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Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature

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ABSTRACT

Objectives: Long-term survival has been observed in patients with oligometastatic non-small cell lung cancer (NSCLC) treated with locally ablative therapies to all sites of metastatic disease. We performed a systematic review of the evidence for the oligometastatic state in NSCLC.
Materials and Methods: A systematic review of MEDLINE, EMBASE and conference abstracts was undertaken to identify survival outcomes and prognostic factors for NSCLC patients with 1–5 metastases treated with surgical metastatectomy, Stereotactic Ablative Radiotherapy (SABR), or Stereotactic Radiosurgery (SRS), according to PRISMA guidelines.
Results: Forty-nine studies reporting on 2176 patients met eligibility criteria. The majority of patients (82%) had a controlled primary tumor and 60% of studies included patients with brain metastases only. Overall survival (OS) outcomes were heterogeneous: 1 year OS: 15–100%, 2 year OS: 18–90% and 5 year OS: 8.3–86%. The median OS range was 5.9–52 months (overall median 14.8 months; for patients with controlled primary, 19 months). The median time to any progression was 4.5–23.7 months (overall median 12 months). Highly significant prognostic factors on multivariable analyses were: definitive treatment of the primary tumor, N-stage and disease-free interval of at least 6–12 months.
Conclusions: Survival outcomes for patients with oligometastatic NSCLC are highly variable, and half of patients progress within approximately 12 months; however, long-term survivors do exist. Definitive treatment of the primary lung tumor and low-burden thoracic tumors are strongly associated with improved long-term survival. The only randomized data to guide management of oligometastatic NSCLC pertains to patients with brain metastases. For other oligometastatic NSCLC patients, randomized trials are needed, and we propose that these prognostic factors be utilized to guide clinical decision making and design of clinical trials.

1. Introduction

The primary treatment for most patients with metastatic NSCLC is palliative chemotherapy, which results in median survivals of 8–11 months [1] and provides minimal chance of long-term survival. Despite these generally dismal outcomes, encouraging reports of long-term survival in select patients with low-volume metastatic NSCLC treated with curative intent have emerged in the recent literature [2]. The rationale for this approach is based on a theory of cancer spread proposed by Hellman and Weichselbaum. Along the spectrum of locally confined to widely metastatic cancer, there exists an intermediate "oligometastatic state" where metastases are limited in number and location [3]. It has been hypothesized that in select oligometastatic patients, locally ablative therapies given with the intent of eradicating all sites of known metastatic disease could result in long-term survival, or even cure [4].

Much of the evidence supporting the oligometastatic state exists within the surgical literature. The international registry of lung metastases reported the outcomes of 5206 patients with resected lung metastases from a variety of primary cancers and reported a 5 year survival of 36% [5]. Analogously, hepatic resection is considered a standard treatment option for metastatic colorectal cancer and can result in 10-year survival rates of 20–26%, and potential cure [6]. However, neither intervention is supported by level 1 evidence from randomized trials. Furthermore, some have suggested that the long-term survival outcomes observed in such studies may be more reflective of patient selection, rather than treatment effect [7].

There is an increasing body of literature describing the use of less invasive ablative techniques for the treatment of oligometastases, such as Stereotactic Radiosurgery (SRS) and Stereotactic Ablative

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Radiotherapy (SABR), a novel radiotherapy technique that utilizes highly conformal, ablative doses, usually delivered in 8 or fewer fractions. SABR is a standard treatment option for medically inoperable patients with early-stage NSCLC, yielding local control and survival rates superior to conventionally fractionated radiotherapy techniques and comparable to those achieved with surgical resection [8–12]. Emerging data on the use of SABR in patients with oligometastatic cancer report high rates of local control and, in select patients, long-term survival. A systematic review reporting on 334 patients with pulmonary oligometastases (from a variety of primary tumors) treated with SABR from 13 institutions reported a 2 year local control rate of 77.9% and a 2 year OS of 53.7% [13]. SABR has also been utilized for metastases of the liver [14,15] and adrenal gland [16], with rates of local control and survival outcomes comparable to those reported for surgical metastatectomy. Several studies have described the use of SABR in patients with mixed metastatic sites from a variety of primary cancers, and report local control rates of 74–80% and 2 year OS of 39–56% [17–19].

Other pertinent findings from these studies provide insight into the natural history of oligometastatic disease, such as the observation that approximately 80% of patients will develop further metastases, 2–4 years after SABR [20]. Conversely, approximately 20% of patients may achieve long-term survival without developing additional metastases and appropriate selection of patients for aggressive treatment is of paramount importance.

There is uncertainty as to whether the oligometastatic state truly exists in NSCLC, since the outcomes for NSCLC have historically been significantly poorer than other cancers. Though multiple retrospective case series have reported long-term survival in oligometastatic NSCLC patients treated with curative intent, outcomes and patient populations are variable and there are no clearly defined parameters to identify which patients might benefit most from ablative treatment of oligometastases. We performed a systematic review of the evidence for the oligometastatic state in NSCLC, to describe outcomes and prognostic factors that identify patients who may benefit from aggressive strategies.

2. Materials and methods

2.1. Literature search strategy

A systematic review of the literature was performed according to PRISMA systematic review guidelines (www.prisma-statement.org). The Medline and EMBASE databases were searched for relevant papers between 1985 and 2012 that met the study inclusion/exclusion criteria:

2.2. Inclusion and exclusion criteria

We identified reports containing the survival outcomes and prognostic factors of NSCLC patients with 1–5 synchronous or metachronous metastases with a "controlled" primary (with "local control" defined as concurrent or previous curative intent/definitive treatment to the primary lung cancer) or an "uncontrolled" primary (defined as treatment of the primary tumor with palliative radiotherapy, palliative chemotherapy, or no treatment) who received ablative treatment of all metastatic sites via surgical metastatectomy, SABR, or radical external beam radiotherapy to a dose of ≥50 Gy Equivalent Dose in 2-Gray Fractions (EQD2). Reports were excluded if the outcomes of NSCLC patients could not be ascertained or separately analyzed, or if insufficient detail was provided. Studies that contained patients with controlled and uncontrolled primary cancers where the outcomes of patients with controlled primary tumors were not reported separately were excluded, unless the proportion of patients with uncontrolled primary tumors was <50%. To minimize publication and reporting bias, single case reports or case series that comprised fewer than 10 cases were excluded.

Potential articles were identified using the National Library of Medicine's (NLM) medical subject headings (MeSH):

"(carcinoma, non small cell lung[mh] OR small cell lung carcinoma[mh]) AND surviv*[tw] AND (radiotherapy[mh] OR radiation therapy[tw] OR stereotactic[tw] OR SBRT[tw] OR SABR[tw] OR surgery[tw] OR resection[tw] OR surgical[tw] OR metastasectomy[tw] OR radiotherapy[sh]) AND (neoplasms/sc[mh] OR metast*[tw] OR oligomet*[tw] OR stage 4[tw] OR stage IV[tw] OR stage four[tw] OR late stage[tw])".

To capture articles not indexed with MeSH, a search was performed on a set of keywords appearing in either the title and/or abstract of potential articles:

"oligomet*[tw] AND lung[tw] AND (publisher[sb] OR in process[sb] OR pubmednotmedline[sb])".

Additional studies were identified by searching bibliographies of candidate articles and searching abstracts of the 2012 Proceedings of the American Society for Radiation Oncology (ASTRO).

2.3. Data abstraction

The following information was abstracted from all primary reports: primary author, reference, year of publication, number of patients, patient population, age, study design, performance status, treatment of metastases, treatment of primary lung cancer, dose and fractionation of radiotherapy, T and N-stage of the primary lung cancer (AJCC 6th edition), histology of the primary lung cancer, median follow up, survival outcomes (overall survival, median survival), local control, disease free interval, prognostic factors (univariate and multivariate), toxicity and quality of life data.

2.4. Reporting of outcomes

Survival outcomes were described by reporting the number of studies that reported median survival, the range of median survivals and the overall median of the un-weighted median survivals. Estimates of overall survival values were obtained from Kaplan–Meier curves in studies where these values were not specifically reported. Prognostic factors for overall survival assessed by multivariate analyses were reported as being "highly significant" if they were assessed in more than 2 studies and were significant in ≥50% of studies. "Moderately significant" prognostic factors were defined as those assessed only in two studies and found to be significant in ≥50% of studies. "Occasionally significant" prognostic factors were defined as those factors assessed in >2 studies and found to be positive in <50% of the studies.

3. Results

3.1. Literature search results

The search identified 1897 potentially eligible articles (1880 MeSH only and 17 keyword only; Fig. 1). After applying the exclusion criteria, 135 publications remained potentially eligible. Twenty-one additionally pertinent papers were identified from a bibliography review of these papers and two abstracts were identified from the ASTRO 2012 conference proceedings, leading to a total of 158 potentially eligible articles. These articles underwent

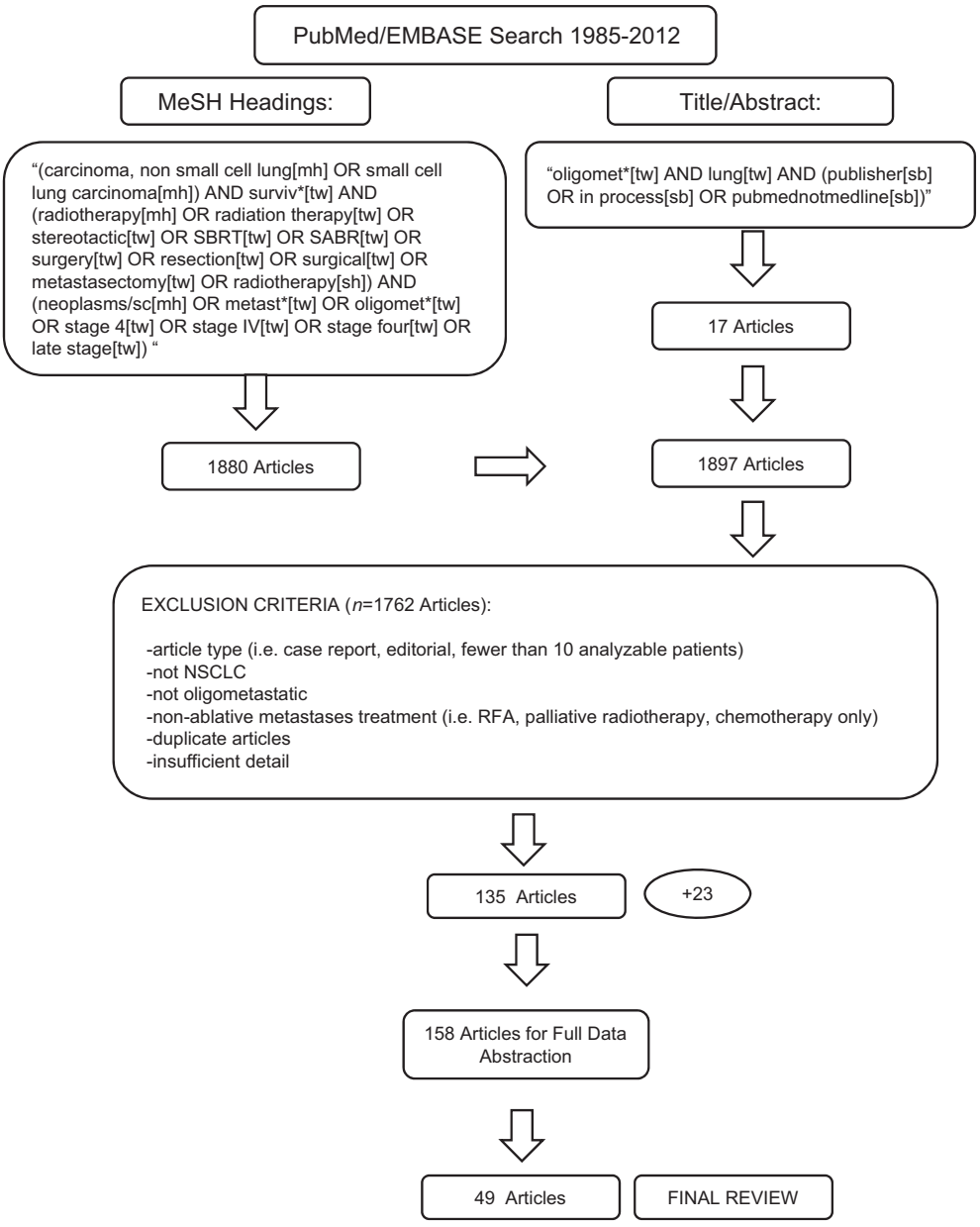

Fig. 1. PRISMA flow diagram related to electronic search strategy.

full data abstraction to ensure final eligibility and 49 publications (47 articles and 2 conference abstracts), reporting on 2176 NSCLC patients who received locally ablative treatment to oligometastases were deemed to be relevant to the topic of oligometastatic NSCLC and are the subject of this systematic review.

All studies were observational; no randomized controlled trials were identified. The majority of studies were retrospective case series (84%). Four studies were retrospective cohort studies. One prospective case series, one prospective single arm phase II trial and two systematic reviews of the literature were identified.

3.2. Patient and tumor characteristics

Patient and tumor characteristics are summarized in Table 1. Of the 2176 patients included in the 49 eligible studies who received locally ablative treatment to oligometastases, 1793 patients (82.4%) had a controlled primary tumor. Patients were younger than the general NSCLC population: approximately half of the studies reported median age (52–69 years, overall median 60 years) and half of the studies reported mean age (52–67.8 years). Twenty-four studies reported performance status, 67% of these included only patients with a performance status of KPS 70/ECOG1 or better. The overall median disease-free interval, defined variably as the time from diagnosis or treatment of the primary tumor to diagnosis or treatment of oligometastases, was approximately 14 months.

3.3. Sites of metastases

Approximately 60% of studies reported on patients with brain metastases only. Studies that included patients with a variety of metastatic sites comprised almost one-quarter of the total and a significant proportion of patients in these studies (35.7%) had brain metastases. The total number of patients with brain metastases was 1236 or 68.9% of all eligible patients. A total of 43 out of 49 studies

Table 1
Patient and tumor characteristics.

	# Studies reporting/49	Range (months)	Number of patients (*n*)
Age	49		1793
Median	25	52–69	
Mean	24	52–67.8	
		Studies reporting (%)	Number of patients (*n*)
Performance status	24		617
≥KPS70 or ≤ECOG 1	16	66.7	
<KPS70 or >ECOG 1	8	33.3	
		Range (months)	Overall median (months)
Disease free interval	15	8–60	14.1
		Number of patients (*n*)	Total patients (%)
Location of metastases	49	1793	
Brain only	29	1082	60.3
Mixed	11	431	24.0
Adrenal only	7	190	10.6
Lung only	29	90	5.0
		Number of patients (*n*)	Total patients (%)
No. of metastases/patient	43	1327	
single/solitary	23	711	53.6
1–3	13	414	31.2
1–5	7	202	15.2
		Number of patients (*n*)	Total patients (%)
Histology of primary tumor	39	1585	
Adenocarcinoma		932	58.8
SCC		316	19.9
Other		337	21.3
		Studies reporting (%)	Number of patients (*n*)
Timing of metastases	46		1766
Synchronous only	18	39.1	614
Metachronous only	6	13.0	142
Synchronous or metachronous	22	47.8	1010

reported the total number of metastases. Most patients had limited metastatic disease: more than half had a solitary metastasis, and at least 85% of patients had 3 or fewer metastases. Seven studies (16.3%) included patients with 1–5 metastases.

3.4. Primary tumor histology

Primary tumor histology was reported in 39 studies. Adenocarcinoma was the most common tumor histology, comprising 59% of cases. The proportion of squamous cell carcinoma was 20% and the remaining 21% were "other" histologies (large cell/neuroendocrine/not specified).

3.5. Ablative treatment of oligometastases

Surgical metastatectomy was the most common ablative technique for oligometastases (55% of studies). Stereotactic radiosurgery (SRS) for brain metastases and SABR were used in 35% and 10% of studies, respectively. Radical external-beam radiotherapy for oligometastases was utilized in 1 study.

3.6. Survival outcomes

Of the 49 eligible studies, 31 studies (63.3%) reported survival outcomes from the time of diagnosis or treatment of metastases, 14 studies (28.6%) reported survival from the time of diagnosis or treatment of the primary lung cancer, and 3 studies (6.1%) did not clearly define how survival outcomes were measured. Median survival was reported in 40 of 49 studies ($n = 1855$) with a range of 5.9–52 months (overall median, 14.8 months, SD 9.8 months) (Fig. 2a). The subset of patients with controlled primary tumors ($n = 1299$) had a median OS range of 6.2–52 months (overall median 19 months, SD 9.7) (Fig. 2b). OS outcomes were heterogeneous, with 1 year OS: 15–100%, overall median at one year 57.2% (reported in 33 studies), 2 year OS: 18.5–90%, overall median 42% (reported in 28 studies) and 5 year OS: 8.3–86%, overall median 23.3% (reported in 26 studies). For patients with exclusively brain metastases, 1, 2, 3 and 5 year OS ranged considerably and were 15–100%, 15.6–87.5%, 10–50% and 0–60%, respectively.

3.7. Survival by location of oligometastases

Survival outcomes by location of oligometastases are summarized in Table 2. All patients with mixed metastatic sites, adrenal metastases and lung metastases had controlled primary tumors. Patients with mixed metastatic sites had the longest median survivals, and patients with adrenal metastases had the shortest median survivals. Control of the primary tumor was associated with better survival in patients with brain metastases. Only one

Table 2
Survival by location of oligometastases.

Location of oligometastases		No. patients (*n*)	MS range (months)	Overall MS (months)
Brain	Status of primary lung tumor			
All patients	Controlled or uncontrolled	1436	5.9–52	13.6
All patients	Controlled	1082	6.8–52	19.7
Solitary Metastasis	Controlled or uncontrolled	294	5.9–52	9.3
Solitary Metastasis	Controlled	215	6.2–52	19.7
Mixed	Controlled (all)	431	13–30.9	20
Adrenal	Controlled (all)	190	11–21	17
Lung (one study only)	Controlled (all)	76	40	n/a

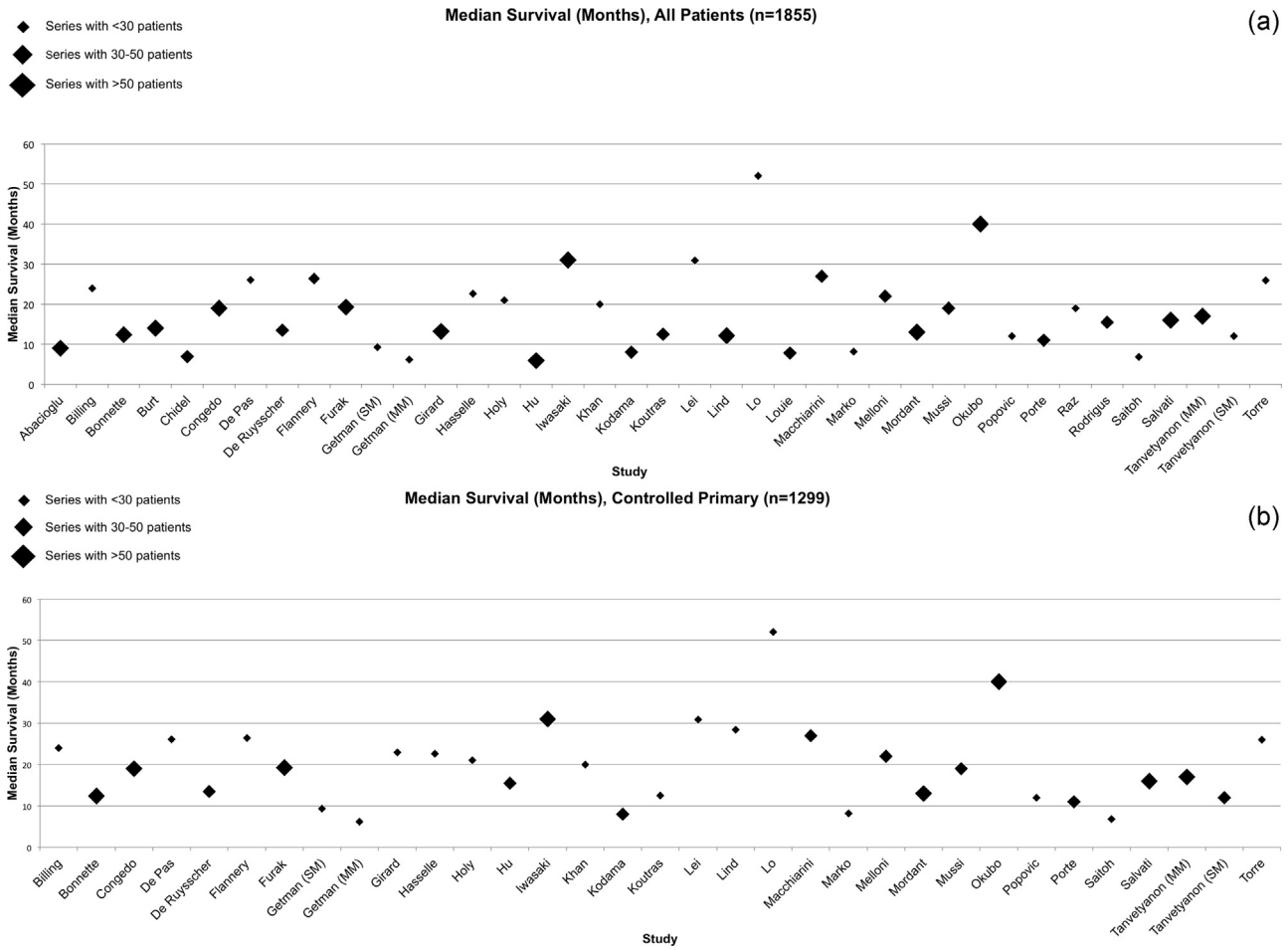

Fig. 2. (a) Median survival for all patients who received locally ablative treatment of oligometastases ($n = 1855$) (b) median survival for patients with controlled primary lung tumors ($n = 1299$). SM: synchronous metastases, MM: metachronous metastases. Please refer to Supplementary Content, published online only, for corresponding appendix of references of authors listed in this figure.

of two studies reporting on patients with lung metastases reported median survival; all patients in this study had controlled primary tumors.

3.8. Time to progression

The median time to any progression (distant or local), reported in 14 studies ($n = 446$), was 4.5–23.7 months (overall median 12 months). Three studies reported overall progression free survival at 1 year: range 42–78%, overall median 51.3% ($n = 117$).

3.9. Prognostic factors

A total of 23 studies ($n = 1064$ patients) performed multivariable analyses (MVA) of prognostic factors for survival (Table 3). Prognostic factors deemed to be highly significant (see Section 2.4 for definitions) on MVA (Group 1), were: control of primary tumor, N-stage and disease free interval of >6–12 months. Moderately significant prognostic factors (Group 2) were: presence of extracranial metastases, use of PET-CT, RPA classification primary tumor size, and type of thoracic resection. Occasionally significant prognostic factors (Group 3) were: primary tumor histology, age, AJCC stage of primary lung cancer, number of oligometastases, and use of chemotherapy.

3.10. Toxicity and quality of life

Toxicity and quality of life outcomes were reported in four studies. Two studies evaluating SABR for oligometastases reported only mild acute toxicity; long-term toxicity was not reported. One study evaluating patients who had radical surgical or radiotherapeutic management of the primary tumor and oligometastases found acceptable rates of acute toxicity, no severe long-term side effects, and no reduction in patient-reported quality of life. Another study evaluating extra-thoracic metastatectomy reported post-operative complications in approximately 1/3 of patients and in-hospital mortality and morbidity rates of 7% and 27% respectively.

4. Discussion

Although there have been calls for aggressive treatment of oligometastatic NSCLC, [21] this systematic review has revealed that survival outcomes reported in the literature for patients with oligometastatic NSCLC treated with curative intent are extremely variable, with 5-year survivals ranging from very poor (<10%) to excellent (>80%). In most studies included herein, the patients were highly selected, most often with a controlled primary tumor, 1–3 metastases, most often located in the brain, a good performance status and a relatively young age. As such, comparisons of survival between oligometastatic patients and the general unselected population of stage IV NSCLC patients (with OS in the range of 8–11

Table 3
Prognostic factors for survival assessed by multivariate analyses (MVA) in at least two studies.

	Prognostic factor	# Studies reporting	# Studies significant/#studies reporting	Comments
Group 1	Controlled primary tumor	13	7/13	Better OS with radical/definitive treatment/controlled primary/complete resection vs. supportive/palliative treatment/uncontrolled primary/incomplete resection
	Primary tumor N-stage	12	6/12	*N*0 better OS than *N* + (5 studies) *N*0/1 better OS than N2/3 (1 study)
	Disease free interval	4	3/4	Better OS with DFI > 360 days vs. < 360 days (brain metastases) with DFI > 1 year vs. < 1 year (multiple metastatic sites), better OS if DFI > 6 months vs. less (adrenal metastases)
Group 2	Presence of extra-cranial metastases	2	2/2	Decreased OS with presence of extra-cranial metastases
	Use of PET-CT	2	2/2	PET CT associated with better OS than CT alone
	RPA classification	2	1/2	RPA 1 better OS than RPA 2
	Primary tumor size	2	1/2	1–3 cm vs. 3–5 cm vs. > 5 cm, better OS with smaller primary tumor
	Type of thoracic resection	2	1/2	Lobectomy vs. pneumonectomy (better OS with lobectomy)
Group 3	Primary tumor histology	16	5/16	Adenocarcinoma better OS than other histologies
	Age	11	2/11	Age ≤50≥ or age ≤70≥ better OS
	Use of chemotherapy	8	1/8	Use of peri-operative chemotherapy associated with better OS
	# of oligometastases	7	2/7	1 vs. > 1 (1 study: lung mets), 1 vs. 2–3 vs. 4–6 (1 study: brain mets)
	Thoracic AJCC stage group	5	1/5	Stage I better than stage III or IV (no stage II pts in study)
	Sex	9	0/9	
	Primary tumor T-stage	7	0/7	
	Synchronous vs. metachronous oligometastases	4	0/4	
	Location of oligometastases	5	0/5	(visceral vs. non-visceral, ipsilateral vs. contralateral lung, ipsilateral vs. contralateral adrenal)
	Use of whole brain radiotherapy	3	0/3	

months) may be subject to bias and are insufficient to definitively prove the oligometastatic state.

Although some patients do enjoy extended survival, a high proportion of oligometastatic NSCLC patients fail locally or distantly soon after treatment, with a median time to any recurrence of approximately 12 months. Whether the minority of patients who remain disease-free beyond two years are truly oligometastatic patients whose disease has been completely eradicated, or instead, are patients with indolent disease who will recur at later date, is a question that remains unanswered. At present, there are no reliable prognostic models to permit this differentiation. This review identified several prognostic factors for survival that were consistently found to be significant on multivariate analyses in the literature, and these mostly reflect the status of intra-thoracic disease: definitive treatment/control of the primary tumor, intra-thoracic N-stage and a disease free interval of at least 6–12 months. We propose that these factors be used in future prognostic models to identify those oligometastatic patients who are most likely to be long-term survivors.

By examining survival results across studies, this review also suggests that the location of metastases may also be prognostic for survival. Survival outcomes in studies that included patients with a variety of metastatic sites were better than those of patients with exclusively brain metastases, and the presence of adrenal gland metastases tends to confer a poorer overall survival. These findings require prospective validation, as they may be prone to biases inherent in comparing results across different studies. The patient populations included in the eligible studies were heterogeneous, and variability in the definition and reporting of outcome measures limits comparisons of outcomes across studies. An individual-patient data meta-analysis would allow for more robust comparisons, may reduce bias, and allow for assessments of prognostic and predictive factors.

A critical question surrounding the concept of oligometastatic cancer is whether the prolonged survival observed in this select group is a result of a carefully selected patient population with indolent tumor biology, or whether it is a result of treatment intervention [22,23]. Much of the evidence to support pulmonary metastatectomy, for example, is based on retrospective single arm studies, without appropriate controls [24]. The only randomized controlled trials to support the ablative treatment of oligometastases exist within the brain metastasis literature, and are not specific to NSCLC. The Radiation Therapy and Oncology Group trial 9508 compared whole brain radiotherapy (WBRT) with WBRT + SRS for patients with 1–3 brain metastases, and found a OS advantage only in patients with a single metastasis [25]. The Patchell study, which randomized patients with a single brain metastasis to WBRT alone versus surgical resection + WBRT, found a survival benefit in those patients who received surgical resection [26]. Further prospective studies are needed to establish the benefit of ablative treatment strategies in other oligometastatic patient populations. Ultimately, randomized trials are needed to prove or disprove the

presence of the oligometastatic state in patients with NSCLC. Apart from patients presenting with brain metastases, such evidence is not yet available.

Two randomized phase II trials for patients with oligometastatic NSCLC were initiated in recent years. One sought to randomize patients with NSCLC and ≤5 metastases (with stable disease after two cycles of chemotherapy) to high-dose radiotherapy all sites of disease vs. 2 cycles of further chemotherapy (NCT00887315). The second sought to randomize patients presenting with NSCLC and ≤3 oligometastases (with stable disease after 2–6 cycles of chemotherapy) to high-dose radiotherapy to all sites of disease vs. observation (NCT00776100). Unfortunately, both trials closed due to slow accrual. The SABR-COMET randomized phase II trial (NCT01446744) is randomizing patients with controlled primary tumors of various histologies, with up to 5 metachronous oligometastases, to SABR to all sites of disease vs. palliative standard-of-care chemotherapy and/or radiotherapy [27] and is accruing in Canada and the Netherlands.

5. Conclusion

There is a paucity of randomized data to guide the management of patients with oligometastatic NSCLC. The preponderance of evidence suggests that the patient selection is a key determinant of long-term survival in patients with oligometastatic NSCLC. Although some highly selected patients do achieve long-term survival, most develop progression with the first-year post-treatment. Key determinants of long-term survival include definitive treatment of the primary tumor, a long disease-free interval between treatment of the primary tumor and development of metastases, and lack of intra-thoracic nodal metastasis. These factors should be utilized to guide clinical decision making and the design of future prospective randomized studies.

Conflict of Interest Statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2013.07.026.

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