centres) replied: 62% discussed the cases in their MDT. One case had 100% consensus on the diagnosis of oligometastatic disease, 3 cases had > 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 below.

1. 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 local treatment modality, that may modify the course of the disease and be considered as an opportunity for long-term disease control (Table 2, consensus questions 1.1, 2.1, 2.2).

The need for "modification of the disease course" was felt to be important, as it was noted that sOM-NSCLC patients might have a better prognosis compared to patients with more widespread disease, even without the addition of radical intent treatment. Hence, the addition of radical treatment should improve the outcome of sOM-patients, irrespective of the pre-treatment prognosis. The term "long-term disease control" was preferred over cure, it was felt that patients could benefit from radical treatment resulting in prolonged disease control without gaining a cure. However, it was discussed that 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, due to the location of the metastasis or comorbidities of the patient. As the definition is not determined by the type of radical treatment (only its feasibility), histology and genomic background are not taken into account in this definition.

2. **Definition of oligometastatic NSCLC**

2.1 Maximum number of metastases and organs

The maximum number of metastases/organs involved depends on the possibility of offering a radical intent treatment strategy. Based on the systematic review, a maximum of 5 metastases and 3 organs was agreed on. The presence of diffuse serosal metastases or bone marrow involvement excludes cases from this definition (Table 2, consensus questions 2.4-2.6).

Despite extensive discussion, expert opinion significantly varied and no consensus was reached on the maximum number of metastasis or organs. While there was agreement that

the number of metastasis and organs involved is important, it was felt 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 / organs that can be technically treated with radical intent and result in improved outcome (i.e. not clear whether radically treating 10 metastases results in improved outcome or not when radical treatment is technically feasible). In the survey conducted, a maximum of 3 metastases was the most frequent answer, but a maximum of 5 metastases was the most frequent definition found in the systematic review. In order to provide a workable definition, we combined the maximum number of metastases and organs to the aim of the treatment of sOM-NSCLC and the results from the survey. We also discussed 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.

2.2 Nature of organs involved

All organs are allowed, except diffuse serosal metastases (meningeal, pericardial, pleural, mesenteric) as well as bone marrow involvement as these cannot be treated with radical intent (Table 2, consensus questions 2.8, 2.9).

Brain and adrenal metastases were not considered to be special sites, even though there is more data on sOM in these two organs. The group felt that there could be publication bias regarding data from these 2 sites, and that more prospective data on influence of specific site on outcome is necessary.

2.3 Pulmonary metastases

Pulmonary metastases are counted as a metastatic site (Table 2 consensus question 2.10)

For pulmonary metastases, the 8th TNM classification should be followed. An M1a lesion counts as one metastatic site with regards 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 can influence the possibility to administer treatment with radical intent, depending on the treatment modality / modalities planned.

2.4 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 if radical local treatment of the primary may be applied (table 2, consensus questions 2.11).

Given that in some trials mediastinal lymph nodes counted among the number of metastatic sites[15] and N0 patients seem to have the best prognosis[2], it was discussed whether mediastinal lymph node involvement should modify the metastatic sites count, provided it could be amenable to radical treatment. Again, the agreement was that TNM8 criteria should be followed. It was suggested that future clinical trials should consider stratification according to the N0-1 versus N2-3 status.

2.5 Data to be collected in future trials

Other definition questions were discussed (use of risk classification groups, total tumor volume (table 2, consensus questions 2.7 and 2.12), there was consensus that these finding are of interest but that 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.

3. Staging

3.1 Imaging work-up

^{18}F-FDG-PET-CT and brain imaging are mandatory. For brain imaging, MRI is preferred (Table 2, consensus questions 3.1, 3.2).

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

3.2 Mediastinal staging

Mediastinal staging with ^{18}F-FDG-PET-CT is needed, with pathological confirmation required if this influences treatment strategy (Table 2, consensus question 3.3).

There was extensive discussion whether mediastinal staging with endobronchial/oesophageal ultrasound (EBUS/EUS) and/or mediastinoscopy should be performed to obtain the most reliable staging information (i.e. follow same principles as for early stage disease)[23]. However, for practical reasons it was agreed upon to only request pathological confirmation if this influences the treatment strategy (e.g. lobectomy or not, inclusion of mediastinal lymph nodes in the radiation field or not).

3.3 Pathological confirmation

Pathological confirmation of at least one metastasis is required unless the MDT decides that the risk outweighs the benefit. (Table 2, consensus question 3.4, 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.

3.4 Solitary metastasis

In addition to sections 3.2-3.3, 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 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 (table 2, 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 standardise inclusion criteria in future clinical trials as well as 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 to avoid controversial extremes, in order to settle a clinically relevant consensus. Whereas there is no high-level evidence for a definition or staging of sOM-NSCLC,

we followed a rigorous multi-step process to formulate this consensus. Based on the process we followed, and the extensive discussions with all the experts during the consensus meeting, we believe 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 the definition of sOM-NSCLC might change over time when more prospective data will become available, while this work provides a framework for such future research.

One of the important disagreements in the survey and during the consensus meeting was the maximum number of metastases and organs allowed in the definition. Due to new treatment techniques, a large number of metastases can often be treated with radical intent. However, it is not known whether LRT improves outcome in these patients. 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 4 metastases were included we think did this not impact on the outcome as the restriction to a single or to two metastases was also common in the provided answers to the real-life cases[21]. In the end, we agreed that more than five metastases should not currently be allowed in the definition of oligometastatic disease, considering that oligo means “few”, and with support from published data. 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 evaluate outcome with LRT also in non-oligometastatic patients (example:. “EORTC / EORTC-RP-1822 “E²-RADIatE - OligoCare: a pragmatic observational cohort study to evaluate radical radiotherapy for oligo-metastatic cancer patients”) in order 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 8th TNM classification [25]. We agreed that metastatic mediastinal lymph nodes are allowed in the oligometastatic definition, but are 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.

Five year overall survival (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. Five and six-year OS were disappointingly low, being only 7.7% and 5.1%, respectively [26]. From 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-NSCLC[27]. In this trial, *EGFR/ALK* negative NSCLC patients with sOM-disease will be registered before treatment and , when no progression occurs after 2 cycles of chemotherapy, patients will be randomized between 2 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 3 metastatic lesions is allowed. The primary outcome measure is OS. Patients are stratified according to presence/absence of mediastinal lymph node metastasis (N0/1 versus N2/3), number of metastasis (1 versus 2/3) and presence/absence of brain metastasis.

Besides the number of metastases, number and type of organs with metastases and involvement of mediastinal lymph nodes, based on our results other areas for future research are:

1. The prognostic significance of total tumor volume, and the histological subtype
2. The significance of dividing sOM-NSCLC in risk groups (e.g. group 1: 1 metastasis / 1 organ, group 2: 2-3 metastasis / 1 organ, group 3: 2-3 metastasis / 2 organs etc.).

Ideally ongoing registries and trials (e.g. EORTC OligoCare, SARON) should collect prospective data on these topics.

In addition in addition to working towards an agreed upon definition of sOM-NSCLC, clarifying the staging requirements is also essential. The EORTC Imaging Group published recently imaging recommendation for oligometastatic NSCLC, in order to correctly identify these patients[22]. For lung cancer, a ^{18}F-FDG-PET scan and a dedicated brain MRI 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 non-oligometastatic patients.

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 and this might not reflect the opinion of experts outside of Europe.

In conclusion, following a rigorous multi-step 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-NSCLC was formulated. This statement will help to harmonising inclusion criteria in future clinical trials.

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Table 1 Definition and staging procedures recommended in recently published and ongoing clinical trials on synchronous oligometastatic non-small cell lung cancer (search clinicaltrials.gov 14.12.2018 "oligometastatic AND lung cancer | Recruiting Studies")

Trial	Published	Country	Trial number	Phase	Definition: number of metastasis	Mandated FDG-PET	Mandated Brain imaging
Concurrent and Non-concurrent Chemo-radiotherapy or Radiotherapy Alone for Patients With Oligo-metastatic Stage IV Non-small Cell Lung Cancer (NSCLC)	De Ruysscher 2012 (ref 12)	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 2016 (ref 15)	USA	NCT01725165	2	≤3[1] LN count as 1 metastatic site	no[3]	no[3]
Phase II Study of Pembrolizumab After Curative Intent Treatment for Oligometastatic Non-Small Cell Lung Cancer	Bauml 2018 (ref 13)	USA	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 2018 (ref 16)	USA	NCT02045446	2	≤6[2]	no[3]	NR

Stereotactic Ablative Radiotherapy for Oligometastatic NSCLC (SARON)	-	UK	NCT02417662	3	≤ 3	yes	yes
Local Non-salvage Radiotherapy for Synchronous Oligometastatic Non-small-cell Lung Cancer.	-	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	-	USA	NCT03275597	1b	≤ 6 extracranial sites[4]	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)	-	China	NCT02893332	3	≤ 5 (inclusive primary site; lymph nodes are considered as a metastatic site)	NR	NR

NR: not reported on clinicaltrials.gov; LN: lymph nodes; [1]After first line systemic therapy , [2]6 active extracranial sites after with no more than 3 sites in liver or lung, [3]PET-CT and/or brain MRI were suggested, but not mandated, [4]A site may have multiple tumor lesions within it as long as the gross tumor volume (GTV) of the site is 8 cm or less and can be covered in an acceptable SBRT field

Table 2 Consensus Questions discussed at Dublin meeting

AIM OF TREATMENT sOM-NSCLC	
1.1	Is it the aim of treatment of patients with OM-NSCLC cure (obtain long term survival)?
DEFINITION of sOM-NSCLC	
2.1	Is it the aim of treatment of patients with OM-NSCLC to cure (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 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 in stages (i.e.OL1-Ol2-OL3-OL4)?
2.8	Are 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?

Table 3 summary of consensus definition sOM-NSCLC

Consensus questions	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 its feasibility), histology 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. Based on 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 that there is a lack of data to formulate a statement*
2.8, 2.9	*All organs are allowed, except diffuse serosal metastases (meningeal, pericardial, pleural, mesenteric) as well as bone marrow involvement 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 if 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 at least one metastasis is required unless the MDT decides that the risk outweighs the benefit.*
3.5	*In addition to sections 3.2-3.3, 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 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.*