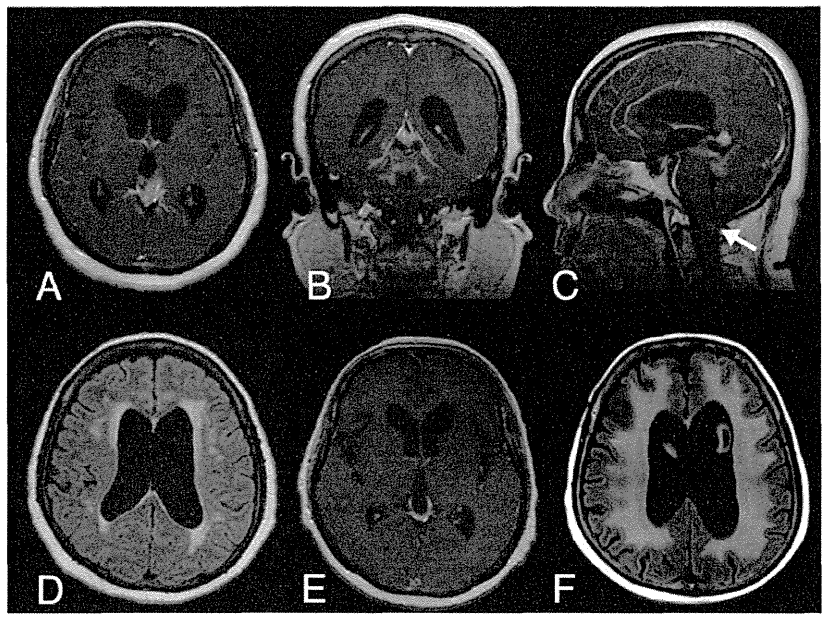

Figure 1. Example of treatment response and a late adverse effect. (A-D) Magnetic resonance imaging at the time of diagnosis (Tables I and II, case 3). (A, B and C) Contrast-enhanced T1-weighted imaging prior to treatment revealed spinal dissemination on the dorsal side of the medulla oblongata, appearing as a contrast-enhanced region (arrow). (D) The patient had slight periventricular white matter abnormalities on fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging. (E) Contrast-enhanced T1-weighted magnetic resonance imaging 2 months after treatment demonstrated a complete response. (F) The patient clearly showed exacerbated periventricular white matter abnormalities on FLAIR imaging and gradually developed a neurocognitive disorder in the 6 years following treatment.

As regards treatment selection and outcome, the two patients who received craniospinal and whole-ventricular irradiation after biopsy-only surgery exhibited a long-term survival of ≥6 years (Table II, cases 3 and 4). However, two patients experienced relapses consisting of cerebrospinal dissemination after treatment and eventually succumbed to the disease (Table II, cases 1 and 4). Of the two patients with recurrence, one had only received local irradiation at the site of the pineal tumor without chemotherapy after R2-resection. These outcomes suggest that the irradiation field may affect recurrence, although we cannot clearly establish an association between the irradiation field and the outcome, due to the limited number of cases.

Toxicity. All the patients recovered from surgery without significant problems. No lethal events or serious intracranial bleeding were recorded in the perioperative period.

Table II outlines the late adverse effects after treatment. The two patients who received 36 Gy of craniospinal irradiation and 18 Gy of whole-ventricular irradiation had evidence of cerebral white matter abnormalities in MRI and grade 3 cognitive disturbance according to RTOG and CTCAE toxicity grading, at 5-7 months and at 4-6 years after radiation therapy (Table II, Fig. 1). Although the patient who received only 34.2 Gy of whole-ventricular irradiation had evidence of cerebral white matter abnormalities at 6 months after radiation therapy, the patient exhibited no evidence of a neurocognitive disorder, even 9 years after the treatment. The patients who were irradiated locally had no evidence of cerebral white matter abnormalities or neurocognitive disorders. The two patients who received craniospinal and whole-ventricular irradiation also exhibited evidence of hypopituitarism after treatment: one developed a growth hormone deficiency 8 months after radiation therapy and the other developed a thyroid-stimulating hormone deficiency 7 years after radiation therapy. However, the latter patient already had a lack of growth hormone when he was diagnosed with PPTID. There were no reported cerebrovascular disorders after treatment.

Discussion

As the number of available studies on the treatment of PPTID is limited, the present study may add noteworthy evidence regarding viable treatment outcomes with radiation therapy and chemotherapy in PPTID. In our cohort, two patients experienced relapses with cerebrospinal dissemination and eventually succumbed to the disease; this was consistent with previous studies suggesting the potentially aggressive behavior of PPTID and its tendency for CSF seeding (8,11). In a previous report analyzing patterns of prognostic factors and treatment failures, five of 37 patients with PPTID relapsed >5 years after the initial treatment (11). The role of craniospinal and whole-ventricular irradiation for patients with PPTID remains to be determined. However, the importance of irradiation for patients with pineal parenchymal tumors, excluding pineocytoma, was investigated in a previous study on a series of 30 patients with pineal tumors and 105 with other germ cell tumors (12). That study demonstrated an association between the radiation dose administered and survival time in patients with pineal parenchymal tumors: the patients who received doses >50 Gy had a significantly higher 3-year survival rate compared to those who received lower doses (94 vs. 56%, respectively; P=0.03). In the present study, almost all the patients, even those with cerebrospinal dissemination

at diagnosis, survived long-term after radiation therapy (Table II). In our cohort, one of the two patients diagnosed with cerebrospinal dissemination received a total of 54 Gy of craniospinal and whole-ventricular irradiation with a combination of sequential chemotherapy after biopsy-only surgery and survived for >7 years. Doses >50 Gy and wide irradiation fields, such as craniospinal and whole-ventricular irradiation, combined with sequential chemotherapy, may be an effective treatment for PPTID with dissemination, although the number of cases analyzed was limited.

Whether all PPTID patients should be treated with chemotherapy remains controversial. Among the five PPTID patients in the present study, one did not receive chemotherapy; this patient developed spinal seeding after treatment and succumbed to the disease. In this patient, a radiation dose of 54 Gy was directed at the pineal region. Given the CSF seeding potential of PPTID and the outcome of this case, either systemic chemotherapy or a wider irradiation field may be required to prevent recurrence, although a definitive conclusion cannot be reached from only five cases regarding the exact indication of chemotherapy and the width of the irradiation field.

There is currrently no standard systemic therapy for PPTID patients. In this study, we used a combination regimen of vincristine, nimustine, carboplatin and interferon β as a systemic treatment for PPTID. The safety of the regimen used in this study was previously confirmed by a phase II study in patients with glioblastoma multiforme (13). Previous studies demonstrated promising results with the combination of vincristine, nitrosoureas and platinums in children diagnosed with primitive neuroectodermal tumors and low-grade gliomas (14,15). Interferon β was reported to act as a drug sensitizer for nitrosourea and alkylating agents, whereas interferon β and nitrosourea combination therapy has been used for the treatment of gliomas in Japan (16). Moreover, interferon β was shown to enhance chemosensitivity to alkylating agents by downregulating the expression of a DNA repair protein, O^6-methylguanine DNA methyltransferase, via p53 induction (17).

A previous study used combination chemotherapy with cisplatin and vinblastine as systemic treatment of pineal parenchymal cell tumors (18), whereas a clinical study on childhood pineoblastoma used a regimen including ifosfamide, etoposide, high-dose methotrexate, cisplatin and cytarabin followed by radiation therapy, or a regimen including vincristine, lomustine and carboplatin (19). These regimens may represent other chemotherapeutic options for pineal parenchymal tumors. A recent study suggested that molecular-targeted therapies, in addition to chemotherapy, may be a viable treatment option for PPTID tumors. A mutation of epidermal growth factor receptor (in-frame deletion of exons 2-7) was detected in PPTID tumors by flow cytometry, western blot analysis and reverse-transcription polymerase chain reaction (20). Patients with PPTID may benefit from a combination of chemotherapy and molecular-targeted therapy in the future.

Although almost all the patients in the present study were long-time survivors, they experienced some late adverse effects. The two patients who received craniospinal irradiation exhibited severe cognitive impairment (grade 3, RTOG and CTCAE toxicity grading) 4-6 years after radiation therapy. This result is consistent with previous reports regarding neurobehavioral outcomes following cranial irradiation (21). Neurocognitive disorder due to treatment is a multifactorial consequence, although data suggest that injury to neural progenitor cells plays an important role in treament-related neurocognitive toxicity (22,23). Associations between radiation dose to neural progenitor cell niches and the temporal lobes were previously reported (24). From this viewpoint, radiation delivery technique modifications, including hippocampal avoidance, may carry the potential to mitigate cognitive neurotoxicity by sparing normal neural stem cells, as in the RTOG 0933 trial, which was a phase II trial investigating whether avoiding the hippocampus during whole-brain radiation therapy lowers the incidence of long-term neurocognitive toxicity in the management of brain metastases.

In addition to the neurocognitive toxicity effect of radiation therapy, certain types of chemotherapy potentially contribute to neurocognitive toxicity due to the different sensitivity of normal neural stem cells (25). Newer chemotherapy agents, such as the epidermal growth factor receptor tyrosine kinase inhibitor and the proteasome inhibitor, were reported as potentially neurotoxic, compared to conventional chemotherapeutic agents (25). Moreover, irradiation may enhance chemotherapeutic neurocognitive toxicity. The majority of chemotherapeutic agents do not effectively penetrate the blood brain barrier; however, there is evidence that brain irradiation causes radiation-induced damage to the capillary bed (26). The concurrent or subsequent administration of neurotoxic chemotherapy while the blood brain barrier is disrupted by radiation therapy is likely to result in the sensitization of the brain to chemotherapy (21). As PPTID patients have the possibility of long-term survival even after recurrence, as shown in this study, whether patients should receive systemic chemotherapy and craniospinal and whole-ventricular irradiation should be carefully considered, depending on the patient's pathological characteristics, disease extent and potential to develop severe late adverse effects. As there are several available methods to enhance treatment intensity and reduce the possible effects on long-term toxicity, more detailed prospective future studies with a larger number of cases are required to investigate the optimal irradiation field and chemotherapeutic strategy for PPTID.

There were potential limitations to this study. First, we could not prospectively evaluate the cognitive disorders with a general neurocognitive function assessment, such as the Mini-Mental State Examination, the Montreal Cognitive Assessment, the Hopkins Verbal Learning Test and Trail Making Tests, or a more detailed objective patient-reported quality of life outcome assessment. Second, this was a retrospective study with a limited case series. Although this disease entity is rare, we should prospectively investigate larger cohorts to determine the appropriate treatment options.

In conclusion, we evaluated the outcomes of multimodality treatment for PPTID. Patients with PPTID in this study survived long-term, even after experiencing a recurrence. However, some patients developed serious neurocognitive disorders a few years after the treatment. Taking into account the rarity of this disease and the long-term survival of recurrent patients, a prospective multi-institutional study including a large patient cohort is required to determine the optimal width of the irradiation field and the use of chemotherapy after surgery, weighing the serious late adverse events and survival time.

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DIAGNOSTIC NEURORADIOLOGY

Quantitative imaging values of CT, MR, and FDG-PET to differentiate pineal parenchymal tumors and germinomas: are they useful?

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Abstract
Introduction Quantitative values of CT attenuation, apparent diffusion coefficient (ADC), and standardized uptake value (SUV) were investigated for differentiation between pineal parenchymal tumors (PPTs) and germinomas. Differences in age, sex, and calcification pattern were also evaluated.
Methods Twenty-three patients with PPTs and germinomas in 20 years were retrospectively enrolled under the approval of the institutional review board. CT attenuation, ADC, and SUV (20, 13, and 10 patients, respectively) were statistically compared between the two tumors. Differences in sex and patterns of calcification ("exploded" or "engulfed") were also examined. Mean patient ages were compared among three groups of pineoblastoma, pineal parenchymal tumor of intermediate differentiation, (PPTID) and pineocytoma and germinoma.
Results None of the quantitative values of CT attenuation, ADC, and SUV showed significant differences between PPTs and germinomas ($p>.05$). However, there was a significant difference in age ($p<.05$) among the three groups of pineoblastoma (mean age ± standard deviation 7.0±8.7 years), PPTID, and pineocytoma (53.7±11.4 years) and germinoma (19.1±8.1 years). Sex also showed significant differences between PPTs and germinomas ($p=.039$). Exploded pattern of calcification was found in 9 of 11 PPT patients and engulfed pattern in 7 of 9 patients with germinomas. No reverse pattern was observed, and the patterns of calcification were considered highly specific of tumor types.
Conclusions None of the quantitative imaging values could differentiate PPTs from germinomas. Age, sex, and calcification patterns were confirmed useful in differentiating these tumors to some degree.

Keywords Pineal tumor · Germinoma · CT attenuation · Apparent diffusion coefficient · Standardized uptake value

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Introduction

Tumors of the pineal region are uncommon and account for approximately 0.4–1 % of all intracranial tumors in American and European literatures, but higher incidence of up to 3.2 % is reported from Japan [1]. Pineal tumors consist of a very heterogeneous group of tumors including germ cell tumors (GCTs) (40 %), pineal parenchymal tumors (PPTs) (14–27 %), and neuroepithelial tumors, such as astrocytoma, ependymoma, and papillary tumor of the pineal region [1–3]. In GCTs, germinoma accounts for the majority of intracranial GCTs (68–86 %) [2, 4, 5], which can be treated successfully with a combination of chemotherapy and radiotherapy. Therefore, biopsy is sufficient for the diagnosis of germinoma [6], which is different from PPTs that are categorized into three subtypes: pineocytoma (grade 1), pineal

parenchymal tumor of intermediate differentiation (PPTID) (grade 2 or 3), and pineoblastoma (grade 4) [3, 7]. Surgical resection is mainly selected for pineocytoma occasionally combined with adjuvant chemotherapy and/or radiotherapy [8]. Treatment of PPTID varies from surgery to radiotherapy (radiosurgery or craniospinal irradiation) alone and chemotherapy [9, 10]. Standard care of pineoblastoma includes maximal surgical resection with adjuvant craniospinal radiation and systemic chemotherapy [11]. Therefore, the differentiation between germinoma and PPTs before surgical procedure is highly important.

For the differentiation between PPTs and germinomas, age, sex, and patterns of calcification, i.e., "exploded" or "engulfed", have been reported useful [2, 4, 12], and physiological pineal calcifications are frequently observed on CT [13].Other imaging characteristics of these tumors at the pineal region have been described on CT and MRI, but their qualitative evaluations could not differentiate the two entities [14, 15]. However, there have been only few studies on ^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET). There were only two case reports on FDG-PET findings in pineoblastoma [16] and mixed GCT [17]. No comprehensive imaging study including all conventional imaging methods of CT, MRI, and FDG-PET has been conducted to differentiate germinomas and PPTs.

The purpose of this study was to make a comprehensive evaluation on differential capability between germinomas and PPTs using the quantitative values of CT attenuation, apparent diffusion coefficient (ADC), and standardized uptake value (SUV). We also evaluated their age, sex, and patterns of calcification as exploded or engulfed, if calcification was present on CT.

Materials and methods

Patients

This study was approved by the institutional review board. Informed consent was waived due to retrospective nature of this study. The institutional medical recording system and the pathology database were searched for patients who had CT, MR, and FDG-PET imaging with histological verification of germinoma and PPTs between January 1993 and December 2012. Twenty-three patient records (12 female and 11 male subjects; mean 31 years old, ranged from 1 to 68 years) were found and analyzed for this study. Twelve patients had PPTs (five pineocytomas, four PPTIDs, and three pineoblastomas), and 11 patients had pure germinomas. Imaging was conducted using CT, MRI, and FDG-PET in 23, 14, and 10 patients, respectively, but three and one patients were excluded from CT and MRI, respectively, because they were scanned after biopsy. Patient characteristics are summarized in Table 1.

CT imaging

CT images were obtained with a 64-channel multi-detector row CT (MDCT) scanner for 5 patients, a 16-channel MDCT scanner for 4 patients (Aquilion 64 and 16, respectively, Toshiba Medical Systems, Otawara, Japan), and a 4-channel MDCT scanner for 11 patients (W-3000, Hitachi Medical Co., Tokyo, Japan). Resolutions of all the CT images were 0.4×0.4×7–8 mm.

MR imaging

MR scans were conducted with a 3T scanner for six patients and a 1.5T scanner for five patients (MAGNETOM Trio and MAGNETOM Symphony, respectively, Siemens Medical Systems, Erlangen, Germany). The other 1.5T scanner was used for two patients (Signa Genesis, GE Medical Systems, Milwaukee, WI, USA). In addition to axial T1-weighted, T2-weighted, and FLAIR images, contrast-enhanced axial T1-weighted images were acquired after the administration of a Gadolinium contrast agent (0.1 mmol/kg). Diffusion-weighted imaging (DWI) was acquired with the following parameters: TR=3,700–10,000 ms; TE=80–101 ms; slice thickness=3–5 mm; slice spacing=1–1.8 mm; pixel spacing=0.9–1.7 mm×0.9–1.7 mm; FOV=220×220 mm. DWI was conducted with two different motion-probing gradient values (b=0 and 1,000 s/mm^2) applied in three orthogonal directions. The acquired images were combined to form a single composite DWI, and their ADC values were calculated for each pixel to make ADC images.

FDG-PET imaging

FDG-PET scans were conducted using a PET/CT scanner for seven patients and a PET scanner for three patients (Discovery ST Elite and Advance, respectively, GE Healthcare, Waukesha, WI, USA). Patients fasted for at least 4 h prior to the scans. After intravenous administration of 4 MBq/kg of FDG, the patients rested in a waiting room for 30 min. Emission scans of the brain were conducted for 15 min with 128×128 matrix and 47 slices and 128×128 matrix and 35 slices, resulting in resolutions of 2.0×2.0×3.27 mm and 2.0×2.0×4.25 mm, respectively, for the scanners.

Data analysis

All images were evaluated independently by two experienced neuroradiologists (T.K. and R.S., both had experience in diagnostic imaging for 9 years) blinded to clinical data. Region of interests (ROIs) for the tumors were defined on an analysis console (Advantage Workstation 4.4, GE Medical Systems, Milwaukee, WI, USA) to measure maximum and mean nonenhanced CT attenuation values (CTmax and CTmean,

Table 1 Patient characteristics and quantitative imaging values

No.	Age	Sex	Pathology	CTmean (HU)	CTmax (HU)	Calcification	ADCmean ($\times 10^{-6}$ mm^2/s)	ADCmin ($\times 10^{-6}$ mm^2/s)	SUVmean	SUVmax
1	55	F	Pineocytoma	33.8	48.5	Exploded	912.3	606.5	5.1	7.72
2	63	F	Pineocytoma	40.6	54	–	813.2	570	NA	NA
3	62	F	Pineocytoma	36.2	48	Exploded	523.1	391	16.82	28.82
4	30	M	Pineocytoma	36.1	47.5	Exploded	653.1	488.5	9.39	11.76
5	68	M	Pineocytoma	39	58.5	Exploded	747.2	574	5.59	6.67
6	55	F	PPTID	39.3	57	Exploded	NA	NA	NA	NA
7	55	F	PPTID	32.8	48	Exploded	1,406.4	1,160	5.53	6.26
8	43	F	PPTID	39.8	57	–	NA	NA	NA	NA
9	52	F	PPTID	40.4	53	Exploded	996.1	705	NA	NA
10	17	F	Pineoblastoma	45	58	Exploded	NA	NA	NA	NA
11	1	F	Pineoblastoma	43.4	67	Exploded	750.1	321.3	NA	NA
12	3	M	Pineoblastoma	NA	NA	NA	NA	NA	5.87	6.43
1	8	F	Germinoma	40.4	53	–	NA	NA	NA	NA
2	8	F	Germinoma	40	55.5	–	NA	NA	NA	NA
3	22	M	Germinoma	43.6	57.5	Engulfed	NA	NA	NA	NA
4	33	M	Germinoma	45.1	59.5	Engulfed	813.6	321.3	NA	NA
5	14	M	Germinoma	NA	NA	NA	758.6	550	NA	NA
6	21	M	Germinoma	49.5	62	Engulfed	NA	NA	NA	NA
7	26	M	Germinoma	NA	NA	NA	NA	NA	5.43	9.4
8	22	M	Germinoma	37.1	52	Engulfed	639.5	414	8.26	9.88
9	17	M	Germinoma	41.2	64	Engulfed	NA	NA	9.05	12.42
10	12	F	Germinoma	39.4	53.5	Engulfed	825.7	325	2.74	3.58
11	27	M	Germinoma	40	60	Engulfed	725.4	470	NA	NA

ADC apparent diffusion coefficient, *HU* Hounsfield unit, *NA* not available, *PPTID* pineal parenchymal tumor of intermediate differentiation, *SUV* standardized uptake value

respectively), mean and minimum ADC values (ADCmean and ADCmin, respectively), and mean and maximum SUV (SUVmean and SUVmax, respectively). ROIs were drawn on one slice with the largest enhancement area by referring to the MR or CT images. Regions suggestive of a cystic change, necrosis, or calcification were excluded from the ROIs. When only FDG-PET imaging existed (one patient of pineoblastoma and one patient of germinoma), ROIs were drawn by referring to FDG uptakes. We evaluated the presence and the pattern of calcification as exploded or engulfed on axial nonenhanced CT.

Statistical analysis

Interobserver variability was evaluated using intraclass correlation coefficient (ICC) [18] for measuring the quantitative values and ROI sizes. The measured values obtained by the two evaluators were averaged and compared between germinoma and PPTs using the Mann-Whitney test. Age difference was compared among the three groups of germinomas, pineoblastomas, and PPTIDs and pineocytomas using Kruskal-Wallis test because the pineoblastoma is found in much younger patients than the pineocytoma or PPTID. Sex difference was examined with Fisher's exact test. A p value less than .05 was considered statistically significant. Statistical analysis was conducted with a commercially available statistical software package (MedCalc version 12.5.0, MedCalc software, Mariakerke, Belgium).

Results

ICCs were 0.76 to 0.99, which were recognized as good to excellent interobserver reproducibility [19] for all the quantitative values and ROI sizes. Statistically significant difference was not found between germinoma and PPTs for any of the measured quantitative values (p=.17, .08, .72, .09, .61, and .91, respectively, for CTmax, CTmean, ADCmean, ADCmin, SUVmean, and SUVmax; see Tables 1 and 2 and Figs. 1, 2, 3, and 4).

Calcification was detected in 9 of 12 patients (75 %) with PPTs, and all cases showed exploded calcification. Seven of 11 patients with germinoma had calcification, and engulfed calcification was found in all cases (Fig. 4). No discrepancy was observed between the observers.

The mean ages ± standard deviations were 19.1±8.1, 7.0± 8.7, and 53.7±11.4 years old for patients with germinoma,

Table 2 Differences between PPT and germinoma in CTmax, CTmean, ADCmean, ADCmin, SUVmean, and SUVmax

Quantitative values	*n*	PPT Median (interquartile range)	G Median (interquartile range)	*p* value
CTmax (HU)	20	54.0 (48.1–57.8)	57.5 (53.4–60.5)	.17
CTmean (HU)	20	39.3 (36.1–40.6)	40.4 (39.8–44.0)	.08
ADCmean ($\times 10^{-6}$ mm^2/s)	13	781.6 (700.1–954.2)	758.6 (703.9–816.6)	.72
ADCmin ($\times 10^{-6}$ mm^2/s)	13	572.0 (439.8–655.8)	414.0 (324.1–490.0)	.09
SUVmean	10	5.73 (5.53–9.39)	6.85 (4.09–8.66)	.61
SUVmax	10	7.20 (6.43–11.76)	9.64 (6.49–11.15)	.91

ADC apparent diffusion coefficient, *G* germinoma, *HU* Hounsfield unit, *PPT* pineal parenchymal tumor, *SUV* standardized uptake value

pineoblastoma, and PPTIDs and pineocytomas, respectively. When these three groups were compared, significant difference was observed among all the three groups ($p<.05$, post hoc analysis, Fig. 5). Eight out of 11 patients were male in germinoma, and 9 out of 12 were female in PPTs. The difference was statistically significant ($p=.039$).

Discussion

This is the first study that investigated quantitative imaging values of CT attenuation, ADC, and SUV, comprehensively, for differentiation between germinomas and PPTs. The imaging spectrum of these tumors has been described [2, 4, 12, 14, 15], but most findings are limited to CT or MRI. There are two case reports on its very high uptake by FDG-PET imaging in pineoblastoma [16] and little uptake in mixed GCT [17], but no report exists on pineocytoma and PPTID on FDG-PET. Moreover, no comparison has been conducted comprehensive of all modalities between PPT and germinoma, which was conducted in this study. We focused on pure germinoma because GCTs except germinoma can be generally differentiated using serum and cerebrospinal fluid (CSF) levels of tumor-produced oncoproteins (α-fetoprotein, β-human chorionic gonadotropin (β-hCG), and placental alkaline phosphatase) [2].

On CT, the pineoblastoma and germinoma are frequently recognized as hyperattenuating masses, which reflect highly cellular histologic features compared with the pineocytoma and PPTID [2]. However, the difference in the CT value between the germinoma and PPT was around 3 Hounsfield unit (HU) (see Table 2), which was not statistically significant.

Dumrongpisutikul et al. [20] have proposed the utility of ADC values between the germinoma and PPT. They found that germinoma had higher ADC values than the pineal cell tumors; however, we found no significant difference in ADC values between PPTs and germinoma. They drew the ROIs covering the entire lesions inclusive of cystic or necrotic regions, while we put them on areas with contrast enhancement because such region size may vary. The ADC value of the solid portion of the tumor is considered to have limited role in making differential diagnosis.

In FDG-PET, no study that compared between PPTs and germinomas has been reported. This is the first study to investigate the difference, but no significant difference was found

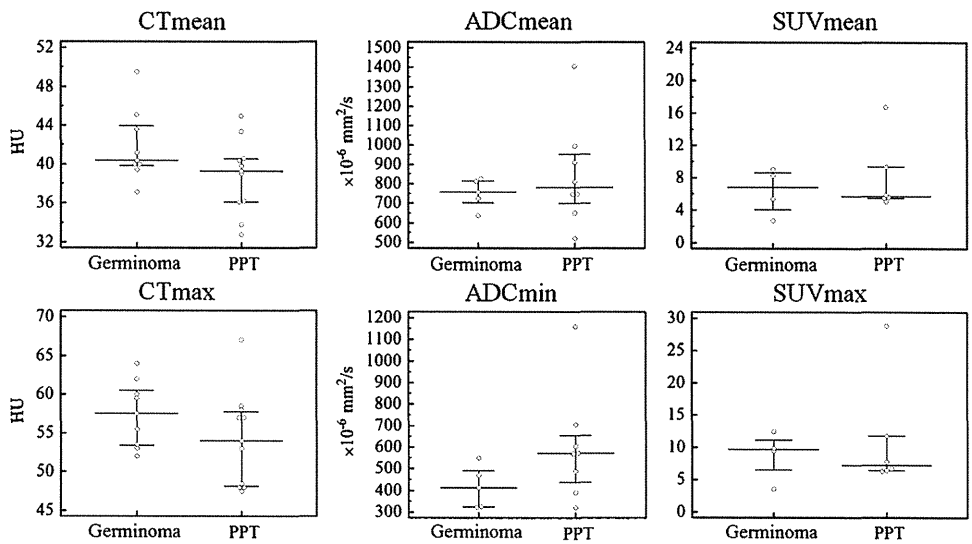

Fig. 1 Plots of quantitative values for comparisons between PPT and germinoma. No significant difference was observed between them. The *long horizontal bars* indicate median values, and the *short horizontal bars* show interquartile range. *ADC* apparent diffusion coefficient, *HU* Hounsfield unit, *PPT* pineal parenchymal tumor, *SUV* standardized uptake value

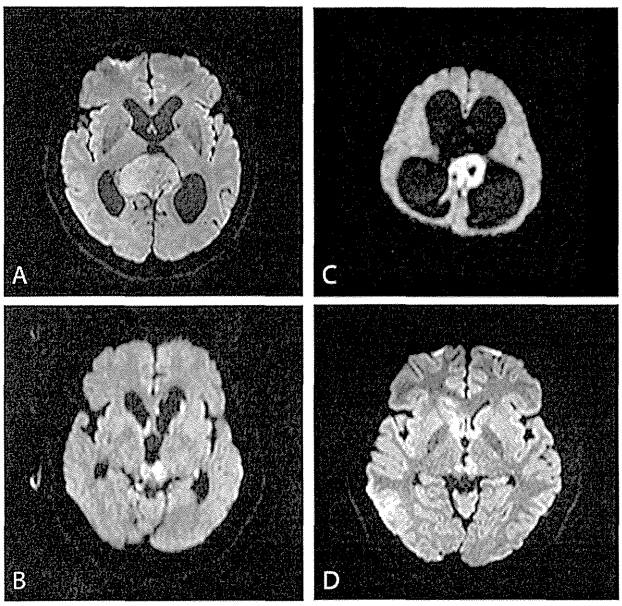

Fig. 2 Diffusion-weighted images of pathologically proven **a** pineocytoma, **b** PPTID, **c** pineoblastoma, and **d** germinoma. They have minimum ADC values of 574, 705, 343, and 325×10^{-6} mm^2/s, respectively. *ADC* apparent diffusion coefficient, *PPTID* pineal parenchymal tumor of intermediate differentiation

between germinomas and PPTs. In average, germinomas had higher SUVs than PPTs, although two cases of pineocytoma had very high SUVs (see Table 1).The pineocytoma is a low-grade tumor and may retain functionality. FDG uptake reflects not only cell density and mitotic activity of pineal tumors but also other activities such as regulation of certain circulating

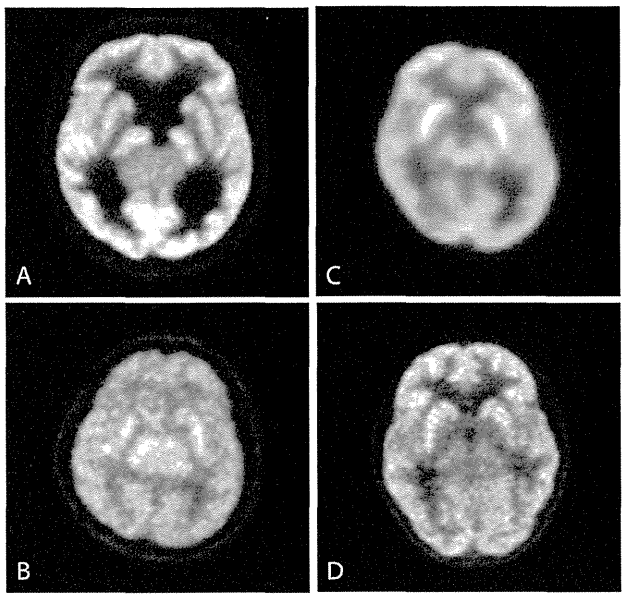

Fig. 3 FDG-PET images of **a** pineocytoma, **b** PPTID, **c** pineoblastoma, and **d** germinoma. They have maximum SUV values of 6.67, 6.26, 6.43, and 9.88, respectively. *PPTID* pineal parenchymal tumor of intermediate differentiation, *SUV* standardized uptake value

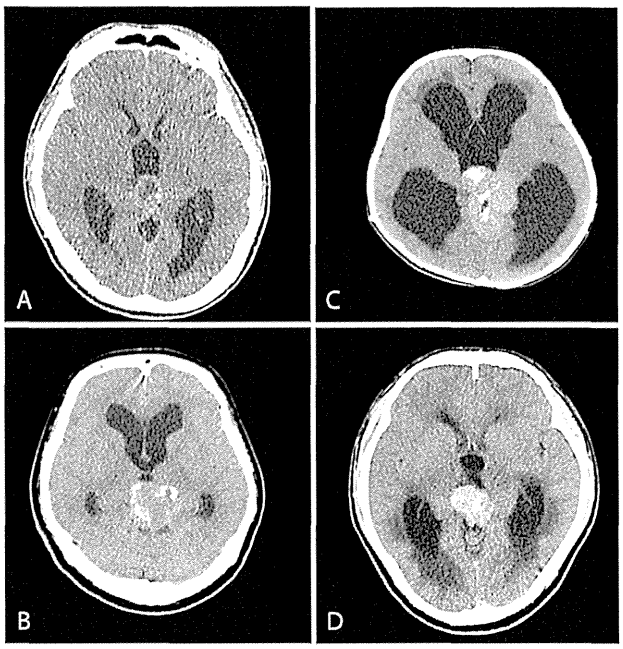

Fig. 4 CT images of pathologically proven **a** pineocytoma, **b** PPTID, **c** pineoblastoma, and **d** germinoma. They have mean CT values of 36.1, 32.8, 45.0, and 49.5 HU, respectively. Cases **a**, **b**, and **c** show "exploded" calcfication, whereas case **d** shows "engulfed" calcification. *HU* Hounsfield unit, *PPTID* pineal parenchymal tumor of intermediate differentiation

hormone levels and short-term (e.g., diurnal or circadian) biologic rhythm [13]. Such complex activity of the pineal tumor may result in failure of differentiation using SUV values.

It has already been reported that germinomas "engulf" physiological calcifications, whereas PPTs scatter or "explode" calcifications [2, 4]. When calcification existed, the

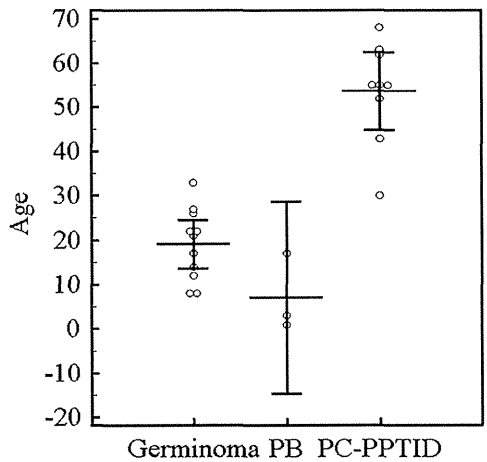

Fig. 5 Age difference among germinomas, pineoblastomas, and PPTIDs and pineocytomas. Significant differences observed in all pairs of the three groups ($p<.05$, *post hoc* analysis). The *long horizontal bars* indicate mean values, and the *short horizontal bars* show 95 % confidence intervals. *PB* pineoblastoma, *PC* pineocytoma, *PPTID* pineal parenchymal tumor of intermediate differentiation

pattern classification was considered to have high differentiation capability of the two. In this study, these two tumors were completely differentiated by the patterns with no disagreement between the two evaluators. However, calcification was detected in 75 % on nonenhanced CT. Other clues for differentiation might be required.

The pineocytoma and PPTID occur predominantly in adults from the third to sixth decades of age [13], whereas the pineoblastoma most commonly occurs in the first two decades [7].Ninety percent of patients with germinoma are less than 20 years old [4, 7]. The mean ages of the three tumor groups were statistically significant, but there was a large overlap between pineoblastoma and germinoma (see Fig. 5), and the differentiation was considered difficult between them.

No gender predilection is reported in pineocytoma and pineoblastoma, but a slight female preponderance is reported in PPTID [2, 7]. Germinoma in the pineal region are 10 times more common in men [7]. In this study, all of the PPTID patients were female, and male predominance was found in germinoma. Statistically, there was a significant difference between PPT and germinoma in sex. However, there were three female patients out of 11 germinoma patients, and its differentiation from pineoblastoma is considered difficult.

There is a limitation in this retrospective study that the numbers of patients with PPTs and germinomas were relatively small, which is inevitable considering the relative rarity of these tumors. As the other limitation, we have to consider errors caused by the difference in MR imaging methods, such as magnetic field strengths (i.e., 1.5T vs 3T), MR vendors, and imagers for measuring the ADC values, which were 4–9, 7, and up to 8 %, respectively [21]. ADCmin had a weak tendency ($p=0.09$) to differentiate PPT from germinoma. Variability in MR imaging methods might obscure the potentially existing difference between these two tumors, but images that only form a single MR imaging method may not be technically feasible due to the aforementioned reason.

Conclusions

Roles of the quantitative values of CT attenuation, ADC, and SUV were investigated in differentiating between PPTs and germinomas, but none was found useful. However, as was previously reported, age, sex, and calcification patterns had statistically significant differences and were confirmed useful in differentiating these tumors to some degree. In PPTs, we may distinguish pineocytomas and PPTIDs from pineoblastomas because their age distributions are highly different. However, differentiation between pineoblastomas and germinomas is difficult, when there is no calcification.

Conflict of interest We declare that we have no conflict of interest.

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Original Article

Characteristics of brain metastases from esophageal carcinoma

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Abstract

Background: Esophageal carcinoma (EC) is a major malignancy with a poor prognosis. Although esophageal cancers rarely metastasize to the brain, the number of patients diagnosed with brain metastases (BM) from EC is steadily increasing. Therefore, the risk factors for BM from EC should be known. Here we reviewed our experiences and the previous literature regarding BM from EC.

Methods: Between 2000 and 2013, we retrospectively reviewed the clinical features and neurological findings of 19 patients diagnosed with and treated for BM from EC to determine the clinical risk factors and features.

Results: In all patients, the lesions were partially or completed located in the thoracic esophagus, and the average size of the EC lesion at diagnosis was 5.8 ± 2.9 cm, which was smaller than the previously reported size of EC lesions accompanied by BM. Patients without lung metastases were more common than those with lung metastases. The lesions in the 13 patients included squamous cell carcinoma (SqCC) in 9 (69.2%) and small cell carcinoma (SmCC) in 3 (23.0%). Six patients were not examined. Although there was no trend toward a higher incidence of BM in patients with adenocarcinoma and SqCC, this trend was observed in patients with SmCC. Excluding a single patient with SmCC, all patients had beyond stage III disease at EC diagnosis.

Conclusions: Our study suggests that BM can occur in patients with EC lesions smaller than those previously reported; moreover, SmCC may be a risk factor for BM from EC.

Key Words: Adenocarcinoma, brain metastases, esophageal carcinoma, small cell carcinoma, squamous cell carcinoma

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INTRODUCTION

Esophageal carcinoma (EC) is a major malignancy with a poor prognosis and a 5-year survival rate of 23%.[22] According to the comprehensive registry of EC in Japan, EC often develops in the 7th decade in males, with a male-to-female ratio of approximately 7:1.[11] EC frequently metastasizes to the lymph nodes, liver, lung, and bone, but

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rarely to the brain; the incidence of brain metastases (BM) from EC is approximately 0.6-1.5%.[11,16,22,23] Therefore, it is a rare occurrence, with as few as 150 cases reported worldwide [Table 1].[1-7,9,12-14,16-22] However, the number of patients diagnosed with BM from EC is increasing, probably because of advances in diagnostic imaging and treatment of the primary EC lesion.[18,21] Therefore, there has been a steady increase in the number of clinical reports of BM from EC, with well-described treatments and outcomes in particular.[11-13,16,18,22,23] Till date, however, there has been insufficient discussion of the clinical risk factors and features of BM from EC. Therefore, we reviewed our clinical experiences together with the existing literature to evaluate recent trends in the occurrence of BM in patients with EC.

MATERIALS AND METHODS

Between 2000 and 2013, 19 patients with BM from EC were diagnosed and treated at Kumamoto University Hospital and Saiseikai Kumamoto Hospital in Kumamoto City in southern Japan. All patients with BM were diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI). To determine the clinical risk factors and features of BM in patients with EC, we retrospectively reviewed their clinical features and neurological findings. Specifically, the following information was collected: Patient age and sex, time from EC diagnosis to BM occurrence, EC size, EC stage at diagnosis, treatment, EC location, BM location and imaging characteristics, neurological symptoms, histology, concurrent metastatic sites, and survival data. Time from EC diagnosis to BM occurrence was actuarially calculated using the Kaplan-Meier method. A probability level of 0.05 was set for statistical significance. Statistical analysis was performed using StatMate III, Version 3.19 (ATMS, Tokyo, Japan).

Table 1: Published reports of brain metastases (BM) from esophageal carcinoma (EC)[1, 3-19]

Syudy	Year	Patients with BM
Appelqvist	1975	1
Bosch *et al.*	1979	1
Mandard *et al.*	1981	5
Anderson and Lad	1982	1
Sons and Borchard	1984	3
Chan *et al.*	1986	2
Kaneko *et al.*	1991	4
Gabrielsen *et al.*	1995	12
Quint *et al.*	1995	3
Takeshima *et al.*	2001	8
Ogawa *et al.*	2001	36
Weinberg *et al.*	2003	27
Almasi *et al.*	2004	1
Yoshida *et al.*	2007	17
Agrawal *et al.*	2009	1
Kanemoto *et al.*	2011	12
Smith and Miller	2011	7
Song *et al.*	2014	26
Present study	2014	19

BM from EC is a rare occurrence, with approximately 150 cases reported worldwide
EC: Esophageal carcinoma, BM; Brain metastases

RESULTS

Table 2 provides the clinical summary of all 19 patients. Table 3 summarizes the EC-related clinical data and characteristics. The average age at EC diagnosis was 65.5 ± 6.9 years (range 52-78 years), and the male-to-female ratio was 18:1.

The average EC size at diagnosis was 5.8 ± 2.9 cm in the 15 patients whose size data were collected. EC location ranged from cervical esophagus (Ce) to abdominal esophagus (Ae). The data on EC location were collected in 17 patients. EC that was partly or completely located in the middle thoracic esophagus (Mt) was the most common (12/17 patients), and the lesions were partly or completely located in the thoracic esophagus (Te) in all patients. In the 15 patients whose staging data were collected, EC at diagnosis was stage IV in 10 patients, stage III in 4 patients, and stage II in 1 patient; therefore, excluding 1 patient with small cell carcinoma (SmCC), all patients had beyond stage III disease.

The clinical data and characteristics of BM in the 19 patients are summarized in Table 4. The median time from EC diagnosis to BM occurrence was 7.0 months (range - 4 to 36 months. Time from EC diagnosis to BM occurrence was statistically significant, regardless of whether or not surgery was performed for EC [HR, 0.31 (0.038, 0.60); P = 0.007]. At diagnosis, 8 patients were asymptomatic and 11 had various neurological symptoms, including hemiplegia, seizure, visual disturbance, memory disturbance, and aphasia. Multiple BM lesions were found in eight patients. Among these, one patient had multiple metastases throughout the brain and the remaining seven had a total of 28 lesions: 9 each in the frontal and parietal lobes, 4 in the occipital lobe, 3 in the cranium, 2 each in the cerebellum and temporal lobe, and 1 in the corpus callosum. With regard to the features of BM on CT and/or MRI, 6 of 19 (31.5%) patients exhibited a cystic mass with an enhanced rim, 11 of 19 (57.8%) patients exhibited a solid mass with necrosis, and 2 of 19 (10.5%) patients exhibited a mass with bone destruction. Surgical resection of BM and/or EC was performed in 13 patients. Histological examination for these 13 patients revealed squamous cell carcinoma (SqCC) in 9 (69.2%), SmCC in 3 (23.0%), and basal cell carcinoma in 1 (7.6%). Six patients were without surgical resection and histological examination. Of note, the proportion of patients without lung metastasis was higher (57.8%) than that of patients

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Table 2: Summary of the 19 patients with brain metastases from esophageal carcinoma (EC)

Age/ sex	Histology	Location of EC	Size of EC (cm)	Time from EC	Neurological symptoms	Lung metastases	Outcome (months)
67/M	SqCC	Te (Ut, Lt)	4	1Y, 11M	No symptoms	Yes	Died (8)
68/M	SmCC	Te (Mt)	2	2Y	No symptoms	Yes	-
67/M	SqCC	Te (Ut-Mt)	6	2Y	Convulsion	Yes	Died (18)
67/M	SqCC	Te (Lt)	6	3Y	Hemiplegia	No	Died (12)
68/F	SqCC	Te (Mt-Lt)	3	4M before	Memory disturbance	No	Died (12)
73/M	SqCC	Ce-Te (Mt)	7	6M	Hemiplegia	No	Died (2)
72/M	SqCC	Te (Mt-Lt)	6	1Y, 10M	No symptoms	No	Died (2)
59/M	-	Te (Mt)-Ae	5	1M	No symptoms	Yes	-
58/M	SqCC	Ce-Te (Ut)	5	3M	No symptoms	No	Died (2)
60/M	-	Te (Mt)-Ae	13	Same time	Hemiplegia, aphasia	No	Died (3)
60/M	-	Te (Mt), Lt	5	Same time	Hemianopsia	Yes	Died (4)
52/M	BasalCC	Te (Mt)	-	1Y	Disturbance of consciousness, hemianopsia	Yes	Died (34)
66/M	SmCC	-	-	4Y	Headache	Yes	Died (11)
69/M	SqCC	Te (Ut-Mt)	-	2M	Headache	No	-
52/M	-	-	-	3Y	No symptoms	No	-
70/M	-	Te (Mt)	3	Same time	No symptoms	No	Died (1)
71/M	SqCC	Te (Mt-Lt)	10	2Y	Headache, hemiplegia	No	Died (17)
69/M	-	Te (Lt)-Ae	9	7M	No symptoms	Yes	Alive (3)
78/M	SmCC	Te (Lt)	4	6M	Convulsion	No	Alive (1)

M: Male, F: Female, SqCC: Squamous cell carcinoma, SmCC: Small cell carcinoma, Ce: Cervical esophagus, Te: Thoracic esophagus, Ut: Upper thoracic esophagus, Mt: Middle thoracic esophagus, Lt: Lower thoracic esophagus, Ae: Abdominal esophagus, EC: Esophageal carcinoma

with lung metastasis. The survival period from diagnosis in the 13 patients whose survival data were collected ranged from 1 to 34 (average 9.7 ± 9.4) months.

DISCUSSION

According to the comprehensive registry of EC in Japan, EC progresses in 2% males and 0.4% females.[11] There are significant racial variations in the histological types of EC. According to the study of Chalasani *et al.*, SqCC was predominant (92%) while adenocarcinoma was rare among black patients. On the other hand, adenocarcinoma was more common (66%) than SqCC (32%) among white patients.[8] With regard to the histological type of primary EC in the Japanese population, SqCC is more common (86.9%) than adenocarcinoma (4.3%).[11] In a study by Weinberg *et al.*, histology did not appear to be a risk factor for BM, and among the patients with BM in that study, 82% had adenocarcinoma and 7% had SqCC.[22] Although Gabrielsen *et al.* reported that adenocarcinomas were more prone to metastasize to the brain compared with SqCC, their data were not significant ($P = 0.16$).[9] In contrast, there were no cases of adenocarcinoma in the present study; SqCC accounted for 9 of the 13 patients (69.2% BM cases), while SmCC and basal cell carcinoma accounted for 3 (23% BM cases) and 1 (7.6% BM cases) of the 13 patients, respectively. According to the comprehensive registry of EC in Japan, where SqCC occurs in 87.5% patients and adenocarcinoma in 4.3%, there is no trend toward a higher incidence of BM with adenocarcinoma or SqCC.[11] The proportion of patients with SmCC in our study was higher than that of EC in Japan, suggesting that SmCC is a specific risk factor for BM from EC. Further research is required to confirm this assertion. The features of BM on CT and/or MRI were not significantly correlated with histology (OR, 2.0; $P = 0.85$). However, compared with BM from lung cancer (cystic, 15%; solid, 85%), BM from EC show a greater tendency to become cystic masses with necrosis.[15]

Although it is well known that EC rarely metastasizes to the brain, the number of patients diagnosed with BM from EC is increasing. Metastases are thought to occur via local invasion and hematogenous spread,[22] with the latter being the most likely mechanism for BM. Typically, lung metastasis is rarely found in patients with BM from EC. Indeed, of the 27 patients in the study by Weinberg *et al.*, 7 (26%) had lung metastases.[22] In our study, 8 of the 19 patients (42.1%) had lung metastases, probably because hematogenous spread to the brain occurred via the Batson venous plexus. The Batson venous plexus is a network of valveless veins that connect the systemic veins to the internal vertebral venous plexuses.[5] Because of their location and lack of valves, they are thought to be a route for the lesion to metastasize to the brain without metastasizing to the lungs.[16,22] In particular, because the esophagus contains the esophageal venous plexus, EC lesions are likely to metastasize to the brain through the Batson venous plexus. This is supported by

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Table 3: Clinical data and characteristics of esophageal carcinoma (EC) in the 19 patients

Clinical data and characteristics (total number of patients)	Number of patients	(%)
Age at EC diagnosis		
Range	52-78 (years)	-
Average±SD	65.5±6.9 (years)	-
Sex		
Male	18	(94.7)
Female	1	(5.2)
Size of EC (n=15: No data in 4 patients)		
Range	2-13 (cm)	-
Average±SD	5.8±2.9 (cm)	-
Location of EC (n=17: No data in 2 patients)		
Ce	2	(11.7)
Te		
Ut	5	(29.4)
Mt	12	(70.5)
Lt	9	(52.9)
Ae	3	(17.6)
Stage of EC at the diagnosis (n=15: no data in 4 patients)		
Tumor staging		
0 -I	0	(0)
II	1	(6.6)
III	4	(26.6)
IV	10	(66.6)
TNM classification		
Tx	2	(13.3)
Tis-T1	0	(0)
T2	2	(13.3)
T3-T4	11	(73.3)
Nx	1	(6.6)
N0	1	(6.6)
N1	13	(86.6)
Mx	0	(0)
M0	5	(33.3)
M1	10	(66.6)
Treatment for EC		
S+R+C	6	(31.5)
R+C	6	(31.5)
S+C	1	(5.2)
S+R	1	(5.2)
R	1	(5.2)
C	1	(5.2)
BSC	3	(15.7)

Stage: using TNM classification, SD: Standard deviation, S: Surgery, R: Radiotherapy, C: Chemotherapy, BSC: Best supportive care, EC: Esophageal carcinoma

Table 4: Clinical data and characteristics of brain metastases (BM) in the 19 patients

Clinical data and characteristics (Total number of patients)	Number of patients	(%)
Time from EC diagnosis and BM occurrence		
Range	−4-36 (months)	-
Average±SD	14.2±15.0 (months)	-
Median	7	-
Neurological symptoms		
No symptoms	8	(42.1)
Hemiplegia	4	(21.0)
Headache	3	(15.7)
Visual disturbance	2	(10.5)
Seizure	2	(10.5)
Memory disturbance	1	(5.2)
Aphasia	1	(5.2)
Location of BM		
Brain		
Frontal	9	(50)
Parietal	9	(50)
Occipital	4	(22.2)
Temporal	2	(11.1)
Cerebellar	2	(11.1)
Corpus callosum	1	(5.6)
Cranium	3	(16.7)
Feature of BM on images		
Cystic mass with enhanced rim	6	(31.5)
Solid with central necrosis	11	(57.8)
Bone destruction	2	(10.5)
Treatment for BM		
S+R	5	(26.3)
R	8	(42.1)
S	3	(15.7)
BSC	3	(15.7)
Histological type of BM and/or EC (n=13: No data in 6 patients)		
Squamous cell carcinoma	9	(69.2)
Small cell carcinoma	3	(23.0)
Basal cell carcinoma	1	(7.6)
Other metastatic sites		
Without lung metastasis	11	(57.8)
With lung metastasis	8	(42.1)
With LN metastasis	12	(63.1)
Survival period from BM diagnosis (n=13: No data in 6 patients)		
Range	1-34 (month)	-
Average±SD	9.7±9.39 (month)	-
Median	8 (month)	-

BM: Brain metastasis, EC: Esophageal carcinoma, BSC: Best supportive care, LN: Lymph node, SD: Standard deviation

the fact that the thoracic esophagus, which lies in the region of the esophageal venous plexus, was the most common location for EC in our study. This phenomenon may account for the low rate of lung metastases in patients with BM from EC.

In the study by Ogawa *et al.*, the primary lesions were stage III or stage IV in 81% patients with BM.[16] Our

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study supported this finding, with 93.2% patients having stage III or stage IV disease. If we further restrict the sample to only patients with SqCC, all had stage III or stage IV disease. One patient with SmCC had stage II disease. In the study of Gabrielsen *et al.*, the mean size of EC in patients with and without BM was 8.6 ± 2.8 cm and 5.1 ± 2.5 cm, respectively, suggesting a highly significant correlation between increased EC size and BM risk ($P < 0.001$).[9] On the basis of this study, Go *et al.* concluded, "preoperative neuroimaging is not indicated for routine staging of patients with EC except large tumors (>8 cm)."[10,11] However, in our study, the mean EC size in patients with BM was 5.8 ± 2.9 cm, suggesting that BM can occur in association with EC lesions that are smaller than those generally estimated.

This study was limited by the fact that the risk factors for metastases were not statistically evaluated because no data was available for EC patients without BM. However, our retrospective review of patients with BM from EC revealed valuable findings.

CONCLUSION

Our study suggests that BM can occur in association with EC lesions that are smaller than those previously reported and that SmCC may be a risk factor for BM from EC. The findings from this study and previous studies suggest that BM should be considered in patients with beyond stage III EC lesions, those with EC lesions located partly or completely in the thoracic esophagus, which cannot be removed by surgery, and those with local invasion or lymph node metastasis,[10,11] regardless of the presence or absence of neurological symptoms or lung metastasis. Further research and case reports are necessary to clarify the clinical risk factors for BM in patients with EC.

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CLINICAL STUDY

Risk factors for early death after surgery in patients with brain metastases: reevaluation of the indications for and role of surgery

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Abstract Surgical resection remains an important option for the treatment of brain metastases despite recent advancements in radiotherapy and systemic therapy. When selecting surgical candidates, it is important to exclude terminal cases who will receive neither a survival benefit nor an improvement in their quality of life. We reviewed a total of 264 surgical cases of brain metastases and analyzed the clinical characteristics of early death in order to clarify the indication for and the role of surgery. The median survival time (MST) after surgery in all cases was 12.4 months. Early death was defined as death within 6 months, and 23 % (62 cases) of this series were succumbed to this. A decrease in postoperative Karnofsky performance status (KPS) (<70) ($P = 0.041$), lack of systemic therapy after surgery ($P < 0.0001$), and uncontrolled extracranial malignancies ($P = 0.0022$) were significantly related to early death in multivariate analysis, while preoperative KPS (<70) and recursive partitioning analysis (RPA) class were related to early death only in univariate analysis ($P < 0.05$). When analyzing patients with uncontrolled extracranial malignancies and those with a postoperative KPS score of 70 or greater (who were generally candidates for systemic therapy), the MST was significantly longer in the systemic therapy (+) group compared with the systemic therapy (−) group (12.5 vs. 5.6 months; $P = 0.0026$). Our data indicate that the postoperative RPA class and treatment strategy were associated with early death. Deterioration of patients by surgery should be avoided in the treatment of brain metastases.

Keywords Brain metastases · Surgery · Early death · Leptomeningeal metastases

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Introduction

Brain metastasis is a life-threatening event for cancer patients and indicates that cancer has reached the advanced stages. Surgical resection remains an important option for treatment despite recent advancements in radiotherapy and chemotherapy. The aims of surgical resection are mass reduction and rapid improvement of neurological status.

Knowledge regarding the prognosis of extracranial lesions is important when making decisions about surgery. Several studies have attempted to identify prognostic factors, and various classification systems including recursive partitioning analysis (RPA) classification and graded prognostic assessment (GPA) have been developed [1, 2]. These classification systems have mainly been validated in patient populations treated with radiotherapy; however, some reports have indicated that these systems are useful for predicting survival time after surgery [3–9]. Considering the risks associated with treatment, terminal cases who receive neither a survival benefit nor an improvement in their quality of life (QOL) should be excluded during the selection of surgical candidates.

Herein, we describe a retrospective analysis of the relationship between clinical characteristics and the

outcome of surgery for brain metastases, and we discuss the indications for and the role of surgery.

Materials and methods

Patients

In total, we included 264 cases (156 men and 108 women) who underwent resection as their first surgery for brain metastases at the National Cancer Center Hospital in Japan between January 2000 and December 2011. The mean age of the included patients was 57.5 years (range 19–87), and their clinical characteristics were extracted from their medical records. Overall survival was calculated from the first resection surgery to death. The Karnofsky performance status (KPS) was determined as recorded or was retrospectively estimated from information obtained from the clinical chart by three neurosurgeons (Y.N., Y.M., and S.S.) who performed surgery on the patients. RPA classification of each patient was performed using published criteria [1]. Preoperative status, including performance status and RPA, was evaluated at the time of surgery, while postoperative status was evaluated approximately 1 month after surgery. The performance status and RPA class of patients who died within 1 month after surgery were recorded as 0 and III, respectively. Information regarding the RPA class and status of extracranial malignancy was not available for 1 case.

The cause of death was determined by clinical evaluation. Neurological deaths were defined as cases with neurological deterioration and stable extracranial disease as well as cases with apparent fatal progression of intracranial lesions or leptomeningeal metastases (LMM) regardless of systemic conditions.

The analysis in this study was approved by the local institutional review board (reference no. NCC16-066).

Treatment

Our basic surgical indications for brain metastases were described in a previous report [10]. Surgical candidates included patients with the following characteristics: (1) a post-surgery life expectancy of 6 months or more based on information from medical oncologists, (2) no clinical symptoms or apparent radiological findings indicating LMM, and (3) single metastases measuring $\geqq 3$ cm, or multiple or smaller tumors associated with severe neurological symptoms such as cerebellar metastases. In principle, adjuvant radiotherapy usually began 8 days after surgery. Adjuvant stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) was undergone only for the treatment of the surgical remnant or unresected lesion(s) in patients with multiple metastases. After brain metastases were controlled, patients received further systemic therapy or best supportive care (BSC) according to decisions made by medical oncologists.

A total of 37 patients received RT prior to surgery. In patients who experienced tumor recurrence after radiotherapy, surgical indication was judged via discussion with senior radiologists.

Early death

Early death was defined as death within 6 months after the first surgery for brain metastases, and the clinical profiles between the early death group and the non-early death group were compared. This definition is based on a comparison between the outcome of whole brain radiation therapy (WBRT) and surgery. The median survival time (MST) after WBRT alone is approximately 6 months [11–13]; therefore, if surgery confers a survival benefit, it should extend this time period.

Statistical analysis

Statistical analysis was performed using JMP version 10 (SAS Institute, Cary, NC, USA). The data for survival time were analyzed using the Kaplan–Meier method. A P value below 0.05 was considered statistically significant.

Results

Analysis for all cases

When all cases were analyzed, the median follow-up, MST, 1-year overall survival rate, and 5-year overall survival rate were 11.2, 12.4 months, 52, and 12 %, respectively. The 3 and 6-month overall survival rates were 89 and 75 %, respectively. When patients were divided according to preoperative RPA class, we determined that MST was 21.8 months for class I (59 cases, 22 %), 12.4 months for class II (148 cases, 56 %), and 6.5 months for class III (56 cases, 21 %) (Fig. 1a). When we reevaluated the data using postoperative RPA classification, MST was 20.8 months for class I (66 cases, 25 %), 11.2 months for class II (176 cases, 67 %), and 4.3 months for class III (21 cases, 8 %) (Fig. 1b). Both of pre- and postoperative RPA class were significantly related with survival ($P < 0.0001$, log-rank test). The relationships between preoperative and postoperative RPA class are shown in Supplementary Table 1.

KPS improved in 53 %, was unchanged in 40 %, and worsened in 7 % of all cases after surgery. Surgical complications were observed in 20 cases (7.6 %) including 8 instances of neurological deterioration due to surgical

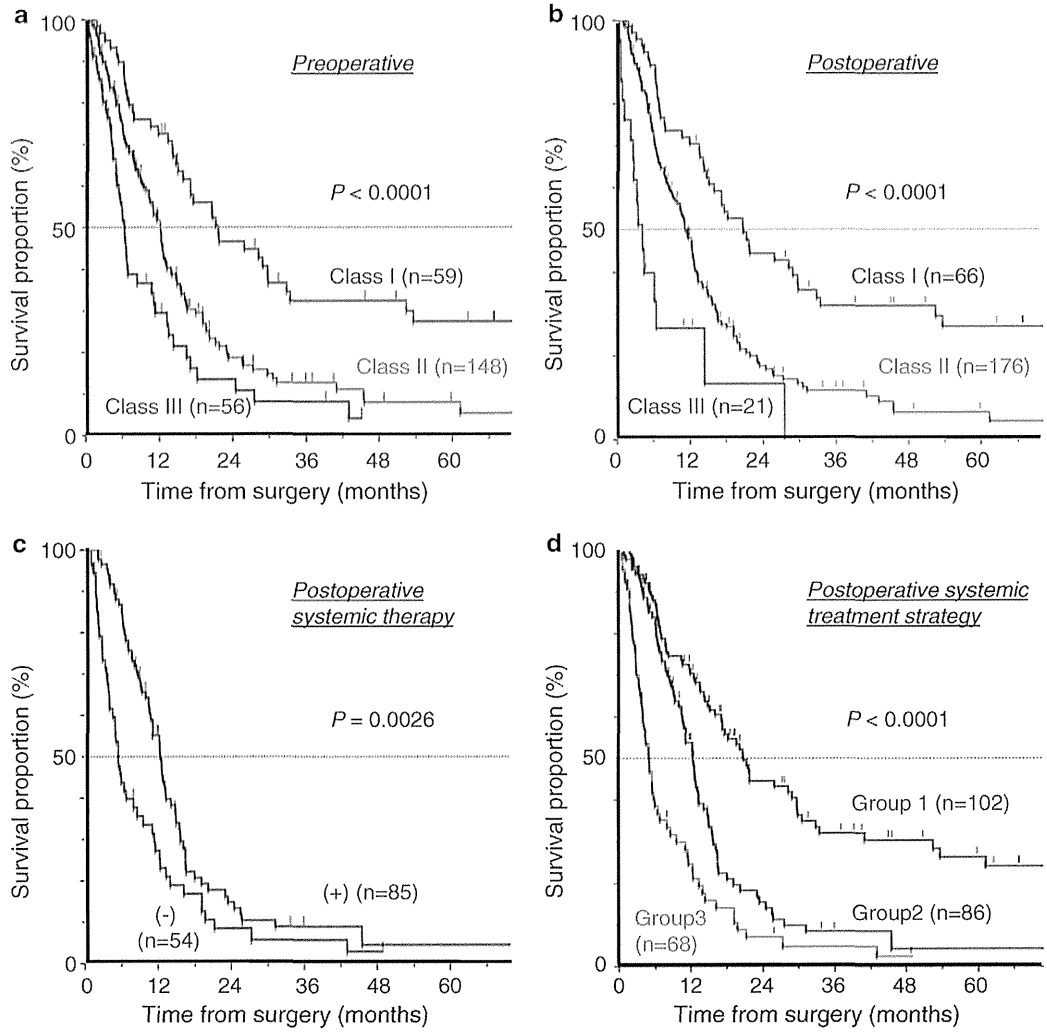

Fig. 1 Survival analysis. **a** Survival curves according to preoperative RPA class. MST was 21.8 months for class I, 12.4 months for class II, and 6.5 months for class III. **b** Survival curves according to postoperative RPA class. MST was 20.8 months for class I, 11.2 months for class II, and 4.3 months for class III. **c** Survival curves according to type of adjuvant therapy in patients with high KPS (70 or more) and uncontrolled extracranial malignancies. MST was 12.5 months for the systemic therapy (+) group and 5.6 months for the systemic therapy (−) group. **d** Survival curves according to postoperative systemic therapy. Group 1 consisted of patients without systemic disease, group 2 consisted of patients undergoing systemic therapy for uncontrolled extracranial disease, and group 3 consisted of patients who had extracranial disease but did not receive systemic therapy. MST was 20.8 months for group 1, 12.4 months for group 2, and 5.1 months for group 3

manipulation, 3 cerebral infarctions, 2 cases requiring evacuation of intraparenchymal hemorrhage, 1 case requiring evacuation of epidural hematoma, 1 case treated conservatively for intraparenchymal hemorrhage, 1 case requiring ventricular drainage for obstructive hydrocephalus, 1 instance of pulmonary embolism, 1 instance of surgical site infection, 1 sudden cardiopulmonary arrest, and 1 instance of vocal paralysis related to intubation. A permanent neurological deficit occurred in 11 (4.2 %) patients, but did not lead to early death in any case. Four patients (1.5 %) succumbed to surgery-related death (i.e., death within 30 days after surgery). Of these, two died of advanced systemic diseases 22 and 30 days after surgery, respectively. The other patients experienced neurological death: 1 died of LMM 23 days after surgery, while the other died of brainstem infarction 17 days after surgery for frontal lobe metastases.

Clinical characteristics of the early death group

A total of 62 patients (23 %) were included in the early death group. The early death rates were 10, 22, and 41 % in preoperative RPA class I, II, and III patients. When patients were divided according to postoperative RPA class, the

Table 1 Patient characteristics

	Total	Early death	Non-early death	*P* value[a]
Patients no.	264	62	202	
Multiple BM	67	24	43	0.0058
Infra-tentorial lesions	79	18	61	0.86
Age 65 or more	82	16	66	0.31
Preoperative KPS <70	57	24	33	0.0002
Postoperative KPS <70	22	13	9	<0.0001
ECM and/or uncontrolled primary lesion[b]	161	50	111	0.0003
Preoperative RPA[b]				0.0059[c]
I	59	6	53	
II	148	33	115	
III	56	23	33	
Postoperative RPA[b]				0.0041[c]
I	66	7	59	
II	176	43	133	
III	21	12	9	
Primary cancer				
Lung	102	24	78	
Breast	48	11	37	
GI	46	14	32	
Malignant melanoma	13	5	8	
Renal	8	2	6	
Others	47	6	41	
GTR	232	53	179	0.51
Any RT prior to surgery	37	11	26	0.33
Adjuvant RT(+)	216	46	170	0.075
Systemic therapy after operation for BM				
(+)	119	16	103	<0.0001
(−)	129	46	83	

BM brain metastases, *ECM* extra-cranial metastases, *GI* gastrointestinal, *GTR* gross total removal, *KPS* Karnofsky performance status, *RPA* recursive partitioning analysis, *RT* radiation therapy, *WBRT* whole brain radiation therapy

[a] Pearson's Chi square test

[b] Data of one case was absent

[c] Analyzing with dividing into RPA I and II-III

early death rates were 11, 24, and 57 % in class I, II, and III patients, respectively.

Table 1 shows the results of univariate analysis of data from the early death group and the non-early death group. The early death group contained a significantly higher ratio of patients with multiple brain metastases, KPS <70, uncontrolled primary cancers, and advanced RPA (II or III). The distribution of primary cancers did not differ significantly between these 2 groups. Fewer patients received systemic therapy after the resection of brain metastases in the early death group than in the non-early death group (26 vs. 55 %).

Table 2 Multiple logistic regression analysis for early death

	Odds ratio	*P* value
Postoperative systemic therapy (−)	4.91	<0.0001
Uncontrolled extra-cranial malignancy (+)	5.22	0.0022
Postoperative poorer KPS (<70)	3.61	0.041
Multiple brain metastases	(2.04)	0.051
Preoperative poorer KPS (<70)	(1.84)	0.18
Preoperative advanced RPA (class II or III)	(0.79)	0.84
Postoperative advanced RPA (class II or III)	(0.96)	0.98
Adjuvant radiotherapy (not performed)	(1.69)	0.21

KPS Karnofsky performance status, *RPA* recursive partitioning analysis

Multivariate logistic regression analysis was performed to identify which factors were most closely related with early death. Only clinical factors with $P < 0.1$ in univariate analysis (as described above) were used for this analysis. As shown in Table 2, uncontrolled primary tumors or extracranial metastases, lack of postoperative systemic therapy, and a postoperative decrease in KPS (<70) were significantly related to early death.

The impact of postoperative systemic therapy on the survival of patients with uncontrolled extracranial disease

The impact of treatment strategy on survival was further analyzed because postoperative systemic therapy was significantly related with early death in the univariate and multivariate analyses described above. Survival analysis using the Kaplan–Meier method did not reveal a difference in survival between patients in the systemic therapy (+) group (119 cases) and the (−) group (129 cases) (12.9 vs. 10.7 months; $P = 0.68$, log-rank test). Because systemic therapy is not usually administered to patients with poor performance status or without extra-cranial malignancies, we performed a further analysis including only patients with uncontrolled extracranial malignancies and those with a postoperative KPS of 70 or more. Based on this analysis, the MST was significantly longer in the systemic therapy (+) group (85 cases) than in the systemic therapy (−) group (54 cases) (12.5 vs. 5.6 months; $P = 0.0026$, log-rank test) (Fig. 1c).

The impact of postoperative treatment strategy on survival

All patients were divided into 3 groups according to treatment course after surgery for brain metastases: group 1

(102 cases) included patients without systemic disease, group 2 (89 cases) included patients who underwent systemic therapy for uncontrolled extracranial disease, and group 3 (65 cases) included patients who had extracranial disease but did not receive systemic therapy. Group 3 patients were treated with best supportive care. The MSTs of groups 1, 2, and 3 were 20.8, 12.4, and 5.1 months, respectively, and the difference among the groups was significant ($P < 0.0001$, log-rank test) (Fig. 1d). The early death rate was 12 % in group 1, 16 % in group 2 and 55 % in group 3, and the early death rate of group 3 was significantly higher than that of the other groups ($P < 0.0001$, Pearson's Chi square test).

Cause of death

Data regarding cause of death was available for 55 of the early death cases. Twenty patients (32 %) died from neurological causes, while 35 patients (56 %) died from systemic diseases. Thirteen of the neurological deaths were attributed to LMM. The adjuvant radiation therapies used in LMM cases were WBRT in 5 and local brain radiation therapy in 3 cases. Five cases did not receive either therapy. Other neurological deaths were due to progression of brain metastases after RT (6 cases) and brain stem infarction (1 case).

Postoperative status and survival time in preoperative RPA class III patients

Patients assessed as preoperative RPA class III ($n = 56$) typically have shorter survival times; therefore, the clinical courses of these patients were further analyzed in order to evaluate the potential treatment benefit. Of these patients, 8 (14 %), 31 (55 %), and 17 (30 %) were postoperative RPA class I, II, and III, respectively. When patients were divided according to postoperative RPA class, MST was 13.6, 6.5, and 3.6 months in class I, II, and III patients, respectively. MST was significantly longer in patients who experienced an improvement in postoperative RPA class ($n = 39$) compared with patients who remained in class III ($n = 17$) (6.9 vs. 3.6 months; $P = 0.019$, log-rank test). KPS was improved in 43 (77 %), unchanged in 10 (18 %), and worsened in 3 (5.4 %) preoperative RPA class III cases after surgery.

We further analyzed the cases showing RPA class III preoperatively but better RPA class postoperatively (I, 8 cases; II 31 cases) in order to discuss the operative indication for preoperative RPA class III patients (Supplementary Table 1). Twelve cases (31 %) of this cohort (39 cases) succumbed to early death after surgery, and their postoperative RPA class was I in one and II in 11. The causes of their early death were mainly consisted of systemic death; systemic disease in 8 cases, leptomeningeal metastasis in 2 cases and unknown in 2 cases. To identify what factor contributed to the early death in this cohort (39 cases), the postoperative treatment strategy was compared between the early death cases (12 cases) and the non-early death cases (27 cases). Eight of the 12 early death cases received best supportive care while 7 of the 25 non-early death cases (2 cases lacked the data) did. Thus, lack of postoperative systemic therapy was also statistically related with the early death in this cohort despite improvement in RPA class (8/12 vs. 7/25; $P = 0.025$, Pearson's Chi square test).

Discussion

In this study, we reviewed a surgical series from a single center and focused on the clinical characteristics of cases with poorer prognosis. Comparing with the recent studies presenting their surgical outcome, our series showed the comparable survival time [3, 6, 7, 9] according to RPA class and the comparable complication rate (7.6 vs. 4.5–14 %) despite the high ratio of RPA class III (21 vs. 5.7–6.8 %) [6, 14, 15]. We showed that postoperative treatment strategy and performance status were the significant factors for early death in multivariate analysis.

Systemic therapy after surgery was previously reported as being significantly related to survival time, but this was contradicted by the result in multivariate analysis [6]. This result simply seems to reflect the bias of the analysis: systemic therapy is usually avoided in patients with poorer performance status or patients without uncontrolled extracranial malignancy. We further analyzed only patients with favorable postoperative KPS scores and uncontrolled extracranial malignancies to ensure that we were only analyzing patients who truly needed further treatment for primary cancer. We showed that postoperative systemic therapy had a significant effect on survival in this population (Fig. 1c). Similarly, multivariate analysis showed that a lack of postoperative systemic therapy was a significant factor for early death, which was mainly analyzed in this study (Table 2). Thus, the treatment strategy for extracranial malignancies should be considered when determining operative indication, and this is supported by the results described in Fig. 1d. In other words, patients who cannot undergo chemotherapy (e.g., due to multidrug resistance to systemic therapy) are at high risk of early death after surgery. We also subjected our cohort to further analysis for survival by dividing three groups time according to the operative period (2000–2003, 2004–2007 and 2008–2011), but the difference in OS or early death rate was not apparent (data not shown). Despite the recent advances in systemic therapeutic agents, brain metastases