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REVIEW ARTICLE

The Role of Thoracic Surgery in the Therapeutic Management of Metastatic Non–Small Cell Lung Cancer

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ABSTRACT

Introduction: In most patients with NSCLC, the disease is diagnosed in an advanced stage, the prognosis is poor, and survival is typically measured in months. Standard therapeutic treatment regimens for patients with stage IV NSCLC typically include chemotherapy and palliative radiation. Despite newer regimens that may include molecularly targeted therapy and immunotherapy, the overall 5-year survival for stage IV disease remains low at 4% to 6%. Although therapeutic surgery is performed in a minority of cases, accumulating data suggest that thoracic surgery may play several beneficial roles for these patients.

Methods: In this narrative review, we summarize the literature on surgical intervention in the multimodality management of stage IV NSCLC, focusing on the potential evidence for and against therapeutic or curative intent procedures to affect outcomes for patients with oligometastatic disease and pleural metastasis.

Results: In selected patients, surgical resection can result in a 5-year survival rate of 30% to 50%, but this is heavily influenced by the presence of mediastinal nodal disease, which should be evaluated before therapeutic surgical procedures are undertaken. Additionally, diagnostic or palliative surgical procedures can play an important role in the personalized management of stage IV disease. These data suggest that for carefully selected patients with advanced stage NSCLC, surgical intervention can be an important component of combined modality treatment.

Conclusions: Given the advances in molecular targeted therapy and immunotherapy, further studies should focus on the possible use of surgery as a strategy of therapeutic "consolidation" for appropriately selected patients with stage IV NSCLC who are receiving combined modality care.

Keywords: Metastatic NSCLC; surgery; resection; multimodality treatment; survival

Introduction

NSCLC remains the leading cause of cancer-related mortality in the United States. In most patients with NSCLC, the disease is diagnosed in an advanced stage, which carries a particularly poor prognosis with few long-term survivors. The median overall 5-year survival rate for NSCLC is only 18%, and it is substantially lower for patients with stage IV disease, at 4% to 6%.[1] Standard treatments often rely on complex multidisciplinary regimens, which typically include cytotoxic chemotherapy, frequently in combination with palliative radiation, as well as molecularly targeted therapy and immunotherapy.[1] Traditionally, stage IV treatment regimens have not included curative intent surgical treatments, given

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therapeutic goals that have focused on disease control, optimization of quality of life, and palliation.[2,3]

Yet, it is becoming increasingly clear that patients with metastatic NSCLC are a heterogeneous group. Despite all such patients being characterized as having stage IV disease, some will have a high disease burden whereas others will have isolated metastatic lesions. In 2017, updates to the TNM staging system have reclassified metastatic disease into M1a (separate tumor nodule in a contralateral lobe, tumor with pleural or pericardial nodules, or malignant pleural or pericardial effusion), M1b (single extrathoracic metastasis in a single organ), or M1c (multiple extrathoracic metastases in one or several organs) on the basis of the heterogeneity of this group, with median survival differing significantly (22.5 months for M1a, 17.8 months for M1b, and 13.6 months for M1c [$p < 0.001$]).[4] Given the diversity in the population of patients with stage IV NSCLC, it is not surprising that treatment regimens are heterogeneous.

In 2004, notable therapeutic advances in the care of patients with advanced stage NSCLC occurred when *EGFR* driver mutations were identified in tumors from a subset of patients with NSCLC, and these were associated with durable responses to EGFR tyrosine kinase inhibitors (TKIs).[5–7] These findings have led to parallel discoveries of ALK receptor tyrosine kinase gene (*ALK*), and in other tumor subsets, *ROS1* rearrangements that sensitize patients with NSCLC to crizotinib.[8–10] This transformation in therapeutic options for patients with metastatic NSCLC has led some to reconsider the role of surgical resection for patients with metastatic NSCLC. A study of patients in the California Cancer Registry demonstrated that unmatched patients with stage IV NSCLC who underwent surgical procedures as part of multimodality therapy had a significantly lengthened median overall survival, ranging from 9.4 to 28 months depending on inclusion of chemotherapy and radiotherapy as opposed to 2 to 10 months in patients receiving nonsurgical treatments.[11] This improved survival could result from benefits of surgical treatment, or they could represent selection bias. Despite this survival benefit, the inclusion of surgery in treatment regimens decreased from 2004 to 2012, a finding corroborated by a study of English cancer registries.[11,12] The incorporation of surgical management for patients with stage IV NSCLC is very slowly gaining traction in the United States, but there may be a role for increased local control of intrathoracic disease progression without systemic progression with the improvements seen in aforementioned new systemic treatments.

The results of the first trial considering the effects of local consolidative therapy in combination with systemic treatment was published in 2016 by Gomez et al.[13] Patients with three or fewer sites of metastatic disease were treated with standard first-line systemic therapy and randomized to local consolidative therapy (surgery or radiation) or to maintenance therapy. Median progression-free survival was 11.9 months in the patients who received local consolidative therapy versus 3.9 months in the maintenance group ($p = 0.0054$). Multimodality therapy including surgery may lead to a further prolongation of survival for what has previously been a dismal prognosis.

The central focus of this review is to examine the role of surgery in the management of metastatic NSCLC. The available studies will be evaluated to determine which, if any, effects of surgery in patients with advanced NSCLC can be attributed to direct therapeutic effects versus selection bias, because patient selection is clearly a key component of favorable oncologic and surgical outcomes for these patients. Yet, the diversity of the population of patients with stage IV NSCLC makes large prospective surgical studies challenging to design and accrue. As a result, much of our knowledge of surgical interventions about outcomes for surgical management of metastatic disease is largely limited to small single-institution series, and this affects the quality of the evidence evaluating its role.[14–20] The current literature lacks a review that includes the palliative, diagnostic, and therapeutic roles of surgery in patients with metastatic NSCLC. To address this subject cohesively, we conducted a narrative review of the surgical literature on this topic.

Methods

PubMed was searched for the terms *metastatic*, *NSCLC*, *surgery*, *resection*, *oligometastatic*, and *pleura*. The resulting articles were reviewed by E. A. D. for their applicability and referenced to create this review of the literature. Additional articles were included to summarize the existing literature or provide sufficient background.

Results

Surgery for Diagnosis and Palliation

The role of surgery for advanced-stage malignancies is now commonplace for diagnostic and palliative purposes for many cancers, including NSCLC.[21–26] Surgeons have routinely been involved in the care of patients with metastatic NSCLC to assist with diagnosis and staging with procedures such as mediastinoscopy, endobronchial ultrasound transbronchial needle aspiration, navigational bronchoscopy, video-assisted thoracoscopic surgery for biopsy, or other surgical biopsy.[27] The role for surgery in the setting of metastatic disease continues to expand, as surgeons are frequently asked to assist with palliation of symptoms such as malignant pleural effusion by pleurodesis or indwelling pleural catheters, which are proven to be safe and effective.[22,24–26]

In the last 5 years, as personalized medicine has taken a more prominent role in the care of patients with metastatic NSCLC and treatment decisions are now based on molecular subtypes, surgeons are more frequently performing diagnostic operations to provide adequate tissue to enable detailed molecular and genetic subtyping of NSCLC or enrollment into clinical trials.[21,28–31] Additionally, for patients who experience disease progression during targeted therapy, there is a role for rebiopsy to test for targetable mechanisms of acquired resistance.[32] Multidisciplinary management is crucial for these patients to expedite treatment, minimize low-yield procedures, and balance the risks and benefits of invasive procedures with the anticipation of a meaningful change in treatment plan.

Oligometastatic Disease

In 1995, Hellman and Weichselbaum stated the following regarding an oligometastatic state: "for certain tumors, the anatomy and physiology may limit or concentrate metastases to a single or a limited number of organs."[33] They suggested that patients with tumors in this "state" may be "amenable to curative therapeutic strategy." Although the number of patients with metastatic NSCLC is large, the number of patients with NSCLC with oligometastatic disease is harder to characterize. Mordant et al. reported a retrospective series of more than 4668 patients who underwent lung cancer surgery over a 23-year period and observed that only 94 patients (2%) had oligometastatic disease.[34] This percentage is lower than in the report by SWOG, in which 7% of all patients with lung cancer who underwent surgery had oligometastatic disease comprising between two and five malignant lesions.[35]

Hanagiri et al. demonstrated that the heterogeneity in the extent of oligometastatic disease has conferred strong survival implications after surgical resection.[36] For patients with only one metastatic lesion, the 5-year survival rate was approximately 50% after surgery, compared with only 17% for patients with five metastatic lesions who underwent a surgical procedure ($p < 0.001$). The nodal status of patients with oligometastatic lung cancer also significantly affects their survival status. In patients with stage IV NSCLC who underwent surgery, those with clinical N0 disease had an 18 month median 5-year survival compared with 11 months for those with any nodal disease, highlighting the importance of neoadjuvant chemoradiation in diminishing nodal disease in surgical candidates with advanced-stage NSCLC ($p < 0.001$).[37] In a study by Collaud et al., a similar trend is seen with tumor size, with patients with T1 or T2 stage IV NSCLC who undergo resection having a median 5-year survival of 26 months compared with only 8 months in patients with T3 or T4 disease ($p = 0.007$).[38] Additionally, data suggest that the timing of metastatic disease development may affect survival, with patients with metachronous oligometastatic stage IV NSCLC having improved survival as opposed to those with synchronous oligometastatic disease.[39,40] However, other studies have reported no difference in outcomes between metachronous and synchronous oligometastatic disease in NSCLC, likely reflecting that these studies are underpowered for these analyses.[41]

Numerous single-institution series dating back several decades have demonstrated that surgical management of patients with oligometastatic NSCLC to the brain or adrenal gland is associated with superior long-term survival. In fact, authors of these studies have reported long-term survivors despite the diagnosis of metastatic NSCLC, and in some cases 5-year survival after resection of oligometastatic disease has been reported to be as high as 50% (Table 1).[15–20,38,41–46] Some series have also suggested that for patients with early-stage intrathoracic disease whose oligometastatic disease is managed with definitive intent local therapy involving either radiation or surgical resection, survival can be similar to that of patients with stage II disease.[47,48]

Mercier et al. reported a series of 23 patients who underwent resection of an adrenal gland metastasis after resection of their primary tumor.[16] In this relatively small series, the median disease-free interval was 12.5 months and the overall 5-year survival rate was 23.3%. However, for patients with metachronous oligometastatic disease who presented with an isolated adrenal metastasis more than 6 months after lung resection, the 5-year survival was a favorable 38%. Perioperative outcomes were not reported by these authors, and this is an important consideration because acute surgical morbidity may not only counteract the potential oncologic benefits of resection of oligometastatic disease but also interfere with the ability to receive additional systemic therapy should disease relapse occur. In a similar series of patients with isolated adrenal metastasis, Raz et al. report 5-year overall survival rates of 34% for patients who underwent resection of adrenal metastasis and 0% for those managed nonoperatively ($p = 0.002$).[42] Importantly, there were no perioperative deaths in this series and no major complications after adrenalectomy in any patients. The authors also reported significantly worse 5-year survival in patients with contralateral adrenal metastasis (83% versus 0% [$p = 0.003$]) or mediastinal nodal involvement (52% versus 0% [$p = 0.008$]). These series highlight the potential benefits of resection for patients with oligometastatic disease to the adrenal glands and illustrate the need for careful patient selection.

Similar results have been observed for patients with oligometastatic disease to the brain. For example, a retrospective study by Daniels et al. demonstrated remarkable 5-year survival for patients with NSCLC with brain metastases treated with surgery, although the study was limited to only 12 patients. The 5-year survival was 60% in patients who underwent resection of their cerebral metastases, a survival statistic that was nearly equivalent to the 5-year survival of their entire cohort of patients with NSCLC undergoing pulmonary resection.[19] Bae et al. analyzed a larger cohort of 86 patients with NSCLC with metachronous brain metastases undergoing a surgical procedure or radiation of their oligometastatic intracranial disease; these patients had less robust survival outcomes than seen in other studies, with an overall 5-year survival rate of 22%, suggesting that for patients with intracranial metastases metachronous presentation results in diminished survival.[43] However, this study still indicated that aggressive treatment of the metastatic disease with resection or stereotactic radiosurgery was associated with improved survival compared with that of patients with higher disease burdens.

Little consensus has been reached on treatment of oligometastatic disease involving sites such as bone, contralateral lung, or other organs. Several groups have recently published small series detailing outcomes of the management of patients with oligometastatic NSCLC to sites other than the brain and adrenal glands (see Table 1).[17,20,36,38,41,47] For example, Congedo et al. describe a series of 53 patients with oligometastatic disease to diverse sites, including the brain, adrenal gland, bone, vertebrae, liver, and contralateral supraclavicular lymph nodes. All patients were treated with resection of the primary tumor and aggressive local therapy to all sites of metastatic disease with either surgical resection or radiation.[17] For patients undergoing an operation, perioperative outcomes were as follows: 30-day mortality was 1.9% (one of 53 patients); severe complications (pneumonia, pulmonary embolism, and bleeding requiring reoperation) were seen in five of 53 patients (9.4%), and mild complications (arrhythmias, air leak, and mucus retention) were seen in 11 of 53 patients (20.8%). Complete resection was achieved in 79% of patients, and this was shown to be strongly associated with overall survival (hazard ratio [HR] = 4.75, 95% confidence interval [CI]: 1.87–12.10, $p = 0.001$). In contrast, pretreatment weight loss greater than 10% was associated with poor long-term survival (HR = 8.01, 95% CI: 2.73–23.51, $p < 0.001$) and distant disease-free survival (HR = 8.67, 95% CI: 2.65–28.40, $p < 0.001$). Interestingly, site of metastasis did not influence survival in this series.

In 2012, Salah et al. conducted a systematic review of outcomes among patients with NSCLC and solitary metastasis to sites other than the brain or adrenal glands who received resection of the metastasis and definitive treatment of the primary lung cancer.[47] The authors were able to identify 62 cases in the literature. The overall 5-year survival rate for the entire cohort was 50%, and perioperative morbidity and mortality were notably low (3% morbidity and 0% mortality). Sites of metastasis were classified as visceral or nonvisceral and included the pancreas, spleen, skin, extrathoracic lymph nodes, kidney, thyroid, bone, liver, stomach, muscle, face, breast, small intestine, and ear. Overall, there was no difference in survival on the basis of site of metastasis. Only mediastinal lymph node involvement by the primary tumor was found to be predictive of poor survival (HR = 8.2, 95% CI: 2.1–32.5, $p = 0.003$). On the basis of these results, the authors of this study advocated an aggressive surgical approach for patients with metastatic NSCLC who have resectable oligometastatic disease after meticulous mediastinal staging to rule out mediastinal involvement. Although these studies have been consistently unable to answer the question of whether the improved oncologic outcomes are surgery are due to selection bias or aggressive surgical management of oligometastatic NSCLC, the reproducible nature of the positive association between surgical management of oligometastatic disease and improved outcomes emphasizes the importance of this topic in ongoing studies and multidisciplinary settings. Importantly, mediastinal nodal involvement has been repeatedly shown to be associated with poor survival, emphasizing the importance of invasive mediastinal staging before therapeutic intent surgical procedures in the setting of oligometastatic disease. There is less definitive evidence regarding the role of neoadjuvant chemotherapy for mediastinal clearance for patients with oligometastatic disease; however, if data from patients with stage IIIA disease are extrapolated to this population, it is reasonable to expect that mediastinal clearance should be attempted before therapeutic intent surgery in this population as well.[49] Future studies need to address this question in a more robust way.

Pleural Metastases

Traditionally, patients with pleural dissemination have not been considered for surgical resection because survival has been extremely poor, with a median survival of 4 months and 5-year survival of 3.1%.[50,51] In the seventh revision of the International Association for the Study of Lung Cancer TNM staging system for NSCLC, recognizing differences in survival on the basis of site of metastases, M1a disease was revised to include contralateral lung nodules (in which median survival is approximately 10 months) and pleural and pericardial dissemination (in which median survival is approximately

Table 1. Characteristics of Studies of Oligometastatic NSCLC Managed with Surgery

Study	n	Age, y	Performance Status (ECOG)	Location of Oligometastatic Disease	Perioperative Outcomes	Significant Factors on Multivariate Analysis	Survival
Raz et al., 2011[42]	20	56	0-1	100%, adrenal	NR	None	34%, 5-y
Mercier et al., 2005[16]	23	54	NR	100%, adrenal	4%, bronchopleural fistula 4%, covered evisceration	Disease-free interval >6 mo	23%, 5-y
Collaud et al., 2012[38]	29	62	NR	66%, brain 27%, intrapulmonary 7%, adrenal	NR	pT stage	36%, 5-y
Gray et al., 2014[15]	38	55	NR	100%, brain	NR	Aggressive thoracic therapy	29%, 5-y
Daniels and Wright, 2005[19]	15	54	NR	100%, brain	NR	None	60%, 5-y
Bae et al., 2015[43]	86	60	NR	100%, brain	NR	Adenocarcinoma, disease-free interval >10 mo, surgery, and stereotactic radiosurgery	15%, 5-y
Yuksel et al., 2014[44]	28	53	NR	100%, brain	NR	T1/T2 tumors	8%, 5-y
Hanagiri et al., 2012[36]	17	66	0-1	14%, bone 11%, brain 11%, adrenal 8%, axillary lymph node 6%, liver 3%, contralateral pulmonary	NR	NR	25.1%, 5-y
Congedo et al., 2012[17]	53	61	0-1	71%, brain 15%, adrenal 5%, bone 5%, vertebrae 2%, liver 2% contralateral lymph node	6%, pneumonia 2%, pulmonary embolism 2%, bleeding requiring reoperation	R0, weight loss, PET-CT	24%, 5-y
De Ruysscher, 2012[45]	39	62	0-2	44%, brain 18%, bone 10%, adrenal 10%, intrapulmonary 5%, soft tissue 3%, liver	NR	None significant	18%, 3-y
Khan et al., 2006[18]	23	NR	0-1	61%, brain 13%, intrapulmonary 9%, adrenal 9%, bone 4%, celiac node 4%, soft tissue	None	NR	20-mo median follow-up
Endo et al., 2014[41]	34	66	0-1	50%, brain 35%, intrapulmonary 12%, adrenal 3%, renal	NR	None	47%, 5-y

(continued)

Table 1. Continued

Study	n	Age, y	Performance Status (ECOG)	Location of Oligometastatic Disease	Perioperative Outcomes	Significant Factors on Multivariate Analysis	Survival
Yamaguchi et al., 2016[46]	23	56	0-1	57%, brain 13%, bone 9%, adrenal 9%, extrathoracic lymph node 4%, liver 4%, small intestine 4%, subcutaneous	9%, prolonged air leak	NR	42%, 5-y
Griffioen et al., 2013[20]	61	62	0-2	59%, brain 18%, bone 6%, adrenal 6%, contralateral lung 6%, extrathoracic lymph node 3%, skin 2%, colon	NR	Surgical resection of intrathoracic disease, decreased radiation, and planned target volume	38%, 2-y

ECOG, Eastern Cooperative Oncology Group; NR, not reported; PET-CT, positron emission tomography-computed tomography.

8 months), whereas M1b or distant metastases are associated with a 6-month median survival.[52] Currently, therapeutic intent surgical procedures are not recommended by National Comprehensive Cancer Network guidelines for management of metastatic NSCLC with pleural dissemination, but they are offered in isolated patients.[3] The surgical treatment of patients with pleural dissemination can include pleural disease detected at the time of thoracotomy or patients who undergo multimodality treatment including neoadjuvant or adjuvant chemotherapy or chemoradiotherapy.

Similar to the series reporting surgical outcomes for patients with oligometastatic disease, the large majority of studies evaluating patients with pleural dissemination who undergo a surgical procedure are small and retrospective (Table 2).[36,46,53–59] In a report by Hanagiri et al. there were 36 patients who underwent resection for metastatic NSCLC, of whom 17 patients had ipsilateral pleural dissemination.[36] For their entire cohort, the 5-year survival rate was 26.8%, and in the patients with pleural dissemination it was 25.3%. In the context of metastatic NSCLC, these results are favorable given that survival for historical controls is on the order of 3 to 6 months. However, important questions of selection bias and generalizability of the results remain. These authors routinely perform intraoperative chemotherapy, and this practice also introduces bias. Notably, six of 19 patients (31.6%) were 3-year survivors, and it seems reasonable to hypothesize on the basis of these data that patients with pleural dissemination may derive some therapeutic benefit from extirpative surgery.[36]

However, an important limitation of the study by Hanagiri et al. is that perioperative outcomes were not reported, and this remains a significant concern in studies of this type.[36] Liu et al. retrospectively analyzed 80 patients who underwent surgical resection for M1a disease. The authors included patients with pleural nodules, pleural effusion, contralateral lung metastasis, diaphragm nodules, and pericardial nodules.[55] The overall 5-year survival rate was 31% and the median survival time was 34.3 months. On multivariate analysis of overall survival, only smoking status ($p = 0.006$) and adjuvant treatment ($p = 0.013$) were independent prognostic factors. Importantly, site of metastasis and type of resection were not significantly associated with survival.

An important theme of these series is that although potential surgical patients overall represent a minority of patients with advanced/metastatic NSCLC, there is increasing experience with the concept of surgical intervention in these patients for whom surgical intervention was previously considered contraindicated. Therefore, further examination of the risks, benefits, and appropriate indications appears warranted. Contingent on this will be a careful analysis of the extent to which

Table 2. Characteristics of Studies of NSCLC Pleural Metastases Managed with Surgery

Study	n	Age, y	Performance Status (ECOG)	Operative Procedures	Perioperative Outcomes	Significant Factors on Multivariate Analysis	Survival
Hanagiri et al., 2012[36]	17	65.8	0-1	Anatomic and nonanatomic resection[a]	NR	NR	25.1%, 5-y
Fukuse et al., 2001[53]	49	62.3	NR	Exploratory thoracotomy, anatomic and nonanatomic resection[a]; intraoperative chemotherapy	NR	Tumor size and pleural dissemination	26.7%, 3-y
Ichinose et al., 2001[54]	100	63	NR	Anatomic and nonanatomic resection[a]; intraoperative chemotherapy (n = 47)	NR	Sex, clinical and pathologic nodal status, intrapleural treatment, and intrapleural and adjuvant treatment	31.8%, 3-y; 22.8%, 5-y
Liu et al., 2015[55]	80	58	NR	Anatomic and nonanatomic resection[a]	NR	Smoking status and adjuvant treatment	31%, 5-y
Okamoto et al., 2012[56]	100	62.7	NR	Anatomic and nonanatomic resection[a]; intraoperative chemotherapy (n = 37)	NR	Pathologic nodal status and pneumonectomy	41.4%, 3-y; 23.7%, 5-y
Mordant et al., 2011[57]	32 study group, 38 controls	59	NR	Pneumonectomy or lobectomy vs. exploratory thoracotomy	Study: 5 deaths, 11 complications; Control: 0 deaths, 0 complications	No significant factors	Study: 16%, 5-y Control: 0, 5-y
Kimura et al., 2010[58]	19	67.9	NR	Anatomic and nonanatomic resection[a]; intraoperative chemotherapy (n = 12)	NR	NR	MST 28.5 mo
Yamaguchi et al., 2015[46]	11	55	0-1	Induction chemoradiation followed by extrapleural pneumonectomy	No perioperative deaths	NR	33.3%, 3-y; 22.2%, 5-y

[a]Includes wedge resection and segmentectomy.
ECOG, Eastern Cooperative Oncology Group; NR, not reported; MST, median survival time.

selection bias versus therapeutic benefit accounts for this positive association. In a retrospective chart review of 1623 patients with NSCLC who underwent resection from 1990 to 2007, 100 (6.2%) were found to have either malignant pleural effusion without nodules or metastatic pleural nodules.[56] The 3-year and 5-year survival rates for these surgical patients were 41.4% and 23.7%, respectively. In patients with pleural dissemination, N2 or N3 nodal status was predictive of decreased survival (HR = 2.39, 95% CI: 1.21–4.74, $p = 0.01$) and no patient with N2 or N3 disease was a long-term survivor. Median survival time was 24.1 months. Patients with pleural effusion and N0 or N1 disease had a significantly better prognosis (with a 5-year survival rate of 63.6%) than patients with N2 or N3 disease ($p = 0.003$). These authors argue that patients with malignant pleural effusion who are in N0 or N1 may be candidates for definitive surgical resection if complete resection can be achieved. Again importantly, perioperative outcomes were not reported by these authors.

The extent and timing of procedures that should be offered to patients with pleural dissemination remains unclear, and important safety questions remain, particularly as few series have reported perioperative outcomes after these procedures. Mordant et al. suggest that surgical procedures more extensive than lobectomy may negatively affect median survival, but other authors suggest that radical operations such as extrapleural pneumonectomy or other intraoperative therapies may provide a survival benefit.[46,57–59] For example, Wolf et al. suggest that in the hands of experienced centers and teams, patients with pleural disease but no evidence of mediastinal nodal disease or distant metastasis can be considered for extrapleural pneumonectomy with curative intent.[59] Intraoperative chemotherapy administration has also been suggested as an adjunctive treatment option for patients with pleural dissemination.[58] Kimura et al. reported a retrospective series of 19 patients with malignant pleural effusion or dissemination to the ipsilateral hemithorax who underwent surgical resection of the primary lesion with additional intraoperative intrathoracic hyperthermotherapy (group A) or hyperthermochemotherapy (group B). They compared the results in these patients with those in an unmatched control group of patients who underwent surgical resection without additional therapy (group C).[58] They did not find a significant difference in overall survival between their groups, but the median survival times were 19.4, 41, and 25 months, respectively.

Discussion

With the improved disease response and control rates seen with molecular targeted agents and immune checkpoint inhibitors, we are seeing patients living longer with advanced stage NSCLC. This trend is likely to continue and even grow. The data presented in this review illustrate the benefits that can be seen for patients with metastatic NSCLC who a undergo thoracic surgical procedure as part of a multimodality treatment regimen and should raise a question about the role of thoracic surgery for patients who demonstrate intrathoracic disease progression or persistence when systemic disease is controlled. This review has focused on therapeutic intent surgical procedures for primary tumors. There may be a role for surgical control of metastatic disease as well, but a detailed discussion of such a role is beyond the scope of this manuscript. Additionally, for patients who are not surgical candidates, local control of intrathoracic disease with radiotherapy should also be considered for both primary and metastatic lesions. Multidisciplinary treatment planning is critical for patients with multiple oligometastatic lesions, as a combination of surgical treatment and radiotherapy may provide optimal treatment for these patients.

The data presented in this review suggest that the survival benefits of surgical management of intrathoracic disease are significant and should be carefully considered when weighing treatment options for patients with metastatic disease. Patient selection may influence outcomes through selection of patients with better prognosis or selection of patients for whom surgery will improve outcomes. Early-stage intrathoracic disease is a key contributor to long-term survival in many of studies referenced in this review and should emphasize the importance of invasive mediastinal staging for these patients. Because of the retrospective nature of the studies summarized in this review and the available data on the use of systemic therapy for the patients discussed, meaningful discussion of the role of systemic treatment for oligometastatic disease is limited, but should be addressed in future studies. Accordingly, multidisciplinary treatment planning is critical for patients with metastatic NSCLC. Additionally, although these patients represent a very heterogeneous group, collaborative multicenter clinical trials are needed to provide meaningful answers regarding the role of surgery for patients with metastatic NSCLC.

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