Title: Prognosis after brain metastasis from differentiated thyroid carcinoma

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Abstract

Background

In patients with differentiated thyroid carcinoma (DTC), lung and bone metastasis sometimes occur. However, brain metastasis (BM) is extremely rare. Because most previous reports about BM from DTC included a relatively small number of cases, the clinical characteristics and outcomes of BM are still unclear.

Patients and Methods

Between 1965 and 2013, among 961 patients who had died because of DTC, 24 patients were diagnosed with BM from DTC. One patient with BM from DTC is still alive. To identify the prognostic factors for longer survival after BM, the medical records of these 25 patients were retrospectively reviewed.

Results

The median age at BM diagnosis was 66 years. Typical symptoms associated with BM had appeared in 20 patients (80%). The Karnofsky Performance Status (KPS) was good (≥70) in 10 patients and poor (≤60) in 15 patients. Seven patients had a single intracranial lesion of BM, 6 patients had 2 or 3 lesions, and 9 patients had 4 or more. Eleven patients did not receive any treatment for BM,

and 14 patients underwent surgical resection, radiation therapy, or both. One-year and 5-year disease-specific survival rates were 28% and 10.6%, respectively. Good KPS (≥70), small number of intracranial lesions (≤3), and treatment for BM were prognostic factors for long survival on univariate analysis ($p<0.05$). On multivariate analysis, only treatment for BM was significant.

Conclusion

Treatment of BM from DTC is indicated in patients who have a good KPS and fewer intracranial lesions, and some of them may achieve long survival.

Introduction

At initial diagnosis, differentiated thyroid carcinoma (DTC) is more often intrathyroid or spread only to cervical lymph nodes because of its typical slow-growing pattern. Distant metastasis from DTC is reported in about 4-15% of cases [1]. The most common site of distant metastasis is the lung, followed by bone (1-15%) [2].

In contrast, brain metastasis (BM) is extremely rare, and BM occurs in approximately 1% of all DTC cases [3]. However, Dinneen et al noted that, of all rare metastases (brain, breast, liver, kidney, muscle, and skin), brain was the most frequent locus of secondary metastasis from DTC[3].

The presence of distant metastasis is the most significant poor prognostic factor for survival, with only 50% survival after 10-years for patients with metastasis[4]. Although there is a general consensus in the literature that BM is associated with a poor prognosis with a tendency for recurrence [5], the clinical characteristics and outcomes of BM are still unclear.

Therefore, the medical records of DTC patients with BM were retrospectively reviewed, and their clinical features were evaluated to identify the prognostic factors for long survival after BM from DTC.

Methods

The prospectively maintained institutional database at Ito hospital was retrospectively searched for patients who had already died because of DTC between January 1965 and December 2013. Of the 961 fatalities, 24 patients had been diagnosed as having BM when they were alive. In addition, one patient with BM from DTC is still alive. Thus, 25 patients were included in the present study.

The medical records were reviewed and the following data were evaluated: patients' sex and age (at initial diagnosis and BM diagnosis), histopathology, initial DTC stage according to the UICC (Union for International Cancer Control), treatment for initial DTC, presenting symptoms associated with BM, diagnostic modality for BM, other coexistent distant metastasis, Karnofsky Performance Status (KPS), treatment modalities for BM, and patient outcome.

Statistical analyses were performed using a statistical software program (JMP8.0; SAS Institute, Inc. Cary, NC). Disease-specific survival (DSS) was calculated using the Kaplan-Meier method, and survival time was measured from the date of BM diagnosis to the date of death or last follow-up. Univariate analysis was conducted for DSS by the Kaplan-Meier method for the variables

sex, age at initial diagnosis, age at BM diagnosis, histopathology, KPS, other coexistent distant metastasis, symptoms, number of intracranial lesions, and treatment for BM. Differences between groups were analyzed for significance by the log-rank test. A multivariate analysis was performed using the Cox proportional hazard model. Hazard ratios for each category were calculated, and p-values <0.05 were regarded as significant.

A literature review was performed through a PubMed search for “differentiated thyroid carcinoma” and “brain metastasis”, in addition to reviewing the citations in the resulting articles.

Results

Patients' characteristics

Table 1 summarizes the patients' characteristics. Of the 25 patients, 17 were women, and 8 were men. One patient was still alive, and 24 patients had died. The median age at initial diagnosis was 57 years (range 20-91 years). Only one patient already had BM at the time of the initial diagnosis of DTC.

Histopathological findings of primary DTC

All cases were confirmed by histopathological examination of the lesion from surgical resection or needle biopsy. Of these, 18 were diagnosed as papillary thyroid carcinoma and 7 as follicular carcinoma (2 minimally invasive, 2 widely invasive, and 3 unknown).

According to the UICC 7th classification, the stages were pT1-2 for 5 patients, pT3-4 for 14, and unknown for 6. Nodal involvement was present in 13 patients, absent in 5, and unknown in 7. Four of 13 patients who had lymph node metastasis included large lymph node metastasis over 3cm. Four patients had distant metastasis at initial diagnosis, 19 patients did not, and 2 were unknown. The extent of the cancer was confined to the thyroid in 9 patients, beyond the thyroid capsule into the sternothyroid muscle or soft tissues in 3, beyond the

sternothyroid muscle or soft tissues in 8, and unknown in 5.

In all patients but one, thyroidectomy was performed. Fourteen patients underwent total or sub-total thyroidectomy, 9 patients underwent less than subtotal thyroidectomy, and 1 patient was unknown. Lymph node dissection was performed for 20 patients (9 were modified neck dissection, 11 were central node dissection). Four patients did not undergo lymph node dissection, and 1 was unknown.

Clinical features of the BM from DTC

Table 2 summarizes the clinical features of the BMs.

The median age at BM diagnosis was 66 years (range 28-91 years). The median duration from initial diagnosis to BM diagnosis was 73.3 months (range 0-182 months), and from BM diagnosis to death was 41.5 months (range 0-83 months). Typical symptoms associated with BM appeared in 20 patients. Four patients had paresis or gait disturbance, 3 patients presented with unconsciousness, and 2 patients complained of headache, vertigo, or vomiting. Language disorder, deafness, appetite loss, incontinence, visual field defect, and tumor of the head skin were seen at the time of BM diagnosis in one patient each. Only 3 patients (8%) had no symptoms associated with BM and were diagnosed by chance

when they underwent the survey for other metastatic sites.

The diagnosis of BM was made by CT scan in 19 patients, by MRI in 3, by angiography in 1, and by eyeground findings in 1.

Other coexistent distant metastasis at the time of BM diagnosis were found in 20 cases (80%). Lung metastasis appeared in 15 cases. Bone metastasis was seen in 7 cases, and liver metastasis was seen in one. On the other hand, 5 cases (20%) did not have any other distant metastasis at the time of BM diagnosis.

KPS was used as a predictive factor for metastatic brain tumor in the American Society for Radiation Oncology evidence-based guideline. With the KPS, the patient's condition is classified into 10 levels (Table 3), while with the Performance Status (PS), the patient's condition is classified into five levels. Ten patients (40%) had good KPS scores (70-100 points), and 15 patients (60%) had poor KPS scores (0-60 points).

Seven patients had a single intracranial lesion of BM, 6 patients had 2 or 3 lesions, and 9 patients had 4 or more lesions.

Treatment for BM from DTC

In the treatment of the BM, 11 patients did not receive any active treatment because of their poor general condition, and treatment was limited to best

supportive care.

Surgical resection alone for the intracranial lesions was performed in 4 patients, stereotactic radio surgery (SRS) alone was performed in 5 patients, and whole-brain radiation therapy (WBRT) alone was performed in 2 patients. The 2 other patients underwent combination treatment, surgical resection plus WBRT, or SRS plus WBRT.

After all, 6 patients underwent surgery and they were histologically confirmed as BM from DTC.

Clinical course and outcome

At the time of the last follow-up, 24 patients were dead, and one patient was still alive. Information regarding the cause of death was available for 15 patients. Six patients were reported as having died due to the associated BM. Four patients died from pneumonia, and four patients died from respiratory dysfunction. It was supposed that BM had no small influence on the occurrence of pneumonia, because the patients were immuno-suppressed by the corticosteroids for the treatment of brain edema.

The prognosis of BM was usually poor. The one-year disease-specific survival rate for BM was only 28%, with a five-year rate of 10.6% (Fig. 1). For some

selected fortunate patients, the treatment for BM contributed to their longer survival.

The longest survivor was alive 83 months after BM diagnosis. He diagnosed as PTC when he was 58 years-old. At 29 months after initial surgery, single intracranial metastasis was found. His KPS score was 90 at the time of BM diagnosis. Treatment for BM was only surgical resection. Over 6 years after BM treatment, he is still alive without appearance systemic recurrences.

Table 4 summarizes the results for the prognostic factors for longer survival. Survival comparisons were performed between subgroups of patients according to baseline characteristics and treatment received. On univariate analysis, 3 factors (KPS, number of intracranial lesions, and treatment for BM) had a huge impact on survival. The median survival time after BM diagnosis was 34.5 months if KPS was over 70 and only 3 months if KPS was under 70 ($p=0.01$). Similarly, the median survival time after BM diagnosis was 9.5 months if there were less than 4 intracranial lesions, and 3 months if there were more than 4 intracranial lesions ($p=0.04$). The median survival time after BM diagnosis was 15.5 months if treatment for BM was performed and 3 months if treatment was only best supportive care. On multivariate analysis, only treatment for BM was

significant.

Discussion

For DTC, regional lymph node metastasis are common, and they are not immediately life-threatening. Although distant metastasis from DTC are usually slow-growing compared with other malignancies, some of the patients with these conditions die from disease-specific causes.

The most common sites of distant metastasis from DTC are lung and bone. Brain metastasis is relatively rare.

In the present study, 60% of the patients have synchronous lung metastasis. In previous reports, the frequency of the synchronous lung metastasis with BM was similar to our result[6-8]. An appearance of lung metastasis is not a predictive factor significantly, while BM patients tended to have lung metastasis when BM was diagnosed.

According to the research between 1984 and 2000 in Japan, of all metastatic brain tumors, the prevalence of BM from lung cancer is estimated to be 51.9%, breast cancer is 9.3%, and rectal cancer is 5.4% [9].

In the present study, the one-year DSS rate after BM from DTC (28%) was the poorest compared with BM from other organ cancers (lung cancer 40.7%, breast cancer 50.2%, gastric cancer 31.7%) [4]. This result is unexpected, because DTC

usually glows more slowly than other malignancies such as lung cancer, breast cancer, and intestinal cancer. However, more cases are needed to evaluate the differences in clinical outcomes of BMs from different primary sites.

Park HY[10] recommended the routine screening of BM by MRI after surgery for lung adenocarcinoma. Approximately 10-25% of lung cancer patients had BM at initial diagnosis and about 40-50% of them developed BM during the course [11].The incidence of BM from lung carcinoma is relatively high. Therefore, it may be useful to evaluate BM routinely. In contrast, BM from DTC is quite rare. We regard that the routine screening by brain CT or MRI to find BM from all DTC patients is not useful to improve the outcome of the patients with DTC. But, according to the present study and previous reports, most of BM patients had other coexisting distant metastasis when BM was diagnosed. Therefore, the active surveillance to find BM for limited patients who had already distant metastasis (e.g. lung and bone metastasis) may be considerable.

In the present study, the most frequent locus of the BM was not analyzed, because the image at the time of BM diagnosis was missing for several cases. However, Al-Dhahri et al. noted that BM occurs more frequently in the cerebral hemispheres; other sites for intracranial metastasis are the cerebellum and

pituitary[5].

In general, minimally invasive follicular carcinoma (MIFTC) has favorable prognosis and low risk of recurrence. But in our case series, two MIFTC patients progressed to brain metastasis. One of two was operated at 1965, and the detail of the pathology was unclear. The other patient was diagnosed Graves disease at first. After the operation, the nodular goiter was found in the resected thyroid and incidentally diagnosed as MIFTC. We are not sure why these two low risk patients were suffered from BM.

We also investigated the serum thyroglobline (Tg) levels of our study population. Because most cases had distant metastasis when BM was diagnosed, serum Tg levels had been already high. Therefore, it was not useful to predict BM by the increase of serum Tg levels. (data were not shown)

Eight patients received radioactive iodine treatment or whole-body scintigraphy within two years before BM diagnosis. But all the patients had not been detected BM. Several studies have investigated RI treatment for distant metastasis of DTC. However, the most common lesion of distant metastasis of DTC was lung or bone. The effect of RI for brain metastasis was unclear. In the study by Tahmasebi et al[12], 8 patients underwent RI for BM, and overall survival varied

from 3 months to 4 years.

In our experience, brain CT or MRI are more useful for early detection of BM than radioactive iodine scintigraphy.

The NCCN guideline 2014 recommended that surgical resection followed by WBRT or SRS plus WBRT was appropriate for patients who had stable systemic disease or were newly diagnosed, WBRT or SRS was appropriate for patients who had multiple (>3) metastatic lesions, and for patients who had disseminated disease, systemic treatment options were considered best supportive/palliative care or WBRT.

In fact, in the present study, not a few long-time survivors were found in the patients who underwent treatment for BM. There were significant differences in the survival rate between treatment and no treatment for BM. However, there was no difference in the type of treatment for BM, surgical resection, WBRT, SRS, or radioactive iodine therapy (RI). These results were probably because of the small numbers of patients.

Chiu [7] reported that patients who underwent surgical resection had significantly longer survival than patients who did not. However, in their study, treatment was external beam radiotherapy, RI, or chemotherapy; SRS was not included.

In Japan, SRS became available for the treatment of metastatic brain tumors from 1996. Not many cases have undergone SRS for BM from DTC. We expect that SRS will be useful for BM, but more cases are needed to evaluate the advantages of SRS.

In the American Society for Radiation Oncology evidence-based guideline, KPS was used as a prognostic factor for BM. They defined a KPS score of over 70 points as having a good prognosis. Akiba [13] and Izumi [14] reported that a KPS score over 70 points was a good prognosis factor for metastasis of brain tumor. In the present study, a good KPS was correlated to longer survival on univariate analysis, but not on multivariate analysis. KPS (≥70), as well as the number of BMs (≤4), should be useful to select the patients who should be treated for brain metastasis.

In our review using PubMed, there were three reports [6-8] that analyzed over 10 cases who had BM from DTC (Table 5). Each report concluded that BM occurred at a high rate concurrently with lung and bone metastasis, and survival time after BM diagnosis was nearly one year. Chiu et al concluded that surgical treatment for BM extended the prognosis[7].

Conclusion

In conclusion, BM from DTC has a poor prognosis. However, if the patient has good KPS or only 1 to 3 intracranial lesions, the physician should suggest treatment for BM with surgical resection, SRS, WBRT, or RI.

Conflict of interest None

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Table 1. Clinical characteristics at the time of initial diagnosis of DTC

Sex	Male	8
	Female	17
Age at initial diagnosis (y)	Median (range)	57 (20-91)
Histopathology	Papillary thyroid carcinoma	18
	Follicular thyroid carcinoma	7
	Minimally invasive	2
	Widely invasive	2
	Unknown	3
Thyroidectomy	Total/sub-total	14
	Less than sub-total	9
	No	1
	Unknown	1
Lymph node dissection	MND*	9
	CND**	11
	No	4
	Unknown	1
T（UICC 7th edition）	1	1
	2	4
	3	3
	4	11
	Unknown	6
N（UICC 7th edition）	0	5
	1a	4
	1b	9
	Unknown	7
M（UICC 7th edition）	0	19
	1	4
	Unknown	2
Extrathyroidal invasion	Confined to thyroid	9
	Beyond thyroid capsule into sternothyroid muscle or soft tissues	3
	Beyond sternothyroid muscle or soft tissues	8
	unknown	5

*MND: modified neck dissection **CND: central node dissection

Table 2. Clinical characteristics at the time of diagnosis of brain metastasis

Age at BM diagnosis (y)	Median (range)	66 (28-91)
Duration from initial diagnosis to BM (months)	Median (range)	73.3 (0-182)
Duration from BM to death (months)	Median (range)	41.5 (0-83)
Symptoms associated with BM	Paresis/gait disturbance	4
	Unconsciousness	3
	Headache/ vertigo/ vomiting	2
	Language disorder/deafness/appetite loss/incontinence/visual field disorder/ tumor of the head skin	1
	Nothing	3
	NA	2
Modality of diagnosis	CT	19
	MRI	3
	Angiography	1
	Eyeground examination	1
	NA	1
Other coexisting distant metastasis	Lung	15
	Bone	7
	Liver	1
	None	5
KPS*	Good (100-70)	10
	Poor (60-0)	15
Number of intracranial lesions	1	7
	2 or 3	6
	≥4	9
	NA	3
Treatment for BM	Surgical resection	5
	Stereotactic Radio Surgery (ex, r-knife)	6
	Radioactive iodine (^{131}I)	1
	Whole-Brain Radiation Therapy	4
	Best supportive care only	11
Cause of death (N=24)	Associated with brain metastasis	6
	Pneumonia	4
	Respiratory dysfunction	4
	Unknown	10

NA: not available ＊KPS: Karnofsky Performance Status

Table 3. Karnofsky Performance Status (KPS) scale definitions rating (%) criteria

	%	
Able to carry on normal activity and to work; no special care needed	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Oxford Textbook of Palliative Medicine, Oxford University Press. 1993;109

Table 4. Univariate and multivariate analyses of the predictive factors for long survival after brain metastasis

Category		N	p value		
			Univariate	Multivariate OR	95%CI
Sex	Male	8	0.09	-	
	Female	17			
Age at initial diagnosis	≥45 y	22	0.96	-	
	<45 y	3			
Age at BM diagnosis	≥70 y	8	0.34	-	
	<70 y	17			
Histopathology	PTC	18	0.17	-	
	FTC	7			
KPS*	≥70	10	0.01†	0.16	
	<70	15		0.47	0.14-1.32
Other coexisting distant metastasis	yes	20	0.94	-	
	no	5			
Symptoms associated with BM	yes	20	0.2	-	
	no	3			
Number of intracranial lesions	<4	13	0.04†	0.25	
	≥4	9		1.74	0.66-4.54
Treatment	yes	14	<0.01†	0.02	
	no	11		0.31	0.10-0.84

OR: odds ratio CI: confidence interval
*KPS: Karnofsky Performance Status
†:$p<0.05$

Table 5. Review of case series (>10 patients) of BM from DTC

Author	No. of cases	Histology	Duration from primary to BM diagnosis (months)	Survival time after BM diagnosis (months)	Other coexisting distant metastasis	Treatment modalities
Samuel AM, et al.	15	P:5 F:9 H:1	61.8	12.4	lung 9 bone 6	surgery 5
Chiu AC, et al.	32	P:32	73.2	12.4	lung 18 bone 10	surgery 7 WBRT 13 CT 6
Henriqurs de Figueiredo B, et al.	21	P:5 F:9 H:1	114.9	7.1	lung11 bone 10 peritoneum 2 bladder 1 liver 1 adrenal 1	surgery 1 WBRT 7 SRS 2
Our report	25	P:17 F:8	146.5	17.8	lung 15 bone 7 liver 1	surgery 5 SRS 7 RI 1 WBRT 4

P: papillary thyroid carcinoma F: follicular thyroid carcinoma H: Hürthle cell carcinoma
WBRT: whole-brain radiation therapy SRS: stereotactic radio status
RI: radioactive iodine therapy

Fig.1

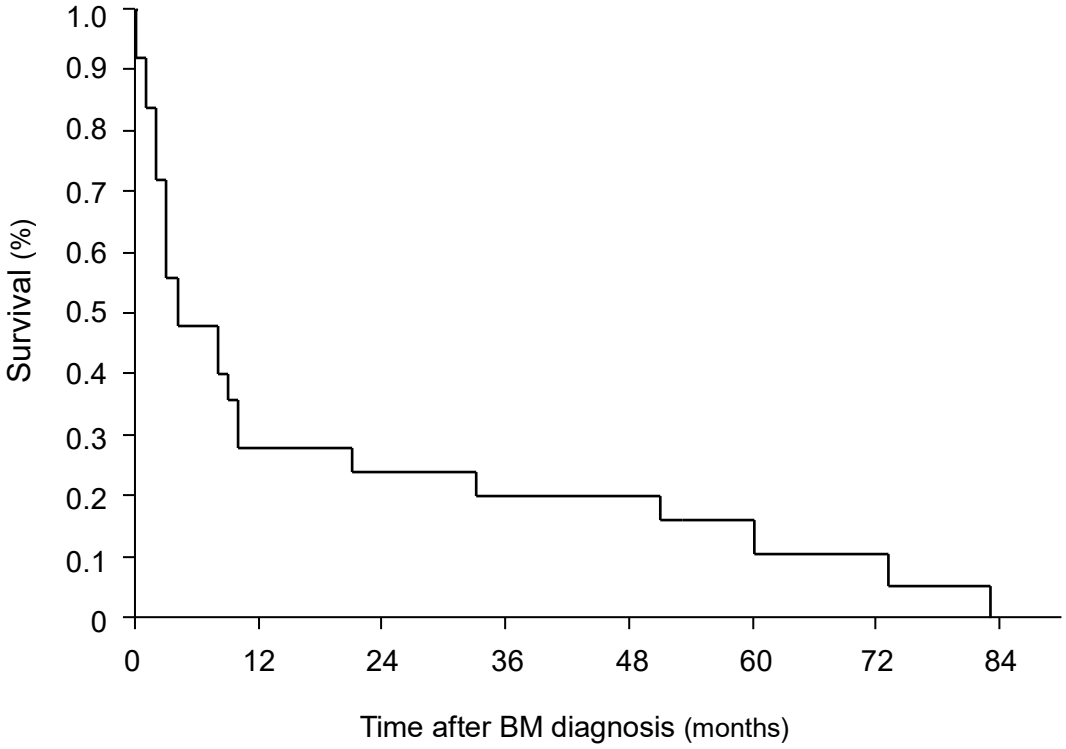
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Survival (%)
0
12
24
36
48
60
72
84
Time after BM diagnosis (months)

Fig.2

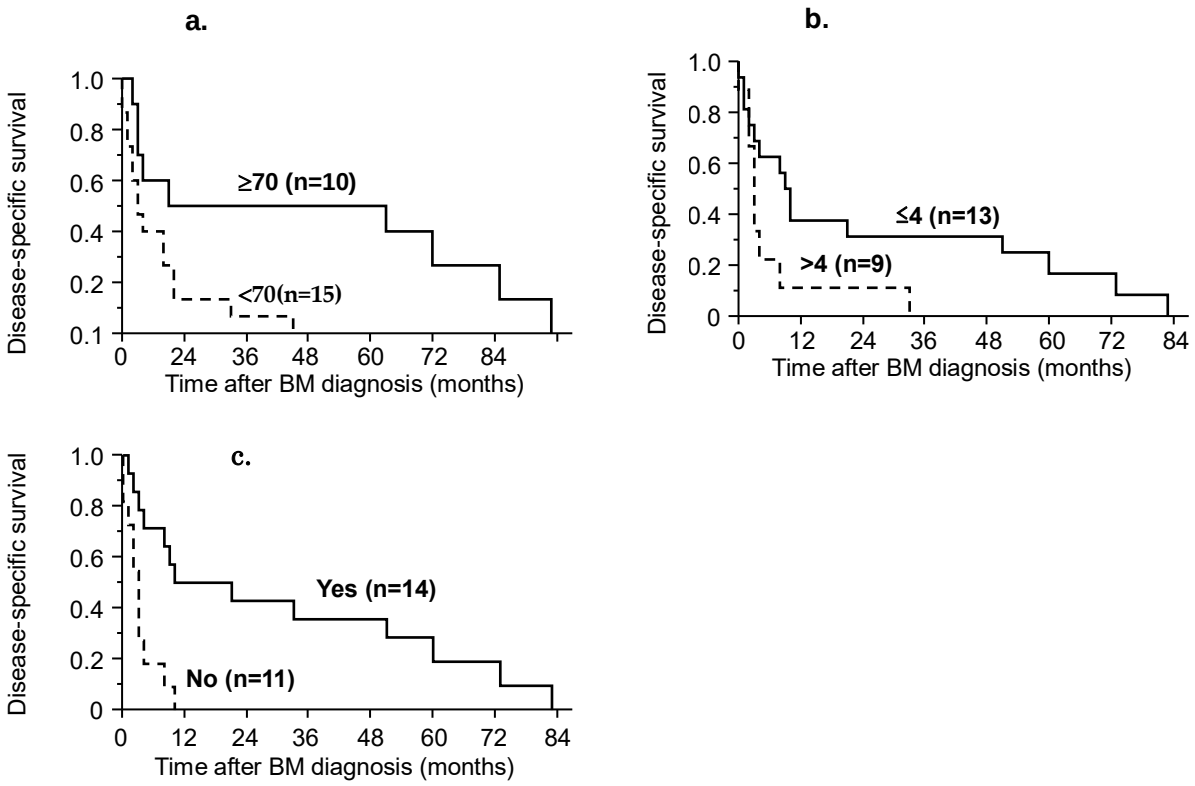
a.
Disease-specific survival
1.0
0.8
0.6
0.4
0.2
0.1
≥70 (n=10)
<70(n=15)
0
24
36
48
60
72
84
Time after BM diagnosis (months)
b.
Disease-specific survival
1.0
0.8
0.6
0.4
0.2
0
≤4 (n=13)
>4 (n=9)
0
12
24
36
48
60
72
84
Time after BM diagnosis (months)
c.
Disease-specific survival
1.0
0.8
0.6
0.4
0.2
0
Yes (n=14)
No (n=11)
0
12
24
36
48
60
72
84
Time after BM diagnosis (months)

Figure legends

Fig. 1. Overall survival after diagnosis of brain metastasis (n = 25). One patient is still alive, and 24 patients died.

Fig. 2. Survival curves of three significant prognostic factors on univariate analysis. Comparison of disease-specific survival rates between KPS good or poor (a), between number of intracranial lesions ≤4 or over 4 (b), and between treatment or no treatment for brain metastasis (c).