Surgery in oligometastatic NSCLC patients in the targeted therapy era

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Practice points

- Oligometastatic status can be identified by full image evaluation (including whole-body PET or abdominal computed tomography combined with bone emission computed tomography are recommended) and mediastinoscopy to exclude metastases in other organs and N2 disease.
- For all curative-intent paradigms for stage IV disease, control of the primary tumor should be a prerequisite to proceeding with a local therapy to the oligometastatic organ.
- Metastasectomy can be done only when R0 resection is available, or else only a diagnostic biopsy is reasonable for oligometastatic patients.
- The careful and full evaluation by an experienced multiple disciplinary tumor board to guide diagnosis and treatment strategy will be an optimal way for possible oligometastatic patients.
- Wisely making full use of both local therapy and systematic therapy in selected stage IV NSCLC patients will definitely extend survival.
- Biomarkers that effectively distinguish truly limited metastases and indolent tumors are urgently needed.

More than 50% of NSCLC patients present with metastatic disease at first diagnosis, with a median survival of 8–11 months. However, selected patients with oligometastatic disease who receive appropriate local therapy for both the primary lesion and metastases enjoy long-term survival or are even cured. The new (eighth) edition of the tumor, node and metastasis classification of lung cancer suggests that patients with a single metastatic lesion in one distant organ should be placed into a new category, M1b, which will certainly lead to more applications of local therapy in such subpopulations. Moreover, as the applications of targeted therapy increase, surgery will play an evermore critical role in eliminating drug-resistant cancer clones of patients who exhibit mixed responses to tyrosine kinase inhibitors. The lung, brain and adrenal gland are the most common oligometastatic organs, and are reviewed separately.

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Of all patients diagnosed with NSCLC, more than 50% present with metastatic disease [1,2]. And in the synchronous setting, about 15% NSCLC patients suffer from oligometastases [3]. As advanced NSCLCs are incurable and there are a few available treatment strategies, the expected median survival of such patients is a dismal 8–11 months [4]. However, selected patients with oligometastatic disease who undergo appropriate local therapy of both the primary lesion and metastases

KEYWORDS

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have enjoyed long-term survival or have even been cured [5,6]. The Guideline from European Society of Medical Oncology in 2014 also states that radical local therapy including high-dose radiotherapy or surgery is promising for this subpopulation [3]. Moreover, as the use of targeted therapy increases, some retrospective studies have reported improvements in survival when local therapy and agents targeting driver gene mutations are combined in patients with limited metastasis [7,8]. On this basis, the eighth edition of the tumor, node and metastasis (TNM) classification of lung cancer suggests that patients with a single metastatic lesion in one distant organ should be placed into a new category, M1b, because such patients have better prognoses (the new M1b patients exhibit a median survival of 11.4 months) than those with multiple metastatic lesions in one or multiple organs (the new M1c patients, with a median survival of 6.3 months) [9]. It is expected that this innovative proposal will increase the use of local therapies to treat solitary metastases in stage IV patients. This review addresses some important surgical issues for the treatment of oligometastatic NSCLC in the era of targeted therapy.

Rationale of surgery to treat oligometastases & treatment strategies

Three successive hypotheses on the nature of oligometastases have been proposed (Figure 1): the early Halstead hypothesis, the systemic hypothesis and (currently) the spectrum hypothesis [10]. After Paget [11] first put forward the ‘seed-and-soil’ theory in 1889, metastases came to be viewed as a form of nonrandom behavior. Later, Halsted [12] proposed the evolutionary hypothesis of an ‘orderly disease’ (using breast cancer as a model) to describe the mode by which tumor cells spread directly from primary lesions to lymph nodes through the lymphatics and then to distant organs. 12 years later, the theory was improved by Ewing [13]. This classic theory afforded a rationale for the use of local therapies such as radical surgery and radiosurgery in cancer patients. Later, Keynes and Fisher [10,14–15] developed a hypothesis contrary to that of Halsted, holding that clinical cancer was systemic in nature and that small tumors were actually early manifestations of systemic disease. This suggested that only systemic therapy could be used to treat metastatic disease. The spectrum theory of cancer metastasis emerged in 1994; this proposed that the nature of a tumor at the time of first diagnosis fell into a

spectrum ranging from indolent to the presence of widespread metastases [16]. In other words, if a patient had an indolent tumor, a possible survival benefit might be afforded by combining local and systemic treatment to conquer metastatic disease. In the context of this theory, the term ‘oligometastasis’ was coined to indicate an intermediate metastatic state (metastases to one or a limited number of organs) [17]. More recently, the concept of indolent lung cancer has been proposed; the tumor grows and spreads slowly, accompanied by a few symptoms. Furthermore, Chen *et al.* [18] found that the primary lesions and metastases of both treatment-naïve patients and those treated with EGFR tyrosine kinase inhibitors (TKIs) exhibited heterogeneous EGFR mutations and mixed responses to TKIs. This suggested that it was rational to combine local treatment with systemic TKIs to eliminate cancer subclones resistant or insensitive to EGFR-TKIs. In parallel with application of the basic theories, resection of metastases yielded sufficient high-quality tissue for genetic analysis, which today plays an essential role in furthering our understanding of the drug-resistance mechanisms in play and the overall nature of the tumor.

Two types of oligometastases should be distinguished in the era of targeted therapies: oligometastases in treatment-naïve patients and oligorecurrences in patients nonresponsive to TKIs. No consensus on an optimal disease-free interval (DFI) distinguishing synchronous from metachronous disease has emerged but the DFI is associated with longer term survival [19]. The numbers of lesions have varied from one to five in retrospective studies. According to our clinical model of EGFR-TKI failure, oligorecurrence of TKI-resistant tumors reflects local progression if the following criteria are met: disease control for ≥ 3 months upon EGFR-TKI treatment; progression of a solitary or a few extracranial lesions (all lesions can be covered with a single radiation field) and a symptom score ≤ 1 [20]. For such patients, continuation of EGFR-TKIs plus local intervention raised the overall survival (OS) to 17.1 months [20]. Another two retrospective studies found an additional survival benefit in patients with *EGFR* mutations and *ALK* rearrangements who remained on TKI therapy after undergoing local therapy [7,8].

Local treatments for oligometastatic lesions mainly include surgery, modern external radiotherapy and interventional ablation therapy. No matter which method is used, minimal invasiveness

Figure 1. The three metastasis hypotheses and the appropriate treatment strategies. Hypotheses seeking to explain oligometastasis have evolved over time; three models have been developed: the Halstead hypothesis, the systemic hypothesis and most recently the spectrum hypothesis. (A) Paget first advanced the ‘seed-and-soil’ theory in 1889, and Halsted proposed the evolutionary concept of ‘orderly disease’ in 1894. In 1928, this theory was improved by Ewing, who believed that tumor cells were directed by blood and lymphatic flows into specific organs. This theory rationalized local therapy. (B) In 1956 and 1980 (respectively), Keynes and Fisher proposed that small tumors were early manifestations of systemic disease, supporting the notion that only systemic therapy was required. (C) In 1994, Hellman developed the spectrum theory. The nature of a tumor at the time of first diagnosis lies within a spectrum ranging from indolent to widespread metastasis; the term ‘oligometastasis’ was coined. In 2012, Chen *et al.* found that tumors within individuals exhibited heterogeneity in terms of *EGFR* mutations and tyrosine kinase inhibitor responses, indicating that local treatment and systemic therapy should be combined when treating such patients.

B: Blood; L: Lymphatic flow; M: Metastasis.

is key. With recent great improvements in optical, stapling and energy devices as well as in perioperative management, surgery has become safer and less invasive, and increasing numbers of patients with somewhat poor performance status have become surgical candidates [21]. Surgery should be performed on patients whose stable primary lesions and metastases are completely resectable. Before surgery, full-body imaging (whole-body PET or abdominal computed tomography combined with bone emission computed tomography are recommended) and mediastinoscopy must be performed to exclude metastases to other organs and N2 disease. Four key groups of prognostic factors affect surgical outcomes and the survival of oligometastatic patients. These are the number of sites of metastatic disease, the pathological stage of lymph node involvement, the status of the primary lung lesion and the DFI from metastatic lesions. Specific survival data on patients with oligorecurrences in different organs are discussed below.

Lung metastases

Both the seventh [22] and eighth [23] TNM staging systems assign NSCLC patients with

more than one nodule in the same lobe to stage T3, and those with nodule(s) in the ipsilateral nonprimary lobe to stage T4. If there is a nodule in the contralateral lobe, the disease stage is M1a. In fact, lung metastasis does not differ greatly from a synchronous second primary lung tumor. In the time since the first Martini standard was proposed in 1975 [24] that standard has been revolutionized by the application of many multiple clinicopathological techniques (including detection of driver gene mutations) to enhance the accuracy of the standard [25–27]. Given the complexity of the issue, both the eighth TNM stage international subcommittee and the American College of Chest Physicians recommended that, optimally, all available information should be reviewed by a multidisciplinary tumor board [28,29].

In this study, we used the terms ‘metachronous’, ‘synchronous’, ‘primary NSCLC’ and ‘surgery or surgical treatment’ to search PubMed for studies with more than 50 patients who underwent surgery to treat lung oligometastases (Table 1). No randomized trials were retrieved, and the survival outcomes of the retrospective studies varied. Although most patients

Table 1. Survival and prognostic factor of oligo-lung metastatic NSCLC patients treated by surgery in retrospective series.

Study (year)	Sample size (n)	Temporal association of nodule (patient, n)	Median OS (months)	5-year survival rate (%)	Positive prognosis factors of survival	Ref.
Stella <i>et al.</i> (2016)	56	Synchronous (20) Metachronous (36)	27.2 (synchronous) 66.5 (metachronous)	NR	NR	[39]
Tonnies <i>et al.</i> (2014)	57	Synchronous	56	48.5	Without thoracic lymph node involvement	[31]
Riquet <i>et al.</i> (2008)	234	Synchronous (118) Metachronous (116)	26 (synchronous) 39 (metachronous)	23.4 (synchronous) 31.6 (metachronous)	Tumors located in the same lobe	[40]
Rostad <i>et al.</i> (2008)	94	Synchronous	23	27.6	Female, younger age, nonpneumonectomy, nonadenocarcinoma	[41]
Chang <i>et al.</i> (2007)	92	Synchronous	NR	35.3	No lymph node metastasis	[32]
Battafarano <i>et al.</i> (2004)	69	Metachronous	NR	33.4	NR	[42]
Aziz <i>et al.</i> (2002)	51	Synchronous (10) Metachronous (41)	31 (synchronous) 49 (metachronous)	10 (synchronous) 44 (metachronous)	Longer DFI, different histology and lower stage of the second tumor	[30]
Rea <i>et al.</i> (2001)	80	Synchronous and metachronous	NR	20 (synchronous) 51 (metachronous)	NR	[43]
Van Rens <i>et al.</i> (2001)	127	Metachronous	NR	26	Stage IA of the second primary tumor	[33]
Okada <i>et al.</i> (1998)	57	Synchronous (28) Metachronous (29)	NR	70.3 (synchronous) 32.9 (metachronous)	Stage I and stage II of the second tumor	[34]
Adebonojo <i>et al.</i> (1997)	51	Synchronous and metachronous	NR	0 (synchronous) 37 (metachronous)	NR	[44]
Antakli <i>et al.</i> (1995)	54	Synchronous and metachronous	NR	12.25 (synchronous) 23.4 (metachronous)	NR	[45]
Faber (1993)	114	Metachronous	NR	33	NR	[46]
Rosengart <i>et al.</i> (1991)	111	Synchronous (33) Metachronous (78)	NR	44 (synchronous) 23 (metachronous)	Complete resection	[35]
Deschamps <i>et al.</i> (1990)	80	Synchronous (36) Metachronous (44)	NR	15.7 (synchronous) 33.8 (metachronous)	NR	[47]

DFI: Disease-free interval; NR: Not reported; OS: Overall survival.

enrolled in the retrospective works had solitary lung metastases or second primary lung tumors (defined in various ways), we focused only on whether tumors were treated with curative intent and whether any survival benefits were evident. Thus, we simply divided patients in terms of the temporal associations (synchronous or metachronous) between nodules (nodules: refer to both secondary tumors and metastatic nodes) and primary cancers. A pooled analysis showed that the median OS and 5-year survival rate ranges were 23–56 months and 10–70.3% for metachronous patients, and the corresponding data for synchronous patients were 39–66.5 months and 23.4–51%. Although most studies investigated many nodules histologically, the consistency of such data across nodules was not significantly associated with survival, except in one controversial study that reported an actuarial 5-year survival of 51% (median OS: 61 months) in metachronous patients with various histologies compared with a 5-year survival of 31% (median OS: 34 months) in patients with similar histologies ($p = 0.03$) [30]. In the synchronous setting, the patients who did not have tumor invasion in mediastinal lymph node may survive longer [31,32]. In the metachronous setting, a lower recurrent tumor stage seems to predict survival well [33]. Of studies that enrolled patients with both synchronous and metachronous lung lesions, two early works [34,35] yielded opposite results; synchronous patients enjoyed better survival. The inconsistencies may be attributable to bias in patient selection and a higher incomplete resection rate in metachronous patients with poor functional lung reserves. As surgical techniques have improved in recent years, survival times and cure rates have increased in such subpopulations. Moreover, if a patient is medically inoperable, stereotactic ablative radiotherapy is emerging as a valuable and less invasive local treatment option for pulmonary oligometastases; the 2-year survival rate is 49–65% [36–38].

Generally speaking, the stages and locations of tumors, and the cardiopulmonary functional reserve, determine the order and method of operation. In a synchronous setting, tumors of later stages and with more solid tissue component must always be handled first. If patients have poor lung function after the first operation, radiotherapy of the contralateral lobe is acceptable. If the oligometastases are metachronous, the second surgical approach varies by patient status. Minimally invasive video-assisted thoracoscopic surgery has

been widely used, particularly to treat peripheral nodules; a single 3- to 4-cm incision permits single-port lobectomy. Video-assisted thoracoscopic surgery affords oncologic outcomes comparable to those of thoracotomy but with fewer complications, a shorter hospital stay, a better quality of life and superior tolerance of adjuvant therapies [48].

Brain metastasis

Brain metastases have always been considered fatal during the course of NSCLC; the median survival time in the natural course of events (without intervention) is only 2 months [49], and is no more than 6 months after whole-brain radiotherapy (WBRT) [50]. However, in 10% of stage IV patients, the brain is the only site of metastatic disease [29], and local therapy has afforded encouraging survival benefits. We searched PubMed using the terms ‘oligometastase(i)s or mono-metastase(i)s or solitary metastase(i)s,’ ‘NSCLC,’ and ‘surgery or metastasectomy’. Prospective and retrospective studies that enrolled more than 50 locally treated oligo-brain-metastatic patients were retrieved; the survival data are shown in Table 2.

In the 1990s, two benchmark randomized trials revealed the survival benefit afforded by combined surgery and radiotherapy in patients with solitary brain metastases. The combination groups had OSs of 8.5 and 10 months compared with 3 months in those who received radiotherapy alone [55–56]. Another randomized trial showed that radiotherapy alone afforded inconsistent survival outcomes [54], and was associated with patient bias (in terms of those [73%] with either extracranial metastases or uncontrollable primary disease). Thus, differences in the primary tumor distributions among the two trial groups may contribute to the observed discrepancy [66]. Aoyama *et al.* conducted a randomized controlled trial in 132 patients (including 88 with primary lung cancer) with one to four brain metastases to evaluate the effects on survival of WBRT-plus-stereotactic radiosurgery (SRS) versus SRS alone. The addition of WBRT reduced the brain tumor recurrence rate (46.8% in the combination group and 76.4% in the SRS-alone group; $p < 0.001$) but did not afford any survival benefit [53]. In patients with asymptomatic cerebral oligometastases, no superior OS was found after SRS followed by chemotherapy (14.6 months in the SRS group and 15.3 months in the chemotherapy alone group) [51]. Furthermore, an important randomized trial from the European Organisation

Table 2. Prospective studies on local therapy treating oligo-brain-metastatic patients and the representative retrospective data for NSCLC in this setting.

Study (year)	Prospective or retrospective	Sample size (local treated cases; n)	Definition of oligometastases	Therapy	Median OS (months)	5-year survival rate (%)	Positive prognosis factors of survival	Ref.
Lim <i>et al.</i> (2015)	Prospective randomized Phase III trial	105 (98)	One to four brain metastases	SRS + chemotherapy versus upfront chemotherapy	14.6 (SRS group) 15.3 (upfront chemotherapy group)	NR	Nonadenocarcinoma, lower extracranial metastases (<2), lower number of brain metastases (<2) and <i>EGFR</i> mutation	[51]
Kocher <i>et al.</i> (2011)	Prospective randomized Phase III trial	359 (359) [†]	One to three brain metastases	WBRT versus observation for surgery or SRS treated patients	10.9 (WBRT group) 10.7 (observation group)	NR	NR	[52]
Aoyama <i>et al.</i> (2006)	Randomized controlled trial	132 (132) [‡]	One to four brain metastases, each less than 3 cm in diameter	WBRT + SRS versus SRS alone	7.5 (combination group) 8 (SRS alone)	NR	Stable primary tumor status and extracranial metastases, age <65 years, KPS score of 90–100	[53]
Mintz <i>et al.</i> (1996)	Randomized controlled trial	84 (84) [§]	Single brain metastasis	Surgery + radiotherapy versus radiotherapy alone	5.62 (combination group) 6.28 (radiotherapy alone)	NR	No evidence of primary tumor	[54]
Vecht <i>et al.</i> (1993)	Randomized controlled trial	33 (33)	Single brain metastasis	Surgery + radiotherapy versus radiotherapy alone	8.5 (combination group) 3 (radiotherapy alone)	NR	Age <60 years	[55]
Patchell <i>et al.</i> (1990)	Randomized controlled trial	37 (37)	Single brain metastasis	Surgery + radiotherapy versus radiotherapy alone	10 (combination group) 3.75 (radiotherapy alone)	NR	Surgery to brain metastases, longer DFI between primary and metastases	[56]
Collen <i>et al.</i> (2014)	Prospective Phase II single-arm trial	26 (26)	≤5 synchronous and metachronous metastatic lesions	SBRT	23	NR	Synchronous metastases and induction chemotherapy	[57]
De Ruysscher <i>et al.</i> (2012)	Prospective Phase II single-arm trial	17 (17)	Synchronous metastases lesions less than five	SRS, surgery	13.6 [†]	17.5 [#]	NR	[58]

[†]This study enrolled 190 NSCLC patients.

[‡]This study also including other primary tumors.

[§]This study only included 45 NSCLC patients.

^{††}These data including other oligometastatic organs, there were no specified data of brain alone to be reported.

^{‡‡}This is the 3-year survival rate.

DFI: Disease-free interval; KPS: Karnofsky performance status; NR: Not reported; OS: Overall survival; PS: Performance status; SRS: Stereotactic radiosurgery; SBRT: Stereotactic body radiation therapy; WBRT: Whole-brain radiotherapy.

Study (year)	Prospective or retrospective	Sample size (local treated cases; n)	Definition of oligometastases	Therapy	Median OS (months)	5-year survival rate (%)	Positive prognosis factors of survival	Ref.
Bougie <i>et al.</i> (2015)	Retrospective	115 (115)	Metachronous and synchronous single brain metastases	Surgery, SRS	13.3 (surgery group) 7.8 (SRS group)	NR	Aggressive treatment of the primary NSCLC metachronous metastasis	[59]
Parlak <i>et al.</i> (2014)	Retrospective	63 (63)	Synchronous solitary brain metastasis	Surgery + WBRT, SRS + WBRT	27.8 (surgery group) 28.6 (SRS group)	NR	T1–T2 stage, N0–N1 stage, no weight loss	[60]
Xu <i>et al.</i> (2013)	Retrospective	98 (98)	Synchronous solitary metastases	Surgery, SRS, WBRT	15.4 (surgery or SRS) 11.5 (WBRT alone)	6.7 (surgery or SRS) 0 (WBRT alone)	Gender, the stage of the primary tumor, PS and removed primary tumor	[61]
Hu <i>et al.</i> (2006)	Retrospective	84(84)	Synchronous solitary brain metastases	Surgery or SRS	7.4 (SRS group) 12 (surgery group)	7.6	Thoracic stage I	[62]
Flannery (2003)	Retrospective	72 (72)	Synchronous and metachronous solitary brain metastasis	Gamma knife SRS ± WBRT	33.3 (metachronous) 8.6 (synchronous)	13.2 (metachronous) 8.1 (synchronous)	Metachronous disease	[63]
Salvati <i>et al.</i> (1996)	Retrospective	91 (91)	Synchronous and metachronous solitary brain metastases	Surgery	16	NR	Staging of the primary tumor	[64]
Burt <i>et al.</i> (1992)	Retrospective	185 (185)	Synchronous and metachronous solitary brain metastases	Surgery	14	13	Complete resection of the primary disease	[65]

[†]This study enrolled 190 NSCLC patients.

[‡]This study also included other primary tumors.

[§]This study only included 45 NSCLC patients.

[¶]These data including other oligometastatic organs, there were no specified data of brain alone to be reported.

[‡]This is the 3-year survival rate.

DFI: Disease-free interval; KPS: Karnofsky performance status; NR: Not reported; OS: Overall survival; PS: Performance status; SRS: Stereotactic radiosurgery; SBRT: Stereotactic body radiation therapy; WBRT: Whole-brain radiotherapy.

for Research and Treatment of Cancer showed that adjuvant WBRT after the SRS or surgery decrease the intracranial recurrence but have no improvement in OS [52]. However, as this trial was not only for NSCLC patients, and the condition of primary lesion is various, the benefit of surgery combined with WBRT in this subpopulation should be tested further. Another single-arm prospective trial of radical therapy for synchronous oligometastases achieved a median OS of 13.5 months and the 3-year survival rate of 17.5%, but the small sample size rendered it difficult to derive conclusive findings [58]. Almost all retrospective studies have used multiple treatment paradigms. Surgery or SRS alone afforded median OSs of 12–27.8 and 7.4–28.6 months, respectively (Table 2). Factors positively prognostic of survival in retrospective series have varied but have commonly included complete resection, a longer DFI, favorable performance status, lower N status and a lower thoracic stage (Table 2).

In general, brain metastases were evident on diagnosis in 23–31.4 and 24% of *EGFR*-mutated and *ALK*-rearranged patients, respectively, and increased over time after diagnosis [67–69]. Metastases that developed in patients with *EGFR*-mutated NSCLC were smaller, and tended to be multiple in nature and to exhibit leptomeningeal dissemination compared with patients with the wild-type gene [68]. Even given the high rate of brain metastasis and the invasive nature of the cancer, the OS of such subpopulations was longer than that of wild-type patients [68]. Specific surgical data are limited. One retrospective study enrolled ten patients with brain metastases (six with fewer than four lesions) exhibiting *EGFR* mutations or *ALK* rearrangements; an additional 7.1 months of progression-free survival (PFS) was afforded by SRS after progression during the use of related TKIs [8]. The median OS in a Phase II trial featuring prescription of TKIs combined with WBRT in patients with *EGFR* mutations was 19.1 months [70]; combined SRS and TKI treatment was not superior than SRS monotherapy in brain metastasis patients carrying *EGFR* mutations [71]. Such retrospective findings need to be confirmed in prospective trials with larger sample sizes.

Adrenal metastases

The adrenal gland commonly hosts NSCLC metastases; the incidence of solitary metastases of tumors of this gland ranges from 1.62 to 3.5% [72]. Adrenal metastases can be synchronous or metachronous; bilateral masses develop

in 10% of all lung cancer patients and are usually asymptomatic [73].

We used the terms ‘oligometastase(i)s or monometastase(i)s or solitary metastase(i)s’, ‘NSCLC’ and ‘surgery or adrenalectomy’ to search PubMed and references in retrieved articles (Table 3). Data from studies with more than 20 patients who underwent surgery to treat adrenal oligometastases and that reported survival data are shown in Table 3. No prospective clinical trials were retrieved. In pooled analyses, the median OS and 5-year survival rates of all patients with solitary adrenal metastases treated via adrenalectomy were 11–19 months (23.3–34% of patients; Table 3). Only one study contained detailed survival data on synchronous and metachronous patients; the 5-year survival rates were 41 and 27% respectively; the difference was not significant. In addition, 83% of patients with ipsilateral tumors were alive at 5 years, compared with no patients with a contralateral tumor ($p = 0.002$) [74]. The small sample sizes and the retrospective nature of these studies render it impossible to identify patients who might be assisted, but certain factors including absence of mediastinal nodal invasion, an ipsilateral tumor, a longer DFI and a stable or absent primary tumor may predict better survival after adrenalectomy. Other local therapies such as SBRT have been used to treat patients with adrenal metastases. In one retrospective study, 18 patients with NSCLC and adrenal metastases underwent SBRT and enjoyed survival benefits, particularly those with solitary adrenal metastases (PFS: 12 months; OS: 23 months) [75]. Although the limited data render it difficult to draw conclusions, a role for SBRT in such settings should be further explored.

Other extrathoracic metastasis

Surgical data for other extrathoracic NSCLC oligometastases are minimal; such conditions are rare. The skeletal system as another common site of metastases had always been thought of as a poor predictor for survival. However, some retrospective analysis showed that NSCLC patients with single bone metastases demonstrate a better prognoses than those with multiple ones [80,81]. Moreover, in the synchronous setting, radical resections of both bone and lung tumor afford a long-term survival for patients with solitary bone metastases [82,83]. Although these results come from limited case reports, it could suggest an appealing role of surgery for selected solitary bone metastatic NSCLC patients.

Table 3. Survival and prognostic factor of oligo-adrenal metastatic NSCLC patients treated by surgery in retrospective series.

Study (year)	Sample size (local treated cases, n)	Definition of oligometastases	Median OS (months)	5-year survival rate (%)	Positive prognostic factors of survival	Ref.
Howell <i>et al.</i> (2013)	29 (29)	Synchronous and metachronous isolated adrenal metastasis [†]	17	27	Metachronous disease, DFI >12 months	[76]
Raz <i>et al.</i> (2011)	37 (20)	Synchronous and metachronous isolated adrenal metastases	19	34 (83 for ipsilateral metastases and 0 for contralateral metastases) 41 (synchronous) 27 (metachronous)	No mediastinal nodal disease, ipsilateral metastases	[74]
Strong <i>et al.</i> (2007)	39 (39)	Synchronous and metachronous isolated adrenal metastasis	17	29	Lack of local recurrence and size of lesion being less than 4.5 cm	[77]
Mercier <i>et al.</i> (2005)	23 (23)	Synchronous and metachronous isolated adrenal metastasis	13.3	23.3	DFI >6 months	[78]
Porte <i>et al.</i> (2001)	43 (43)	Synchronous and metachronous homolateral, contralateral to the primary, bilateral	11	NR	NR	[79]

[†]This study also included 8 (14%) oligometastatic patients in whole analysis group.

DFI: Disease-free interval; m: Month; NR: Not reported; OS: Overall survival.

Data of surgery to other extrathoracic metastases such as extrathoracic lymph nodes, soft tissue or other viscera are limited in case reports. For example, an early retrospective study in 1995 enrolled 14 extrathoracic patients (metastatic organs including extrathoracic lymph nodes, skeletal muscle bone and small bowel) whose 10-year actuarial survival rate achieved 86% [84]. A systematic review of oligometastatic lung cancer progression to the pancreas showed that pancreatic resection with curative intent appeared to be associated with an increased (but not statistically significant) OS benefit compared with nonresection (29 vs 8 months) [85]. On the other hand, we have found that uncommon solitary metastases are a poor prognostic factor for survival, but the median OS of uncommon metastasis patients who receive systemic therapy combined with local treatment is longer than that of uncommon metastasis patients who receive systemic therapy alone or who receive best-supportive therapy (median OS: 12.5 vs 7.4 vs 3.4 months; $p < 0.01$) [86].

Conclusion & future perspective

Bias is unavoidable in retrospective studies, but the relatively low incidence of clinically encountered oligometastases renders it very difficult to conduct a large-scale randomized clinical trial. As reported recently at the 2016 American

Society of Clinical Oncology annual meeting, a multicenter Phase II randomized trial showed that nonprogressive oligometastatic patients enjoyed encouraging PFS benefits when given local therapy after earlier standard chemotherapy or relatively targeted therapy (the PFS of patients given local therapy was 11.9 months vs 3.9 months for those who did not undergo local therapy) [87]. However, the sample size was small and the study lacked the power to explore the true OS benefit; dilution attributable to crossover between the arms was in play.

According to recognized theoretical hypotheses, oligometastasis patients may be considered intermediate in terms of cancer status, and may benefit from radical therapy. Additionally, we should note that although an oligometastatic patient may have a better OS than a patient with diffuse disease to several compartments, if we do not give wise and timely local therapy to these oligometastatic patients, this kind of better prognoses may not convert into real survival benefits. However, given the interindividual complexities that are in play, careful evaluation using the multiple disciplinary tumor is required to guide the diagnosis and treatment of possibly oligometastatic patients optimally. Moreover, appropriate definitions of slow or indolent progression of oligometastasis or oligorecurrence are urgently required. Although indolent

NSCLC is characterized by a volume-doubling time of more than 600 days [88], more genetic biomarkers of truly indolent tumors are needed. The expression levels of certain miRNAs may be associated with various oligometastasis phenotypes [89–91]; further studies are required. In addition, advances in imaging techniques are needed to allow timely identification of early metastatic lesions.

As the numbers of targeting agents validated in clinical trials increase, surgery and other local treatments combined with prescription of low-toxicity and high-efficiency targeted drugs will extend survival. However, the optimal local treatments remain unknown; randomized clinical trials are required. New radiotherapy techniques (such as SBRT) minimize morbidity and may lessen the need for surgery in oligometastatic patients who historically would have required surgery. In patients with changes in the *EGFR* and *ALK* genes, new-generation TKIs such as alectinib [92] and AZD3759 [93] that effectively target the CNS may control brain metastases. A combination of surgery and the use of such CNS-specific agents will certainly prolong PFS in patients with brain metastases. However, the economic costs of therapies must be considered. When the cost–effectiveness of surgery, SBRT and systemic therapy for NSCLC

patients with pulmonary oligometastases were recently compared, Markov modeling showed that the optimal strategies were SBRT for adenocarcinoma patients without *EGFR* mutations, paclitaxel/carboplatin for patients with squamous cell carcinoma and erlotinib for patients with *EGFR* mutation-positive adenocarcinoma [94]. The new agents and techniques are expensive; it is necessary to balance efficacy with cost, and to deliver only truly optimal therapies prudently.

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