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Original Research

Defining oligometastatic non-small cell lung cancer: A simulated multidisciplinary expert opinion

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Abstract ***Introduction:*** Synchronous oligometastatic non-small cell lung cancer (NSCLC) definition varies from 1 metastasis in 1 organ (tumour-node-metastasis 8 [TNM8]), 1–3 metastases (European Society for Medical Oncology [ESMO]), ≤3 metastases (including mediastinal nodes [MLN]) after systemic treatment to 3–5 metastases in ongoing trials. A single definition is however needed to design/compare trials. To assess oligometastatic NSCLC definitions used by clinical experts in daily practice and its evolution, we redistributed a 2012 case-based survey (Dooms, the World Congress of Lung Cancer 2013).

Methods: In December 2017, 10 real-life multidisciplinary team (MDT) discussed patients (good condition, no significant comorbidities, ^{18}F-fluorodeoxyglucose positron emission tomography/brain magnetic resonance imaging staged, all < 5 metastases, 9/10 ≤ 3 metastases, oncogene-addicted or wild-type) were distributed to 33 international NSCLC experts involved in the European Organisation for Research and Treatment of Cancer oligometastatic NSCLC consensus group, questioning is this oligometastatic disease and if oligometastatic, which treatment proposal. The answers provided in 2017 were compared with the 2012 answers; real-life treatment and survival of the patients was added.

Results: Twenty-six of 33 experts (24 centres) replied: 8 medical oncologists, 7 pulmonologists, 7 radiation oncologists, 4 thoracic surgeons. Sixty-two percent of respondents discussed the cases with their MDT. One case had 100% oligometastatic consensus, and 3 cases had >90% consensus; the number of treatment proposals varied between 3 and 8. Radical treatment was more often offered in case of single metastasis or N0. Compared with 2012, there was a trend towards a more conservative oligometastatic definition and chemotherapy was more frequently included in the treatment proposal.

Conclusions: Oligometastatic NSCLC definition was conservative. The number of organs, MLN status and radical treatment possibility seem to be components of daily practice oligometastatic definition.

1. Introduction

Patients with metastasised non-small cell lung cancer (NSCLC) are generally considered incurable. However, it is suggested that some patients have an intermediate state, between localised disease and widespread metastases, and that they could benefit from more aggressive treatment. The term 'oligometastases' has first been proposed in 1995 by Hellman *et al.* [1], describing a clinically significant state with a limited number of metastases in a single or a limited number of organs. They also suggested that oligometastatic patients can be treated with local radical therapy (LRT) with radical intent but that further studies are needed to identify patients who will benefit the most [1]. Synchronous oligometastases is defined as a diagnosis of oligometastases at the first diagnosis of metastatic NSCLC.

Several, mainly retrospective series showed that a subset of these radically treated patients can indeed obtain a long-term survival, especially those with a single brain or adrenal metastasis and N0 disease [2–8]. The first prospective trial (single arm, phase II) was published in 2012 [9]. Eligible patients were those with stage IV NSCLC with less than five synchronous metastases, amenable for LRT. Eighty-seven percent of the included patients had a single metastasis, and 95% of them received chemotherapy as part of their primary treatment. Two- and three-year survival rates were 23.3% and 17.5%, respectively [9]. With the published series and the widespread introduction of minimal invasive surgery and stereotactic radiotherapy, the concept of delivering LRT in patients with oligometastatic NSCLC gained increasing interest and was also incorporated in NSCLC guidelines. For example, the European Society for Medical Oncology guideline states that definition for oligometastatic disease varies but that patients with one to three synchronous metastases can be treated with radical intent, preferably in a clinical trial [10]. The National Comprehensive Cancer Network guideline states that patients with NSCLC with limited metastases can receive LRT [11]. The 8th TNM classification of lung cancer also included the concept: M1b defines a single metastasis in a single site, and M1b patients were shown to have a superior prognosis than M1c patients, although treatment was not known for these patients [12]. After the first prospective phase II trial, three other trials including patients with synchronous oligometastatic NSCLC have been reported with promising progression-free survival (PFS) data [13–15]. Only for one trial, overall survival (OS) results have been reported, with a median OS of 41.2 months for the LRT arm and 17 months for the control arm [15]. The inclusion criteria such as the

Table 1
Summary of completed and reported oligometastatic trials in non-small cell lung cancer.

Author, year, phase trial	Nr of patients with NSCLC included	Max nr of metastatic sites	Max nr of organs with metastases	Primary/ LN counted	Treatment	Outcome	Characteristics included patients
De Ruysscher (update 2018), II single arm	40 All histologies	5	5	No	LRT ± chemotx	OS at 2 years: 23.3% OS at 3 years: 17.5% OS at 5 years: 7.7% OS at 6 years: 2.5%	87% single met 41.1% N0-1
Gomez (update 2019), II randomised	49 All histologies	Counted after first-line systemic tx: 3	3	Yes (MLN)	A: LRT + maintenance B: maintenance	Median PFS 11.9 (LRT) versus 3.9 months (HR 0.35; p = 0.0054) median OS 41.2 (LRT) versus 17 months<	68% 0–1 non-regional mets 48% N0-1
Iyengar 2017, II randomised	29 Non-*EGFR*/*ALK*	6 including primary Max 3 in liver/ lung	5	Yes	Chemotx followed by A: LAT + maintenance chemo B: maintenance chemo	Median PFS 9.7 (LRT) versus 3.5 months (HR 0.30; p = 0.01)	Median sites of disease: 3 MLN not mentioned
Bauml 2018, II single arm[a]	45 All histologies	4	4	No	LRT to all sites followed by pembrolizumab	12-month PFS 728% 18-month PFS 54% 24-month PFS 50%	63.6% single met 61.4% N0-1

Abbreviations: NSCLC: non-small cell lung cancer; max: maximum; nr: number; MLN: mediastinal lymph nodes; LRT: local radical therapy; OS: overall survival; mets: metastases: tx: therapy; PFS: progression-free survival; vs: versus; HR: hazard ratio; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; chemo: chemotherapy.
[a] No limits on prior lines of therapy, but patient should be programmed death-(ligand)1 inhibitor naive.

number of metastases, considering the primary and/or mediastinal lymph nodes, eligibility of patients with driver mutations and treatment sequence varied (Table 1) [16].

As it is clear from these summarised trials and guidelines, definition of synchronous oligometastatic NSCLC varies. Furthermore, even though most trials allow at least three metastatic sites and do not restrict on mediastinal lymph nodes, most enrolled patients have only one metastatic site and N0-1 disease (Table 1) [13–15]. A single oligometastatic definition is, however, needed to design and compare trials. The European Organisation for Research and Treatment of Cancer Lung Cancer Group (EORTC-LCG) initiated a consensus process. A consensus group was formed aiming to agree on a common NSCLC synchronous oligometastatic definition that could be used in future clinical trials. In preparation for this meeting, a systematic review [17] and a survey [18] were performed. Furthermore, we redistributed a 2012 case-based survey (Dooms *et al.*[19], presented at the World Congress of Lung Cancer 2013) to a larger expert panel. This is to assess synchronous oligometastatic NSCLC definitions used by clinical experts in daily practice and its evolution. Results of this case-based survey are reported here.

2. Materials and methods

2.1. Cases

The original 2012 case-based survey was developed in preparation for a workshop on oligometastatic NSCLC in Leuven, Belgium, and consisted of ten real-life multidisciplinary team (MDT) discussed patients. These patients were in a good clinical condition, had no significant comorbidities and were all ^{18}F-fluorodeoxyglucose positron emission tomography (^{18F}FDG-PET) and brain magnetic resonance imaging (MRI) staged. All patients had less than five metastases, and nine of them had three or less metastases. Both oncogene-addicted (epidermal growth factor receptor [*EGFR*]–mutated) and wild-type NSCLC cases were included. The 7th TNM edition was initially used for these cases but was recoded to the 8th edition for this analysis [20,21]. The cases can be found in the supplementary material (appendix 1). These patients were diagnosed with stage IV NSCLC between 2009 and 2012; the last date of follow-up was January 5, 2018.

2.2. Distribution of cases

In 2012, this survey was sent to 11 experts in the field with the following questions: (1) Is this oligometastatic disease? And (2) Can you state what your preferred treatment is?

In December 2017, the same cases were distributed to 33 international NSCLC experts involved in the European Organisation for Research and Treatment of Cancer (EORTC) oligometastatic NSCLC consensus group (including four young investigators), with the following questions: (1) What is your working environment? (2) Can you please discuss these cases in your MDT? (3) Do these patients have oligometastatic disease? And (4) What is your treatment proposal for each

Table 2
Summary of clinical cases and expert answers.

Case TNM8	OMD agreement (% positive answer) 2012/2017	Number of tx proposals[a] 2012/2017	% of treatment proposals including systemic tx[a] 2012/2017	% of radical tx answers[a] 2012/2017	Real-life radical tx intent	Real life tx	Real-life survival (mo) alive at 5 yrs (+: yes, -: no)/with or without active disease
(1) *EGFR* + cT2aN3M1c (3 brain mets)	55/38	3/5	100/100	50/60	No	EGFR-TKI	40.1-/NA
(2) *EGFR* + cT4N0M1a (ground glass)	36/35	4/3	60/78	100/100	Yes	VATS lobectomy RUL + wedge ML, adjuvant chemotx 2016 PD: EGFR-TKI	65.2+/with
(3) cT2bN1M1b (solitary renal)	91/96	5/5	80/91	100/96	Yes	cCRT chest and partial nephrectomy	8.3-/NA
(4) cT1cN3M1b (solitary adrenal)	73/58	4/5	100/100	75/93	Yes	Induction chemotx, radical RT chest, adrenalectomy	66.1+/without
(5) cT3N1M1c (adrenal + pelvic node)	55/50	3/5	100/92	67/92	No	Chemotx	18.6-/NA
(6) cT2aN0M1c (3 liver mets)	64/69	4/5	71/83	43/89	No	Chemotx	51.5-/NA
(7) cT2aN2M1b (solitary bone)	91/92	4/5	80/100	80/92	Yes	Induction chemotx, lobectomy RLL, adjuvant chest RT, scapula RT	13.4-/NA
(8) cT2bN1M1c (2 brain mets)	91/96	3/8	100/84	80/88	Yes	SRT brain, cCRT chest	39.6-/NA
(9) cT2bN0M1c (1 lung, 1 pancreas)	82/69	6/4	78/94	78/72	Yes	VATS lobectomy LUL, SRT pancreas, adjuvant chemotx	74.0+/without
(10) cT1bN0M1b (solitary bone)	100/100	3/5	9/54	91/92	Yes	VATS lobectomy RUL, SRT C6, adjuvant chemotx	11.6-/NA

Abbreviations: TNM: tumour-node-metastasis; OMD: oligometastatic disease; tx: treatment; mo: months; yrs: years; EGFR: epidermal growth factor receptor; mets: metastases; TKI: tyrosine kinase inhibitor; VATS: video-assisted thoracoscopic surgery; RUL: right upper lobe; ML: middle lobe; PD: progressive disease; cCRT: concurrent chemoradiotherapy; RT: radiotherapy; RLL: right lower lobe; SRT: stereotactic radiotherapy; NA: not applicable.

[a] Only results given for respondents who answered that the case was oligometastatic.

oligometastatic case? Responders had the option to add remarks or comments regarding the way their decision was made. The responders were not aware of the actual treatment of the cases and did not know the 2012 answers. Current results were compared with the 2012 answers, and the real-life applied treatment and survival data of the patients were added (the last date of follow-up was January 5, 2018).

2.3. Statistics

Statistical analysis was performed with Excel 2016. Descriptive statistics were used to describe all answers to the cases, and the Fisher exact test was used to evaluate if the answer in 2017 (oligometastatic yes/no) was related to whether a case was discussed in the MDT.

3. Results

2012 and 2017 results plus real-life outcomes are summarised in Table 2. Detailed treatment answers (type of LRT, type of systemic treatment, sequence of treatment [if mentioned in the answer]) can be found in Supplemental Table 1.

3.1. 2012

In 2012, 11 experts (three radiation oncologists, three thoracic surgeons, three pulmonologists, one pathologist and one specialist in nuclear medicine) answered all ten cases. The answers are summarised in Table 1. Only one case (case 10) had 100% consensus that this was oligometastatic disease. For the other cases, agreement ranged from 36 to 91%. The number of treatment options per oligometastatic case ranged from two to six. The percentage of responders that included systemic treatment in their treatment proposal for the cases they considered oligometastatic ranged from 9 to 100%. The lowest percentage of systemic treatment use was found for the 100% oligometastatic consensus case 10 (cT1bN0M1b). Even though responders considered a case oligometastatic,

the percentage of treatment with radical intent (i.e. LRT given to all disease sites) for oligometastatic cases varied from 43 to 100%. The lowest percentage was found for case 6.

3.2. 2017 and comparison with 2012

In 2017, 26 of 33 (78.8%) experts from 24 different institutions (11 countries) responded and answered all cases. Six worked in a cancer centre, 19 in a university centre and one in a general hospital. One was a clinical oncologist, seven were medical oncologists, seven pulmonologists, seven radiation oncologists and four thoracic surgeons. Sixteen of them (62%) discussed all cases in their local MDT.

In general, remarks were made that in case of a solitary metastasis, pathology proof should be obtained when feasible. One respondent stated that mediastinoscopy was necessary in patients with N0/1 disease when mediastinoscopy was not already performed. When a case was not considered oligometastatic, reasons were the extent of locoregional disease, the number of metastases or their location (i.e. LRT not possible).

For the same patient case (number ten) as in 2012, there was 100% consensus in 2017 that this was oligometastatic disease. For the other cases, agreement ranged from 38 to 96%. The four cases with an agreement of more than 90% were cases with N0 or N1 disease (and one N2 case with a solitary micrometastasis in lymph node station 4R) and a single metastasis (one case with 2 brain metastases). There was no association between the decision that a case was oligometastatic and discussing the case in the MDT except for case 5. In case 5, 45% of those presenting the case in the MDT stated that it was oligometastatic disease while 80% not discussing in the MDT stated it was oligometastatic disease ($p = 0.04$).

For seven cases, the percentage of oligometastatic agreement did not differ for more than 5% when 2012 and 2017 answers were compared. For the other three cases, the percentage of oligometastatic agreement was 13–17% lower in 2017 than in 2012. In 2017, the number of treatment options ranged from three to eight, and for seven cases, this number was higher in 2017 than in 2012. The percentage of responders that included systemic treatment in 2017 was 54–100%. Systemic treatment was proposed as neoadjuvant, concurrent and adjuvant approaches (Supplemental Table 1). For two cases, the use of systemic treatment percentage was more than 5% lower than in 2012 (8% and 16%, respectively); for six, it was more than 5% higher (range, 11–45%). In 2017, the percentage of treatment with radical intent for the oligometastatic cases ranged from 60 to 100%, was 5% lower than in 2012 in one case and more than 5% higher in six cases (range 10–46%).

3.3. Real-life outcomes

In real life, seven patients were treated with radical intent (Table 2). Two of them were treated with induction chemotherapy followed by LRT, and the others were treated with LRT and concurrent or adjuvant systemic treatment. Three of these seven patients were alive at five years, and none of the non-radically treated patients were alive at five years. Patient six was treated with palliative chemotherapy only and died after 51.5 months of a second primary metastatic cholangiocarcinoma. In hindsight, it was possible that the liver lesions were metastases of a cholangiocarcinoma although median OS of a non-radically treated cholangiocarcinoma is less than one year [22] Patient ten, with 100% oligometastatic consensus received radical treatment but died after 11.6 months (Table 1).

4. Discussion

With the introduction of minimally invasive LRT techniques and the superior survival outcomes with LRT added to systemic treatment [13,15,23], there is increased interest in radically treating (synchronous) patients with oligometastatic NSCLC. However, definition for synchronous oligometastatic NSCLC varies across guidelines and trials where only selected patients are included. Furthermore, more oligometastatic patients are treated with LRT in daily practice, and it is not known whether this type of oligometastatic patients treated mirrors that of the clinical trials.

We showed that the oligometastatic definition in daily clinical practice was conservative: even though all cases had less than five metastases and 90% had three or less metastases, only one case had 100% consensus that this was oligometastatic disease. Three other cases had more than 90% oligometastatic consensus: two of these cases had a solitary metastasis, the other had two brain metastases and all cases had N0 (or micrometastatic N) disease. The oligometastatic definition was more restrictive in 2017 than in 2012, but cases with the highest agreement on oligometastatic disease remained the same. The number of metastatic sites, mediastinal lymph node status and possibility for LRT seem to be components that are taken into account by experts for oligometastatic definition and treatment in daily practice.

Interestingly, there seems to be a discrepancy between a theoretical definition of oligometastatic disease (i.e. not linked to a specific patient case) and the practical definition of oligometastatic disease. This is shown for clinical trials as well as daily practice. Despite that most trials allow up to three or five metastatic sites (some even more) and do not restrict on the presence of mediastinal lymph node metastases, most enrolled patients have only one metastatic lesion and N0 or N1

disease [9,13,15,23,24]. Similar results are seen in daily practice as demonstrated in a European survey on synchronous oligometastatic NSCLC definition that we performed at the end of 2017 – beginning of 2018 (444 responders). Forty-two percent included up to three metastases in their definition, 16% included up to five metastases and 16% had no upper limit, if LRT was possible. Only 25% stated that mediastinal lymph node involvement was not allowed to be classified as oligometastatic NSCLC [18]. Despite these relatively broad inclusion criteria for oligometastatic disease, our cases showed that mainly the patients with a single metastasis and N0-1 disease were considered oligometastatic and were treated with LRT. However, to be able to design and compare trials, a single definition is needed. The EORTC oligometastatic definition group has formulated a consensus statement on the definition of synchronous oligometastatic NSCLC [16]. This definition should be prospectively tested in future randomised trials and in the EORTC-ESTRO (European Society for Therapeutic Radiation and Oncology) OligoCare project (a pragmatic observational basket study to evaluate radical radiotherapy for oligometastatic cancer patients). As such, this definition might change with continuing new insights. Another factor that is important for the definition is the required staging for these patients. This was not addressed in this survey as all patients were ^{18F}FDG-PET and brain MRI staged as proposed by the EORTC imaging group [25]. However, staging requirements vary in ongoing trials.

Another finding from this survey is the number of treatment options per oligometastatic case. For most cases, four to five different treatment scenarios were mentioned, and up to eight in one case. Treatment options varied with respect to the LRT technique (surgery, S(B)RT and radiofrequency ablation) and also for systemic treatment (type and sequence [induction, concurrent and adjuvant]). However, the therapeutic sequence seems important for oligometastatic disease, as usually only the patients who do not progress with induction systemic treatment are selected for LRT (cf Gomez and Iyengar trials) [13,15,23]. Maybe some of the patient cases in this survey would not have been treated with LRT when systemic treatment had been given upfront. The trial by Iyengar *et al* [13] was published just after the completion of our case-based survey, and it is possible that more experts would have selected upfront systemic treatment followed by LRT if this article had been published before the distribution of the cases. However, even though sensitivity to systemic treatment can enrich the oligometastatic patient population for long-term benefit, treatment sequence (sequential versus concurrent) was not associated with the outcome in another trial [9,26]. Moreover, in the updated analysis of this trial, with a minimal follow-up of more than seven years, five- and six-year survival rates were only 7.7% and 2.5%, respectively [26].

Better selection methods are needed to identify oligometastatic patients who will benefit from LRT in addition to systemic treatment. The number and sometimes also location of metastasis, volume of disease and nodal status are associated with the outcome in oligometastatic patients [3,6,7]. In the trial by Gomez *et al.* [15,23], only treatment type (LRT versus no LRT) and presence of driver mutations were associated with improved PFS. Other patient-related factors could not be identified, but the number of included patients in this trial was small. Iyengar *et al.* [13] analysed only prognostic factors for PFS within the LRT group. Hopefully the Stereotactic Ablative Radiotherapy for Oligometastatic Non-Small Cell Lung Cancer (SARON) trial (NCT02417662) will provide some of these answers because patients are stratified as per mediastinal lymph node status (N0-1 versus N2-3), histology (adenocarcinoma versus non-adenocarcinoma), brain metastases (present versus absent) and the number of oligometastatic sites (1 versus 2 versus 3) [27]. Other interesting factors such as (metabolic) volume of disease, radiomics features, molecular signatures (e.g. microRNA's) and use of circulating tumour DNA to predict benefit of LRT in patients with oligometastatic NSCLC should be evaluated in future trials [9,28–35]. In addition, it should be evaluated whether the same predictive factors exist in patients treated with immunotherapy, as this will also be more incorporated in the treatment of patients with oligometastatic NSCLC.

5. Conclusion

In this case-based survey, oligometastatic NSCLC definition in daily practice was conservative. The number of metastases and organs involved, extent of locoregional disease and the possibility for radical treatment seem to be components of the daily practice oligometastatic definition. Efforts such as by the EORTC oligometastatic definition consensus group should be made to provide a uniform definition. This definition should be tested in future trials and in the OligoCare project. Furthermore, predictive factors for benefit of LRT should prospectively be evaluated.

Conflict of interest statement

T.B. reports no conflict of interest regarding the content of this manuscript. A.L., N.G.L., J.V., B.H., M.G.L. and C.D. report no conflict of interest. L.E.L.H. reports no conflict of interest related to the current manuscript. Outside of the current manuscript L.E.L.H. received research funding from Roche and Boehringer Ingelheim (both institution); has been a member of the advisory board of Boehringer and BMS, (both institution, BMS also self); has received travel reimbursement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.09.013.

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