Long-term Survival Following Surgical Treatment of Solitary Brain Metastasis in Non-small Cell Lung Cancer*

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Dissemination of lung cancer beyond the intrathoracic lymph nodes (stage IV disease) implies surgical unresectability. However, solitary brain metastases (SBMs) from non-small cell lung cancer (NSCLC) have often been treated by combined resection of the primary tumor and its metastasis. Such an aggressive approach appears to substantively improve patient outcome and provide better quality of life in selected cases. A search of the literature reveals extended survival (10 years or longer) in 16 patients following combined surgical excision. We report three patients with NSCLC and isolated central nervous system involvement who achieved exceptionally long survival. The existing literature on SBMs from NSCLC is reviewed.

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NSCLC=non-small cell lung cancer; SBM=solitary brain metastasis; WBRT=whole-brain radiation therapy

Key words: combined surgical approach; long-term survival; non-small cell lung cancer; solitary brain metastasis

Cerebral metastasis is a feared complication of lung cancer and is generally believed to represent the final step in the natural history of the patient’s malignancy. Because of the short median survival after diagnosis, in the past, patients with brain metastases have frequently been treated with palliative intent. Although some patients with metastatic brain disease have a rapid downhill course, sporadic cases of prolonged survival after surgical resection of brain metastases have been reported. In 1954, Knights,1 in a study of 6,900 autopsies at this institution, found evidence of intracranial spread in 55% of patients with lung cancer.1 He also noted that a significant number of patients had solitary brain metastases (SBMs) in areas amenable to surgical removal. Twenty years later, Magilligan et al2 presented their experience with combined surgical excision of both the primary lung cancer and its brain metastasis, followed by whole-brain radiation therapy (WBRT). They noted significant prolongation of survival time and better quality of life in most patients, with negligible operative mortality. Their report was subsequently followed by numerous retrospective studies that yielded comparable results.

Since then, patients with SBMs from a primary lung cancer have been identified as a subgroup in which an aggressive surgical approach provided a favorable outcome. Herein, we present three patients with non-small cell lung cancer (NSCLC) and SBMs who survived more than 10 years following combined surgical excision.

CASE REPORTS

PATIENT 1

In March 1967, a 50-year-old man was evaluated for a 1-month history of new-onset seizures and progressive weakness of the right arm. On examination, he was found to have expressive aphasia and decreased motor strength in the right upper extremity. An EEG showed a focal irritative lesion in the left frontal region. A subsequent cerebral angiogram confirmed the presence of a 3-cm lesion in the left frontal lobe. A radiograph of the chest revealed a 3-cm well-circumscribed mass in the upper lobe of the left lung. The patient underwent left frontoparietal craniotomy, and a 2.5x3x2-cm mass was completely removed. Histologic examination revealed metastatic adenocarcinoma.

Three weeks later, he underwent thoracotomy and wedge resection of the tumor of the upper lobe of the left lung. Histologically, the lesion proved to be moderately differentiatied adenocarcinoma of the lung. The patient had an uneventful postoperative course and was discharged with marked relief of neurologic deficits. He then received a total of 5,000 cGy external beam radiation to the chest.

He remained symptom-free and maintained gainful employment as a sales representative for 13 years. Routine screening tests during this period disclosed no abnormalities. In 1980, he developed progressive difficulty in swallowing. A barium swallow test and endoscopy revealed an esophageal sticture. Multiple biopsies and brushings for cytologic examination were nondiagnostic. A CT scan of the chest and head showed no evidence of recurrent disease. Thereafter, he required intermittent esophageal dilatation for symptomatic relief of dysphagia.

In May 1985, he presented with massive hematemesis and chest pain. After initial stabilization, an esophagogram revealed leakage of contrast medium into the mediastinum consistent with esophageal perforation. He died of exsanguination in June 1985. No autopsy was performed. He survived 18 years 3 months following craniotomy.

PATIENT 2

In 1972, a 34-year-old woman presented with onset of new occipital morning headaches. On a routine chest radiograph, she was noted to have a 4x4-cm mass in the upper lobe of the right lung. Nuclear isotope brain scanning and cerebral arteriographic study identified a single tumor in the left parieto-occipital region. She underwent craniotomy, and a 2.5-cm mass from the left occipital lobe was excised in toto. Postoperatively, she received 4,000 cGy WBRT. The resected tumor proved to be metastatic adenocarcinoma.

Two months later, she underwent a lobectomy of the right up-
per lobe followed by 4,000 cGy external beam radiation to the chest. Histologic examination revealed moderately differentiated adenocarcinoma. The patient had an uneventful recovery and was followed up, until 1985, with routine diagnostic procedures that failed to show evidence of recurrent local or systemic disease.

In 1985, the patient presented with the complaints of progressive shortness of breath and a cough productive of blood-streaked sputum. A CT scan of the chest revealed a 3-cm lobulated mass in the lingula and another 2-cm mass at the level of the carina, partially occluding both mainstem bronchi. There were no enlarged mediastinal lymph nodes.

In June 1985, she underwent bronchoscopy that showed an endobronchial mass partly occluding the distal trachea by creating a ball-valve effect. The mass was resected using a YAG laser. After removal of the lesion, another mass was found obstructing the lingular bronchus that also was resected. Histopathologic examination revealed poorly differentiated squamous cell carcinoma at both sites.

She then received two courses of chemotherapy consisting of cis-platin and vinblastine sulfate, followed by 2,000 cGy external beam radiation to the chest. Three months later, she presented with difficulty walking and diplopia. A myelogram showed complete block to contrast dye at the level of L4-5. Cerebrospinal fluid cytologic studies were positive for malignant cells. In August 1985, the patient died. Postmortem examination was denied by the family. She survived 13 years 4 months after craniotomy.

**Figure 1.** Photomicrographs depicting metastatic adenocarcinoma of the brain, clear cell type, of the left temporal lobe (A); primary adenocarcinoma of the lung (B); recurrent adenocarcinoma of the lower lobe of the left lung (C); papillary adenocarcinoma of the middle lobe of the right lung (D) (hematoxylin-eosin, original magnification ×40).

**Patient 3**

In October 1973, a 45-year-old woman was seen for evaluation of severe headaches and slurred speech. On examination, she was found to have right central facial nerve palsy and right hemiparesis. A chest radiograph revealed a 3-cm well-circumscribed opacity in the upper lobe of the left lung. A cerebral arteriogram showed a mass in the left posterior temporal lobe. Metastatic workup revealed no other site of disease. She underwent craniotomy of the left temporal lobe. A superficial “walnut-sized” tumor was easily identified in the temporal lobe, and a gross total resection was performed. Histologic examination revealed metastatic adenocarcinoma (Fig 1, A).

Three weeks later, she underwent a thoracotomy and wedge resection of the subpleural tumor. It too proved to be adenocarcinoma (Fig 1, B). There were no grossly involved hilar lymph nodes. She had an uneventful postoperative recovery. The patient did not receive any adjuvant postoperative therapy.

She remained disease-free until 1982 when she presented with new-onset seizures. Her seizure disorder was treated with diphenylhydantoin; later, the dosage was tapered and finally therapy was discontinued. A CT scan of the head showed no evidence of recurrent tumor. Routine screening tests did not disclose recurrent local or systemic disease, or both, during this period.

One year later, a CT scan of the chest disclosed an irregular, pleural-based density along the posterior aspect of the upper lobe of the left lung. Percutaneous thin-needle aspiration biopsy of this...
mass was consistent with adenocarcinoma. She received three courses of chemotherapy consisting of vinblastine and cis-platin that resulted in partial regression of tumor.

Subsequently, she underwent a lobectomy of the left upper lobe. A 4 x 2 x 2-cm tumor was identified in the upper lobe of the left lung that was posteriorly adherent to the fifth rib. There was no gross involvement of hilar or mediastinal lymph nodes. Histologic examination revealed adenocarcinoma (Fig 1C). Thereafter, she received 5,000 Gy external beam radiation to the upper lung region. The patient remained free of symptoms for another 5 years.

In November 1988, she presented with complaints of productive cough, fever, and chills. The chest radiograph revealed an infiltrate of the middle lobe of the right lung. A presumptive diagnosis of pneumonia was made, and she was treated with intravenously administered antibiotics for 3 weeks, resulting in the disappearance of her symptoms. Despite this treatment, her chest radiograph showed no resolution. She then underwent an open-lung biopsy of the right lung. Histopathologic examination revealed papillary adenocarcinoma (Fig 1D). Three months later, the patient died at the age of 62 years. She survived 15 years 6 months following craniotomy.

**Discussion**

The brain is a common site of treatment failure following curative resection of NSCLC. In large autopsy series, the incidence of cerebral metastases from lung cancer ranges from 30 to 60%.5-8 Once brain metastasis is clinically apparent, median survival ranges from 1 to 6 months.5-8 WBRT may achieve neurologic palliation but has a limited role in prolonging survival.

In a third of the patients, brain metastases are solitary, and of these, nearly 50% will be resectable and potentially “cureable” after removal of the primary lung tumor and its metastasis. Nonetheless, intracranial metastasis has long been viewed as a desperate situation by patients as well as clinicians.9,10 In 1926, Grant,10 in a review of 49 patients with brain metastases, concluded that “surgery is of no ultimate benefit as far as prolongation of life is concerned.” Others expressed similar skepticism concerning the results of surgery in patients with brain metastases.11 Thereafter, however, anecdotal reports of patients with lung cancer who were effectively treated after resection of their cerebral metastases appeared in the literature (Table 1).12-24

In 1976, Magliigan et al3 reviewed the survival data of patients with lung cancer and SBM who underwent combined curative resection. In their original study, they reported a mean survival of 14 months with improvement of the neurologic symptoms in the majority of the patients. In a subsequent report, they reexamined the survival and quality of life in the same patient group after 25 years of follow-up. They described a 5-year survival rate of 21% and a 2% operative mortality.25 They concluded that combined surgical excision is an effective and well-tolerated procedure and encouraged an aggressive surgical approach to solitary cerebral metastases.25 Subsequently, the frequency of SBM and the failure of other therapeutic modalities to satisfactorily alter survival26-27 prompted many investigators to study their individual institutional experience.28-37

Such studies mostly constituted post hoc analyses of data in a well-selected group of patients and were often biased in that they used dissimilar selection criteria or employed different methods of survival analysis,38 thereby precluding valid assessment and comparison of their results. Also, most of the studies predated the widespread use of CT scans in the preoperative evaluation of patients; thus, their results may fail to reflect the true efficacy of surgery in this setting. Recognizing the inherent constraints of retrospective studies, however, the data from published series indicated that pa-
patients treated by surgical resection of the primary NSCLC and isolated brain metastases enjoyed a substantially longer disease-free survival than those treated with either radiotherapy or chemotherapy. Furthermore, most series reported an operative mortality rate of less than 5%, suggesting that an aggressive surgical approach is relatively safe. These studies also sought to determine the patient characteristics that were predictors of long-term survival. They examined the impact of such variables as cell type, location of the brain metastases, stage of the primary lung lesion, metachronous versus synchronous presentation, and preoperative neurololgic status during survival.

Many authors noted the preponderance of adenocarcinoma in the majority of late survivors. In all our cases, the initial histologic type was adenocarcinoma, although one patient later developed multiple primaries of squamous cell type. It is unclear why patients with adenocarcinoma seem to have a survival advantage compared with those who have nonadenocarcinoma histologic features. Slow cell-doubling time and greater immunologic response to malignancy have been variously considered as likely explanations. It is possible, however, that the preponderance of this cell type is incidental, reflecting its greater tendency to spread to the central nervous system. Thus, adenocarcinoma may be more common among late survivors because it gives rise to a greater number of cerebral metastases. In fact, adenocarcinoma of the lung has been found to produce more metstatic deposits than other histologic types of NSCLC and even more cerebral metastases than small cell carcinoma.

The tendency of the primary tumor of the lung to preferentially involve the upper lobes in patients developing SBM has been described by many authors. In a review of “long-term survivors” after excision of SBM from NSCLC, Weilbaecher found that 10 of 11 patients (91%) had upper lobe primary sites. Read et al. too noted that 70 of the 92 patients with SBM (76%) had primary lung lesions in the upper lobes. The prevalence of upper lobe NSCLC in patients with SBM is probably more apparent than real, because lung cancer in general has a propensity to involve the upper lobes of the lung. Indeed, a recent analysis indicated that the apparent association of upper lobe primary sites with distant metastases (including the brain) reflected such a tendency.

Reports in the literature also are contradictory with respect to the prognostic importance of metachronous vs synchronous brain metastases. Our cases demonstrated synchronous onset of the brain lesions. The metastases to the brain were detected first and treated before the resection of the primary lung cancer. Although some authors maintained that metachronous onset of metastases to the brain indicates a less aggressive tumor and is associated with a better prognosis, this has not been uniformly confirmed in other studies. Torre et al. noted that synchronous cerebral metastases did not necessarily confer a worse prognosis.

The role of postoperative WBRT as an adjuvant to surgery is uncertain. While WBRT is likely to have a value as far as local control is concerned, as yet no prospective randomized study has proven a clear benefit of WBRT in improving survival in patients with SBM from NSCLC treated with staged combined surgical resection. Nonetheless, most patients continue to receive WBRT after craniotomy to eradicate residual disease at the operative site, as well as metastatic deposits elsewhere in the brain. This may prove an important therapeutic issue, considering that the number of long-term survivors after surgical resection of single metastatic lesion is not negligible and that WBRT has been associated with significant short-term and delayed toxicity.

In 1990, the publication by Patchell et al. of a prospective randomized trial to evaluate surgical extirpation plus WBRT vs WBRT alone conclusively established the superiority of surgical treatment. The investigators evaluated 48 patients with SBM that were not highly radiosensitive (mainly NSCLC, but also other primary tumors). Twenty-five patients underwent surgical excision followed by WBRT, while the remaining 23 were treated with radiotherapy alone. In this study, patients treated with surgery plus WBRT achieved a median survival of 40 vs 15 weeks achieved in the group treated with WBRT alone. Further, patients in the surgical group maintained a good quality of life (Karnofsky score ≥ 70) much longer than those treated with WBRT alone (38 vs 8 weeks). Finally, this study also demonstrated that the incidence of neurologic relapse was significantly less in the surgical group (20%) than in the irradiation-alone group (52%).

More recently, Burt et al. reviewed 185 patients who had undergone craniotomy for resection of brain metastases from NSCLC. The majority of the patients also received postoperative WBRT. A single brain lesion was present in 89% of the patients. No survival difference was noted in patients with metachronous vs synchronous presentation. In addition, neither the histologic type nor the locoregional extent of the primary lung lesion (TN stage) had an impact on survival. Importantly, however, adequate control of the locoregional disease had the greatest influence on the length of survival. Patients who underwent complete resection of their primary lung lesions survived significantly longer (median survival, 21 months) than those in whom complete resection could not be performed (median survival, 10 months). While the authors provided no data as to the cause of death in this study (progressive systemic cancer vs death from neurologic causes), they concluded that resectability of the primary lung lesion is the chief determinant of survival in patients with NSCLC undergoing resection of brain metastases.

Although an aggressive surgical approach in the treatment of SBM appears to confer a distinct survival advantage, only 10% of cerebral metastases from NSCLC are solitary, and fewer than one half of the patients with SBM are surgical candidates due to inaccessibility of the lesion, advanced systemic disease, or comorbid medical conditions. Therefore, cranial irradiation still remains the mainstay of therapy for most patients with brain metastases. In fact, surgical management of patients with two or more brain metastases has been associated with a high operative complication rate and poorer survival.

**Conclusion**

Advances in neuroimaging techniques coupled with the rising incidence of NSCLC will result in early detection of a greater number of brain metastases among survivors. It is,
therefore, likely that in the coming years many patients with NSCLC and SBM will be seen by physicians. Incorporation of surgery in the front-line care of patients with SBM in the setting of NSCLC has led to an impressive improvement in patient outcome. Unfortunately, however, the nihilistic attitude of many physicians continues to result in delay or failure to seek prompt surgical evaluation.\textsuperscript{36,33}

The patients described in this report serve to illustrate the rewarding results of adopting an aggressive therapeutic approach. It is hoped that heightened awareness of the potential for “cure,” timely referral, and well-planned operative intervention will result in enhanced survival in this growing patient population.

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Pulmonary Botryomycosis in a Patient With AIDS*

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We describe the clinical and pathologic findings of the first reported case of pulmonary botryomycosis in a patient with AIDS. Botryomycosis is an uncommon, chronic, suppurative disease that is often mistaken clinically and historically for a fungal infection. The patient responded to systemic antibiotic therapy.

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Key words: AIDS; pathology; pulmonary botryomycosis

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Botryomycosis, which closely mimics fungal infections both clinically and histologically, is an uncommon chronic suppurative and sometimes granulomatous infection generally involving the skin, tela subcutanea (subcutis), and occasionally the viscera and is caused by bacteria. The hallmark of the disease is the presence of eosinophilic fungal granules in a suppurative lesion; the granules consist of the causative bacteria.

Recently, three cases of cutaneous botryomycosis have been reported in AIDS patients. In the present article, we report what is to our knowledge the first case of pulmonary botryomycosis in a patient with AIDS.

Case Report

Clinical Data

A 36-year-old heterosexual male, chronic smoker presented with a history of blood-streaked sputum and cough for 3 days. He had no history of fever, chills, shortness of breath, persistent cough, weight loss, nor any exposure to tuberculosis.

The physical and clinical examination disclosed no abnormalities except for severe human papilloma virus infection involving the penis. The CBC count and differential cell counts were within normal limits. A chest x-ray film showed a single mass, 5 cm in diameter, located in the upper lobe of the right lung with a central area of low attenuation (Fig 1). A CT scan showed the mass to be

Figure 1. Chest x-ray film showing a single mass (5 cm) in upper area of right lung (arrow).

Figure 2. CT scan of the chest showing a pleural-based mass in the upper area of right lung with central low attenuation area (arrow).