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CURRENT TOPICS REVIEW ARTICLE

Approach for oligometastasis in non-small cell lung cancer

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Abstract Non-small cell lung cancer (NSCLC) harboring a limited number of distant metastases, referred to as the oligometastatic state, has been indicated for surgery for the past several decades. However, whether the strategy of surgical treatment results in a survival benefit for such patients remains controversial. Experientially, however, thoracic surgeons often encounter long-term survivors among surgically resected oligometastatic NSCLC patients. In this article, the current situation of surgical approach and potential future perspective for oligometastatic NSCLC are reviewed.

Keywords Oligometastasis · Oligo-recurrence · Non-small cell lung cancer · Radiotherapy · Surgery · Molecular-targeted therapy

Oligometastatic state

Cancer patients with distant metastasis are deemed to be incurable and generally not indicated for radical local treatments with a curable intent, and required palliative treatments such as chemotherapy, palliative radiation and supportive care to maintain their quality of life (QOL). Stage IV NSCLC remains poorly controlled, with a median survival of up to 12 months [1, 2]. However, selected patients with limited metastasis in the lung, brain, or unilateral adrenal gland have been treated by local treatments such as surgery or radiotherapy, including heavy ion therapy or proton therapy, for many decades [3, 4, 5]. Long-term survivors of lung metastasectomy for colon cancer or malignant bone and soft tissue tumor have been reported [6]. In 1995, Hellman and Weichselbaum proposed the term "oligometastasis", which is a state between local and systematic disease, and advocated potential curative intent with local treatments [7]. Niibe et al. added the concept of oligo-recurrence, which is defined as 1–5 distant metachronous metastases that can be treated by local treatment, with controlled primary cancer [8]. Several lines of evidence from basic cancer biology support these concepts. Wan et al. [9] demonstrated that pulmonary metastases lie behind a "niche" that is formed by interaction with the matrix and by the mesenchymal-to-epithelial transition. Lussier et al. reported that oligometastatic cancers have a distinct microRNA expression profile from that of polymetastatic cancers [10]. The recent advancement of staging modalities, such as magnetic resonance imaging (MRI) for brain metastasis, positron emission tomography using fluorodeoxy-3 glucose (FDG-PET) for nodal and distant metastases, and the transbronchial needle aspiration technique under endobronchial ultrasound (EBUS-TBNA) for mediastinal nodal metastasis [11] have enhanced the radical strategy for oligometastatic NSCLC since the guidelines recommend strict exclusion of the N2 status and multiple distant metastases in other organs [12].

Local treatments for oligometastatic NSCLC

In NSCLC, both synchronous and metachronous oligometastases in the lung, brain or adrenal glands have occasionally been resected in clinical practice if other distant

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metastases are ruled out and the primary site is resectable or controllable. However, most reports concerning oligometastasectomy are retrospective studies, some of which have showed that NSCLC with oligometastasis can benefit from aggressive local therapy due to less biologically aggressive cancers [13, 14]. Following the recommendation by Hellman and Weichselbaum [7], a phase II study of surgical interventions for oligometastatic NSCLC was conducted by Ginsberg and Rusch [15]. The authors enrolled 23 patients with synchronous solitary organ metastasis who underwent surgery for both primary and metastatic lesions; however, the complete resection rate was 43 % and the median survival time was only 11 months. The 23 patients included 14 brain metastasis and 13 mediastinal metastasis. De Ruysscher et al. reported their result of non-surgical treatments (chemotherapy or chemoradiotherapy) for cases with less than five oligometastases [16]. Among the enrolled 39 patients, 74 % had local stage III, 44 % had brain metastasis, 10 % had adrenal gland metastasis, 87 % had a single metastatic lesion, and 95 % received chemotherapy. The overall median survival time was 13.5 months. These two prospective studies suggest that chemotherapy is the main therapy for stage IV NSCLC even when the metastatic lesions are limited. Among stage IV NSCLC, it is known that the number of metastatic lesions is associated with the survival, even if the same treatment modalities are given [17, 18]. Niibe et al. proposed the Niibe–Onishi–Chang classification for metastases and recurrence according to their review of the literature [19]. They also reviewed previous studies of oligometastatic NSCLC and advocated that local treatment approaches such as surgery or ablative radiation are only indicated for isolated brain or adrenal gland metastasis in terms of the survival results, and the most favorable lesion is 1–2 metachronous (recurrent) metastases [19]. Punglia et al. demonstrated the hypothetical benefit of local therapy on the survival with increasing effectiveness of systemic therapy [20]. Recently, Endo et al. reported a prospective phase II study of surgery for primary lesions (cT1-2N0-1) and surgery or radiotherapy for synchronous or metachronous single organ metastases (e.g., brain, lung or others) [21]. Thirty-six patients were enrolled, and 59 % underwent complete resection for both primary and metastatic lesions. The 5-year survival rate was favorable (approximately 40 %), however, 18 % of the lesions was revealed to be benign lesions in surgical pathology, and second primary lung cancer was contaminated by pulmonary metastasis.

Isolated brain metastasis of NSCLC

Even with lower-level evidence, the guideline from the American College of Chest Physicians (ACCP) recommends surgery for the primary lesions and surgery or radiation for isolated brain metastasis in both synchronous and metachronous situations (recommendation level 1C) [12] if N2 is excluded by FDG-PET or EBUS-TBNA. The National Comprehensive Cancer Network (NCCN) guideline recommended with a uniform consensus (recommendation level 1 or 2a) local treatments, such as surgery followed by whole brain radiation or stereotactic radiotherapy. If the thoracic lesion is T1-2N0-1 or T3N0, then lung resection, stereotactic ablative radiotherapy or chemotherapy is recommended (recommendation level 2a). According to previous retrospective studies regarding isolated brain metastasis, the 2- and 5-year survival rates were approximately 30 and 10–20 %, respectively, when the primary tumors were resected and synchronous metastasis was treated with surgery or stereotactic radiation (Table 1) [4, 22, 23]. From our institution, 24 patients with oligometastatic metachronous brain metastasis were examined and the disease-free interval between pulmonary resection and

Table 1 Outcome of stage IV NSCLC patients who underwent resection of solitary brain metastases

First author	Year	No. of patients	5-year survival (%)	Mean survival (months)	Prognostic factor
Saitoh [24]	1999	24	8.3	6.8	Disease free interval, Surgical methods
Bornnette [34]	2001	103	12	11	Histology
Billing [4]	2001	28	21	24	*N* status
Abrahams [35]	2001	36	0	9.9	Performance status
Granone [36]	2001	20	14	23	Histology, *N* status
Iwasaki [25]	2004	28	3 years: 22.9	Not stated	Histology, *N* status, CEA
Furak [27]	2005	65	19.3	19	–
Girard [37]	2006	29	18	13.2	Response to pre-operative chemotherapy
Hu [26]	2006	53	7.6	12	Stage without brain metastases
Flannery [22]	2008	42	21	18	Performance status
Louie [38]	2009	35	2 years: 22	7.8	Stage without brain metastases
Mordant [23]	2012	57	13	14	Age, histology, tumor size, *N* status

the diagnosis of brain metastasis significantly impacted the long-term survival [24]. In several retrospective studies, not only the disease-free interval, but also histology, performance status, *N* status, and stage without brain metastasis were reported to be predictive factors [4, 25, 22, 26]. Even in cases of metachronous oligometastasis, the clinical outcome of local treatment was similar to that of the synchronous condition, with 2- and 5-year survival rates of approximately 30 and 10–20 %, respectively [27, 28].

Isolated adrenal gland metastasis of NSCLC

Regarding isolated metastasis to the unilateral adrenal gland, the 5-year survival rate was approximately 30 % when both primary tumors and synchronous metastasis were resected. Similar to isolated brain metastasis, N0 or N0-1 cases showed a better prognosis than N2, and such unilateral isolated adrenal gland metastasis cases are recommended for surgery for the primary and metastatic lesions according to the ACCP guidelines (recommendation level 1C) and NCCN guidelines (recommendation level 2a). Previous studies have reported more than 20 patients with isolated synchronous adrenal metastasis of NSCLC, which showed 5-year survival rates of 7 % [29], 26 %, [30] and 34 % (Table 2) [3]. Raz et al. reported that there were no long-term survivors among their non-adrenalectomy cases [3]. They also demonstrated that contralateral metastasis and upper lobe primary cancer cases showed a significantly unfavorable prognosis compared with their counterparts and they discussed their speculations of local extension to the adrenal gland.

Isolated metastasis except for brain or adrenal metastasis of NSCLC

Salah et al. reviewed the results of local therapy for extracranial and extra-adrenal NSCLC solitary metastases, which demonstrated a 5-year survival rate of approximately 50 % and indicated that N2 was a worse prognostic factor [31]. Their findings might indicate a potential oligometastatic state except for brain or adrenal metastasis of NSCLC patients. One limitation associated with previous retrospective studies for oligometastasis of NSCLC is the difficulty in evaluating and summarizing useful evidence on the effectiveness of radical local treatment due to selection bias.

Potential future perspectives

More recently, the 8th staging system of lung cancer has been proposed by the International Association for the Study of Lung, in which the metastasis factor is categorized as follows: M0 (no distant metastasis or disseminated metastasis), M1a (disseminated metastasis), M1b (single metastasis in a single organs) and M1c (multiple metastasis in a single or multiple organs) [32]. The prognosis for M1a and M1b are similar and better than that of M1c. T1-2 N0-1M1b in the new staging system would be indicated for local therapies (Table 3). Additionally, adjuvant or neoadjuvant chemotherapies are reasonable options, although there is currently no

Table 2 Outcome of stage IV NSCLC patients who underwent resection of solitary adrenal metastases

First author	Year	No. of patients	5-year survival (%)	Mean survival (months)	Prognostic factor
Porte [29]	2001	43 (32 synchronous, 11 metachronous)	7	11	None
Tanvetyanon [30]	2008	114 (48 synchronous, 66 metachronous)	26 (synchronous), 25 (metachronous)	12 (synchronous), 31 (metachronous)	None
Raz [3]	2011	20	34		Ipsilateral metastasis, *N* status

Table 3 Treatment strategy for oligometastatic NSCLC

Metastasis	Thoracic condition	Treatment for metastasis	Treatment for primary tumors
Single/isolated brain M1b	T1-2, N0-1 T3, N0	Surgery/stereotactic ablative radiotherapy followed by whole brain radiation	Thoracic surgery followed by chemotherapy or chemotherapy only or chemotherapy followed by thoracic surgery
Single/isolated adrenal gland M1b	T1-2, N0-1 T3, N0	Surgery	Thoracic surgery followed by chemotherapy or chemotherapy only or chemotherapy followed by thoracic surgery

supporting evidence. In patients given molecular-targeted agents, such as epidermal growth factor-thymidine kinase inhibitors or anaplastic lymphoma kinase inhibitors, local therapy for oligometastasis may yield a greater survival benefit. In 2007, Punglia et al. demonstrated the significance of local treatment for breast cancer by reanalyzing a previously reported meta-analysis [20]. Clinical trials which included locally intensive treatments showed a lower risk of local recurrence and a favorable 15-year survival than those which did not include locally intensive treatments. The authors suggest that the significance of local management of primary tumors is affected by the effectiveness of systematic treatments, such as molecular-targeted agents, i.e., the role of local therapies is insignificant if the systematic therapies are very weak or very strong, whereas it is very significant if the systematic therapies are moderately strong. In renal cell cancer, Flanigan et al. performed a combined analysis of two randomized trials to investigate the efficiency of nephrectomy for stage IV disease and demonstrated that the nephrectomy group showed a significantly superior survival to the interferon alone group [33]. Several molecular-targeted agents are currently available in daily practice, and the NCCN guidelines recommended nephrectomy and optional metastasectomy for stage IV renal cell cancer patients. The molecular-targeted strategy for NSCLC patients has been rapidly developed and diagnostic modalities that are now able to exclude metastasis have also been established. Therefore, the role of surgery for highly selected stage IV NSCLC patients is anticipated to increase in this modern medical environment, although clinical trials are required to confirm the survival benefits and accurately select appropriate patients.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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