



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

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1 **Defining synchronous oligometastatic non-small cell lung cancer: a systematic review**

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88 **Abstract**

89 **Introduction:** Synchronous oligometastatic disease (sOM) is an oncological concept, characterized by
90 a limited cancer burden. Oligometastatic patients could potentially benefit from local radical
91 treatments. Despite the fact that the sOM condition is well recognized, a universal definition, including
92 a specific definition for non-small cell lung cancer (NSCLC), is not yet available. The aim of this
93 systematic review is to resume sOM definitions and staging requirement used in NSCLC.

94
95 **Methods:** The key issue was formulated in one research question according to the PICO strategy. The
96 question was introduced in MEDLINE (OvidSP). All articles dealing with sOM-NSCLC and providing a
97 definition of sOM-NSCLC were selected and analyzed.

98
99 **Results:** A total of twenty-one eligible articles focusing on sOM NSCLC were retrieved and analyzed. In
100 17 studies (81%), patients had to be staged with magnetic resonance or computed tomography (CT) of
101 the brain, thoracic and abdominal CT and positron emission tomography. The total number of
102 metastases allowed in the definitions ranged between 1 and 8, but in 38.1% of studies the maximum
103 number was 5. Most of the publications did not define the number of involved organs and the
104 maximum number of metastases per organ. For mediastinal lymph-node involvement, only 5 (27.8%)
105 articles counted this as a metastatic site.

106
107 **Conclusions:** No uniform definition of sOM-NSCLC could be retrieved by this systematic review.
108 However, extended staging was mandated in the majority of studies. An accepted oncological
109 definition of sOM is essential for patient selection in order to define prospective clinical trials.

110
111 **Keywords:** NSCLC; oligometastatic disease definition; synchronous; systematic review

112

113

114 **Introduction:**

115 Approximately half of all patients with non-small cell lung cancer (NSCLC) present with metastatic
116 disease, with a median overall survival (OS) of 12 months¹. However, metastatic NSCLC is a
117 heterogeneous status, characterized by different clinical presentations and prognoses according to
118 anatomical sites and number of metastases. In 1995, Hellman and Weichselbaum defined
119 oligometastatic disease² as a state of limited systemic metastatic burden, in which eradication of
120 oligometastases with local radical therapies (i.e. surgery and radiotherapy) could be curative in
121 selected patients³.

122 Currently, no single, uniform and reliable definition of synchronous oligometastatic disease (sOM) in
123 NSCLC does exist. In the ESMO guidelines a paragraph is dedicated on oligometastatic disease, without
124 a clear definition of this status, reporting that many clinical trials investigating local treatment of
125 oligometastatic disease have limited inclusion to patients with ≤ 5 metastases, but the vast majority of
126 the trials included patients with ≤ 3 metastases¹. In the NCCN guidelines oligometastatic patients are
127 defined as isolated or limited metastatic disease⁴.

128 A uniform definition is of importance as new effective local ablative therapies are developed. Their
129 integration in therapeutic algorithms for sOM NSCLC is tested in different prospective clinical trials^{5,6}.

130 In an attempt to provide a definition of sOM NSCLC, the European Organisation for Research and
131 Treatment of Cancer - Lung Cancer Group (EORTC-LCG) developed a consensus definition based on
132 clinical sOM cases, a European sOM survey and a systematic review of the currently requested staging
133 methods and sOM definitions used in clinical trials⁷⁻⁹. Here we report the results of the systematic
134 review.

135

136 **Material and Method:**

137 The key issue was formulated in one question according to the PICO criteria (population, intervention,
138 control, and outcomes). The standard reporting guidelines (PRISMA statement – <http://www.prisma-statement.org/>) has been used for this systematic review. The research question was strictly
139 concentrated on the clinical definition of sOM-NSCLC. The research equation composed of MeSH
140 descriptors and free-text keywords, as reported in **Supplement 1**, have been launched in MEDLINE
141 (OvidSP) in October 2017.

143 A time cut-off of January 1st, 1996 has been used in order to identify publications with patients staged
144 according to the 5th TNM classification and above¹⁰. Titles and abstracts were screened independently
145 by two authors (MGL and NGL) and reviewed by two other authors (AMD and TB) to determine
146 potentially relevant articles for the systematic review. The selection process was divided in two parts:
147 abstract and full articles selection.

148 Abstracts were selected as follow: i) focusing only on lung cancers (NSCLC or SCLC), ii) dealing with
149 synchronous oligometastatic tumors, whatever the definition used by the authors, iii) providing a

150 definition of oligometastatic status, iv) any retrospective or prospective study, v) for retrospective
151 study, the number of patients had be at least 14 (adapted from the statistical Simon's design).
152 Full articles were evaluated according to the previous criteria and contributes in French, English,
153 Dutch and Italian were accepted.
154 Series focusing on a specific single metastatic organ (e.g. only brain or adrenal gland) were excluded,
155 as the focus of the review was oligometastasis instead of solitary metastasis. Also systematic reviews,
156 meta-analysis and editorials were not included.
157 Additional publications were identified through examination of references cited in the eligible
158 publications and were added if they also fulfilled the selection criteria. Disagreements were resolved
159 by consensus.
160 The following variables were extracted from the publications for the definition of the sOM NSCLC: (1)
161 number of metastases, (2) number of organs with at least one metastasis, (3) number of metastases
162 per organ, (4) lymph node status, (5) metastatic sites that were excluded.
163 Additional data describing the population, intervention and outcomes were also extracted: (1) type of
164 study; (2) single or multi centre experience; (3) number of patients enrolled; (4) staging system; (5)
165 radiological assessment (thoracic, mediastinal, cranial and extracranial metastatic staging); (6)
166 pathological proof of malignancy; (7) primary outcome; (8) curative therapeutic intent.

167

168

169 **Results:**

170 The search strategy and potentially eligible abstracts are shown in **Supplement 2**. A total of 1125
171 potentially eligible titles were identified and 80 duplicates were removed. Among 1045 titles, 348
172 respected the abstract selection criteria (ASC) and another 9 articles were added by reviewing the
173 references from the included articles. Seventy-three articles fulfilled the full publications selection
174 criteria (FPSC) and among them we selected those that were focused on the sOM (i.e. article focussing
175 only on oligoprogression and oligorecurrence were excluded). We accepted articles if evaluating both
176 sOM (main issue of the systematic review) and oligoprogression/recurrence. A total of 21 articles
177 were eligible for this systematic analysis ^{5,6,11-28} as reported in **Figure 1**.

178

179 *Population:*

180 The main studies' characteristics are reported in **Table 1**. Most of the published data were
181 retrospective (n = 14; 66,6%) and single centre (n= 17; 81%). The total number of sOM-NCLC patients
182 described in the 21 studies was 1215 (range: 18-198) with a median number of 39.

183

184

185 *Mandated staging:*

186 In the majority of studies (n = 17; 81%), staging with thoracic and abdominal CT-scan, positron
187 emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with CT (¹⁸F-FDG
188 PET/CT) and brain Magnetic Resonance Imaging (MRI) or CT was mandated. In particular, in 16
189 studies baseline brain imaging was mandated and baseline brain MRI was preferred in 14 articles
190 (66.7%). Mediastinal staging was predominantly clinical (n = 13; 62%) with ¹⁸F-FDG PET/CT while
191 only 5 articles (23.8%) mandated a pathological mediastinal staging by endobronchial ultrasound
192 (EBUS). A pathological proof of metastases was not requested in 3 articles (14.3%), was mandated for
193 all sites in one study (4.8%), and for at least one metastatic site in 2 studies (9.5%). In the majority of
194 studies (n = 15; 71.4%) this information was not available (**Table 1**).

195

196 *Outcomes:*

197 The main information about the applied definitions of sOM NSCLC is reported in the **Table 2**. The total
198 number of metastases used in the definition of sOM ranged between 1 and 8, and in 8 studies (38.1%)
199 the maximum number of metastases allowed was 5. In most of the series (n = 13; 61.9%), we did not
200 find any limitation or restriction about the number of organs involved with at least one metastasis,
201 otherwise, when defined, the maximum number of allowed metastatic organs was 3 in 1 article (4.8%),
202 2 in 4 (19%) and 1 in 3 (14.3%).

203 The maximum number of metastases per organ was not defined in 12 articles (51.1%), in 3 (14.3%) a
204 partial definition was given (e.g. no more than two liver metastases, no more than 3 metastases for
205 brain, less than 5 in a single organ other than lung). When a maximum number of metastases per
206 organ was defined it ranged between 1 and 5 (6 articles; 28.6%).

207 We checked whether mediastinal lymph-nodes involvement was counted as a separate metastatic site.
208 This was not specified in 3 studies (14.3%), in 13 (61.9%) lymph-nodal involvement was not counted
209 in the number of metastatic organs allowed, while only in 5 (23.8%) mediastinal lymph-nodes were
210 effectively counted as a metastatic site. In one article all lymph-nodal sites were considered as
211 metastatic sites, while in 4 articles only the N3 stations were counted as a metastatic site.

212 Nineteen of the 21 studies did not exclude any specific metastatic site, while in 2 articles uncontrolled
213 brain, gastrointestinal and skin metastases, or pleural/pericardial metastases were not allowed.

214 Overall survival (OS) was the primary outcome in most of the published articles (n = 18; 85.7%), while
215 in 2 articles (9.5%) this was progression free survival (PFS). In 4 papers both OS and PFS were
216 considered as coprimary endpoints. In 18 articles (85.7%) the authors declared that the treatment of
217 oligometastatic disease had a curative intent. All the variables have been resumed in **Table 2**.

218

219 **Discussion:**

220 Despite the fact that the sOM status is currently recognized in NSCLC, a uniform definition is not
221 available and several issues are still open. Hence, we performed a systematic review of the literature in
222 order to offer a scientific support on the published definitions of sOM NSCLC and to support the

223 EORTC LCG consensus⁸. Based on this systematic review, it emerges that a single clinical definition of
 224 sOM NSCLC does not exist; from the numerous retrieved publications on sOM only a minority provided
 225 a clear definition (**Table 3-4**).

226 Although there is no clear definition of sOM, in the majority of the articles a complete radiological
 227 staging using brain MRI and ¹⁸F-FDG PET/CT was mandated. This is in line with the general consensus
 228 in scientific societies as ESMO, NCCN and EORTC^{1,4,29}. Complete radiological staging remains important
 229 for the definition of sOM, but also the outcome of radical treatment of sOM patients, as stage migration
 230 is a well-known phenomenon when introducing more sensitive diagnostic techniques as ¹⁸F-FDG-
 231 PET/CT and brain MRI. Potentially this could be useful in a better patient selection and consequently
 232 an improvement in clinical outcomes.

233 Furthermore, ¹⁸F-FDG PET/CT was the main method required to stage both systemic disease and
 234 mediastinal lymph-nodal status. On the opposite, it is unclear if a pathological proof of the mediastinal
 235 lymph-nodal involvement in the metastatic process is requested in addition to the metabolic and
 236 morphologic assessment, probably due to excellent sensitivity and specificity of ¹⁸F-FDG PET/CT. A
 237 recent systematic review reported that ¹⁸F-FDG PET/CT is associated with a sensitivity and specificity
 238 in the identification of lymph nodal involvement with value of between 79–85% and 87–92%,
 239 respectively³⁰.

240 In most articles, authors did not report on the histopathological proof of malignancy of the metastatic
 241 site. Apparently, mediastinal lymph node involvement is not uniformly considered relevant in the
 242 definition of sOM-NSCLC and in the selection of patient eligible for combined local and systemic
 243 treatments. It is also uncertain whether involved mediastinal lymph nodes should be counted as a
 244 separate metastatic site. According to the TNM classification¹⁰, mediastinal lymph nodes are
 245 considered locally advanced, but not metastatic. However, from the available literature it is known
 246 that mediastinal lymph node involvement negatively affects outcome of sOM patients [10]. In most of
 247 the studies included in this systematic review, mediastinal lymph node involvement was not counted
 248 as a separate metastatic anatomical site. Future prospective trials should establish or evaluate
 249 whether radical treatment of sOM NSCLC with mediastinal lymph node involvement and which levels
 250 (N1-3) impact on outcomes of these patients.

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

256 The level of evidence and the potential biases of the retrieved publications can limit the information
 257 provided by this review. The majority of the studies were retrospective single center series, and
 258 outside of the maximum number of metastases, other information like the number of organs with at
 259 least one metastasis, the maximal number of metastases per organ was a selection criteria in only a

260 limited number of publications. Even for the maximal number of metastases, which was defined in all
261 studies, no clear cut-off could be found, however, the majority of studies did not allow over 5
262 metastases. From the published papers we cannot deduce whether these data were missing or the
263 authors had not considered them fundamental for their research.
264

265 **Conclusions:**

266 Synchronous oligometastatic NSCLC defines patients, in whom the combination of systemic and local
267 ablative treatments may influence tumour behavior. Although many studies have been published on
268 this subject, evidence from this systematic review suggests that a uniform and reliable definition of
269 sOM does not exist. However, mandated diagnostic staging was very stringent with ¹⁸F -FDG PET/CT
270 and imaging of the brain. Nevertheless, some consensus emerged in the cut-off defining the maximal
271 number of metastases and the staging work-up.

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

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416 **Figures and tables legend:**

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418 **Table 1.** Studies selected, population and intervention in NSCLC synchronous oligometastatic (PICO

419 criteria)

420 **Table 2.** Outcomes in NSCLC synchronous oligometastatic (PICO criteria)

421 **Table 3.** Resume of variables

422 **Figure 1.** Search flowchart

423 **Supplement Table 1.** Research question according to PICO criteria

424 **Supplement Table 2.** Search strategy and potentially eligible abstracts identified by search strategy

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Authors/Year	Population		Intervention							
	Type of study	Single/multi center	Patients (n)	TNM	Work-up	PET-CT	Brain-MRI	Brain-CT	Mediastinal staging	Pathological proof of malignancy
Downey R. 2002 [27]	NRT	Single	23	5 th	Complete	No	Yes	N.A.	EBUS	All sites
Khan A. 2006 [12]	RS	Single	23	N.A.	Partial II	Yes	N.A.	N.A.	PET-CT	N.A.
Inoue St. 2010 [22]	RS	Single	25	N.A.	Complete	No	No	N.A.	PET-CT	No
Cheruvu P. 2011 [23]	RS	Single	38	7 th	Complete	Yes	Yes	N.A.	PET-CT	N.A.
Collaud S. 2012 [24]	RS	Single	29	6 th	Complete	Yes	Yes	N.A.	EBUS	N.A.
Congedo M. 2012 [25]	RS	Single	53	5 th	Complete	Yes	No	Yes	EBUS	N.A.
De Ruyscher D. 2012 [26]	NRT	Single	40	6 th	Complete	Yes	Yes	N.A.	PET-CT	At least one site
Lopez Guerra J. 2012 [13]	RS	Single	78	6 th	Incomplete	N.A.	N.A.	N.A.	N.A.	N.A.
Griffioen G. 2013 [29]	RS	Multicenter	61	5 th -7 th	Complete	Yes	Yes	N.A.	PET-CT	N.A.
Nieder C.S 2014 [14]	RS	Multicenter	23	7 th	Complete	Yes	Yes	Yes	PET-CT	N.A.
Parikh R. 2014 [15]	C	Single	186	7 th	Complete	Yes	Yes	No	PET-CT	N.A.
Sheu T 2014 [18]	DB	Single	90	7 th	Incomplete	N.A.	N.A.	N.A.	N.A.	No
Plones T. 2015 [16]	RS	Single	56	6 th	Complete	Yes	Yes	Yes	EBUS	N.A.
Su Ss. 2015 [20]	NRT	Multicenter	198	6 th	Complete	Yes	Yes	Yes	PET-CT	N.A.
Xanthopoulos E. 2015 [21]	DB	Single	29	7 th	Complete	Yes	N.A.	No	PET-CT	N.A.
Fleckenstein J. 2016 [28]	DB	Single	39	5 th -7 th	Complete	Yes	N.A.	N.A.	N.A.	N.A.
Gomez D. 2016 [6]	RT	Multicenter	49	7 th	Complete	Yes	Yes	N.A.	PET-CT	N.A.
Johnson K. 2016 [11]	DB	Single	37	5 th -7 th	Complete	Yes	Yes	Yes	EBUS	No
Sakai Ks. 2016 [17]	RS	Single	18	7 th	Complete	Yes	Yes	Yes	PET-CT	N.A.
Su Ss. 2016 [20]	NRT	Single	91	6 th	Complete	Yes	Yes	Yes	PET-CT	N.A.
Iyengar P . 2017 [5]	RT	Single	29	N.A.	Complete ‡	Yes	Yes	Yes	PET-CT	At least one site

Table 1. Studies selected, population and intervention in NSCLC synchronous oligometastatic (PICO criteria)

Authors/Year	Outcomes									
	Number of organs with at least one mts	Number of mts	Number of mts per organ	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 R. 2002 [27]	1	1	1	No	No	Other	-	No	No	N.A.
Khan A. 2006 [12]	N.A.	2	N.D.	Yes/N3	No	OS	None	No	No	Yes
Inoue St et al. 2010 [22]	2	5	N.D.	No	Yes	OS/PFS/Other	None	No	No	Yes
Cheruvu P. 2011 [23]	N.A.	8	N.D.	Yes/N3	Yes	OS	GTV	No	No	Yes
Collaud S. 2012 [24]	1	1	1	No	Yes	OS	None	No	Yes (EGFR)/No	Yes
Congedo M. 2012 [25]	2	2	2	No	Yes	OS	Weight loss, PET-CT, surgical resection	No	No	N.A.
De Ruyscher D. 2012 [26]	N.A.	5	N.D.	No	No	OS	None	Pleural or pericardial effusion	Yes (EGFR)/N.A.	Yes
Lopez Guerra J. 2012 [13]	N.A.	4	N.D.	No	Yes	OS	Radiation dose, PS, tumor volume	No	No	Yes
Griffioen G. 2013 [29]	N.A.	3	N.D.	No	Yes	OS/PFS/Other	None	No	No	Yes
Nieder C.S. 2014 [14]	1	3	3	No	Yes	OS	None	No	No	Yes
Parikh R.2014 [15]	N.A.	5	N.D.	Yes/N3	Yes	OS	PS, N status, number of organs,	No	Yes (EGFR)/Yes	Yes
Sheu T. 2014 [18]	N.A.	3	N.D.	N.A.	Yes	OS/PFS	Sex, PS, local therapy	No	No	Yes
Plones T. 2015 [16]	N.A.	5	N.D.	No	Yes	OS	Bone metastases	No	No	Yes
Su Ss. 2015 [20]	3	N.A.	No more 2 liver mets	No	Yes	OS	Radiation dose (>63 Gy), tumor volume, PS	No	Yes (EGFR)/No	Yes
Xanthopoulos E. et al. 2015 [21]	N.A.	4	N.D.	No	Yes	OS	Radiotherapy, female, number of metastatic organs	No	No	Yes
Gomez D. 2016 [6]	N.A.	3	N.D.	Yes/N3	No	PFS	-	No	Yes (EGFR/ALK)/Yes	Yes
Fleckenstein J. 2016 [28]	N.A.	5	3 for brain mts	N.A.	Yes	OS/PFS	None	No	No	Yes
Johnson K. 2016 [11]	2	5	<5	No	No	OS	None	No	No	Yes

Sakai Ks.2016 [17]	2	5	5	No	No	OS	None	No	Yes (EGFR)/Yes	Yes
Su Ss. 2016 [20]	N.A.	4	N.D.	N.A.	Yes	OS	Radiation dose, tumor volume	No	No	Yes
Iyengar P. 2017 [5]	N.A.	5	5 (no more 3 lung or liver)	Yes/Nx	No	PFS	-	Uncontrolled brain metastases	No	Yes

Table 2. Outcomes in NSCLC synchronous oligometastatic (PICO criteria)

Variables	Number of publications (%) Tot:21
Type of study	
Retrospective series	10 (47.6%)
Prospective non randomized 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 number of patients (all studies combined)	1215 [range 18-198]
Median number of patients	39
Staging system	
5 th or 6 th	8 (38.1%)
6 th and 7 th	3 (14.3%)
7 th	7 (33.3%)
8 th	0
Not available	3 (14.3%)
Work up	
Brain MRI/CT + PET (or thorax+abdomen CT and bone scan)	17 (81%)
PET (or thorax+abdomen CT and bone scan) w/o MRI/CT	1 (4.8%)
Uncomplete work-up	3 (14.2%)
PET-TC	
No	2 (9.5%)
Yes	17 (81%)
Not reported	2 (9.5%)
Brain MRI	
No	2 (9.5%)
Yes	13 (61.9%)
Not reported	6 (28.6%)
Brain CT	
No	2 (9.5%)
Yes	7 (33.4%)
Not reported	12 (57.1%)
Mediastinal staging	
PET	13 (62%)
CT only	0 (0%)
EBUS or EUS or mediastinoscopy	5 (23.8%)
Not reported/not assessed	3 (14.2%)
Number of organs with at least one metastasis	
1	3 (14.3%)
2	4 (19%)
3	1 (4.8%)
Any	5 (23.8%)
N.A.	8 (38.1%)
Are mediastinal lymph-nodes counted as an organ	
No	12 (51.1%)
Yes	6 (28.6%)
Not define	3 (14.3%)
Is volume considered as an issue	
No	8 (38.1%)
Yes	5 (23.8%)
Not assessed	8 (38.1%)

Primary outcome measure	
OS	14 (66.7%)
PFS	2 (9.5%)
Response	0 (0%)
QoL	0 (0%)
Other/multiple	5 (23.8%)
Pathological proof of metastasis	
No	3 (14.3%)
Systematic for all sites	1 (4.8%)
Systematic for at least one site	2 (9.5%)
Not reported	15 (71.4%)
Curative therapeutic intent	
No	1 (4.8%)
Yes	18 (85.7%)
Not reported	2 (9.5%)
Is mutational status considered?	
No	15 (71.4%)
Yes	6 (28.6%)
What is the mutationa status analysed?	
EGFR	4
ALK	0
Combination (EGFR/ALK)	2

Table 3. Resume of variables

