Surgical treatment of brain metastases of lung cancer: retrospective analysis of 89 cases

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Abstract

The records of 89 patients who underwent surgery for solitary or multiple parenchymal brain metastases of lung cancer at the Osaka Center for Adult Diseases between 1978 and 1990 were reviewed with follow up until March 1992. The aim of this retrospective analysis was to identify prognostic features that were associated with a favourable outcome. The benefits of brain tumour surgery were evaluated in terms of the cause of death (brain metastasis, tumour in another organ, or treatment related) as well as the postoperative changes in functional state indicated by the Karnofsky scale. The overall mean survival time was 11.6 months, and the one and two year survival rates were 24% and 8%. The brain lesion itself was the cause of death in only 19% of the patients; the other 81% died of systemic disease. Functional state improved after surgical excision of the brain tumour in 36%, remained unchanged in 53%, and worsened in 11%. These data suggest that surgical intervention is beneficial for patients with parenchymal brain metastases. Variables significantly associated with a favourable prognosis included surgical excision of the primary lesion, adenocarcinoma as the histological diagnosis, the use of adjuvant treatment, especially chemotherapy, a preoperative score of over 80% on the Karnofsky scale, and metastasis confined to the brain with no extracranial metastatic foci or residual primary tumour. Additional but non-significant contributors to a good prognosis included age under 65 or 70 years, early tumour stage (stage 1), curative lung cancer surgery, a single metastatic brain tumour (*v* multiple lesions), a solid tumour (*v* cystic), and a supratentorial location of the brain metastasis. The disease free interval and the cerebrospinal fluid cytology were not significant prognostic factors. On the basis of these findings, it is concluded that the surgical removal of brain metastases of lung cancer should be undertaken if the primary tumour has already been removed whether or not there are extracranial metastases, and that postoperative chemotherapy should generally be given.

A general consensus has not yet been reached as to whether surgical resection or conservative treatment, particularly radiotherapy,¹ is preferable for treating metastatic brain tumours. In general, surgical resection followed by radiotherapy is the most widely used approach for a solitary cerebral metastasis.^{2,3} A randomised trial by Patchell *et al* showed that the combination of surgery and irradiation was superior to irradiation alone.⁴ Moreover, an increase in long term survival after tumour excision has been reported by others.^{5,6}

At the Osaka Center for Adult Diseases, our policy is to provide relatively aggressive treatment for patients with metastatic brain tumours. Our criteria for surgical treatment are reasonable stability of both the primary lesion and any metastases outside the brain and the expectation of a fairly high postoperative quality of life for at least two to three months. When the tumour is larger than a certain size (usually 1 cm) and both improvement in neurological symptoms and prolongation of survival are anticipated, total excision is performed in a single operation. This applies even to multiple brain metastases (up to three) and metastases involving both hemispheres. Sometimes a multiple craniotomy is performed, and the patient's wishes and general condition are given full consideration.

The factors affecting the prognosis of patients with metastatic brain tumours have been considered in the medical literature, but these are complex and involve many variables, making it difficult to draw firm conclusions.

We analysed prognostic factors in 89 surgical cases with solitary or multiple parenchymal brain metastases and evaluated the outcome in relation to postoperative adjuvant treatment, preoperative and postoperative functional state, and the cause of death.

Patients and methods

This was an unselected retrospective series and the study comprised 89 patients who underwent surgical removal of solitary or multiple parenchymal brain metastases of lung cancer. These 89 patients were about 44% of the total number of patients with brain metastasis from lung cancer treated at our institution. They were treated at the Osaka Center for Adult Diseases between 1978 and 1990, and the study includes follow up data until 18 March 1992. Surgery was performed when prolongation of survival and improvement of the quality of life were expected, and one

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Table 1 Prognostic factors associated with the survival of patients with brain metastases from lung cancer

1	Age (over or under 70 years)
2	Treatment of lung cancer (surgical or non-surgical)
3	Histological diagnosis of the brain tumour
4	Progressive extracranial malignancy (lung or other organs)
5	Performance state at the time of craniotomy (Karnofsky scale)
6	Time interval between treatment of the primary lesion and excision of the brain metastasis (more or less than one year)
7	Number of brain metastases (single or multiple)
8	Location of the brain lesion (supratentorial or infratentorial)
9	Type of metastatic brain tumour (solid or cystic)
10	Adjuvant treatment (chemotherapy, irradiation or both)
11	Cerebrospinal fluid cytology (positive or negative)

stage removal of single or multiple (up to three) tumours was possible. That is, patients selected for surgery were likely to either overtly or covertly have a better prognosis. Specific factors that might affect the prognosis (table 1) were evaluated in relation to the mean survival time (table 2) after brain tumour excision. The presence of tumours in other organs was assessed by chest radiographs, bone and tumour scintigraphy, ultrasonography, CT, and other examinations as necessary. Metastatic brain tumours that showed clear ring enhancement on CT and those containing more than 80% fluid were classified as cystic. Brain metastases from small cell lung cancer were usually treated by

Table 2 Relationships between prognostic factors and mean survival time

Prognostic factor	Survival (days)	No of patients	p Value*
Age:			
> 70	368 (62)	75	
≤ 70	294 (67)	14	
> 65	408 (76)	56	
≤ 65	248 (37)	27	
Lung cancer treatment:			
Non-surgical	225 (52)	38	
Surgical	500 (98)	51	<0.005
Stage 1	447 (94)	11	
Stage > 3	297 (41)	24	
Histological diagnosis of type of tumour:			
Adenocarcinoma	510 (97)	52	
Squamous cell	205 (32)	17	
Small cell	192 (38)	8	<0.05
Large cell	177 (46)	12	
Extracranial tumour(s):			
Negative	711 (165)	29	
Positive	250 (37)	60	<0.05
Preoperative performance state:			
100–80%	387 (55)	33	
70–50%	353 (84)	40	<0.005
40%	161 (27)	16	
Interval from treatment of lung cancer to brain surgery:			
≥ 1 year	325 (43)	23	
< 1 year	376 (73)	60	
No of brain tumours:			
One	470 (91)	57	
Multiple	232 (30)	32	
Site of brain tumours:			
Supratentorial (one)	494 (99)	52	
Infratentorial (one)	215 (57)	5	
Type of brain tumour:			
Solid	380 (66)	75	
Cystic	277 (74)	13	
Adjuvant treatment:			
Yes	437 (82)	63	
No	250 (73)	26	<0.05
CSF cytology:			
Negative	373 (66)	80	
Positive	467 (185)	9	

* Kaplan-Meier method. Values are means (SEM).

chemotherapy, radiotherapy, or both without surgery, although the histological diagnosis of small cell carcinoma was sometimes only established after removal of the tumour and such cases were included in our analysis. Chemotherapy and irradiation were given on a case to case basis, as there were no fixed criteria for adjuvant treatment. Whole brain irradiation ranging from 20 Gy (10 irradiation sessions with 2 Gy/day) over two weeks to 50 Gy (20 irradiation sessions with 2.5 Gy/day) over four weeks was performed. Chemotherapy was performed with either carcinostatic agents thought to be effective against the primary lesion or with nitrosourea drugs. In 25 patients, chemotherapy with cis-diaminedichloroplatinum (CDDP) was performed as a specific trial between 1988 and 1990 to evaluate its effectiveness. These data were published elsewhere.⁷ Briefly, during surgery, 100 mg/sq m of CDDP was given intravenously or intra-arterially. During the first year after surgery, the patients were admitted to hospital every three months, or whenever possible, for intravenous administration of CDDP at the same dose (100 mg/m²). It was given 3.2 times to each patient on average. Radiotherapy was given to 11 randomly selected patients to evaluate the efficacy of chemotherapy alone and of chemotherapy combined with radiotherapy. The preoperative and postoperative functional state (Karnofsky score⁸) were studied in relation to the survival time. The differences in mean survival time (Kaplan-Meier method) were compared in relation to each of the prognostic factors, and significant differences were determined by the generalised Wilcoxon test and the log rank test. Both tests were applied to between group differences and the log rank test was used for multiple group differences.

Results

The overall mean survival time was 11.6 months (n = 89). Forty eight patients (54%) survived for six months or longer, 37 (42%) for nine months or longer, 21 (24%) for one year or longer, 12 (13%) for 1.5 years or longer, and seven (8%) for two years or longer.

PROGNOSTIC FACTORS AND SURVIVAL TIME

Age

The patients were divided into those aged 70 years or older at the time of detection of the metastatic brain tumour and those under 70 years of age. No significant difference in the duration of survival was noted between these two groups (fig 1), and this was also the case when the patients were divided into those aged 65 years or older, and those under 65 (table 2).

Surgical excision stage and curative nature of the primary lesion

A statistically significant difference was confirmed between the patients with and without lung cancer excision (table 2). The mean survival time was 358 days when excision of the

Figure 1 Prognostic variables showing no statistically significant differences.

primary lung tumour was performed after surgery for the brain metastasis ($n = 9$) compared with 535 days when lung cancer surgery preceded brain surgery ($n = 42$). The mean survival time was 225 days for patients whose lung tumours were not surgically treated ($n = 38$).

Table 3 Survival in relation to the site(s) of extracranial tumours

Extracranial lesions	Survival (days)	No of patients	p Value*
Tumours only in the lungs	328 (79)	24	< 0.01
Tumours in the lungs and other organs	131 (19)	26	
Tumour in the lungs with or without tumours in other organs	225 (41)	50	< 0.05
Tumours in other organs without any lung tumour	375 (58)	10	

* Kaplan-Meier method. Values are means (SEM).

Table 4 Correlations between adjuvant treatment and survival

Treatment	Survival (days)	No of patients	p Value*
Radiotherapy:			
(+)	243 (29)	37	< 0.005
(-)	484 (100)	52	
Chemotherapy:			
(+)	510 (100)	50	< 0.005
(-)	219 (50)	39	
Adjuvant treatment regimen:			
a no adjuvant treatment	250 (73)	26	< 0.05 (a v b)
b chemotherapy alone	709 (179)	27	< 0.05 (b v c)
c radiotherapy alone	157 (27)	13	< 0.05 (c v d)
d irradiation + chemotherapy	301 (37)	23	

* Kaplan-Meier method. Values are means (SEM).

The lung cancers were staged at the time of pulmonary surgery in accordance with the UICC system (1978). Patients with stage 1 tumours survived longer than those whose tumours were stage 3 or higher, but the difference was not significant (table 2, fig 1). There was also no significant difference in mean survival time between curative and non-curative lung surgery (fig 1).

Histological diagnosis

Adenocarcinoma was associated with a significantly longer survival than the other three histological types of metastatic brain tumour (table 2, fig 2).

Presence of extracranial tumours at the time of neurosurgery

A significantly shorter survival was noted in patients with documented extracranial metastases at the time of neurosurgery compared with those without such metastases (patients in whom the brain was the first site of metastasis) (table 2, fig 2). Among the patients with extracranial tumours, the mean survival time was significantly longer if the tumour was outside the lungs than if a lung lesion was present (table 3).

Preoperative performance state

The patients were divided into three groups according to their preoperative Karnofsky scores: 100–80%, 70–50%, and 40% or lower. There was a significant difference in mean survival time between each group, and the patients with scores of 100–80% had the longest mean survival time (table 2, fig 2).

Figure 2 Prognostic variables showing statistically significant differences.

Interval between treatment of the primary lesion and excision of brain metastases

No difference in mean survival time was found between patients with an interval from treatment of lung cancer to neurosurgery of less than one year and those for whom the interval was more than one year (table 2, fig 1).

Number, type, and location of brain metastases

The mean survival time was longer in patients with a solitary brain metastasis than in those with multiple metastases, but the difference was not significant (table 2, fig 1). Solid tumours were associated with a longer mean survival time than cystic tumours (table 2, fig 1). The outcome was better for solitary supratentorial metastases than solitary infratentorial tumours (table 2), but neither of these differences was significant.

Adjuvant treatment

A significantly longer survival was found in the patients who received adjuvant treatment than

in those who did not (tables 2 and 4, fig 2). Although radiotherapy had no significant effect on the mean survival time, chemotherapy significantly prolonged it, and the combination of chemotherapy and radiotherapy was significantly more effective than radiotherapy alone. The mean survival time of patients who received chemotherapy alone was also longer than that of patients who underwent surgery and received no adjuvant therapy (table 4).

For further analysis, the chemotherapy regimens were divided into those involving CDDP, nitrosoureas (ACNU or methyl-CCNU), and other anticancer agents (cyclophosphamide, vincristine, methotrexate, 5-fluorouracil, tegafur, mitomycin-C, and doxorubicin). Nitrosourea agents produced a considerable variation in response and there was a large standard error. Patients given CDDP had a significantly longer mean survival time than patients given other anticancer agents, but there were no other significant differences in terms of the specific agents given (table 5). Among those receiving chemotherapy alone, four patients in the CDDP group showed

Table 5 Chemotherapy agents and survival time after excision of metastatic brain tumour

Anticancer agent	Survival (days)	No of patients	Statistical analysis*
*a CDDP	457 (70)	25	NS (a v b)
Alone	468 (90)	14	
Plus radiotherapy	309 (56)	11	NS
†b Nitrosourea	543 (241)	8	NS (b v c)
Alone	1284 (706)	2	
Plus radiotherapy	296 (87)	6	NS
‡c Others	243 (43)	17	p < 0.05 (a v c)
Alone	173 (35)	9	
Plus radiotherapy	322 (74)	8	NS

Values are means (SEM). Kaplan-Meier method. *CDDP was evaluated from 1988. †ACNU or MeCCNU. ‡Cyclophosphamide, vincristine, methotrexate, 5-fluorouracil, tegafur, doxorubicin, or mitomycin-C were used singly or in combination.

Table 6 Preoperative and postoperative performance state according to Karnofsky scale score

Postoperative score	Preoperative score			
	30-40	50-60	70-80	90-100
30-40	7	3	0	1
50-60	4	11	0	1
70-80	2	6	24	2
90-100	2	1	7	7

Improved 32 cases; stable 47; deteriorated 10; improvement due to surgery: performance state improved in 13 of 56 cases from lower than to higher than 80% on the Karnofsky scale score.

Table 7 Review of the medical literature on prognostic factors associated with survival in patients with metastatic brain tumour

Authors (total number of patients)	Year	Primary cancer; (surgical case)	Prognostic factors
DiStefano <i>et al</i> ⁵ (101)	1979	Breast cancer (solitary 7)	Brain as initial site of metastasis Tumour free interval Resection of brain metastasis
Galicich <i>et al</i> ²⁰ (78)	1980	All cancers (solitary 78)	Tumour free interval Preoperative performance state Primary tumour
Winston <i>et al</i> ²³ (79)	1980	All cancers (solitary 73, multiple 6)	
White <i>et al</i> ¹⁰ (122)	1981	All cancers (solitary 122)	Location Extent of tumour removal Tissue of origin Age and sex Tumour free interval
Zimm <i>et al</i> , ¹¹ (191)	1981	All cancers (solitary 24, multiple 5)	Solitary tumour Brain as initial site of metastasis Preoperative performance state Age Extent of tumour removal
Chan and Steinbok ¹⁷ (57)	1982	All cancers (solitary 57)	Solitary tumour Tumour free interval Presence of systemic metastases Site of primary tumour Response to total treatment No extracranial lesions
Robin <i>et al</i> ¹⁸ (38)	1982	Lung cancer (non-small cell) (non-surgery)	
Sundaresan <i>et al</i> ¹⁴ (35)	1983	Lung cancer (non-small cell) (solitary 34, double 1)	Presence of local or systemic disease Aggressive treatment of primary tumour Metachronous onset of brain metastasis
Yardeni <i>et al</i> ²¹ (74)	1984	All cancers; (solitary 74)	Solitary tumour Tumour free interval Location of brain metastasis
Sundaresan <i>et al</i> ¹⁹ (125)	1985	All cancers; (solitary 119, multiple 6)	Site of primary tumour Location of brain metastasis Extent of systemic disease Preoperative performance state Histological diagnosis
Pellettieri <i>et al</i> ⁹ (134)	1987	All cancers; (solitary 134)	Location of brain metastasis State on admission Age
Pladdet <i>et al</i> ¹⁶ (214)	1989	All cancers (solitary 38)	Solitary tumour Presence of extracranial tumours Resection of brain metastasis Excision of lung tumour
Nakagawa <i>et al</i> (present case) (89)	1992	Lung cancer (solitary 57, multiple* 32)	Histological diagnosis Presence of extracranial tumours Preoperative performance state Adjuvant treatment

* Up to three tumours.

much longer survival (1057, 928, 801, and 770 days) and two more patients survived 600 days. One of two patients in the nitrosourea group survived six years and three months. These prolonged survivals led to the difference of survival time between chemotherapy alone and chemotherapy plus radiotherapy in the group receiving CDDP and nitrosourea and also led to the significantly longer survival in the group receiving chemotherapy alone in comparison with the group receiving chemotherapy plus radiotherapy.

Cerebrospinal fluid (CSF) cytology

There was no difference in mean survival time between patients with and without positive CSF cytology after brain surgery (table 2).

Cause of death

Five of the 89 patients described were still alive at the time of writing. Among the 84 who died during follow up, death was directly attributable to the brain metastases in 16 (19%) and to tumours in other organs (including the primary lesion) in 65 (77.4%). The remaining three patients (3.6%) died of treatment related complications.

Karnofsky scores before and after surgery

Thirty two of the 89 patients (36%) had an improved score after surgery, 47 (53%) showed no change, and the score decreased in 10 cases (11%). Five patients had a postoperative Karnofsky score of 100% (including one whose preoperative score was 100%) and 43 patients (48%) had a postoperative score of 80%. Of the 56 patients with operative scores below 80%, 13 improved to 80% after surgery (table 6).

Discussion

There have been numerous reports concerning the factors influencing the prognosis of metastatic brain tumours (table 7). Our results indicate that the type of tumour (solid or cystic) is a prognostic factor, as there was a trend toward a worse prognosis for cystic tumours. In these patients, multiple brain metastases and subdural tumours tended to develop soon after neurosurgery, suggesting that dissemination of tumour cells occurred through cystic fluid escape during surgery. In this context, CSF cytology also seems to provide important data. Such cytology was not, however, a significant factor in the present study.

Various authors⁹⁻¹¹ have reported that the prognosis worsens with advancing age. This is believed to be due to physical frailty and reduced tolerance of the brain to radiation and chemotherapy. This finding was not supported in our analysis with cut off points of either 65 or 70 years of age.

In terms of the histological type of lung cancer, the prognosis is best for adenocarcinoma, followed in descending order by squamous cell carcinoma, large cell carcinoma, and small cell carcinoma (the prognosis is particularly poor for small cell carcinoma). The reported frequency of brain metastases is greatest for large cell carcinoma, followed by small cell carcinoma, adenocarcinoma, and squamous cell carcinoma.¹² In our study, as in others, the outcome for brain metastases from adenocarcinoma was relatively good, whereas that for large cell carcinoma was poor.

The prognosis of patients with lung cancer and brain metastases is usually poor, and the estimated median survival is only one to six months in the presence of an active lesion in the lung. It has been reported that surgical removal of both the brain metastasis and the lung lesion yields a better prognosis.^{13,15} In the present study, survival was longer when the primary lesion was surgically removed than when it was treated conservatively, regardless of whether its removal preceded or followed excision of the metastatic brain tumour. Although brain metastases may recur even after excision of the primary lesion, it seems that absence of the primary tumour improves the clinical course after removal of the metastases. Zimm *et al*¹¹ and Pladdet *et al*¹⁶ reported that the prognosis was good when there were no metastases to organs other than the brain, and our findings supported this conclusion. Many other authors have cited the absence of primary and metastatic

tumours outside the brain as a favourable prognostic factor.¹⁴⁻¹⁹ Our data suggest that not only is the prognosis significantly poorer if any extracranial lesions are present, but also that the prognosis is significantly further worsened by the presence of tumour in the lungs, as opposed to other organs.

Many investigators have discussed preoperative functional state as a factor influencing prognosis.^{11-19,20} We also found a significant difference between patients with higher and lower Karnofsky scores, particularly those with scores below 40% and above 80%.

Zimm *et al*,¹¹ Yardeni *et al*,²¹ and many other authors^{5-10,17,20,22} have reported that the prognosis improves as the interval between the treatment of the primary lesion and the surgical removal of brain metastases becomes longer. This was not confirmed in our present study.

A single brain metastasis, as opposed to multiple lesions, is widely considered to be a favourable prognostic factor, and patients with a solitary brain metastasis are thought to be the best candidates for surgery. Few reports are available concerning the surgical treatment of multiple brain metastases, and there have been no previous studies on the prognosis after the excision of such metastases. We found no significant differences in survival after the surgical removal of single metastases ($n = 57$, mean survival time = 470 days) and multiple ($n = 32$, mean survival time = 232 days) metastases. Our patients with multiple metastases had been carefully selected by the number and location of the lesions, however, as well as their general condition. The lack of a significant difference between the two groups may also be due to advances in CT and ultrasonic diagnosis, which allow the accurate identification of small tumours, and to advances in surgical techniques that have made it possible to remove small and deeply situated tumours. Furthermore, the survival of a few patients with multiple metastatic brain tumours was possibly prolonged by aggressive chemotherapy or radiotherapy, plus intrathecal chemotherapy when meningeal carcinomatosis developed after tumour removal.

Several investigators have asserted that the prognosis is worse for infratentorial tumours than for supratentorial tumours, due to the inaccessibility of lesions in the posterior cranial fossa or in regions outside the brainstem.^{9-19,21,23} When such tumours enlarge and seed the cerebrospinal fluid, metastasis is facilitated and the lesion rapidly becomes inoperable when it extends further into the brainstem.

Our findings showed that there was a trend toward a worse prognosis for cystic tumours than for solid tumours. This may indicate that cystic tumour is a factor in poor prognosis. The current surgical procedure for cystic tumours in our institution is to completely aspirate the cyst fluid in an attempt to prevent tumour dissemination, and then to pack the tumour cavity with cotton to maintain pressure on the cyst wall during its excision, thus

reducing the chance that part of the tumour will be left behind. Although we cannot conclusively state that the better results found in recent cases are directly attributable to this technique, the outcome of such patients has indeed improved.

In a study involving non-surgical cases, Robin *et al*¹⁸ found that the response to non-surgical treatment is an important factor in the prognosis of patients with metastatic brain tumours. We found the mean survival time to be significantly shorter in surgical patients who were not given adjuvant treatment. In our opinion, adjuvant treatment should generally follow excision of brain metastases, especially considering that metastatic lesions smaller than 1.0 cm which are not seen on CT can often be shown by MRI postoperatively.

Opinions differ regarding chemotherapy for metastatic brain tumours. We have noted that radiation insensitive tumours may disappear on MRI after combined chemotherapy and irradiation due to enhancement of the radiation effect by chemotherapy. We also sometimes found a heightened response to chemotherapy after radiotherapy, which is probably due to increased tumour penetration by the chemotherapeutic agents as a result of modifications in the capillary endothelium due to irradiation. For these reasons, we are apt to use combined chemotherapy and radiotherapy. Survival time was not increased in the group receiving radiotherapy alone or those receiving chemotherapy plus radiotherapy, however, in comparison with that of the group receiving no adjuvant treatment in the present study. Survival was significantly prolonged in the group receiving combined chemotherapy and irradiation compared with that in the group receiving irradiation alone. There are several probable reasons why radiotherapy had the opposite effect to that expected in patients with brain metastases. Firstly, in the group receiving radiation therapy alone and those receiving chemotherapy plus radiotherapy, cancer lesions outside the brain were not well controlled and patients in those groups died from cancer in other organ(s) even though brain metastases were controlled. Secondly, intentional selection of the treatment regimen was a possibility. That is, there was a tendency for patients who were in better condition to refuse radiotherapy and chemotherapy, whereas radiotherapy alone was selected for patients in the worst condition. Moreover, prolonged survivals among patients receiving CDDP and nitrosourea led to the longer mean survival among patients receiving chemotherapy alone compared with that of those receiving chemotherapy plus radiotherapy. As for the effect of CDDP on lung cancer, antagonistic views have been reported.²⁴⁻²⁷ We tried to evaluate the effects of CDDP on brain tumours from lung cancer and found a significantly higher two year survival rate and longer mean interval from resection of the metastatic brain tumour to local or remote recurrence than those in the two groups treated with other drugs and those who received no chemotherapy.⁷

Opinions also differ as to whether it is better to use a carcinostatic agent to which the primary lesion is sensitive, or to use a lipid soluble nitrosourea that can cross the blood brain barrier. As this barrier already seems to be partially disrupted in patients with metastatic brain tumours, it has been reported that drugs that are effective against the primary lesion are also effective against brain metastases.^{28,29} Therefore, most clinicians advocate the use of carcinostatic agents.³⁰ Surgical specimens sometimes show tumour cell nests in the surrounding brain parenchyma where the blood-brain barrier is presumably still intact, and we have encountered postoperative tumour recurrence in the surgical cavity. These experiences led us to use nitrosourea agents, but we found that the response to these drugs varied considerably (table 5).

In summary, the significant prognostic factors were mode of treatment of the lung cancer, histology of the brain metastases, the presence or absence of extracranial tumour, the preoperative performance state, and the use and type of adjuvant treatment. Surgical excision of the lung tumour, a diagnosis of adenocarcinoma, metastases confined to the brain with no carcinoma confirmed in any other organ, a Karnofsky score greater than 80%, and the use of adjuvant treatment (especially chemotherapy) were the major favourable prognostic factors. The patient's age, the stage of the lung cancer at the time of surgery, the number and location (supratentorial or infratentorial) of the intracranial metastases, and type of metastatic brain tumour (solid or cystic) may also affect the prognosis, although a significant influence was not confirmed in the present study.

When the benefit of surgery was evaluated in terms of changes in functional state, 36% of the patients improved, 53% showed no change, and only 11% deteriorated. These results are somewhat better than those obtained by Sundaresan *et al*¹⁴; 75% of their patients improved or were the same after surgery. It is possible that these results are related to recent advances in CT and other diagnostic imaging techniques, including the ability to perform intraoperative ultrasonography of the brain surface. These techniques facilitate the detection of deep brain tumours and permit surgical removal with less damage to normal brain tissue. Even in patients with multiple tumours, surgical excision generally improved, or at least did not worsen their neurological state. Our analysis of the cause of death implicated the brain lesions in only 19% of the patients. This figure is low compared with the results given in other reports,^{5,11} and may be credited to aggressive surgery followed by adjuvant treatment.

In summary, this retrospective analysis of 89 surgical cases indicates that improved survival of patients with brain metastases of lung cancer can be achieved by surgical resection of the metastatic lesions followed by appropriate chemotherapy, provided that the primary lung tumour has already been resected.

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