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The Role of Thoracic Surgery in the Therapeutic Management of Metastatic Non-small Cell Lung Cancer

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Abstract

Introduction—The majority of non-small cell lung cancer (NSCLC) patients are diagnosed with advanced stage disease for whom 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 4–6%. 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/curative intent procedures to impact outcomes for patients with oligometastatic disease and pleural metastasis.

Results—In selected patients, surgical resection can result in a 5-year survival of 30–50%, 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.

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Conclusions—Given 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 receiving combined modality care.

INTRODUCTION

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality in the United States. The majority of NSCLC patients are diagnosed with advanced stage disease which carries a particularly poor prognosis with few long term survivors. Median overall 5-year survival rate for NSCLC is only 18%, and is substantially lower for stage IV patients at 4 to 6 percent.[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 therapeutic goals which 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 being characterized as stage IV, some patients will have 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) based on the heterogeneity of this group with median survival differing significantly (M1a 22.5 months, M1b 17.8 months and M1c 13.6 months, $p<0.001$).[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 epidermal growth factor receptor (*EGFR*) driver mutations were identified in tumors from a subset of NSCLC patients, and these were associated with durable responses to *EGFR* tyrosine kinase inhibitors (TKIs).[5,6,7] These findings have led to parallel discoveries of anaplastic lymphoma kinase (*ALK*) and in other tumor subsets proto-oncogene receptor tyrosine kinase (*ROS1*) rearrangements which sensitize NSCLC patients 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 California Cancer Registry patients demonstrated that unmatched stage IV NSCLC patients undergoing surgical procedures as part of multimodality therapy had significantly lengthened median overall survival, ranging from 9.4–28 months depending on inclusion of chemotherapy and radiotherapy, as opposed to 2–10 months in patients receiving nonsurgical treatments.[11] This improved survival could result from benefits of surgical treatment or represent selection bias. Despite this survival benefit, the inclusion of surgery in treatment regimens has decreased from 2004 to 2012, a finding corroborated by a study of English cancer registries.[11,12] The incorporation of surgical management for stage IV NSCLC patients 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 new systemic treatments mentioned above.

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 3 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 local consolidative therapy patients vs. 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 what, if any, effect of surgery in advanced NSCLC patients can be attributed to direct therapeutic effects versus selection bias since 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 on surgical interventions about outcomes for surgical management of metastatic disease is largely limited small single institution series, and this impacts 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 metastatic NSCLC patients. 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 (EBUS-TBNA), 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 via pleurodesis or in-dwelling 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 metastatic NSCLC patients and treatment decisions are now based on molecular subtypes, surgeons are more commonly 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 while on targeted therapy, there is a role for re-biopsy 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 described an oligometastatic state as “for certain tumors, the anatomy and physiology may limit or concentrate metastases to a single or a limited number of organs”.[33] The authors 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 NSCLC patients with oligometastatic disease is harder to characterize. Mordant et al reported a retrospective series of over 4,668 patients who underwent lung cancer surgery over a 23 year period and observed, only 94 (2%) patients with oligometastatic disease.[34] This percentage is lower than reported by the Southwest Oncology Group in which 7% of all lung cancer patients undergoing surgery had oligometastatic disease representing between 2 and 5 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, 5-year survival was approximately 50% after surgery, compared to only 17% for patients undergoing surgery with five metastatic lesions ($p<0.001$). The nodal status of oligometastatic lung cancer patients also significantly impacts their survival status. In stage IV NSCLC patients undergoing surgery, those with clinical N0 disease had an 18 month median 5-year survival compared to 11 months in 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 T1–2 stage IV NSCLC patients who undergo resection having a median 5-year survival of 26 months compared to only 8 months in T3–4 patients ($p=0.007$).[38] Additionally, data suggest that the timing of metastatic disease development may affect survival, with metachronous oligometastatic stage IV NSCLC patients having improved survival as opposed to 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 following resection of oligometastatic disease has been reported as high as

50%.[15–20,38,41–43] (Table 1.) Some series have also suggested that for patients with early stage intrathoracic disease whose oligometastatic disease is managed with definitive intent local therapy with either radiation or surgical resection, survival can be similar to patients with Stage II disease.[44,45]

Mercier et al. reported a series of 23 patients who underwent resection of an adrenal gland metastasis after resection of their primary tumor.[16] Overall, in this relatively small series, the median disease-free interval was 12.5 months and overall 5-year survival 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 since 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 a 5-year overall survival 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 following adrenalectomy in any patients. The authors also reported significantly worse 5-year survival in patients with contralateral adrenal metastasis (83% vs 0%, p=0.003) or mediastinal nodal involvement (52% vs 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 NSCLC patients with brain metastases treated with surgery. Although 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 NSCLC undergoing pulmonary resection.[19] Bae et al analyzed a larger cohort of 86 NSCLC patients with metachronous brain metastases undergoing surgery or radiation of their oligometastatic intracranial disease had less robust survival outcomes than seen in other studies, with overall 5-year survival rate of 22%, suggesting that for patients with intracranial metastases metachronous presentation results in diminished survival .[46] However, this study still indicated that aggressive treatment of the metastatic disease with resection or SRS was associated with improved survival over 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.[17,20,36,38,41,44] (Table 1) 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 surgery, perioperative outcomes were as follows: 30-day mortality

was 1.9% (1/53); severe complications (pneumonia, pulmonary embolism, and bleeding requiring reoperation) were seen in 5/53 (9.4%) and mild complications (arrhythmias, air leak, and mucus retention) were seen in 11/53 (20.8%). Complete resection was achieved in 79% of patients, and this was shown to be strongly associated with overall survival (HR 4.75; 1.87–12.10, p=0.001). In contrast, pretreatment weight loss over 10% was associated with poor long-term survival (HR 8.01; 2.73–23.51, p<0.001) and distant disease-free survival (HR 8.67; 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.[44] 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 non-visceral and included: 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 based on site of metastasis. Only mediastinal lymph node involvement by the primary tumor was found to be predictive of poor survival (HR 8.2; 2.1–32.5, p=0.003). Based on 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 are consistently unable to answer whether the improved oncologic outcomes following surgery are because of selection bias or because of 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 prior to 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 oligometastatic patients however if data from stage IIIA patients is extrapolated to this population, it is reasonable to expect that mediastinal clearance should be attempted prior to therapeutic intent surgery in this population as well.[47] 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 median survival of 4 months and 5-year survival of 3.1%.[48,49] In the 7th revision of the IASLC TNM staging system for NSCLC, recognizing differences in survival based on site of metastases, M1a disease was revised to include contralateral lung nodules (where median survival is approximately 10 months and pleural and pericardial dissemination where median survival is approximately 8 months), whereas, M1b or distant metastases are associated with a 6 month median survival.[50] Currently, therapeutic intent surgical procedures are not recommended by NCCN guidelines for management of metastatic NSCLC with pleural dissemination, but they are

offered in isolated patients.[3] The rationale for 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 surgery are small and retrospective (Table 2).[36,51–57] 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, 5-year survival 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 – 6 months, although 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 based on 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.[54] Overall 5-year survival was 31% and 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 advanced/metastatic NSCLC patients, 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 selection bias versus therapeutic benefit accounts for this positive association. In a retrospective chart review of 1,623 NSCLC patients undergoing resection from 1990–2007, 100 (6.2%) were found to have either malignant pleural effusion without nodules or metastatic pleural nodules.[53] The 3-year and 5-year survival rates for these surgical patients were 41.4% and 23.7%, respectively. In patients with pleural dissemination, N2–3 nodal status was predictive of decreased survival (HR 2.39; 1.21–4.74, p=0.01) and no patient with N2–3 disease was a long term survivor. Median survival time was 24.1 months. Patients with pleural effusion and N0–1 disease had a significantly better prognosis with a 5-year survival rate of 63.6% than patients with N2–3 disease (p=0.003). These authors argue that patients with malignant pleural effusion who are N0–1 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 following 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 like extrapleural pneumonectomy (EPP) or other intraoperative therapies may provide a survival benefit.[55–58] 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 EPP with curative intent.[57] Intraoperative chemotherapy administration has also been suggested as an adjunctive treatment option for patients with pleural dissemination.[56] 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 hyperthermo-chemotherapy (group B). They compared the results of these patients to an unmatched control group who underwent surgical resection without additional therapy (group C).[56] 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 undergo thoracic surgery 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 focused on therapeutic intent surgical procedures for primary tumors; however there may be a role for surgical control of metastatic disease as well, but a detailed discussion 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 by selecting 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. Due to 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 metastatic NSCLC patients. Additionally, although these patients represent a very heterogeneous group, collaborative, multi-center clinical trials are needed to provide meaningful answers regarding the role of surgery for patients with metastatic NSCLC.

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Table 1

Characteristics of studies of Oligometastatic NSCLC Managed with Surgery

Author, year of publication	N	Age	Performance Status (ECOG)	Location of oligometastatic disease	Perioperative Outcomes	Significant Factors on Multivariate Analysis	Survival
Raz, 2011[43]	20	56	0–1	100%- adrenal	NR	None	34%, 5 year
Mercier, 2005[63]	23	54	NR	100%- adrenal	4%- bronchopleural fistula 4%- covered evisceration	Disease free interval > 6 months	23%, 5 year
Collaud, 2012[39]	29	62	NR	66%- brain 27%- intrapulmonary 7%- adrenal	NR	pT stage	36%, 5 year
Gray, 2014[16]	38	55	NR	100%- brain	NR	Aggressive thoracic therapy	29%, 5 year
Daniels, 2005[20]	15	54	NR	100%- brain	NR	None	60%, 5 year
Bae, 2015[47]	86	60	NR	100%- brain	NR	Adenocarcinoma, disease free interval > 10 months, surgery, and stereotactic radiosurgery	15%, 5 year
Yuksel, 2014[44]	28	53	NR	100%- brain	NR	T1/T2 tumors	8%, 5 year
Hanagiri, 2012[37]	17	66	0–1	14%- bone 11%- brain 11%- adrenal 8%- axillary lymph node 6%- liver 3%- contralateral pulmonary	NR	NR	25.1%, 5-year
Congedo, 2012[18]	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 year
De Ruysscher, 2012[64]	39	62	0–2	44%- brain 18%- bone 10%- adrenal 10%- intrapulmonary 5%- soft tissue 3%- liver	NR	None significant	18%, 3 year
Khan, 2006[65]	23	NR	0–1	61%- brain 13%- intrapulmonary 9%- adrenal 9%- bone 4%- celiac node 4%- soft tissue	None	NR	20 month median follow up
Endo, 2014[42]	34	66	0–1	50%- brain 35%- intrapulmonary 12%- adrenal	NR	None	47%, 5 year

Author, year of publication	N	Age	Performance Status (ECOG)	Location of oligometastatic disease	Perioperative Outcomes	Significant Factors on Multivariate Analysis	Survival
				3%- renal			
Yamaguchi, 2016[66]	23	56	0–1	5 7%- brain 13%- bone 9%- adrenal 9%- extrathoraci lymph node 4%- liver 4%- small intestine 4%- subcutaneous	9%- prolonoged air leak	NR	42%, 5 year
Griffioen, 2013[21]	61	62	0–2	59%- brain 18%- bone 6%- adrenal 6%-contralateral lung 6%- extra-thoracic lymph nodes 3%- skin 2%- colon	NR	Surgical resection of intrathoracic disease, decreased radiation planned target volume	38%, 2 year

Table 2

Characteristics of studies of NSCLC Pleural Metastases Managed with Surgery

Author, year of publication	N	Age	Performance Status (ECOG)	Operative Procedures	Perioperative Outcomes	Significant Factors on Multivariate Analysis	Survival
Hanagiri, 2012[37]	17	65.8	0–1	Anatomic and non-anatomic resection*	NR	NR	25.1%, 5-year
Fukuse, 2001[50]	49	62.3	NR	Exploratory thoracotomy, anatomic and non-anatomic resection* Intraoperative chemotherapy	NR	Tumor size, pleural dissemination	26.7%, 3-year
Ichinose, 2001[51]	100	63	NR	Anatomic and non-anatomic resection* Intraoperative chemotherapy (n=47)	NR	Gender, Clinical and Pathologic Nodal status, Intrapleural Treatment, Intrapleural and Adjuvant Treatment	31.8%, 3-year 22.8%, 5-year
Liu, 2015[53]	80	58	NR	Anatomic and non-anatomic resection*	NR	Smoking Status and Adjuvant treatment	31%, 5-year
Okamoto, 2012[52]	100	62.7	NR	Anatomic and non-anatomic resection* Intraoperative chemotherapy (n=37)	NR	Pathologic Nodal Status, Pneumonectomy	41.4%, 3-year 23.7%, 5-year
Mordant, 2011[54]	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-year Control: 0, 5-year
Kimura, 2010[55]	19	67.9	NR	Anatomic and non-anatomic resection* Intraoperative chemotherapy (n=12)	NR	NR	MST 28.5 mo
Yamaguchi, 2015[57]	11	55	0–1	Induction Chemoradiation followed by Extrapleural pneumonectomy	No perioperative deaths	NR	33.3%, 3-year 22.2%, 5-year

*Includes wedge resection and segmentectomy.