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Original Article / *Özgün Makale*

Results of surgical resection in lung cancer with synchronous brain metastasis

Senkron beyin metastazı bulunan akciğer kanserinde cerrahi rezeksiyon sonuçları

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ABSTRACT

Background: This study aims to investigate the factors affecting the survival of operated non-small cell lung cancer patients with synchronous brain metastasis.

Methods: Clinical outcomes of a total of 16 patients (14 males, 2 females; mean age 60 years; range, 41 to 71 years) who were diagnosed with non-small cell lung cancer and concomitant solitary/oligo brain metastasis and who underwent an intervention primarily for cranium, followed by lung resection in our clinic between January 2012 and January 2016 were retrospectively analyzed. Cranial surgery or gamma-knife radiosurgery was performed in the treatment of brain metastases.

Results: Twelve patients with solitary brain metastasis underwent cranial surgery, while four patients with solitary/oligo metastases underwent gamma-knife radiosurgery prior to pulmonary resection. Definitive pathological examination revealed adenocarcinoma in 13 patients and squamous-cell lung carcinoma in three patients. Mean survival time was 15.3±8.6 months. One-year and two-year survival rates were 56.2% and 32%, respectively. The number of brain metastases, treatment type, tumor cell type, resection type, and status of lymph nodes were not statistically significantly associated with survival (p>0.05).

Conclusion: Cranial surgery or gamma-knife radiosurgery followed by aggressive lung resection can be effectively applied in selected non-small cell lung cancer patients with synchronous brain metastasis. However, the suitability of the primary tumor and brain metastases for complete resection is of utmost importance in patient selection.

Keywords: Lung cancer; oligometastasis; synchronous brain metastasis.

ÖZ

Amaç: Bu çalışmada senkron beyin metastazlı ameliyat edilmiş küçük hücreli dışı akciğer kanseri hastalarının sağkalımını etkileyen faktörler araştırıldı.

Çalışma planı: Kliniğimizde Ocak 2012 ve Ocak 2016 tarihleri arasında küçük hücreli dışı akciğer kanseri ve eşlik eden tek/oligo beyin metastazı tanısı konulan ve primer olarak beyin için girişim yapılan, ardından akciğer rezeksiyonu uygulanan toplam 16 hastanın (14 erkek, 2 kadın; ort. yaş 60 yıl; dağılım, 41-71 yıl) klinik sonuçları retrospektif olarak incelendi. Beyin metastazlarının tedavisi için kraniyal cerrahi veya gamma-knife radyocerahisi uygulandı.

Bulgular: Akciğer rezeksiyonu öncesi tek beyin metastazı olan 12 hastaya kraniyal cerrahi uygulanır iken tek/oligo metastazı olan dört hastaya gamma-knife radyocerrahisi uygulandı. Nihai patolojik inceleme 13 hastada adenokarsinom ve üç hastada akciğerin skuamöz hücreli karsinomu olduğunu gösterdi. Ortalama sağkalım süresi 15.3±8.6 ay idi. Bir ve iki yıllık sağkalım oranları sırasıyla %56.2 ve %32 idi. Beyin metastazlarının sayısı, tedavi tipi, tümör hücre tipi, rezeksiyon tipi ve lenf nodlarının durumu sağkalımla istatistiksel olarak anlamlı şekilde ilişkili değildi (p>0.05).

Sonuç: Senkron beyin metastazlı seçilmiş küçük hücreli dışı akciğer kanseri hastalarında kraniyal cerrahi veya gamma-knife radyocerrahisi sonrası agresif akciğer rezeksiyonu etkili bir şekilde uygulanabilir. Ancak primer tümörün ve beyin metastazlarının tam rezeksiyon için uygunluğu hasta seçiminde son derece önem arz etmektedir.

Anahtar sözcükler: Akciğer kanseri; oligometastaz; senkron beyin metastazı.

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Although resection of primary tumor and metachronous brain metastases is superior to other treatment modalities in terms of long-term survival and disease-free survival, resection of primary non-small cell lung cancer (NSCLC) with synchronous brain metastases is still contradictory.[1,2] The incidence of brain metastasis secondary to lung cancers varies between 40% and 60% in autopsy series.[1,3] Median survival is very poor for brain metastases caused by NSCLC and has been reported as nearly one month, if left untreated. This period of time can be extended to two to three months, when treated only with steroids and three to six months when treated with whole brain radiotherapy (WBR).[3]

Several recommendations are available on the treatment of patients with brain metastasis secondary to NSCLC in the literature. In this study, we aimed to investigate the factors affecting the survival of operated NSCLC patients with synchronous brain metastasis.

PATIENTS AND METHODS

In this study, prospective data entry database was evaluated retrospectively and 16 consecutive NSCLC patients (14 males, 2 females; mean age 60 years; range, 41 to 71 years) with synchronous brain metastasis were examined in our clinic between January 2012 and January 2016. The patient count represents all of the NSCLC patients with synchronous brain metastasis treated in our clinic between the stated time period. No patient was excluded from the study. Medical records were analyzed in terms of age, gender, histological tumor type, postoperative thoracic tumor stage, surgical intervention, postoperative complications, adjuvant treatment, and survival. The factors affecting survival were analyzed. All patients were followed-up in an outpatient setting. The study protocol was approved by the Scientific Study Committee of Sureyyapasa Chest Disease and Thoracic Surgery Training and Research Hospital. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Thoracic computed tomography (CT), cranial magnetic resonance imaging (MRI) and positron emission tomography-CT (PET-CT) were performed preoperatively in all patients. Fiberoptic bronchoscopy or transthoracic fine needle aspiration biopsy was undertaken in ineligible patients for histological examination.

The brain metastases were treated with either cranial surgery or gamma-knife radiosurgery. The decision was established by at least one neurosurgeon and a radiation oncologist. Patients who had brain metastases <3 cm located deep or in the eloquent areas of the brain were treated with gamma-knife surgery, while the rest were treated with cranial surgery. Cervical mediastinoscopy and anatomical lung resection were carried out after cranial interventions.

Only cervical mediastinoscopy was performed for the surgical preoperative evaluation of N_2 lymph nodes. Extended cervical mediastinoscopy is not routinely undertaken in our clinic. Videothoracoscopic evaluation for number 5 and 6 lymph nodes was not carried out as there was no patient with PET-CT positive and/or suspected 5-6 positive lymph nodes in our patient population.

Postoperative staging was carried out according to the seventh edition of the Staging of the International Association for the Study of Lung Cancer.[4] Operative mortality was defined as patients who died within the first 30 days following thoracic and cranial procedures and those who died later but during the same hospitalization.

Survival was estimated using the Kaplan-Meier method. The date of lung surgery was used as the baseline, while the date of mortality or last follow-up (June 2016) as the data cut-off.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed as mean ± standard deviation. Mann-Whitney U and Kruskal-Wallis tests were used to analyze different variables between the two groups. A p value of <0.05 was considered statistically significant.

RESULTS

Six patients (37.5%) were admitted to hospital with neurological symptoms including headache, vertigo, ataxia, and seizure, while 10 patients (62.5%) presented with pulmonary symptoms such as dyspnea, chest pain, cough, and hemoptysis. Two patients had both pulmonary and neurological symptoms.

In all patients, cranial metastasis was operated to control the neurological symptoms and to prevent the central nervous system complications following pulmonary resection. Twelve patients with solitary brain metastasis underwent cranial surgery, while four patients with solitary/oligo metastases underwent gamma-knife radiosurgery prior to pulmonary resection. The symptoms disappeared in

Table 1. Clinical demographic characteristics of patients (n=16)

	n	%	Mean±SD
Mean age (year)			60±8.6
Survival (month)			15.3±8.6
Gender			
Male	14	87.5	
Female	2	12.5	
Number of brain metastasis			
Solitary	15	93.8	
Oligo	1	6.3	
Treatment of brain metastasis			
Cranial surgery	12	75	
Gamma-knife radiosurgery	4	25	
Thoracic surgical method			
Thoracotomy	15	93.8	
Video-assisted thoracoscopic surgery	1	6.3	
Cell type			
Adenocarcinoma	13	81.3	
Squamous-cell carcinoma	3	18.8	
Status			
Exitus	10	62.5	
Alive	6	37.5	
Resection type			
Lobectomy	13	81.3	
Pneumonectomy	3	18.8	
Type of lymph node (N)			
N_0	10	62.5	
N_1	2	12.5	
N_2	4	25	

SD: Standard deviation.

patients with neurological symptoms. Then, routine mediastinoscopy and anatomical lung resection were performed for the treatment of primary lung cancer. Radical resection of the primary tumor and complete mediastinal lymph node dissection were carried out. The median time from craniotomy to thoracotomy was 26 days (range, 18 to 47 days). Resection was completed with thoracotomy in 15 patients and with video-assisted thoracoscopic surgery in one patient. In all patients, histopathological examination confirmed that the metastasis had the same cell type with the primary tumor and was of pulmonary origin. The clinical data of the patients are presented in Table 1.

No patient received neoadjuvant radiotherapy or chemotherapy. The adjuvant therapy decision as well as the type and regimen of adjuvant therapy were based on the postoperative pathological stage and oncology consultation with a medical oncologist and a radiation oncologist. Postoperative adjuvant therapy was given to eight patients (50%): WBR alone in two (12.5%); WBR with systemic chemotherapy in four (25%); and WBR, systemic chemotherapy, and thoracic radiation therapy in two (12.5%). The median dose of WBR was 35 gray (Gy) (range, 25 to 40 Gy).

A total of six patients received systemic chemotherapy. Five of the patients received three or more cycles of either cisplatin plus vinorelbine or carboplatin plus vinorelbine combination. One patient received six cycles of cisplatin and pemetrexed combination plus 21 cycles of pemetrexed maintenance therapy.

The surgical intervention was carried out as right upper lobectomy in five, right lower lobectomy in one, right lower lobectomy+upper lobe posterior segmentectomy in one, left upper lobectomy in two, left lower lobectomy in four, right pneumonectomy in one and left pneumonectomy in two patients (Table 2).

Table 2. Resection types

	n	%
Lobectomy	13	
Right upper lobectomy	4	
Right upper lobe sleeve resection	1	
Right lower lobectomy	1	81.25
Right lower lobectomy + upper lobe posterior segmentectomy	1	
Left upper lobectomy	2	
Left lower lobectomy	4	
Pneumonectomy	3	
Right pneumonectomy	1	18.75
Left pneumonectomy	2	

Histological type was reported as adenocarcinoma in 13 patients and squamous-cell carcinoma in three patients. According to the pathological staging following resection, 10 patients (62.5%) had no lymph node metastasis (N_0), while two (12.5%) had a hilar (N_1) and four (25%) had a mediastinal (N_2) lymph node metastasis. The cranial metastases varied from 2 to 4 cm masses which were mainly located in right frontal, left temporal and left occipital lobes.

Following pulmonary resection, mortality occurred in one patient (6.25%). The patient who received gamma-knife radiosurgery due to solitary brain metastasis and then underwent mediastinoscopy and right pneumonectomy due to an adenocarcinoma died secondary to pneumonia and respiratory failure in the postoperative 10^{th} day. The postoperative pathological stage was reported as $T_3N_1M_1$. This was the only surgery-related mortality in our patient population.

Three patients experienced thoracic surgery-related complications including pneumonia, supraventricular tachycardia, and incision site infection which all were treated medically. No surgery-related morbidity or mortality occurred after cranial interventions.

The median follow-up was 15 months (range, 0 to 32 months). Six patients are still alive and disease-free at 32, 26, 26, 20, 17, and 14 months, respectively, following pulmonary resections. One of these patients who had left lower lobectomy underwent right middle lobectomy due to relapse at 31 months and the patient is still being followed-up as disease-free. Four patients died due to recurrent brain metastases. Hydrocephalus developed in one of these patients at 11 months after surgery. The cause of death was secondary to local relapses and widespread bone metastases in two patients. Other four patients died due to several reasons such as chemotherapy complication and pneumonia, not secondary to relapse, during follow-up.

The median survival time was 15.3±8.6 months (range, 0 to 32 months). The estimated mean survival time was found to be 18.4 months using the Kaplan-Meier plot (Figure 1). One- and two-year survival rates were 56.2% and 32%, respectively.

The number of brain metastases (solitary/oligo), treatment type (craniotomy/gamma-knife), cell type (adenocarcinoma/squamous-cell carcinoma), resection type (lobectomy/pneumonectomy), and status of lymph nodes ($N_0/N_1/N_2$) did not affect survival statistically significantly ($p>0.05$) (Table 3).

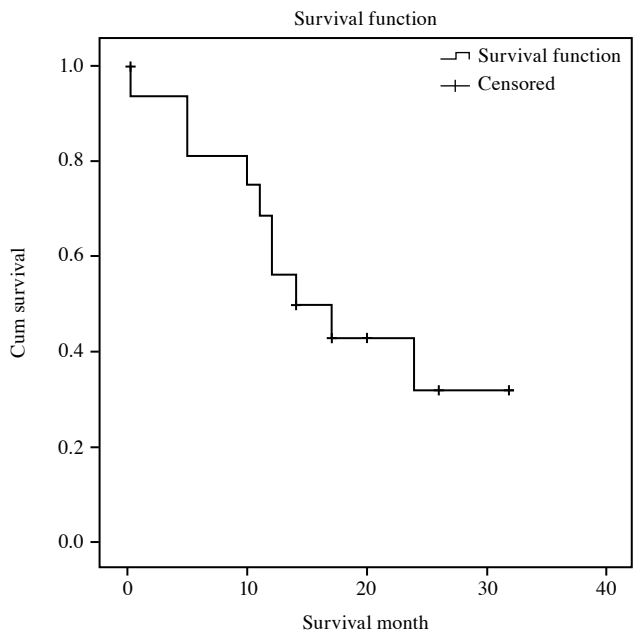

Figure 1. Survival following lung resection.

Table 3. Impact of variables on survival

	n	Mean±SD	*p*
Number of brain metastases			0.66
Solitary	15	15.6±8.9	
Oligo	1	12±0	
Treatment type of brain metastases			0.14
Cranial surgery	12	17.2±8.6	
Gamma-knife radiosurgery	4	9.8±7.0	
Cell type			0.63
Adenocarcinoma	13	15.6±8.6	
Squamous-cell carcinoma	3	14±10.8	
Resection type			0.31
Lobectomy	13	16.5±7.4	
Pneumonectomy	3	10.4±13.7	
Lymph node (N) status			0.30
N_0	10	17.3±8.2	
N_1	2	6.2±8.3	
N_2	4	15±8.8	

SD: Standard deviation.

DISCUSSION

Emergence of brain metastases within the course of NSCLC indicates an ominous prognosis. Median survival time without treatment for brain metastases is usually one to two months. Although the use of corticosteroids contributes to rapid improvement of neurological symptoms, it does not prolong survival more than three months. Whole brain radiotherapy alone considerably improves neurological symptoms; however, it can contribute to median survival time with only three to six months. In addition, this treatment carries the risk of development of dementia.[1,3,5]

Significant reductions in mortality and morbidity have been achieved with the progress of novel techniques in neurosurgery and the rising standards in postoperative care. Therefore, surgical removal of solitary brain metastases prolongs survival and improves the quality of life.[1,3] Currently, stereotactic radiosurgery and gamma-knife radiosurgery can be a reason for preference, when craniotomy is not suitable in patients with multiple metastases and due to the localization of the lesion and to avoid from postoperative complications. Some authors showed that stereotactic radiosurgery and gamma-knife radiosurgery were as effective as surgical resection in local control of brain metastases.[6-8] In our study, gamma-knife technique was used in 25% patients (n=4). One patient with cerebellar metastasis was ineligible for surgery. Another patient with oligometastases with three metastatic sites and other two patients also underwent gamma-knife radiosurgery. According to our results, there was no significant difference in survival rates between craniotomy and gamma-knife radiosurgery ($p>0.05$).

Improved survival and disease-free interval results were reported with combined brain and lung surgery in selected cases with stage IV NSCLC with solitary brain metastasis.[3,9-12] In the literature, various prognostic factors have been proposed for the definition of this patient group who is considered to benefit from bifocal surgery.[1,3,6,10] Therefore, the importance of several parameters is emphasized for prolonged survival in stage IV NSCLC patients with synchronous brain metastases.

Mussi et al.[9] found that N_0 patients had higher survival rates, compared to N_1 and N_2 patients with NSCLC and synchronous/metachronous metastases. In addition, lobectomy was found to be associated with prolonged survival. As N_0 patients who are not suitable for lobectomy would derive more benefit from bifocal surgery, the authors suggested a good staging and careful patient selection. They also revealed that squamous-cell carcinomas were associated with prolonged survival.

Different from the aforementioned study, Granone et al.[10] and Bonnette et al.[13] found statistically significantly higher survival rates in patients with adenocarcinoma ($p=0.019$). However, in the present study, we found no significant effect of the cell type and resection type on survival ($p>0.5$).

In a prospective multi-center study by Endo et al.[14] in which the efficacy of surgery in the treatment of non-N_2 oligometastatic NSCLC patients was investigated, clinically $T_{1-2}N_{0-1}$ lung cancer patients with metastatic lesion in one organ were found to be eligible for surgical resection and that a five-year survival rate around 40% could be expected in this patient group. Also, in this study, the adjuvant therapy following surgery, the cell type and size of the primary tumor did not affect survival significantly. In a review supporting these results, the authors reported that survival after metastasectomy was shorter in intrathoracic stage III patients, compared to stage I and II patients.[15] The authors concluded that the indications should be limited to stage I and II diseases to achieve good results following surgery in oligometastatic NSCLC patients.[15]

In another study, Burt et al.[16] demonstrated that locoregional spread was not effective in patients with synchronous metastases; however, complete resection of the primary disease prolonged survival. Inconsistent with the aforementioned findings, Billing et al.[1] reported that locoregional spread was an important prognostic factor, and N_1 and N_2 metastases adversely affected survival in NSCLC patients with synchronous brain metastases. Of note, many studies supporting these data are available in the literature.[1,3,8,17]

Based on these studies, it is suggested that a selected group of NSCLC patients with brain metastases without lymph node metastasis may gain much more benefit from surgical resection than the other patient groups. There are several studies suggesting mediastinoscopy to meet this goal.[18,19] Therefore, we performed standard cervical mediastinoscopy in all patients to evaluate the status of the mediastinal lymph nodes before pulmonary resection. We completed the lung resections, when the frozen-section examinations of lymph nodes resulted negative. Despite this effort, we found mediastinal lymph node metastasis in four patients in the postoperative staging. However, mediastinal lymph node metastases in three of these patients were in the aortopulmonary lymph node stations that were unreachable with standard cervical mediastinoscopy. Unfortunately, two of four patients with N_2 in the pathological staging died in the postoperative 5^{th} and 12^{th} months. Other two patients are still being followed-up as alive and disease-free at 17 and 26 months, respectively. In our study, we found that lymph node metastases did not have a significant impact on survival ($p>0.05$). However, our sample size was small to establish a definite conclusion.

In a randomized study by Patchell et al.,[20] patients who received WBR following surgery had significantly prolonged survival than those treated with WBR alone without surgery. However, WBR alone should be limited to selected patients due to its high morbidity and undesired effects. In our series, postoperative adjuvant therapy was given in eight patients (50%); WBR alone in two (12.5%), WBR with systemisc chemotherapy in four (25%); and WBR, systemic chemotherapy, and thoracic radiation in two (12.5%). The median dose of WBR was 35 Gy (range, 25 to 40 Gy). Therefore, our findings are inconclusive to propose therapeutic benefits of these treatment options and their definite effects on survival due to our small sample size.

This study has some limitations. First of all, this is a retrospective study. However, patient data were recorded attentively in our hospital. Secondly, the results of the study represent a single center. However, our institution is a reference hospital which accepts patients from many surrounding hospitals.

In conclusion, our results indicate that combined brain and lung surgery in non-small cell lung cancer patients with synchronous brain metastases is an effective treatment method in controlling clinical presentation and prolonging survival. Our experiences and the encouraging data in the literature which increase day by day demonstrate the contribution of bifocal surgery to survival and disease-free interval in this patient population. To provide better survival and disease-free interval, prognostic factors such as N_0 disease, locoregional spread of tumor and complete resection should be taken into consideration as selection criteria for patient subgroups. Further large-scale, prospective studies which will be carried out in the future might strengthen the position of surgery in non-small cell lung cancer patients with synchronous metastases.

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