RESECTION OF SINGLE BRAIN METASTASIS IN NON-SMALL-CELL LUNG CANCER: PROGNOSTIC FACTORS

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Combined resection of primary non-small-cell lung cancer and single brain metastasis is reportedly superior to other treatments in prolonging survival and disease-free interval. To identify prognostic factors that influenced survival we reviewed clinical records and follow-up data of 52 consecutive patients with non-small-cell lung cancer and single brain metastasis who had been evaluated for combined lung and brain operation: 19 had synchronous and 33 metachronous non-small-cell lung cancer and single brain metastasis. Seven patients were excluded from combined operation because of either early brain relapse after craniotomy or single brain metastasis localization in deep brain structures. Forty-one of the 45 patients who underwent combined operation had complete remission of neurologic symptoms. Actuarial 5-year survival from the second surgical intervention was 16% (median 19 months, range 1 to 104 months). N0 status and lobectomy were the only variables associated with longer survival. Actuarial 5-year survivals in patients with synchronous and metachronous presentation were 6.6% and 19%, respectively. In patients with metachronous presentation the length of survival was significantly associated with N0 status, lobectomy, and interval between lung and brain operation equal to or longer than 14.5 months. The subset of patients with N0 status and interval between operations longer than 14.5 months had a 61% 5-year survival. None of the patients with N1-2 disease and shorter interval between operations was alive at 20 months. These data indicate that prognostic factors may help to identify subsets of patients with markedly different outcomes after combined lung and brain operation. (*J Thorac Cardiovasc Surg* 1996;112:146-53)

The brain is a common site of non-small-cell lung cancer (NSCLC) relapse.¹ It has been estimated that in the United States about 40 thousand patients each year will have brain metastasis from NSCLC.² Pathologic studies have shown that single brain

metastasization occurs in one third of the whole population of patients with brain metastasis from NSCLC.³⁻⁷ It is evident, therefore, that a considerable number of patients with NSCLC undergo evaluation for removal of single brain metastasis (SBM). It has been repeatedly demonstrated that combined operation of primary NSCLC and SBM is superior to other treatments in prolonging survival and disease-free interval.^{2, 8-29} The aim of this paper was to ascertain whether survival could be affected by prognostic variables of both NSCLC and SBM and the time interval between the two surgical procedures.

Patients and methods

We reviewed the clinical records and follow-up data of 52 patients with NSCLC and SBM who, between January 1975 and June 1992, were evaluated for radical combined lung and brain operation.

In 19 patients the pulmonary and brain lesions were synchronous with neurologic symptoms as first clinical

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Table I. Clinical characteristics of 15 patients with synchronous presentation of lung cancer and SBM treated by combined operation

	n
Male/female	15/0
Median age (yr)	56.3
Range (yr)	41-68
Lung cancer	
Lobectomy/pneumonectomy	13/2
Right/left site	7/8
Upper/lower location	12/3
Median size (cm)	4
Range (cm)	2-9
Histologic type	
Squamous	6
Adenocarcinoma	7
Undifferentiated	2
T1-2/T3 status	13/2
N0/N1-2 status	8/7
Brain metastasis	
Right/left site	10/5
Supratentorial/infratentorial location	12/3

SBM, Single brain metastasis.

presentation. Fifteen of these patients underwent combined brain and lung resections. Brain operation preceded lung resection in all cases (median interval 1 month) to control neurologic symptoms and to avoid central nervous system complications after pulmonary resection. The clinical characteristics of these patients are reported in Table I. Lung resection was not done in four patients because of early brain relapse after craniotomy.

In 33 patients SBM was diagnosed in a time interval equal to or longer than 2 months after NSCLC resection (metachronous presentation). Thirty of these patients underwent combined lung and brain resection with a median interval of 14.5 months (range 2 to 45 months). The clinical characteristics of these patients are reported in Table II. Brain resection was not done in three patients because of localization of the metastases in deep brain structures (medulla oblongata or basal ganglia).

The lung and brain resection was defined as complete according to standard rules. Margins of brain and lung resections were negative for neoplastic infiltration at microscopic examination. All the resected lung specimens were examined pathologically according to the TNM system.³⁰ Differences between lung and brain histologic types were excluded by careful pathologic review of lung and brain neoplastic tissue of each patient.

Six of seven patients with synchronous presentation and N1-2 status and 5 of 11 patients with metachronous presentation and N1-2 status received various regimens of adjuvant chemotherapy after lung operation. Eight patients, two with synchronous and six with metachronous presentation, underwent whole brain irradiation with 30 Gy in 15 fractions over 4 weeks. Three patients with T3 tumors and metachronous presentation of SBM underwent chest wall radiotherapy after en bloc resection.

Table II. Clinical characteristics of 30 patients with metachronous presentation of lung cancer and SBM treated by lung and subsequent brain operation

	n
Male/female	26/4
Median age (yr)	57.5
Range (yr)	33-72
Lung cancer	
Lobectomy/pneumonectomy	22/8
Right/left site	12/18
Upper/lower location	26/4
Median size (cm)	4
Range (cm)	2-10
Histologic type	
Squamous	9
Adenocarcinoma	12
Undifferentiated	9
T1-2/T3 status	22/8
N0/N1-2 status	19/11
Brain metastasis	
Median interval (mo)	14.5
Range (mo)	2-45
Right/left site	16/14
Supratentorial/infratentorial location	24/6

SBM, Single brain metastasis.

Survival time was measured from the date of the second surgical procedure (lung for patients with synchronous presentation and brain for patients with metachronous presentation) until death or the most-recent date of follow-up (December 1993) for those surviving. Survival was estimated by the Kaplan-Meier method³¹ and comparisons of survival for univariate analysis were estimated by Mantel-Cox and Breslow tests.^{32,33} Frequency data analysis was estimated by Fisher's exact test. The results were considered significant at the 0.05 level ($p < 0.05$).

Results

There were no operative deaths. Complete remission of the neurologic symptoms was obtained in 41 of the 45 patients who underwent combined operation. The actuarial overall 5-year survival was 16% with a median survival of 19 months (range 1 to 104 months) (Fig. 1). Thirty-six patients had relapse and died of the tumor. Table III reports sites of relapse and disease-free interval from the second surgical intervention. A 77-year-old patient with a 47-month disease-free interval from time of brain operation died of cerebral ictus. By the univariate model (Table IV), the following did not affect survival: sex; age; site, size, location, histologic type, and T status of lung cancer; site and location of SBM; synchronous or metachronous presentation; and adjuvant therapy. By contrast, survival was significantly af-

Fig. 1. Actuarial 5-year survival of all patients treated by combined lung and brain operation. Median survival was 19 months for all patients. Patients with synchronous and metachronous presentations had median survivals of 18 and 19 months, respectively.

Table III. Site of relapse and disease-free interval of 36 patients treated by combined lung and brain operation who had relapse

Site of relapse	n (%)	Median disease-free interval in months (range)
Local		
Thorax	14 (39)	13.5 (2-95)
Brain	8 (22)	14.5 (2-23)
Systemic	14 (39)	2 (1-54)

ected by type of lung resection (lobectomy versus pneumonectomy) (Fig. 2) and N status (N0 versus N1-2) (Fig. 3).

The 5-year survival rate of the 15 patients with synchronous presentation was 6.6% with a median survival of 18 months (Fig. 1). Fourteen of the 15 patients died within 30 months. Only one patient survived more than 5 years (63 months). The only variable that was significantly associated with a longer survival was the presence of squamous lung cancer ($p = 0.02$).

The 5-year actuarial survival of the 30 patients with metachronous presentation was 19% with a median survival of 19 months (Fig. 1). The variables

Table IV. Univariate analysis of 45 patients with lung cancer and SBM (synchronous and metachronous) treated by combined operation

Variables	p Value
Male vs female	NS
Age <57 vs ≥ 57 yr	NS
Lung cancer	
Lobectomy vs pneumonectomy	0.040
Right vs left site	NS
Size <4 vs ≥ 4 cm	NS
Upper vs lower location	NS
Squamous vs nonsquamous histologic type	NS
T1-2 vs T3 status	NS
N0 vs N1-2 status	0.009
Brain metastasis	
Synchronous vs metachronous presentation	NS
Right vs left site	NS
Supratentorial vs infratentorial location	NS
Adjuvant therapy	NS

NS, Not significant; SBM, single brain metastasis.

associated with a longer survival (Table V) were the type of lung resection (median survival of patients who underwent lobectomy and pneumonectomy was 27 and 4 months, respectively), the N status (median survival of patients with N0 and N1-2 tumors was 37

Fig. 2. Actuarial 5-year survival according to type of lung operation in 45 patients who underwent combined lung and brain operation. Median survival of patients who underwent lobectomy and pneumonectomy was 20 and 5 months, respectively.

and 4 months, respectively), and the median interval between lung and brain operation (≥ 14.5 months versus < 14.5 months) (Fig. 4).

With grouping of the 30 patients with metachronous presentation according to N status and interval between the two surgical procedures, the longest 5-year survival (61%) was obtained in patients with N0 status and interval between lung and brain operation equal to or longer than 14.5 months ($p = 0.004$) (Fig. 5). All patients with N1-2 status and interval between surgical procedures shorter than 14.5 months died within 20 months. Combining N status with type of lung operation, there was 29% 5-year survival in the 14 patients with N0 status and lobectomy. Only one of the other 16 patients was alive at 5 years. Although statistical significance in survival was not reached among the small subgroups of patients combined according to type of lung intervention and interval between surgical procedures, the 12 patients who underwent SBM removal after a period equal to or longer than 14.5 months after a lobectomy had an actuarial 5-year survival of 58%. On the contrary, none of the remaining 18 patients was alive after 4 years.

Discussion

The results of this paper confirm previous data of the literature that show that combined lung and brain operation is an effective treatment to control symptoms and to prolong survival in patients with NSCLC and SBM.^{2, 8-29} Indeed, in the present series of patients the median survival was 19 months, whereas the reported median survival in untreated patients or in those treated with other therapeutic modalities does not exceed 6 months.²

Furthermore, the present data indicate that survival is greatly affected by the locoregional extension of the lung tumor. In fact, considering the whole population of patients, type of lung resection and N status were associated with significantly different survival probabilities. Survival was higher in patients who underwent lobectomy and in those who had N0 status with respect to survival in patients who underwent pneumonectomy and those with N1-2 status.

The other variables considered, including synchronous or metachronous presentation, did not attain significant differences as far as survival probability was concerned. However, the survival at 5

Fig. 3. Actuarial 5-year survival according to N stage considering 45 patients who underwent combined lung and brain operation. Median survival for N0 and N1-2 tumors was 28 and 12 months, respectively.

Table V. Univariate analysis of 30 patients with metachronous presentation of lung cancer and SBM treated by combined operation

Variables	p Value
Male vs female	NS
Age <57 vs ≥57 yr	NS
Lung cancer	
Lobectomy vs pneumonectomy	0.024
Right vs left site	NS
Size <4 vs ≥4 cm	NS
Upper vs lower location	NS
Squamous vs nonsquamous histologic type	NS
T1-2 vs T3 status	NS
N0 vs N1-2 status	0.026
Brain metastasis	
Right vs left site	NS
Supratentorial vs infratentorial location	NS
Interval between treatments less than median or greater than or equal to median (14.5 mo)	0.045

NS, Not significant; SBM, single brain metastasis.

years was significantly higher ($p = 0.007$) in patients with metachronous presentation (31%, median 35 months) with respect to survival in patients with synchronous presentation (6.6%, median 18 months) when the time lapse from diagnosis of

NSCLC to death or the date of the most-recent follow-up was considered for the computation, instead of the time from the second surgical intervention. The observation that a metachronous presentation could represent a favorable indication for prognosis was further suggested by the results obtained in the analysis of the prognostic factors in the 30 patients with metachronous presentation. Indeed, a significant increase in survival probability was associated not only with a limited extension of NSCLC (lobectomy versus pneumonectomy and N0 versus N1-2), but also with the length of the median interval between the two surgical procedures (≥ 14.5 months).

Furthermore, the presence of more than one favorable prognostic factor in patients with metachronous presentation was associated with an even longer survival. As an example, patients with N0 status and an interval between interventions equal to or longer than 14.5 months had a markedly different prognosis (median 34 months) with respect to the prognosis in patients with N1-2 status and a shorter interval (median 4 months). Although based on small subsets of patients, this observation points to the relevance of the previously mentioned prognostic indicators to the therapeutic decision. Indeed, patients with poor prognostic

Fig. 4. Actuarial 5-year survival according to interval between lung and brain operation in 30 patients with metachronous presentation. Median survival of patients with interval between treatments 14.5 months or longer was 34 months compared with 12 months for patients with interval less than 14.5 months.

factors will probably not receive great benefit from the removal of SBM.

In the patients with synchronous presentation no definite prognostic factors were identified with the exception of a trend to a longer survival in patients with squamous cell carcinoma.

As concerns adjuvant whole brain irradiation, Magilligan,¹⁷ Catinella,²⁶ and Hankins³⁴ and their associates showed a beneficial effect, whereas Burt and associates² did not find any significant increase in survival after postoperative brain irradiation. In a randomized study Patchell and colleagues³⁵ demonstrated that patients who underwent operation plus whole brain irradiation had significantly longer survival in comparison with patients treated only with whole brain irradiation. Our results based on a small number of patients who received adjuvant whole brain irradiation do not permit us to derive firm conclusions about the usefulness of this therapeutic modality. However, in the present study, the great majority of patients died as a consequence of extracranial relapse of the tumor. This points to the superior relevance of the lung tumor local stage, as compared with that of the SBM, in determining the prognosis of these patients. This is further evidenced in patients with metachronous presentation

who at the time of the most-recent follow-up showed only a 13% rate of brain relapse. Given the high morbidity and the undesirable effects connected with whole brain irradiation, it may be advisable to limit this treatment to selected cases.

The small percentage of cases in which the patient underwent adjuvant chemotherapy and the different therapeutic regimens adopted at different times during the course of the study do not permit us to derive general conclusions on this subject.

The observation of an association of the length of survival with the local stage of the lung tumor in the whole population of patients, as well as with the length of the interval from lung operation to brain relapse in patients with metachronous presentation, permits us to draw some considerations on the therapeutic approach to these patients with dismal prognoses. Although based on a small number of subjects, the results obtained in this study clearly indicate that the removal of SBM in patients with NSCLC has to be considered after accurate evaluation of the prognostic factors involved. With an accuracy reasonably acceptable from the clinical point of view, great differences in the outcome can be anticipated in each patient. In general, it can be said that there are patients in whom removal of

Fig. 5. Actuarial 5-year survival of patients with metachronous presentation of SBM stratified according to N stage and interval between lung and brain operation. Median survival was 34 months for N0, 14.5 months or longer; 4 months for N1-2, 14.5 months or longer; 24 months for N0, less than 14.5 months; and 4 months for N1-2, less than 14.5 months.

SBM could be viewed only as an effective means for symptomatic relief. This is particularly true for patients with locally advanced lung tumors, patients with synchronous presentation, and patients with a short interval between lung operation and brain relapse. In the latter group the observed short-term survival after brain operation is not significantly different from that obtainable with alternative therapies. For this reason, removal of SBM in this subgroup of patients is warranted only in accurately selected cases. By contrast, the excellent results obtained in patients with limited locoregional NSCLC involvement and a long interval between lung operation and brain relapse point to a potential curative effect of SBM removal. This subgroup of patients demonstrates long-term survival by brain operation, a result that cannot be achieved by other treatments.

That a limited locoregional stage of the lung tumor had a favorable bearing on the outcome has been already observed by others.^{17, 21, 24, 25} In agreement with this, Burt and associates² found that patients with complete resection of NSCLC survived significantly longer than those with residual locoregional disease. However, comparison of our data with those of Burt and associates² is not possible

because those authors did not report an analysis of the prognostic factors in the subgroup of patients who had completely resectable locoregional disease.

In conclusion, the data obtained provide further support to the therapeutic approach of combined brain and lung operation in patients with NSCLC and SBM and, furthermore, indicate that accurate disease staging and selection of patients may help identify subsets of patients who will obtain the greater benefit from this procedure in terms of length of survival. Confirmation of these results in a greater study population made of larger subsets of patients with different prognostic characteristics is warranted to better define advantages and limits of this therapeutic procedure.

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