

## *Original Articles*

# Clinicopathological Study of Brain Metastasis in Gastric Cancer Patients

YUICHI KASAKURA, MASASHI FUJII, FUMIRO MOCHIZUKI, TETSURO SUZUKI, and TORU TAKAHASHI

Third Department of Surgery, Nihon University School of Medicine, 30-1 Oyaguchi-kamimachi, Itabashi-ku, Tokyo 173-8610, Japan

**Abstract:** Brain metastasis from cancers of the gastrointestinal tract is uncommon; brain metastasis from gastric cancer is rare and its incidence is low. Brain metastasis of gastric cancer is often difficult to treat and is resectable in only a few cases. We have treated three patients who had a solitary brain metastasis after a gastrectomy. These three cases are reviewed along with eight other previously reported cases of brain metastasis to clarify the clinicopathological features and to suggest guidelines for patients with metastatic brain tumors. The clinicopathological features of 11 cases of brain metastasis were analyzed. For comparison purposes, the 11 cases were classified into three groups as follows: a resection group, a chemoradiotherapy group, and a nontreatment group. All the patients had advanced gastric cancer of stage III or more. The resection group had the most survivors, and survival rates decreased in the order of the resection group, the chemoradiotherapy group, and the nontreatment group. There was a statistically significant difference between the resection group and the nontreatment group ( $P = 0.0177$ ). Aggressive multidisciplinary treatment, including a resection, for brain metastasis should improve the quality of life and prolong life expectancy.

**Key Words:** brain metastasis, gastric cancer, treatment indicator

## Introduction

Gastric cancer mostly recurs as peritoneal metastasis. It often recurs in multiple organs and few metastatic lesions are resected. Brain metastasis is often multiple and simultaneous with metastases to other organs, and a resection is uncommon. Most gastric cancer patients with metastasis develop cachexia with peritoneal carcinomatosis and usually die of multiple organ failure.

Reprint requests to: Y. Kasakura  
(Received for publication on Aug. 5, 1999; accepted on Jan. 7, 2000)

Organ failure by metastasis is relatively uncommon as a cause of death, and brain metastasis itself rarely causes death. Generally, the prognosis of patients with metastatic brain tumors is much poorer than that of patients with recurrence in other organs, and the cases of metastasis from gastric cancer are no exception. Many patients die soon after diagnosis, or they suddenly lose consciousness and are later found to have metastasis at autopsy. Brain metastasis of gastrointestinal cancer is infrequent, and metastasis of gastric cancer is also relatively rare.<sup>1-3</sup>

Many studies on brain metastasis from gastric cancer are in the form of case reports.<sup>4-9</sup> We have so far treated three patients who developed a solitary brain metastasis after a gastrectomy, and we were able to prolong their life by resecting the metastatic lesion. These three cases and another eight cases of brain metastasis are reviewed in this study.

## Patients and Methods

### *Patients*

The subjects of this study consisted of 11 patients with brain metastasis of gastric cancer treated at our department over the past 18 years from January 1980 to the end of 1998. They accounted for 0.47% of the total of 2322 cases of gastric cancer treated during the same period at our department.

### *Methods*

The clinicopathological features of all cases were analyzed based on their medical records. The cumulative survival rates were calculated by the Kaplan-Meier method and the difference in survival rates was analyzed by the log-rank test. For all statistical analyses, StatView Version 5.0 software (SAS Institute, Cary,

**Table 1.** Cases with brain metastasis from gastric cancer

Case	Age (years)	Sex	Macroscopic type	Histological type	Type of surgery	Stage	Residual cancer	Curability	Duration from gastrectomy to brain metastasis (months)	Findings of brain metastasis	Treatment of brain metastasis	Survival after brain metastasis (months)
1	53	M	3	Tub 2	DG	III	Margin (+)	C	5.3	Multiple	Chemotherapy	0.2
2	75	F	4	Tub 2	DG	III	Margin (+)	C	5.7	Hemorrhagic	None	0.8
3	69	M	3	Por	DG	IV	Margin (+)	C	2.0	Multiple	Radiotherapy	1.0
4	48	F	3	Por	DG	IV	Margin (+)	C	0.1	Multiple	None	0.5
5	38	M	4	Tub 2	No resection	IV	—	—	2.2 <sup>a</sup>	Multiple	None	0.6
6	74	M	3	Tub 1	TG	III	None	B	18.1	Solitary	Resection + radiotherapy	7.0
7	59	M	4	Por	TG	III	None	B	12.0	Solitary	Resection + chemotherapy	3.4
8	54	M	3	Tub 1	DG	IV	Liver	C	6.7	Multiple	Radiotherapy	2.7
9	53	M	3	Tub 1	DG	IV	None	B	3.8	Solitary	Resection + chemotherapy	6.0
10	46	M	3	Tub 2	DG	III	Liver	C	6.5	Multiple	None	1.3
11	53	M	3	Tub 2	TG	III	None	B	43.7	Solitary	Radiotherapy	6.2

Margin (+), positive surgical margin; Liver, Liver metastasis; Tub 1, well-differentiated adenocarcinoma; Tub 2, moderately differentiated adenocarcinoma; Por, poorly differentiated adenocarcinoma; Curability B, no residual disease but not a high probability of cure; Curability C, definite residual disease

<sup>a</sup>Duration from diagnosis of gastric cancer to brain metastasis

NC, USA) was used, and a *P* value of less than 0.05 was considered to be statistically significant. The histopathological types and classifications were based on the general rules specified in the Japanese Classification of Gastric Carcinoma published by the Japanese Gastric Cancer Association.<sup>10</sup>

## Results

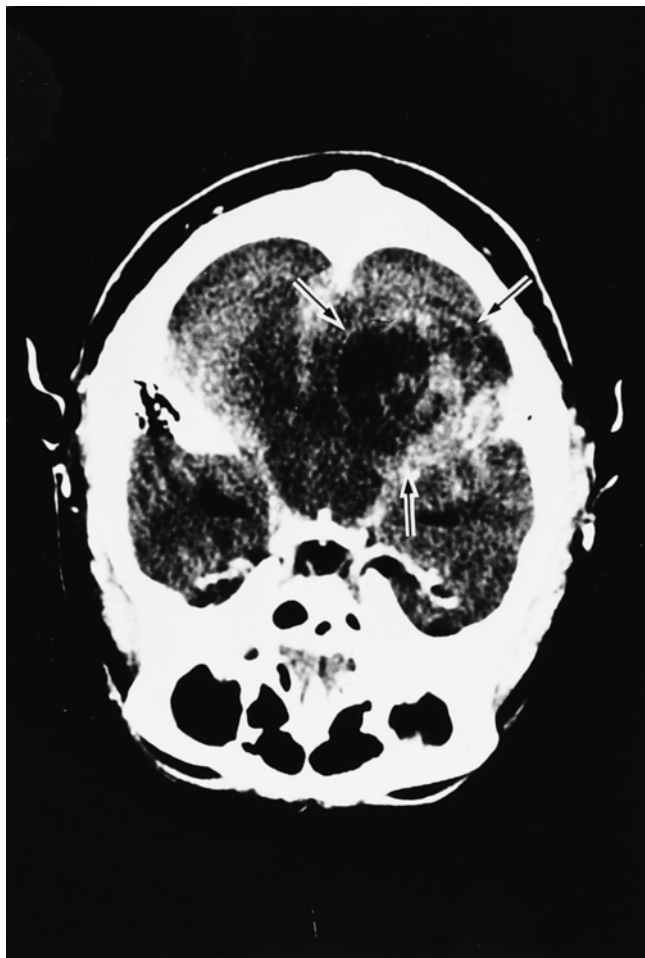
### Clinicopathological Characteristics

There were nine male and two female patients ranging in age from 38 to 75 years (mean age, 54.6 years). Macroscopically, eight cases had type 3 cancers and three had type 4. In addition, eight cases were histologically differentiated while three were undifferentiated. The differentiated type included well- and moderately differentiated adenocarcinoma; the undifferentiated type included poorly differentiated adenocarcinoma and signet-ring cell carcinoma.

All primary lesions of gastric cancer were resected except for one case. All patients had advanced cancer at stage III or more. In six of the ten resected cases, the curability of resection was C (definite residual disease), while in four cases the curability was B (no residual disease but a low probability of cure). Four of the six cases with a curability C resection had a positive surgical margin while the other two cases had liver metastasis. The interval between surgery for the primary lesion and the diagnosis of brain metastasis was less than 1 year in eight cases and over 1 year in three. In seven of the eight patients who developed brain metastasis within 1 year, either surgery resulted in curability C, or the tumor was unresected. In all cases, the diagnosis of brain metastasis was made by a computed tomography (CT) scan after the appearance of cerebral symptoms (headache, mental symptoms, migraine, etc.). Brain metastasis was multiple in seven cases and solitary in four. The curability of resection in all four cases with solitary metastasis was B, and three of them had an interval of more than 1 year between surgery and the occurrence of brain metastasis. One case was complicated by an intracranial hemorrhage.

Three cases were treated with radiotherapy (whole brain irradiation and gamma-knife), one case with solitary metastasis had gamma-knife therapy, and another case received systemic chemotherapy, while four cases could not receive any treatment because of their poor general condition. Metastatic brain lesions could be resected in three cases; two of them received systemic chemotherapy as postoperative adjuvant therapy while the other received radiotherapy.

All the clinicopathological characteristics of individual cases are summarized in Table 1.



**Fig. 1.** Plain computed tomography image of the head (preoperative). A marked tumor with a high-density area and a peritumoral low-density area in the cerebellum (arrows) is observed

#### *Report of a Case Who Underwent a Resection of Brain Metastasis (Case 7)*

A 59-year-old male patient with cancer in the remnant stomach underwent a total gastrectomy achieving a curability B resection. Histological examination of the cancer revealed poorly differentiated adenocarcinoma with invasion into the subserosa with N2 disease (metastasis to the group 2 lymph nodes), but no metastasis to group 3 lymph nodes. He developed para-aortic lymph node metastasis 11 months after surgery, and then 1 month later a solitary metastasis was also discovered in the cerebellum (Fig. 1). As the patient was experiencing headache, nausea, and other symptoms due to cerebral compression, a resection of the brain metastasis was performed (Fig. 2). He received postoperative systemic chemotherapy with a combination of 5-fluorouracil, cisplatin, etoposide, and leucovorin. He died of recur-

rent brain metastasis with bleeding 3.5 months after the brain surgery.

#### *Survival*

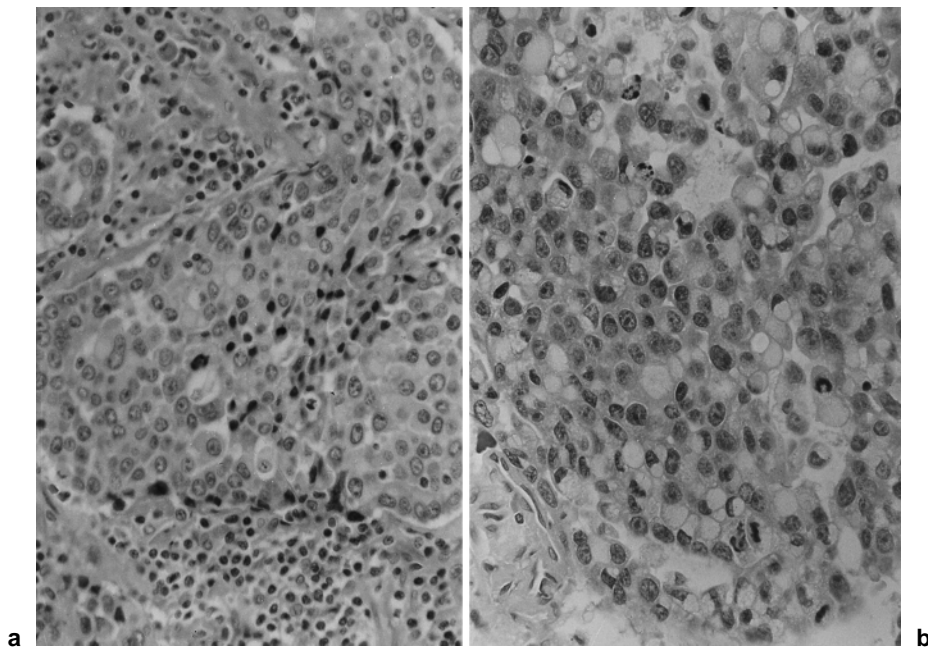
Nine patients died within 6 months after the diagnosis of brain metastasis, five of them within 1 month of diagnosis. The longest duration of survival was 7 months after brain surgery. The 50% survival and mean survival of all 11 cases were 1.3 and 2.7 months, respectively. The 11 cases with brain metastasis were classified into three groups as follows, and between-group comparisons were performed: a resection group (three cases), a chemoradiotherapy group (four cases), and a nontreatment group (four cases). The survival rates decreased in the order of the resection group, the chemoradiotherapy group, and the nontreatment group. The outcome of the resection group was better than that of the nontreatment group ( $P = 0.0177$ ) (Fig. 3).

#### **Discussion**

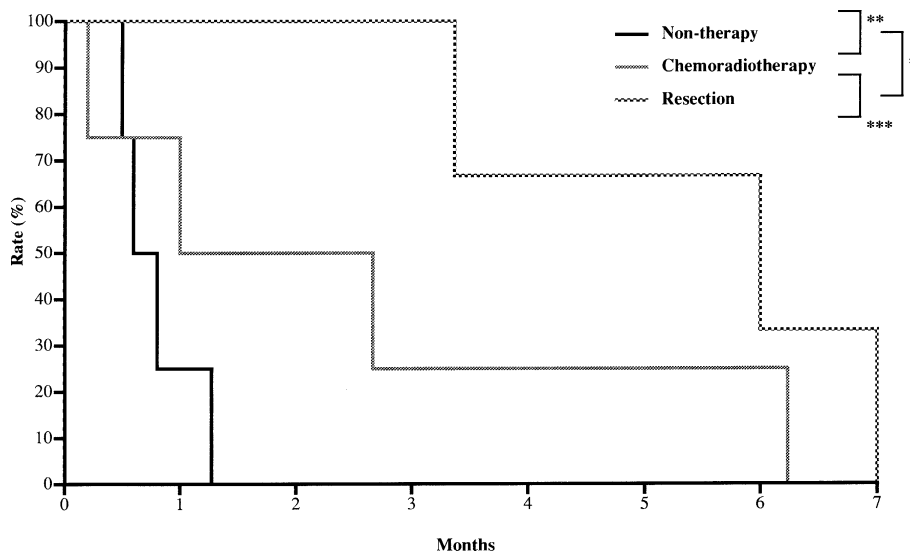
According to the Japanese statistics for brain tumors,<sup>1</sup> metastatic brain tumors account for 13% of all brain tumors. The primary cancer is most often located in the lung, followed by the breast and the gastrointestinal organs. Metastasis to the central nervous system from gastric cancer is mostly lymphogenous and occurs as meningioma, and metastasis to the cerebral parenchyma, which is generally thought to be via the arterial blood flow, is rare.<sup>11</sup> Brain metastasis is most frequent for malignant melanoma (90%), malignant chorioepithelioma (60%), lung cancer (20%), breast cancer (16%), renal cancer (13%), and thyroid cancer (9%). Clinically, brain metastasis of gastric cancer has only been described in about 0.5%–5% of cases.<sup>1,12,13</sup> In a review of autopsies involving carcinomas, intracerebral metastases were found in 8.3% of all cases of gastric cancer.<sup>3</sup> Gastric cancer ranks high as a primary site of metastatic brain tumors, but only because of the large absolute number of patients with gastric cancer. Brain metastasis of gastric cancer occurred in 0.41% of our cases, and these findings are generally similar to the figures in other reports.

In line with other studies,<sup>4–7</sup> all patients in this study had advanced cancer; early postoperative brain metastasis was observed in six cases of curability C resection and one case where no resection of the primary tumor was possible.

A number of reports have described that in many cases (about 50%), gastric cancer with brain metastasis was of a histologically undifferentiated type.<sup>14–16</sup> In this study, however, the proportion of the differentiated type was as high as 72.7%. Since brain metastasis occurs



**Fig. 2.** **a** Primary lesion of the stomach. **b** Metastatic lesion of the brain. Histologically, the primary lesion of the stomach and the metastatic lesion of the brain were both poorly differentiated tubular adenocarcinoma (H&E,  $\times 200$ )



**Fig. 3.** Survival curves after the diagnosis of brain metastasis.  $*P = 0.0177$ ;  $**P = 0.2210$ ;  $***P = 0.2210$

more often in colorectal cancer than in gastric cancer in the United States and Europe,<sup>17</sup> it appears that the incidence of brain metastasis increases in proportion to the absolute number of patients. The ratio of the differentiated type to the undifferentiated type in all of our gastric cancer cases was about one to one, whereas that in advanced cases was about one to two, and undifferentiated type occurred more commonly. From these results, the incidence of brain metastasis should have been higher in the undifferentiated type. However, since all of the cases included in this study were diagnosed by head CT, it seems likely that a large number of patients apparently died before brain metastasis was diagnosed. In other words, the diagnosis of brain metastasis seems

to be made in most cases only after the appearance of some cerebral symptoms.

A case of brain metastasis from submucosal gastric carcinoma has been reported,<sup>8</sup> but this patient had stage IV cancer accompanied by liver metastasis. Most of the reported patients with brain metastasis, including ours, had stage III or more advanced cancer, all of them had lymphovascular invasion or lymph node metastasis, and many also had metastases to other organs. It is difficult to predict brain metastasis, but patients with lymph node metastasis, lymphovascular invasion, or metastases to other organs should be monitored carefully in order to detect brain metastasis.<sup>4-7,9</sup>

Stortebecker<sup>18</sup> reported that the most frequent initial symptoms of brain metastasis are headache, mental symptoms, migraine, vision disorder, and Jackson epilepsy, in that order. The same initial symptoms were also observed in our patients. We used CT scanning to diagnose all of our patients with brain metastasis. One was found to have an intracranial hematoma around the metastatic lesion, while the other ten typically had marked edema around the metastatic lesions.

The selected treatment for metastatic brain tumor depends on whether the metastasis is solitary or multiple. Patients with a solitary metastasis are treated mainly by a resection, and radiotherapy and chemotherapy are the main options for treatment of multiple metastases. Sixty to 70 percent of metastatic lesions are generally believed to be multiple.<sup>19,20</sup> Cases of solitary metastasis are few and, even if metastatic brain lesions are operable, a resection cannot be performed in many patients because of their poor general condition. Yamamoto et al.<sup>21</sup> suggested that, to be suitable for surgery, metastatic brain tumors should satisfy some of the following requirements: (1) a single metastatic lesion in the brain, or if multiple, the lesions should be resectable by a single surgical intervention; (2) a metastatic lesion located in an operable site; (3) no metastasis to any other organs; (4) a good general condition of the patient. In eight of our patients, the metastatic brain lesions were multiple and the tumor was found to have already metastasized to the lymph nodes or other organs at the time of diagnosis. As these patients were at the terminal stage of cancer and in poor general condition, they were inoperable. The three cases resected in the present study satisfied the above requirements. Two cases were found to have abdominal lymph node metastasis, but a resection of brain metastasis was performed in order to improve their quality of life.

Metastatic brain tumors are accompanied by hemorrhages in some cases. Fujita et al.<sup>22</sup> and Mandybur<sup>23</sup> reported that metastatic brain tumors were complicated by intracranial hemorrhages in 4% and 14% of all cases, respectively. An intracranial hemorrhage is not frequent, but it may cause a sudden derangement of consciousness.<sup>22</sup> Many patients with this complication die soon after diagnosis, as we experienced in one patient (case 2).

The prognosis of metastatic brain tumors is generally poor.<sup>9,19,24,25</sup> Harr and Patterson<sup>19</sup> reported a mean post-operative survival of 6 months. Kobayashi et al.<sup>24</sup> reported that, in resected cases, a 3-month survival was 61.5% and 6-month survival was 41.0%. The mean survival of our three patients was 5.4 months after a resection of the metastatic brain lesion. Survival was prolonged in one patient, who returned to his normal

lifestyle without any critical neurological deficits until intra-abdominal recurrence. One study reported that all patients with nonresected metastatic brain tumors died within 2 months.<sup>25</sup> The eight nonresected patients in our study died within 3 months after the diagnosis of brain metastasis.

In this study, we followed 11 cases of brain metastasis of gastric cancer with discouraging outcomes. However, one report described a long-surviving patient who received chemotherapy (FT-207, ACNU) and radiotherapy (<sup>60</sup>Co) and lived for 23 months after a diagnosis of brain metastasis.<sup>26</sup>

In our study, the resection group had a better prognosis than the nontreatment group. One of the factors responsible may have been that the nontreatment group could not receive systemic chemotherapy because of their poor general condition.

## Conclusions

Brain metastasis of gastric cancer is often difficult to treat and it is also rarely resectable. Aggressive multidisciplinary treatment involving surgery, chemotherapy, and radiotherapy is required for both resectable and unresectable cases. The results of this study indicate that a resection of the metastatic lesions both prolongs life while also improving the quality of life.

## References

1. Committee of Brain Tumor Registry in Japan (1990) Brain tumor registry in Japan
2. Weiseberg LA (1979) Computed tomography in intracranial metastasis. *Arch Neurol* 36:630-634
3. Abrams HL, Spiro R, Goldstein N (1950) Metastasis in carcinoma. Analysis of 1000 autopsied cases. *Cancer* 3:74-85
4. Mizushima H, Sasaki K, Hayashi M, Abe T, Doi H, Iwata T, Matsumoto K (1991) Simultaneous operations for primary gastric cancer and metastatic brain tumor. *Showa Univ J Med Sci* 3:175-179
5. Nagahori Y, Sekikawa T, Maeda Y, Ishikawa T, Noguchi A, Sugahara K (1990) Two cases of brain metastasis of gastric cancer (in Japanese with English abstract). *Nippon Rinshogeka Gakkai Zasshi (J Jpn Surg Assoc)* 51:1438-1442
6. Tajima H, Matsuki N, Takeda T, Horichi H, Kumaki T, Shima K (1994) A case of cutaneous and brain metastasis of gastric carcinoma, treated effectively by chemotherapy with CDDP, MMC, etoposide and D' DFUR (in Japanese with English abstract). *Gann to Kagakuryoho (Jpn J Cancer Chemother)* 21:2659-2662
7. Watanabe A, Umehara M, Umehara M, Horiba K, Sasajima K, Yamashita K, Onda M, Node Y (1997) A case of primary squamous cell carcinoma of the stomach with brain metastasis (in Japanese with English abstract). *Nippon Shokaki Geka Gakkai Zasshi (Jpn J Gastroenterol Surg)* 30:1761-1765
8. Nomura T, Yoshikawa T, Kato H, Nikkuni K, Sasaki K, Shira Y, Hatakeyama K (1997) Early gastric cancer manifested as brain metastasis: report of a case. *Surg Today* 27:334-336

9. Kojima Y, Watanabe T, Sanada T, Hiramatsu Y, Nakane Y, Yamamura M, Hioki K, Yamamoto M (1988) A case report of brain metastasis due to an advanced gastric cancer (in Japanese). *Gann no Rinsho (Jpn Cancer Clin)* 34:1731–1734
10. Japanese Gastric Cancer Association (1998) Japanese classification of gastric carcinoma. 2nd English edn. *Gastric Cancer* 1:10–24
11. Levin VA, Dove MF, Landahl HD (1975) Permeability characteristics of brain adjacent to tumors in rats. *Arch Neurol* 32:785–791
12. Kinoshita K (1993) Metastatic brain tumor. In: Takeuchi K (ed) *Hyojun no shinkei gekagaku (Standard textbook of neurosurgery)* 6th edn. Igakushoin, Tokyo, pp 206–208
13. Hanada H (1986) *Noshinkeigekagaku II (Neurosurgery II)* 8th edn. Nagaishoten, Tokyo, pp 661–664
14. Kaibara N, Kimura O, Nishidoi H, Makino M, Kawasumi H, Koga S (1985) High incidence of liver metastasis in gastric cancer with medullary growth pattern. *J Surg Oncol* 28:195–198
15. Noguchi Y (1990) Blood vessel invasion in gastric carcinoma. *Surgery* 107:140–148
16. Adachi Y, Mori M, Maehara Y, and Sugimachi K (1992) Poorly differentiated medullary carcinoma of the stomach. *Cancer* 70:1462–1466
17. Graf AH, Buchberger W, Langmayr H, Schmid KW (1988) Site preference of metastatic tumors of the brain. *Virchows Arch A Pathol Anat Histopathol* 412:493–498
18. Stortebecker TP (1954) Metastatic tumors of the brain from a neurosurgical point of view. A follow-up of 158 cases. *J Neurosurg* 11:84–111
19. Haar F, Patterson RH (1972) Surgery for metastatic intracranial neoplasms. *Cancer* 30:1241–1245
20. Galicich JH, Sundaresan N, Thaler HT (1980) Surgical treatment of single brain metastasis. Evaluation of results by computerized tomography scanning. *J Neurosurg* 53:63–67
21. Yamamoto M, Inagawa T, Kamiya K, Ogasawara H, Monden S (1987) Twenty cases of metastatic brain tumor (in Japanese with English abstract). *Shimanekenritsu Chuobyoin Igaku Zasshi (J Shimane Prefectural Central Hospital)* 14:62–66
22. Fujita K, Matsumoto S (1980) Intracerebral hemorrhage in brain tumors (in Japanese with English abstract). *No Shinkei Geka (Neurol Surg)* 8:935–940
23. Mandybur TI (1977) Intracranial hemorrhage caused by metastatic tumors. *Neurology* 27:650–655
24. Kobayashi S, Kojo N, Miyagi J, Uegaki M, Kobayashi K, Katayama M, Sugita Y, Watanabe M, Kuramoto S (1985) Results of surgical treatment for metastatic brain tumors (in Japanese with English abstract). *No Shinkei Geka (Neurol Surg)* 13:825–830
25. Kim YK, Kawai S, Hisanaga M, Maekawa M, Hirabayashi H, Hattori Y (1985) Results of surgical treatment of metastatic brain tumors (in Japanese). *Osakafuritsu Byoin Igaku Zasshi (Med J Osaka Prefectural General Hospital)* 8:23–25
26. Winston KR, Walsh JW, Fisher EG (1980) Result of operation treatment of intracranial metastatic tumors. *Cancer* 45:2639–2645