REVIEW ARTICLE

Brain metastasis from non-small cell lung cancer: management and prognosis of primary lung tumor resection

Article history:
Received: 06-07-2023
Revised: 07-11-2023
Accepted: 02-12-2023

Donghang Li[a], Hongfeng Tong[b], Yaoguang Sun[b], Qingjun Wu[b], Chao Ma[b], Wenxin Tian[b], Chuan Huang[b], Hanbo Yu[b], Yi Tian[b], Peng Jiao[c]

Abstract: Brain metastases (BM) will develop in 30-50% of non-small cell lung cancer (NSCLC) patients in the course of their illness. Systemic treatment is recommended for most advanced-stage NSCLC patients with BM but the prognosis remains poor. The prognosis and management of primary lung tumor resec-tion are still a debated topic in this complex clinical setting. The present study will gather and review related research evidence. The survival benefit, patient selection and proper surgical strategy of prima-ry lung tumor resection will be summarized and discussed in the treatment for NSCLC patients with BM..

Keywords: brain metastases; non-small cell lung cancer; thoracic surgery.

INTRODUCTION

Most of the brain neoplasm could be attributed to brain metastases (BM), and the most common origin is lung cancer (40%-50%).[1,2] Patients diagnosed with advanced-stage non-small cell lung cancer (NSCLC) with brain metastases represent approximately 10% of newly diagnosed NSCLC cases.[2,3] Synchronous or metachronous BM can develop in 30-50% of NSCLC patients.[4] NSCLC with BM is often considered incurable due to poor prognosis, usually with a 2-year estimated survival rate between 10% and 23%, and 5-year survival varies between 0% and 10%.[5] Emerging treatment strategies such as immunotherapy and targeted therapy may improve the prognosis of a selected group of patients, yet surgery might still have a place in multimodal therapy.

Some studies reported favoring outcomes when local aggressive therapy including surgery to both metastases and primary lung tumors was given to oligometastatic NSCLC patients.[6-13] This resulted in a paradigm shift where metastatic NSCLC would no longer be incurable, and long-term cancer control may be achieved by supplementing surgery and systemic treatment. However, the ability to reach a consensus is limited by the heterogeneous study design and a small number of patients included. To NSCLC patients with BM, it remains unclear about the survival benefit of primary lung tumor resection, who can benefit from such surgery, and what surgery approach should be performed. In this review article, we sought to gather and review recent study evidence and discuss these questions.

[a] Department of Thoracic Surgery, Beijing Hospital, National Center of Gerontology; Institute of Geriat-ric Medicine, Chinese Academy of Medical Sciences, Beijing, People's Republic of China. Corresponding Author: jp_bird@126.com

[b] Department of Thoracic Surgery, Beijing Hospital, National Center of Gerontology; Institute of Geriat-ric Medicine, Chinese Academy of Medical Sciences, Beijing, People's Republic of China.

[c] Department of Thoracic Surgery, Beijing Hospital, National Center of Gerontology; Institute of Geriat-ric Medicine, Chinese Academy of Medical Sciences, Beijing, People's Republic of China.

SURVIVAL AFTER PRIMARY LUNG TUMOR RESECTION

Studying a large database allows analysis with more patients participating, and the outcome of different treatment strategies could be investigated on a larger scale. Kumar[14] assessed the data of 1240 NSCLC patients with synchronous BM from the National Cancer Database (NCDB). 270 patients who received definitive thoracic surgery had better 2-year survival rate than those who did not receive thoracic surgery (50.6%, 95%CI 44.3-56.6 vs 33.8%, 95%CI 30.7-37.0). For the treatment of brain metastases, whole-brain radiotherapy was excluded in this group of patients. Although the number of brain metastatic lesions was not provided, it is supposed that patient with limited tumor burden involving the brain was included, which might contribute to better treatment survival.

Several studies investigated data from the Surveillance, Epidemiology, and End-Results (SEER) database. In a retrospective study, the data of 203 NSCLC patients with BM who received primary pneumonectomy plus mediastinal lymphadenectomy and a 1:2 matching control group were extracted from the SEER database.[15] Propensity scoring match (PSM) was applied to minimize selection bias. It is suggested that patients who get thoracic surgery had a better median survival time than those without thoracic surgery in the control group (27 months, 95%CI 19.3-34.7 vs 6 months 95%CI 4.4-7.6). The surgery approach included in this study was pneumonectomy alone. The extensive surgical resection might have a large impact on the patient's quality of life postoperatively, and even affect survival negatively. In another study, Jia[16] evaluated the survival data of 1857 NSCLC stage IV patients who received thoracic surgery plus chemotherapy from SEER database. PSM was applied and a 1:1 matching control group with patients who received chemotherapy alone was acquired. Improved overall survival (OS) was observed in patients treated with thoracic surgery plus chemotherapy comparing the control group (19 months vs 11 months, HR 0.503, 95% CI, 0.476-0.531). Similar improvement of OS and cancer-specific survival (CSS) was observed in the BM subgroup univariate analysis (HR 1.122, 95% CI, 1.098-1.147 for OS, HR 1.234, 95% CI, 1.204-1.265 for CSS).

Limitation of database-derived study includes a highly selected nature for aggressive therapy, retrospective manner of data collection, and the lack of detailed information regarding systemic treatment and relapse. As studies of immunotherapy and targeted therapy in advanced-stage NSCLC patients have been a research focus recently, most cases included in open-access databases could not provide related information, it remains uncertain whether and how NSCLC patients with BM can benefit from multimodal treatment integrating surgery, and these evolving treatment approaches.

Oligometastatic cancer was introduced as a limited number of identifiable metastatic lesions, usually varying from 1-5, but without a standard definition.[17] Most studies included brain-only oligometastatic NSCLC patients to evaluate the efficacy of primary lung tumor resection. In a retrospective study,[18] 122 NSCLC patients with limited BM (1-3) who received BM surgery were included. 39 patients who had primary lung tumor resection got better survival than those who received chemotherapy or radiotherapy for primary lung tumor control. The median survival time was 11.2 months and 2-year survival rate was 26%. It should be noted that adjuvant immunotherapy was precluded in the study and information regarding EGFR mutation or ALK rearrangement was not provided, patient survival could be underestimated due to these factors. Wang[19] collected data from 172 oligometastatic NSCLC patients including 37 BM patients. In 82 patients who underwent primary lung tumor resection, the median survival time was 48 months, and the 5-year survival rate was 21.1%. Patients with adrenal metastasis had better survival than BM and other distant organ metastasis, but more detailed survival data of BM patients were not mentioned in this study.

Enders[8] retrospectively recruited 141 NSCLC patients with synchronous or metachronous BM, who received BM surgery. 54 patients received primary lung tumor surgery and had a longer median survival time (17.3 months, 95%CI 11.8-30) than those who did not receive lung surgery. 23 patients had extracranial metastases indicating heavier tumor burden and subgroup analysis suggested decreased survival. A subgroup of 21 patients was further analyzed in this study because of long-term survival. Median survival time in this subgroup was 45.9 months, ranging from 26.3 to 75.1 months. Surgery to primary lung tumor was the only significant factor, and several other factors were noticed to be associated with longer survival including younger age, higher Karnofsky performance status score (KPS), metachronous BM, and a longer time between primary tumor diagnosis and BM development.

In a meta-analysis,[20] seven retrospective cohort studies consisting of 668 synchronous oligometastatic NSCLC patients were included and the survival data was pooled and analyzed to assess the survival benefit of aggressive thoracic therapy (ATT) including surgery. A 52% reduction of the death risk (HR, 0.48; 95% CI 0.39-0.60; P<0.00001) was associated with ATT. The pooled cumulative survival rate at 2 years reached 52.1%, compared to 13.7% from those who did not receive ATT. In the brain-only metastases subgroup analysis, the pooled HR for OS in oligometastatic BM patients was 0.44-0.49. Survival data of some retrospective studies was summarized in Table 1.

Study	n	Staging	n. of metastases	BM treatment	Systemic treatment	Survival data
Kumar 2023[14]	270	cT1-3, N0-1, M1b-c	NS	SRS/ metastasectomy	NS	2-y SR 50.6%
Wang 2022[15]	203	pN0-3	NS	NS	NS	MST 27m
Gui 2017[9]	16	cT1-3, N0-2, M1b; EGFR m+	NS	metastasectomy	EGFR-TKI	PFS 16.1m(10.1-21.9); OS 28.0m(19.2-36.8)
Bai 2016[11]	21	IA-IIIA without M stage	1-3	SRS/metastasectomy+WBRT	NS	OS 16.4m(9.6-23.2)
Enders 2016[8]	54	stage IV	NS	metastasectomy	NS	MST 17.3m(11.8-30)
Kanou 2014[21]	29	cT1-4, cN0-1,pN0-2	1-5	SRS/metastasectomy/metastasectomy+WBRT	chemotherapy	MST 9.6m(3-107); 5-y SR 20.6%
Yuksel 2014[12]	28	pT1-4, pN0-2	1	metastasectomy+WBRT	chemotherapy	MST 24m(16.6-31.4); 1-y SR 79%; 2-y SR 42%; 5-y SR 8%
Girard 2006[22]	26	cT1-3, cN0-2	1-5	metastasectomy	NS	MST 23m; 1-y SR 65%; 2-y SR 40%
Biling 2001[23]	28	pT1-4, pN0-2	NS	metastasectomy/ metastasectomy+WBRT	chemotherapy	MST 24m(2-104); 1-y SR 64.3%; 2-y SR 54%; 5-y SR 21.4%

NSCLC: non-small cell lung cancer; BM: brain metastases; NS: not specific; SRS: stereotactic radiosurgery; WBRT: whole brain radiotherapy; EGFR-TKI: epidermal growth factor receptor tyrosine kinases inhibitor; SR: survival rate; MST: median survival time; PFS: progression-free survival; OS: overall survival.

Table 1. Survival of NSCLC patient with BM who receive primary lung tumor resection

Although high level evidence still awaits to be published, improved survival after primary lung tumor resection in NSCLC patients with BM was indicated in many studies. And similar survival benefit was observed in other oligometastatic NSCLC patients involving different organs.[24] Due to the complex nature of the metastatic disease and primary tumor, patient survival could be influenced by many aspects including the overall condition of the patient, tumor load and its biological behavior, and patient response to local and systemic treatment. Patient selection is one of the factors that impede a definite conclusion, as patients who are fit for surgical treatment usually have few comorbidities and less tumor burden. Results from a well-designed randomized trial are still needed to

diminish the bias caused by influencing factors before a clear suggestion can be made to BM NSCLC patients about whether a lung tumor surgery should be performed. Several ongoing clinical trials involving thoracic surgical treatment for NSCLC patients with BM are: NCT03391869, NCT06114108, NCT03410043, NCT03707938, NCT01725165.

PROGNOSTIC FACTORS ASSOCIATED WITH PROLONGED SURVIVAL

As in many studies, primary lung tumor resection was recommended to a highly selected group of advanced-stage NSCLC patients who had BM, it's crucial to screen the appropriate candidate for surgical treatment of primary tumor, to maximize survival benefit and reduce treatment-related risk. In Kumar's study,[14] patients aged younger, white race, who had tumor histology including large cell carcinoma, adeno-squamous, with lower T stage and N stage tended to receive thoracic surgery, and a negative nodal disease or T1-2 disease was associated with greater survival benefit. Liang[25] studied stage IV NSCLC patients from SEER database to develop a model, to search for the optimal candidate for primary lung tumor resection surgery in advanced-stage NSCLC patients. Tumor position, age, tumor differentiation and T stage were found to influence prognosis mostly, followed by N and M stages, histology and gender. A prediction model was established based on these factors and validated internally and externally.

Prognostic factors related to better patient survival in advanced-stage NSCLC patients or BM patients were studied in some database-derived studies and retrospective cohort studies (Table 2). Primary lung tumor resection remains the most frequently studied factors that contribute to patient survival. Factors that related to tumor burden and biological behavior of tumors such as TMN stage, tumor histology, tumor differentiation and metastases pattern were analyzed less commonly. Notably, the influence of N stage on patient survival was well discussed in many other studies. Patients with N2 disease tended to have a worse prognosis and, in some cases, preclude primary lung tumor surgery,[7,11,13,26-29] as mediastinal lymph node involvement might suggest a heavier tumor burden that is not fit for surgery with curative intent.

Systemic therapy including chemotherapy, radiotherapy, immunotherapy and targeted therapy contributed to better patient survival as well, highlighting the widespread nature of the tumor progression and the importance of systemic control. Some studies including phase II randomized clinical trials suggested that response to first-line systemic therapy is a key prognostic factor before a surgery decision is made.[28,30-32] It should be noted that stage IV NSCLC patients were included in these trials rather than merely BM patients. Due to the distinct histological structure of brain tissue and the blood-brain barrier, the response to systemic treatment could be different between the brain and other distal organs involved.[33] Evidence is still lacking in this specific clinical setting of BM patients.

Patients aged younger with less comorbidities and well-supported socioeconomically are more likely to tolerate aggressive local treatment to both primary lung lesions and BM, and thus might warrant better survival.[15,25] When narrowing down the study population to those who received primary lung tumor resection, similar results were indicated as mentioned above (Table 3).

In summary, patients with better overall condition, fewer comorbidities, less tumor burden combined with appropriate systemic treatment and primary lung tumor resection usually have better survival.

APPROPRIATE SURGICAL STRATEGY FOR PRIMARY LUNG TUMOR RESECTION

For the selected group of NSCLC patients with BM, what kind of surgery should be recommended to remove the primary lung tumor remains uncertain. Surgery for this group of patients can be challenging as neoadjuvant systemic therapy might lead to increased frequency of dense fibrotic tissue involving the hilar structures and greater prevalence of firm lymph nodes.[42] The surgical team should be prepared for different surgical approaches. Pneumonectomy, lobectomy and sub-lobar resection including wedge resection and segmentectomy were mentioned in related studies, and lobectomy was the most reported surgical approach among them.

A surgical plan should be made individually based on the patient's overall condition, comorbidities, neoadjuvant systemic therapy, position and extent of the lung tumor, local and overall tumor burden, sequence of thoracic and intracranial tumor treatment, and socioeconomical factors. Survival benefits of different surgical strategies favoring lobectomy but conflicting evidence exists.

Study	n. of study cases	Setting	Patient characteristic	Patient comorbidities	Tumor histology	Tumor differentiation	TNM stage	Metastases pattern	Primary tumor resection	Systemic therapy	Other factors
Database derived study											
Wang 2022[15]	609	BM	≤65 y-o		adenocarcinoma	well moderate	T1-2N0		√	chemo	married
Liang 2021[25]	4872	stage IV	age and gender		√	√	√		√	chemo	race, position of primary tumor, metastasectomy
Hao 2021[34]	1288	stage IV	age and gender		√	√	√		lobectomy	chemo, radio	lymphadenectomy
Retrospective cohort study											
Chen 2021[7]	252	BM		KPS	adenocarcinoma		T1-3N0-1(I-II)		√	√	EGFR mutation, ALK rearrangement, second-line systemic therapies, metastasectomy
Mitchell 2020[35]	194	stage IV		ECOG	squamous				√	√	receipt of systemic therapy
She 2019[18]	122	BM		RPA, KPS				solitary without extracranial		√	infratentorial lesions, complete surgical resection, recurrence treatment
Enders 2016[8]	114	BM							√		
Bai 2016[11]	76	BM					T1-3N0-1(I-II)	solitary			
Gray 2014[36]	66	BM							√/radiation >45Gy*		
Parikh 2014[37]	186	stage IV		ECOG	nonsquamous		N0-1	single organ involved	√/radiation >53Gy		
Xu 2013[38]	213	stage IV	gender	ECOG			√		√		
Louie 2009[39]	35	BM					T1-3N0-1(I-II)		√		time between intracranial and thoracic treatment>8 weeks
Flannery 2008[40]	42	BM		KPS					√		

*After adjusting for age, thoracic stage, performance status and initial CNS therapy; NSCLC: non-small cell lung cancer; BM: brain metastases; KPS: Karnofsky performance status; ECOG: Eastern Cooperative Oncology Group performance status; RPA: recursive partitioning analysis; Chemo: chemotherapy; Raido: radiotherapy.

Table 2. Prognostic factors associated with NSCLC patient survival in different studies.

https://doi.org/10.37819/hb.4.1794

Study	n. of study cases	Setting	Patient characteristic	Tumor histology	Tumor differentiation	TNM stage	Metastases pattern	Primary tumor resection	Systemic therapy	Other factors
Database derived study										
Wang 2022[15]	203	BM	<65 y-o	adenocar-cinoma					chemo	
Zhang 2022[41]	1256	stage IV	age and gender		√	√		surgery types	chemo, radio	metastasectomy, lym-phadenectomy
Jia 2021[16]	NS	stage IV		adeno/ squamous		T1-4N0-3	solitary			
Liang 2021[25]	1374	stage IV	age and gender	√	√	√				position of primary tumor
Retrospective cohort study										
Mitchell 2020[35]	145	stage IV				N0	solitary			without bone metastases

NSCLC: non-small cell lung cancer; NS: not specific; BM: brain metastases; Adeno: adenocarcinoma; Chemo: chemothera-py; Raido: radiotherapy.

Table 3. Prognostic factors related to survival of NSCLC patient with primary lung tumor surgically treated in different studies.

https://doi.org/10.37819/hb.4.1794

In a database-derived study,[34] 1288 stage IV NSCLC patients were divided into two matching groups according to the surgical resection strategy. Lobectomy was more likely to be associated with better survival than sub-lobar surgery, but not in T4 disease. There is no difference in the survival benefit between wedge resection and segmentectomy. While in Kumar's study,[14] patients who underwent nonanatomic thoracic resection still demonstrated better 2-year survival rate than patients who got thoracic radiation (75.9%, 95% CI 61.5-85.5 vs 51.0%, 95% CI, 36.6-63.7). And in Wang's study,[19] 54 patients received wedge resection and 28 patients had lobectomy for lung surgery, and survival analysis demonstrated no differences in two different surgical approach groups. Elder patients with more comorbidities were more likely to receive sub-lobar resection than younger well-fit patients,[34] as the risk of surgery and postoperative life quality should be taken into consideration as well.

Hilar and mediastinal lymphadenectomy has been the standard part of surgical treatment for early and middle-stage NSCLC patients, and it should be taken into consideration during decision making for advanced stage patients with BM.[29] Several studies targeted this setting and got favorable results. Zhang[41] extracted stage IV NSCLC cases from SEER database and grouped the cases according to whether lymph node dissection was performed. After PSM, 628 patients were assigned to the lymph node dissection group and a 1:1 matching group was acquired. The lymph node dissection group had prolonged CSS (23 months) and OS (21 months) than the non-lymph node dissection group (CSS:16 months; OS: 15 months). Numbers of lymph node dissected were related to survival benefits when the examined lymph node ranged from 1 to 25, suggesting systemic lymph node dissection was required to improve patient survival. In Hao's study,[34] multivariate Cox analysis suggested that lymph node dissection was consistently associated with better CSS (HR: 0.76, 95%CI 0.66-0.88, $p<0.001$) and OS (HR: 0.74, 95% CI 0.65-0.86, $p<0.001$), either in lobectomy group or sub-lobar resection group. Further dividing the numbers of lymph nodes dissected showed that ≥9 lymph node dissection was associated with better survival in sub-lobar resection group but not in the lobectomy group. Through systemic lymphadenectomy, a precise nodal disease stage would be acquired, tumor cells spread in the lymphatic draining zone would be removed, facilitating immune response and reducing tumor burden, which might eventually improve patient survival.[43,44]

CONCLUSIONS

NSCLC with BM represents an advanced stage of tumor progression, but in some cases did not preclude aggressive local treatment. Related evidence of retrospective study has been discussed in this study, concerning the prognosis and management of primary lung tumor surgery for NSCLC patients with BM. Primary lung tumor resection might improve the survival of a selected group of advanced stage NSCLC patients with BM. Patient with better overall condition, fewer comorbidities, less tumor burden combined with appropriate systemic treatment and primary lung tumor resection usually has better survival. Surgical strategy should be made individually, and lobectomy along with lymphadenectomy could be recommended when appropriate, to maximize survival benefit. On the other hand, traditional systemic treatment like chemotherapy and emerging systemic treatment such as targeted therapy and immunotherapy are still vital to long-term disease control and survival. A multimodal treatment strategy integrating surgery and evolving systemic therapy is promising in treating this complicated and difficult clinical setting.[45-48] We're looking forward to related studies especially prospectively designed with a large number of patients included to address this topic.

Acknowledgments

None.

Conflict of Interest Disclosures

The authors declare no conflict of interest.

Funding

None.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author upon reasonable request.

REFERENCES

[1] Achrol A S, Rennert R C, Anders C, *et al*. Brain metastases[J]. Nat Rev Dis Primers, 2019,5(1):5.

[2] Goncalves P H, Peterson S L, Vigneau F D, *et al*. Risk of brain metastases in patients with nonmetastatic lung cancer: Analysis of the Metropolitan Detroit Surveillance, Epidemiology, and End Results (SEER) data[J]. Cancer, 2016,122(12):1921-1927.

[3] Proescholdt M A, Schodel P, Doenitz C, *et al*. The Management of Brain Metastases-Systematic Review of Neurosurgical Aspects[J]. Cancers (Basel), 2021,13(7).

[4] Jasper K, Stiles B, McDonald F, *et al*. Practical Management of Oligometastatic Non-Small-Cell Lung Cancer[J]. J Clin Oncol, 2022,40(6):635-641.

[5] Goldstraw P, Chansky K, Crowley J, *et al*. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer[J]. Journal of Thoracic Oncology, 2016,11(1):39-51.

[6] Zhang C, Ma N, Zhang Q, *et al*. Evaluation of local aggressive lung therapy versus systemic therapy in oligometastatic non-small cell lung cancer: a systematic review and meta-analysis[J]. J Thorac Dis, 2021,13(10):5899-5910.

[7] Chen X R, Hou X, Li D L, *et al*. Management of Non-Small-Cell Lung Cancer Patients Initially Diagnosed With 1 to 3 Synchronous Brain-Only Metastases: A Retrospective Study[J]. Clin Lung Cancer, 2021,22(1):e25-e34.

[8] Enders F, Geisenberger C, Jungk C, *et al*. Prognostic factors and long-term survival in surgically treated brain metastases from non-small cell lung cancer[J]. Clinical Neurology and Neurosurgery, 2016,142:72-80.

[9] Gui Q, Liu J, Li D, *et al*. Prolonged survival of patients with EGFR-mutated non-small cell lung cancer with solitary brain metastases treated with surgical resection of brain and lung lesions followed by EGFR TKIs[J]. World J Surg Oncol, 2017,15(1):184.

[10] Mitchell K G, Farooqi A, Ludmir E B, *et al*. Pulmonary resection is associated with long-term survival and should remain a therapeutic option in oligometastatic lung cancer[J]. J Thorac Cardiovasc Surg, 2021,161(4):1497-1504.

[11] Bai H, Xu J, Yang H, *et al*. Survival prognostic factors for patients with synchronous brain oligometastatic non-small-cell lung carcinoma receiving local therapy[J]. Onco Targets Ther, 2016,9:4207-4213.

[12] Yuksel C, Bozkurt M, Yenigun B M, *et al*. The outcome of bifocal surgical resection in non-small cell lung cancer with synchronous brain metastases: results of a single center retrospective study[J]. Thorac Cardiovasc Surg, 2014,62(7):605-611.

[13] Jones G D, Lengel H B, Hsu M, *et al*. Management of Synchronous Extrathoracic Oligometastatic Non-Small Cell Lung Cancer[J]. Cancers (Basel), 2021,13(8).

[14] Kumar A, Kumar S, Potter A L, *et al*. Surgical management of non-small cell lung cancer with limited metastatic disease involving only the brain[J]. J Thorac Cardiovasc Surg, 2023.

[15] Wang Q, Li J, Liang X, *et al*. Improved Survival With Surgical Treatment of Primary Lung Lesions in Non-Small Cell Lung Cancer With Brain Metastases: A Propensity-Matched Analysis of Surveillance, Epidemiology, and End Results Database[J]. Front Oncol, 2022,12:888999.

[16] Jia J, Guo B, Yang Z, *et al*. Outcomes of local thoracic surgery in patients with stage IV non-small-cell lung cancer: A SEER-based analysis[J]. Eur J Cancer, 2021,144:326-340.

[17] Hellman S, Weichselbaum R R. Oligometastases[J]. J Clin Oncol, 1995,13(1):8-10.

[18] She C, Wang R, Lu C, *et al*. Prognostic factors and outcome of surgically treated patients with brain metastases of non-small cell lung cancer[J]. Thorac Cancer, 2019,10(2):137-142.

[19] Wang Z, Gao S G, Xue Q, *et al*. Surgery of primary non-small cell lung cancer with oligometastasis: analysis of 172 cases[J]. J Thorac Dis, 2018,10(12):6540-6546.

[20] Li D, Zhu X, Wang H, *et al*. Should aggressive thoracic therapy be performed in patients with synchronous oligometastatic non-small cell lung cancer? A meta-analysis[J]. Journal of thoracic disease, 2017,9(2):310-317.

[21] Kanou T, Okami J, Tokunaga T, *et al*. Prognosis associated with surgery for non-small cell lung cancer and synchronous brain metastasis[J]. Surg Today, 2014,44(7):1321-1327.

[22] Girard N, Cottin V, Tronc F, *et al*. Chemotherapy is the cornerstone of the combined surgical treatment of lung cancer with synchronous brain metastases[J]. Lung Cancer, 2006,53(1):51-58.

[23] Billing P S, Miller D L, Allen M S, *et al*. Surgical treatment of primary lung cancer with

synchronous brain metastases[J]. The Journal of Thoracic and Cardiovascular Surgery, 2001,122(3):548-553.

[24] Congedo M T, Nachira D, Bertolaccini L, *et al*. Multimodal therapy for synchronous bone oligometastatic NSCLC: The role of surgery[J]. J Surg Oncol, 2022,125(4):782-789.

[25] Liang H, Liu Z, Huang J, *et al*. Identifying optimal candidates for primary tumor resection among metastatic non-small cell lung cancer patients: a population-based predictive model[J]. Transl Lung Cancer Res, 2021,10(1):279-291.

[26] Spaggiari L, Bertolaccini L, Facciolo F, *et al*. A risk stratification scheme for synchronous oligometastatic non-small cell lung cancer developed by a multicentre analysis[J]. Lung Cancer, 2021,154:29-35.

[27] Opitz I, Patella M, Payrard L, *et al*. Prognostic factors of oligometastatic non-small-cell lung cancer following radical therapy: a multicentre analysis[J]. Eur J Cardiothorac Surg, 2020,57(6):1166-1172.

[28] Isbell J M, Li B T, Gomez D R. The emerging role of local therapy in oligometastatic non-small cell lung cancer[J]. J Thorac Cardiovasc Surg, 2022,163(3):819-825.

[29] Eichhorn F, Winter H. How to handle oligometastatic disease in nonsmall cell lung cancer[J]. Eur Respir Rev, 2021,30(159).

[30] De Ruysscher D, Wanders R, Hendriks L E, *et al*. Progression-Free Survival and Overall Survival Beyond 5 Years of NSCLC Patients With Synchronous Oligometastases Treated in a Prospective Phase II Trial (NCT 01282450)[J]. J Thorac Oncol, 2018,13(12):1958-1961.

[31] Iyengar P, Wardak Z, Gerber D E, *et al*. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial[J]. JAMA Oncol, 2018,4(1):e173501.

[32] Gomez D R, Blumenschein G J, Lee J J, *et al*. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study[J]. Lancet Oncol, 2016,17(12):1672-1682.

[33] Rios-Hoyo A, Arriola E. Immunotherapy and brain metastasis in lung cancer: connecting bench side science to the clinic[J]. Front Immunol, 2023,14:1221097.

[34] Hao Z, Liang H, Zhang Y, *et al*. Surgery for advanced-stage non-small cell lung cancer: lobectomy or sub-lobar resection?[J]. Transl Lung Cancer Res, 2021,10(3):1408-1423.

[35] Mitchell K G, Farooqi A, Ludmir E B, *et al*. Improved Overall Survival With Comprehensive Local Consolidative Therapy in Synchronous Oligometastatic Non-Small-Cell Lung Cancer[J]. Clin Lung Cancer, 2020,21(1):37-46.

[36] Gray P J, Mak R H, Yeap B Y, *et al*. Aggressive therapy for patients with non-small cell lung carcinoma and synchronous brain-only oligometastatic disease is associated with long-term survival[J]. Lung Cancer, 2014,85(2):239-244.

[37] Parikh R B, Cronin A M, Kozono D E, *et al*. Definitive Primary Therapy in Patients Presenting With Oligometastatic Non-Small Cell Lung Cancer[J]. International Journal of Radiation Oncology*Biology*Physics, 2014,89(4):880-887.

[38] Xu Q, Wang Y, Liu H, *et al*. Treatment outcome for patients with primary NSCLC and synchronous solitary metastasis[J]. Clin Transl Oncol, 2013,15(10):802-809.

[39] Louie A V, Rodrigues G, Yaremko B, *et al*. Management and Prognosis in Synchronous Solitary Resected Brain Metastasis from Non–Small-Cell Lung Cancer[J]. Clinical Lung Cancer, 2009,10(3):174-179.

[40] Flannery T W, Suntharalingam M, Regine W F, *et al*. Long-term survival in patients with synchronous, solitary brain metastasis from non-small-cell lung cancer treated with radiosurgery[J]. Int J Radiat Oncol Biol Phys, 2008,72(1):19-23.

[41] Zhang Y, Zhang Y, Cheng X, *et al*. The Prognostic Impact of Lymph Node Dissection on Primary Tumor Resection for Stage IV Non-Small Cell Lung Cancer: A Population-Based Study[J]. Front Oncol, 2022,12:853257.

[42] Antonoff M B, Feldman H A, Mitchell K G, *et al*. Surgical Complexity of Pulmonary Resections Performed for Oligometastatic NSCLC[J]. JTO Clin Res Rep, 2022,3(3):100288.

[43] Thomas A, Giaccone G. Why has active immunotherapy not worked in lung cancer?[J]. Annals of oncology, 2015,26(11):2213-2220.

[44] Ohtaki Y, Shimizu K, Suzuki H, *et al*. Salvage surgery for non-small cell lung cancer after tyrosine kinase inhibitor treatment[J]. Lung Cancer, 2021,153:108-116.

[45] Yoo S, Cho W C, Lee G D, *et al*. Long-term Surgical Outcomes in Oligometastatic Non-small

Cell Lung Cancer: A Single-Center Study[J]. J Chest Surg, 2023,56(1):25-32.

[46] Sponholz S, Koch A, Mese M, *et al*. Lung Cancer Resection after Immunochemotherapy Versus Chemotherapy in Oligometastatic Nonsmall Cell Lung Cancer[J]. Thorac Cardiovasc Surg, 2023,71(8):656-663.

[47] Chen Y, Wang Y, Yang Z, *et al*. Local consolidative therapy for synchronous oligometastatic non-small cell lung cancer treated with first-line pembrolizumab: A retrospective observational study[J]. Thorac Cancer, 2022,13(5):732-741.

[48] Smith A, Wali A, Montes A, *et al*. Salvage pulmonary resection in stages IIIb-IV lung cancer after treatment with immune checkpoint inhibitors case series and literature review[J]. J Surg Oncol, 2022,125(2):290-298.