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Analysis of Evolving Clinicopathological Features of Metastatic Brain Tumors Over 30 Years of Surgical Management

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Abstract. *We reviewed 232 cases, in which patients underwent surgical resection and histopathological diagnosis of metastatic brain tumor between 1985 and 2014. We analyzed trends in clinicopathological changes present over three decades in a single institution. The most frequent site of metastatic tumors was the frontal lobe. The average patient age and the percentage of female patients increased over the 30-year study period. The most frequent primary cancer was lung cancer, followed by breast cancer; these were the top two primary cancer types over the three decades. However, use of chemotherapy and radiotherapy as standard treatments for postoperative treatment of metastatic brain tumors has increased over the past 20 years. Development of novel, targeted treatments for these cancer types have created new tools for use in the clinical care of patients with metastatic brain tumors. Incorporation of these tools in a multimodal approach is critical in contemporary management of metastatic brain tumors.*

Metastatic brain tumors (MBTs) are one of the most common intracranial tumors occurring in adults. Previous studies have diagnosed MBT in 9.6% of patients with cancer (1) and in 20-40% of autopsy cases (2). MBTs are typically treated using radiation therapy, including whole-brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS). Based on advances in diagnostic imaging and treatment modalities, the number of patients diagnosed with MBT is expected to increase. In addition, development of new targeted molecular therapies for some types of cancer has increased overall survival in patients with MBT. Therefore, evaluation of tumor pathology is important in treating patients diagnosed with MBT.

In order to evaluate changes in the clinicopathological characteristics of this patient population, we reviewed patients with MBTs that were surgically resected at the Fukuoka University Hospital over the past three decades.

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Materials and Methods

All methods used in this study were reviewed and approved by the Ethics Committee of Fukuoka University (No. 15-5-14).

We reviewed 288 cases in which patients were diagnosed with MBT during treatment in the Department of Neurosurgery, Fukuoka University Hospital, between 1985 and 2014. Surgical resection and histopathological diagnosis of MBT took place in 232 out of 288 patients (80.6%). A total of 56 patients were treated without tumor resection, and these patient cases were excluded from this study.

Tumor resection was performed in order to relieve neurological symptoms and to improve activities of daily living (ADL), but did not have prolongation of survival as a primary aim. Patients who underwent surgical resection of a MBT included those in which: a single large (>3 cm) or symptomatic tumor was present; the primary tumor was well-controlled; life expectancy exceeded 3 months; and consent of the patient or family was obtained.

A total of 92 cases were of a single lesion, and 140 cases were multiple lesions. When multiple lesions were present, WBRT (85 cases, 36.6%) or SRS (55 cases, 23.7%) were administered after surgical resection. The treatment modality employed was dependent on the number of residual tumors and on the patient's age. For 75 patients (32.3%) who were diagnosed with MBTs before identification of the primary tumor, subsequent surgical resection of the primary tumor was performed in 18 cases (7.8%). For patients in which the primary tumor was not resected, chemotherapy (73 cases, 31.5%) or palliative treatment (53 cases, 22.8%) was administered, depending on the patients' age, the number and size of tumors, and the cancer diagnosis. In 11 cases (4.7%), details of postoperative therapy were unknown after patients transferred to a new hospital or were lost to follow-up.

Surgically-resected specimens were fixed in 10% formalin and embedded in paraffin blocks. Tissue sections were cut 4 μm thick and stained with hematoxylin and eosin for histopathological examination.

Results

Patient population. Clinical characteristics of the patient population are summarized in Table I. Of 232 cases in which MBTs were surgically resected and pathologically diagnosed, only 34 cases occurred in the first decade. However, the number of MBT cases increased to 98 cases in the second decade and 100 cases in the third decade.

The average age of all 232 patients considered in this study was 60.7±12.6 years. The average age of patients with MBTs tended to increase slightly over the 30-year interval (59.2±10.3 years in the first decade; 60.0±11.5 years in the second decade; and 61.8±14.1 years in the third decade). Male patients (158 cases, 68.1%) outnumbered female patients (74 cases, 31.9%). The percentage of female patients treated increased from 26.5% in the first decade to 33.0% in the third decade, an increase associated with growth in the number of patients with breast and lung cancer treated. The number of breast cancer cases increased from two (5.9%) in the first decade to 11 (11.0%) in the third decade and lung cancer in females increased from five (22.7%) in the first decade to 18 (32.1%) in the third decade.

Major symptoms. The major symptom reported by patients analyzed in our study was increased intracranial pressure (ICP; 108 cases, 46.6%), often associated with headache or nausea. Focal neurological deficits including hemiparesis, aphasia, speech disturbance, visual loss, and ataxia were reported in 65 cases (28.0%). Nineteen patients (8.2%) suffered one or more seizures. Other clinical symptoms reported included altered mental status (11 cases, 4.7%) and cognitive dysfunction (10 cases, 4.3%). Fourteen patients (6.0%) were asymptomatic. There was no noticeable change in symptoms reported across the duration of the study period (Table I).

Characteristics and timing of diagnosis of primary tumor site versus MBT. At the time of diagnosis, 17 MBTs (7.3%) were associated with intratumoral hemorrhage. Of these, 10 cases were lung adenocarcinoma, three were renal cell carcinoma, two were breast cancer, one was cholangiocarcinoma and a single case was undiagnosed. In 75 cases (32.3%), a MBT was diagnosed before the primary tumor. This occurred in 12 cases (35.3%) in the first decade, 27 cases in the second decade (27.6%), and 36 cases in the third decade (36.0%). There was no noticeable change in the characteristics and timing of diagnosis in three decades (Table I).

Location of metastatic site and surgical method. The most frequent location of MBT was the frontal lobe (68 cases, 29.3%). The cerebellum was the second-most common site (51 occurrences of MBT in a cerebellar hemisphere and four occurrences in the vermis; total of 23.7%) (Table I). Other sites in which MBT occurred included spinal cord (four cases, 1.7%), and basal ganglia (three cases, 1.3%). In two cases (0.8%), the primary tumor was intraorbital. MBT in the brainstem, pituitary gland and cavernous sinus occurred in a single case each (0.4%). There was no noticeable change in the location in three decades.

In 228 cases, a craniotomy was performed in order to resect the MBT. In three cases involving the basal ganglia, a biopsy was performed. Finally, in a single case of a MBT occurring in the cavernous sinus, a trans-sphenoidal approach was used (data not shown).

Pathological diagnosis of primary sites. The primary tumor sites giving rise to MBTs are summarized in Table II. In 127 cases (54.7%) the primary tumor was lung cancer. Its histology included adenocarcinoma (68 cases, 53.5%), squamous cell carcinoma (28 cases, 22.0%), small cell carcinoma (17 cases, 13.4%), and large cell carcinoma (5 cases, 3.9%). In nine cases, the primary tumor was not diagnosed (data not shown). Figure 1 shows typical histopathological findings of frequent MBTs. Interestingly, the frequency of breast cancer diagnoses gradually increased over the course of the study period.

Postoperative treatments. Postoperative MBT treatments are summarized in Table III. Over the 30-year analysis period, surgical resection of the primary tumor decreased from 14.7% (five out of 34 cases) in the first decade to 5.0% (five out of 100 cases) in the third decade. Radiotherapy, including WBRT and SRS, was administered to the largest fraction of patients in the second decade (69 out of 98 cases, 70.4%). Treatment with radiotherapy decreased to 58.0% of patients (58 out of 100 cases) in the third decade. Interestingly, chemotherapeutic treatment increased from 17.6% (six out of 34 cases) to 45.0% (45 out of 100 cases) from the first to the third decade, respectively. However, molecular targeted therapy was only used in three cases in three decades. Patients with poor performance status or patients with non-treatment decision (53 out of 232 cases, 22.8%) received best supportive care.

Clinical outcomes. Regarding functional prognosis, patients with scores of ≥80 on the Karnofsky Performance Status rose from 44.4% before treatment to 50.0% after treatment, signifying an improvement in the ADL. Median overall survival was 15.9 months in the second decade, out 16.7 months in the third decade; for the first decade, this was unknown in detail.

Discussion

Advances in imaging technologies have improved MBT diagnosis. At our facility, use of magnetic resonance imaging beginning in 1989 improved MBT detection and diagnosis.

Table I. *Clinical characteristics of metastatic brain tumors.*

	1985-2014	1985-1994	1995-2004	2005-2014
Number of patients	232	34	98	100
Mean age (±SEM)	60.7±12.6	59.2±10.3	60.0±11.5	61.8±14.1
Gender				
Male	158 (68.1%)	25 (73.5%)	66 (67.3%)	67 (67.0%)
Female	74 (31.9%)	9 (26.5%)	32 (32.7%)	33 (33.0%)
Major symptoms				
Increased ICP	108 (46.6%)	18 (52.9%)	37 (37.8%)	53 (53.0%)
Focal neurological deficit	65 (28.0%)	7 (20.6%)	34 (34.7%)	24 (24.9%)
Seizure	19 (8.2%)	2 (5.9%)	10 (10.2%)	7 (7.0%)
Altered mental status	11 (4.7%)	2 (5.9%)	4 (4.1%)	5 (5.0%)
Cognitive dysfunction	10 (4.3%)	1 (2.9%)	5 (5.1%)	4 (4.0%)
Asymptomatic	14 (6.0%)	4 (11.8%)	3 (3.1%)	7 (7.0%)
Diagnosis characteristics and timing				
Intratumoral hemorrhage	17 (7.3%)	0 (0%)	8 (8.2%)	9 (9.0%)
MBT diagnosed before PT	75 (32.3%)	12 (35.3%)	27 (27.6%)	36 (36.0%)
MBT Location				
Frontal lobe	68 (29.3%)	9 (26.5%)	31 (31.6%)	28 (28.0%)
Cerebellum	55 (23.7%)	8 (23.5%)	21 (21.4%)	26 (26.0%)
Occipital lobe	30 (12.9%)	5 (14.7%)	10 (10.2%)	15 (15.0%)
Parietal lobe	29 (12.5%)	5 (14.7%)	14 (14.3%)	10 (10.0%)
Temporal lobe	24 (10.3%)	3 (8.8%)	10 (10.2%)	11 (11.0%)
Skull	14 (6.0%)	1 (2.9%)	9 (9.2%)	4 (4.0%)

ICP, Intracranial pressure; MBT, metastatic brain tumor; PT, primary tumor; SEM: standard error of the mean.

Use of magnetic resonance imaging has also led to more frequent detection of MBTs before identification of the primary tumor. In the cases analyzed in the present study, MBT was diagnosed before the primary tumor for nearly one-third of all patients (75 cases; 32.5%).

Development of new chemotherapies, including genetically targeted 'precision' medicines, has led to an increase in survival for patients with cancer after diagnosis. In combination with improved detection methods for MBTs, these therapeutic advances have led to increases in the number of patients diagnosed with MBT. MBT now stands as the most frequently diagnosed intracranial tumor in adult patients. In the recent past, treatment for MBT was largely limited to radiation therapy, and the number of patients for which surgery was indicated was limited. Therefore, histological evaluation of MBTs, which was rarely performed in the past, has only recently become more common. This has created a valuable database for analyzing trends in MBT characteristics.

Previous work has found that in Japan, the most common primary cancer source for MBTs is lung cancer (45.7% of MBT cases) (3). The most common histological subtypes of lung cancer include adenocarcinoma (53.0% of lung cancer cases), squamous cell carcinoma (13.0%), small cell carcinoma (5.0%), and large cell carcinoma (1.9%). Other types of primary cancer include breast (12.8%), renal/bladder (6.0%), colon (5.7%), and rectal (3.9%) cancer (3). In countries outside of Japan, lung cancer was also reportedly the most frequent cause of MBT, but malignant melanoma was more frequently a source of MBT than renal carcinoma or breast cancer (1).

Table II. *Primary tumor sites reported for metastatic brain tumors.*

Primary site	1985-2014	1985-1994	1995-2004	2005-2014
Lung	127 (54.7%)	22 (64.7%)	49 (50.0%)	56 (56.0%)
Breast	22 (9.5%)	2 (5.9%)	9 (9.2%)	11 (11.0%)
Renal/Urinary	18 (7.8%)	2 (5.9%)	12 (12.2%)	4 (4.0%)
Colon	12 (5.2%)	2 (5.9%)	4 (4.1%)	6 (6.0%)
Gastric	9 (3.9%)	2 (5.9%)	4 (4.1%)	3 (3.0%)
Rectal	7 (3.0%)	0 (0%)	2 (2.0%)	5 (5.0%)
Esophageal	6 (2.6%)	0 (0%)	3 (3.1%)	3 (3.0%)
Head/neck	5 (2.2%)	2 (5.9%)	2 (2.0%)	1 (1.0%)
Melanoma	4 (1.7%)	0 (0%)	2 (2.0%)	2 (2.0%)
Liver	3 (1.3%)	0 (0%)	1 (1.0%)	2 (2.0%)
Other	19 (8.2%)	2 (5.9%)	10 (10.2%)	7 (7.0%)

In the present analysis, we evaluated the incidence of distinct types of primary tumor over a 30-year period. Relative to previous studies, we found few differences in

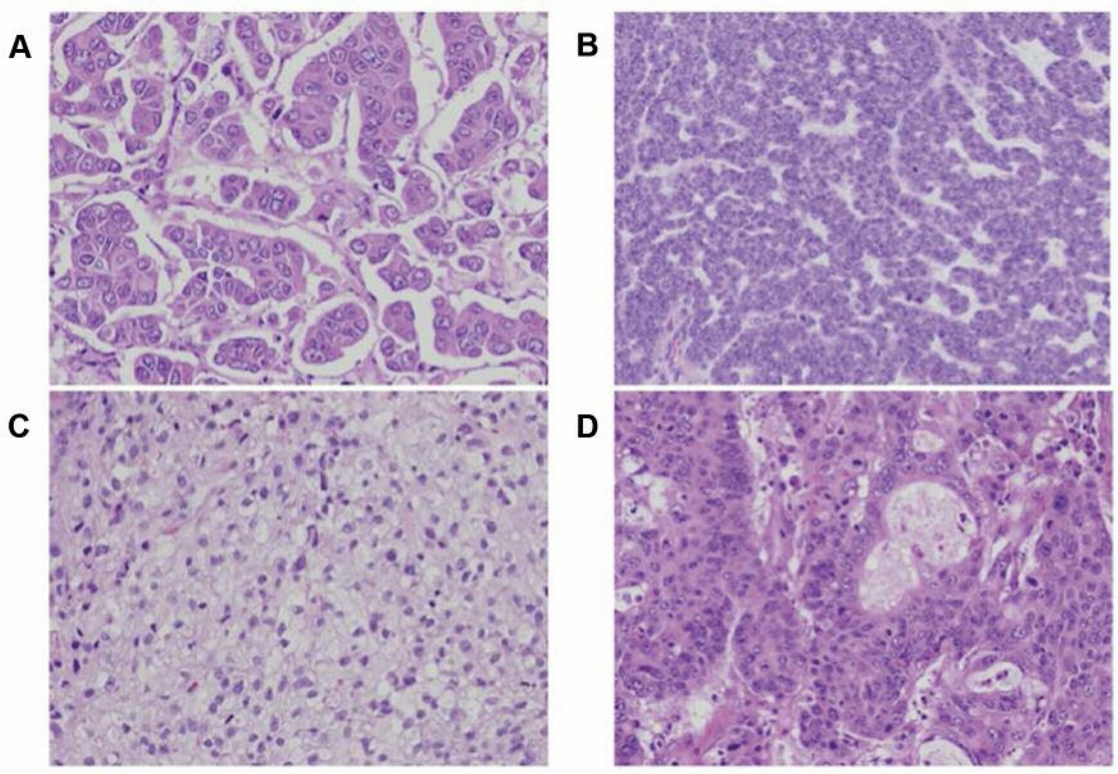

Figure 1. *Histopathological findings of the most frequent types of metastatic brain tumors: lung adenocarcinoma (A), breast cancer (B), renal cell carcinoma (C) and colon cancer (D) (original magnification, ×200).*

Table III. *Postoperative therapy following surgical resection of metastatic brain tumor.*

Postoperative therapy	1985-2014	1985-1994	1995-2004	2005-2014
Surgical resection of primary tumor	18 (7.8%)	5 (14.7%)	8 (8.2%)	5 (5.0%)
Chemotherapy	73 (31.5%)	6 (17.6%)	22 (22.4%)	45 (45.0%)
Radiotherapy	140 (60.3%)	13 (38.2%)	69 (70.4%)	58 (58.0%)
WBRT	85 (36.6%)	13 (38.2%)	37 (37.8%)	35 (35.0%)
SRS	55 (23.7%)	0 (0%)	32 (32.7%)	23 (23.0%)
BSC	53 (22.8%)	7 (20.6%)	21 (21.4%)	25 (25.0%)
Unknown	11 (4.7%)	7 (20.6%)	2 (2.0%)	2 (2.0%)

WBRT, Whole-brain radiation therapy; SRS, stereotactic radiosurgery; BSC, best supportive care. For each value, the total number of patients is indicated, followed by the percentage of patients in parentheses.

the distribution of primary cancer incidence. The sole exception was breast cancer, which increased in incidence. We speculate that increased breast cancer morbidity has led to increased occurrence of this cancer as a source of MBTs (4).

MBT is associated with stage IV primary carcinoma, in which cancer has spread from the source tumor to other parts of the body. Standard treatment for MBT is radiotherapy. In randomized clinical trials conducted in the early 1990s, patients with a single metastatic brain lesion who received combination treatment of surgical resection and WBRT had a better prognosis relative to patients who received radiotherapy only. Improved outcomes associated with the combination treatment included fewer tumor recurrences in the brain and better quality of life. Therefore, combination treatment became the standard treatment approach for single MBTs (5, 6).

In the early 2000s, as commercially developed SRS technologies such as Gamma Knife, CyberKnife, and Novalis Radiosurgery became more widely used, the efficacy of SRS approached that of combination therapy (7). SRS has been particularly important for treating specific patient populations such as elderly people, because the speed of treatment precludes the need for prolonged hospitalization. In addition, low-dose SRS (16-18 Gy) was not significantly inferior to SRS with 20 Gy in elderly patients (8). Radiotherapy continues to be the mainstay for MBT treatment at present. In our analysis, we found that radiotherapy was the most widely employed follow-up treatment after surgical resection of MBT over the course of the 30-year period we analyzed.

New anticancer drugs were introduced in the 1990s. However, chemotherapy was considered to have little efficacy in the treatment of MBTs, because the blood–brain barrier prevented chemotherapeutics from reaching the brain. In both lung and breast cancer, however, development of new, targeted therapies has impacted the incidence and management of MBTs. The presence of epidermal growth factor receptor (*EGFR*) mutations and echinoderm microtubule-associated protein-like 4 (*EML4*)–anaplastic lymphoma kinase (*ALK*) fusion genes in non-small cell lung cancer have been identified, and the high response rate to molecular targeted drug has attracted attention (9-14). Gefitinib, a selective small-molecule tyrosine kinase inhibitor of EGFR, showed efficacy in 32% of patients in a study of 40 patients with MBTs arising from primary lung adenocarcinoma (15). Treatment with tyrosine kinase inhibitor (*e.g.* gefitinib, erlotinib, afatinib) was associated with a median survival time of 15-20 months, and progression-free survival for those with MBT reaches 6.6-11.7 months (16). The incidence of MBT for human epidermal growth factor receptor 2 (HER2)-positive breast cancer is approximately 30-40% (17, 18). Trastuzumab, a monoclonal antibody-based therapy targeting HER2, has become widely used in treatment of HER2-positive cancer, affecting management of MBTs. Lapatinib, a tyrosine kinase inhibitor that disrupts HER2 and EGFR signaling, is a small-molecule that crosses the blood–brain barrier and has shown efficacy in extending survival for patients with MBT (19-21).

In these carcinomas, targeted therapies may improve patient prognosis. Histological and genetic evaluation is essential for these treatments. When obtaining a tissue sample from the primary tumor is difficult, tissue from the MBT may be required.

In many cases in which improved diagnostic imaging tools have led to diagnosis of the MBTs before the primary tumor, surgical treatment of the MBT may be considered. In this study, we found no difference between the second and the third decade in median overall survival because there were only three cases using molecular targeted therapy. In the treatment of the MBT, a multimodal treatment strategy incorporating chemotherapy (included new genetically targeted treatments), surgical treatment and radiotherapy are vital to improving patient outcomes.

We reviewed surgical management of MBTs and clinicopathological features of these tumors treated at our institution over the past 30 years. Lung and breast cancer gave rise to many MBTs, and novel genetically-targeted therapies have provided new treatment options for these conditions. Therefore, it is important to integrate multimodal therapy options including chemotherapy, radiation and surgical therapy based on histopathological diagnosis of tumors in the treatment of MBTs.

Conflicts of Interest

The Authors have no conflicts of interest to declare in regard to this study.

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