Clinical effects of stereotactic radiation surgery in patients with metastatic melanoma

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Abstract

We examined the effectiveness of stereotactic radiation surgery (SRS) in 14 patients with brain metastasis in our hospital. The age of the patients ranged from 45 - 85 years old (mean: 65). Brain metastasis was detected by neurological symptoms in 7 patients and by regularly examined imaging in the remaining patients. The number of metastatic lesions in the brain before SRS ranged from 1 - 11 (median: 2). The treatment number of SRS was 1- 4 times (median: 2). Six of 14 patients had neurological symptoms before SRS. Overall survival (OS) after SRS was 1.7 to 21.2 months (median: 8.2). The progression-free survival (PFS) after SRS was 0.9 to 10.5 months (median: 2.2). The result of univariate analysis showed that the application of 2 or more courses of SRS was significantly related to OS (p=0.005). Single metastatic lesion (p=0.051) and no extracranial lesion (p=0.055) showed a slight tendency to be related to DFS. Neither LDH nor neurological symptoms were significantly related to OS or DFS. Although OS and DFS after SRS were not very long, the treatment of brain metastases has the potential to prevent neurological events. Repeating SRS may be accepted as a local therapy in the multimodal approach including new molecular targeting drugs for metastatic melanoma.

Key words: stereotactic radiation surgery, gamma knife, melanoma, overall survival, disease-free survival

INTRODUCTION

Melanoma has high metastatic ability. Brain metastasis is one of the worst prognostic factors in melanoma and induces disturbance of the central nervous system, which consequently prevents communication between the patient and the family in the terminal stage. Whole brain radiotherapy (WBRT) or stereotactic radiation surgery (SRS) has been used to treat brain metastasis in combination with depressants for cerebrospinal pressure. SRS has the advantages of lower toxicity and a shorter duration of therapy compared with WBRT, which can induce late dystrophy in the gray matter. However, both therapies are usually palliative therapies which improve neurologic symptoms and lead to prolonged survival. Although some clinical effectiveness of radiation targeting brain metastases has been reported, the selection criteria of SRS or WBRT have not been fully determined. Furthermore, Japanese data are limited because of the rarity of the disease. Thus, we examined the effectiveness of SRS in patients with brain metastasis in our hospital.

MATERIALS AND METHODS

The data of patients were gathered from lists at Shishu University Hospital from 2000 to 2010. The following factors were statistically examined to clarify the relationship to

overall survival (OS) and disease-free survival (DFS) by univariate analysis with the log-rank test: the number of treatment courses of SRS, the number of metastatic lesions in the brain, extracranial metastases, lactate dehydrogenase (LDH) and neurological symptoms before SRS .

RESULTS

Fourteen patients (male: 12. Female: 2) received SRS. Their ages ranged from 45 - 85 years old (mean: 65). The duration from the initial surgery of the primary lesion to brain metastasis was 0-95.2 months (median: 9.7, mean: 21.4). Brain metastasis was detected by neurological symptoms in 7 patients and by regularly examined imaging in the remaining patients. The number of metastatic lesions in the brain before SRS ranged from 1 - 11 (median: 2). The number of SRS treatments ranged from one to 4 (median: 2). Six of 14 patients had neurological symptoms before SRS. The symptoms were improved in 2 patients but not changed in 4 patients after SRS. No severe adverse events were observed. One patient had mild impaired consciousness for 6 days after SRS and another patient complained of a short-term spasm in the lower leg for a few days. OS after SRS was 1.7 to 21.2 months (median: 8.2) (Figure 1). PFS after SRS was 0.9 to 10.5 months (median: .2.2) (Figure 2).

The relationship between following factors and OS or DFS examined by univariate

analysis were as follows: The number of treatment courses of SRS (OS: p=0.005, DFS: p=0.237), the number of metastatic lesions in the brain (OS: p=0.599, DFS: p=0.051), extracranial metastases (OS: p=0.092, DFS: p=0.055), LDH (OS: p=0.131, DFS: p=0.345) and neurological symptoms before SRS (OS: p=0.844, DFS: p=0.284). The administration of two or more courses of SRS was significantly related to OS (Figure 3). The number of metastatic lesions up to 2 and the absence of an extracranial lesion showed a slight tendency to be related to PFS (Figures 4 and 5).

DISCUSSION

In our study, the medians of OS and PFS were 8.2 months and 2.2 months, respectively. The results were comparable to those of previous reports which showed an OS of 4.4-10.6 months and a DFS of 2.9-6.8 months[1)-10)]. Additionally, the neurological symptoms were improved in 2 patients but not changed in 4 patients after SRS. Although the durations after SRS were not very long and neurological symptoms were not always improved by SRS, the treatment of brain metastases has the potential to prevent seizures and neurological events caused by the enlargement of tumors, edema and bleeding. The National Comprehensive Cancer Network (NCCN) guidelines recommend that SRS and/or WBRT be administered to brain metastasis of melanoma either as the primary treatment or as an adjuvant following surgical

resection.

Our univariate analysis suggested the possibility of relationship between the number of metastatic lesions, extracranial lesions and DFS, although there was no significant difference. In general, the administration of STR or WBRT has been determined based on the number and size of the lesions. NCCN recommends the use of SRS in patients with limited metastasis (1-3) and SRS or WBRT in patients with multiple metastasis (>3). However, Chang et al. recently reported that the mean of OS after SRS was not statistically different among 4 groups categorized by the number of metastases: 1-5, 6-10, 10-15 and >15[11]. In addition, the treatment of extracranial lesions becomes necessary after the irradiation of a brain metastasis. Most recent advances, including the new molecular targeting therapy including BRAF inhibitor, vemurafenib or dabrafenib, and the anti-CTLA4 antibody, ipilimumab, have brought long-term control of metastatic lesions including in the brain. Knisely et al. reported the results of a prospectively collected cohort study of 77 patients, which showed a median survival of patients who received both ipilimumab and SRS to be 21.3 months, as compared with 4.9 months in patients who received only SRS[12]. In these contexts, the late adverse effect of WBRT on cognitive function may favor the use of SRS.

The number of courses of SRS administered was the only significant factor related to

survival in our study. Because the analysis performed was univariate analysis, the difference in the progression speed of metastatic lesions between patients could have influenced the result. However, a multimodal approach in individual metastatic organs is required in patients with metastatic melanoma. Thus, repeating SRS may be accepted as a local therapy in the multimodal approach to metastatic melanoma if extracranial lesions are controlled. Because the number of cases in our study was not sufficient for the above suggestion to be conclusive, further examination is needed.

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FIGURE LEGENDS

Figure 1. Overall survival after first therapy by stereotactic radiation surgery

Figure 2. Progression-free survival after first therapy by stereotactic radiation surgery

Figure 3. Overall survival and the number of treatment courses of stereotactic radiation surgery

Figure 4. Progression-free survival and the number of brain metastases

Figure 5. Progression-free survival and extracranial metastasis

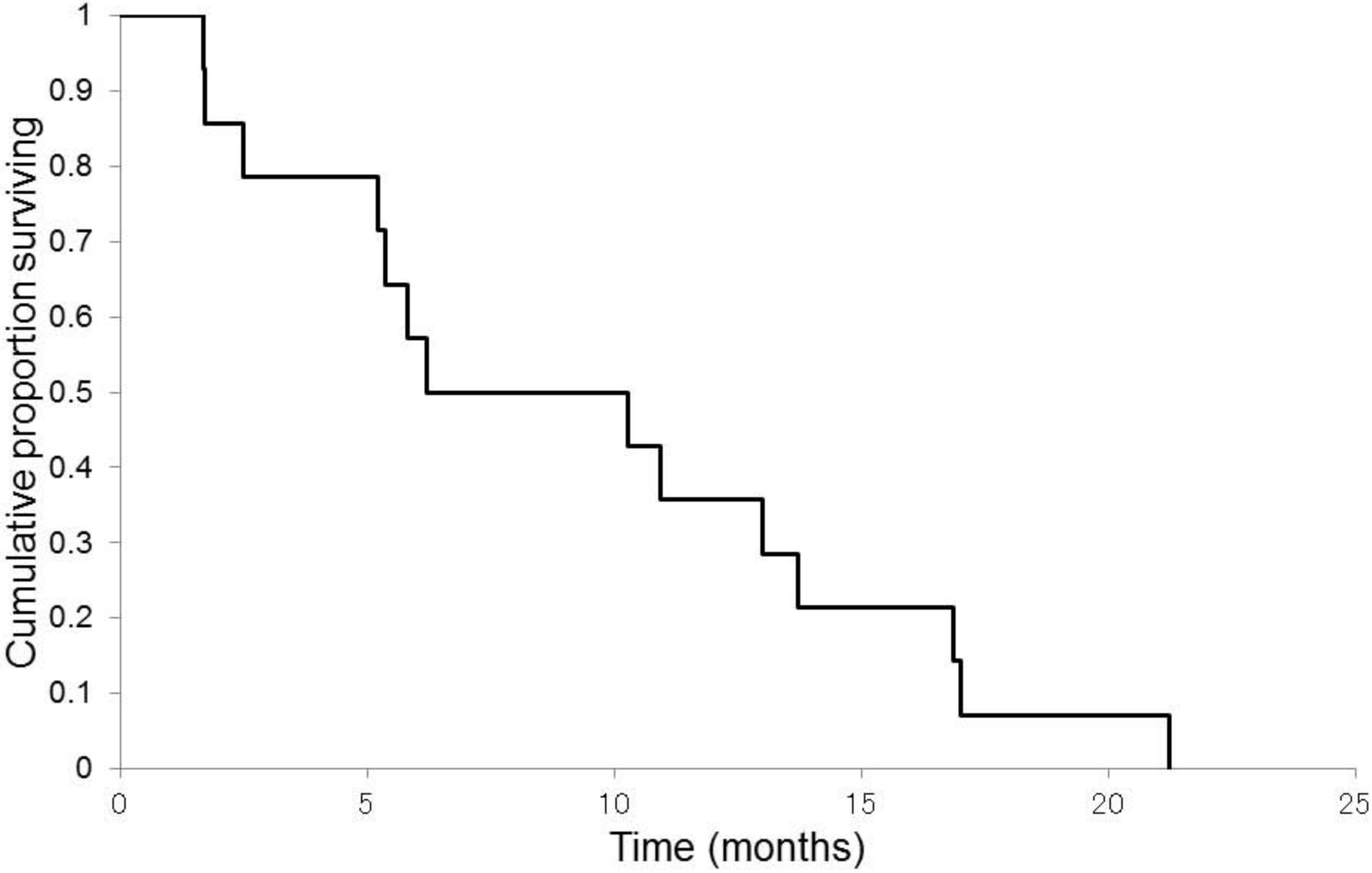
Cumulative proportion surviving
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
Time (months)

Figure 1

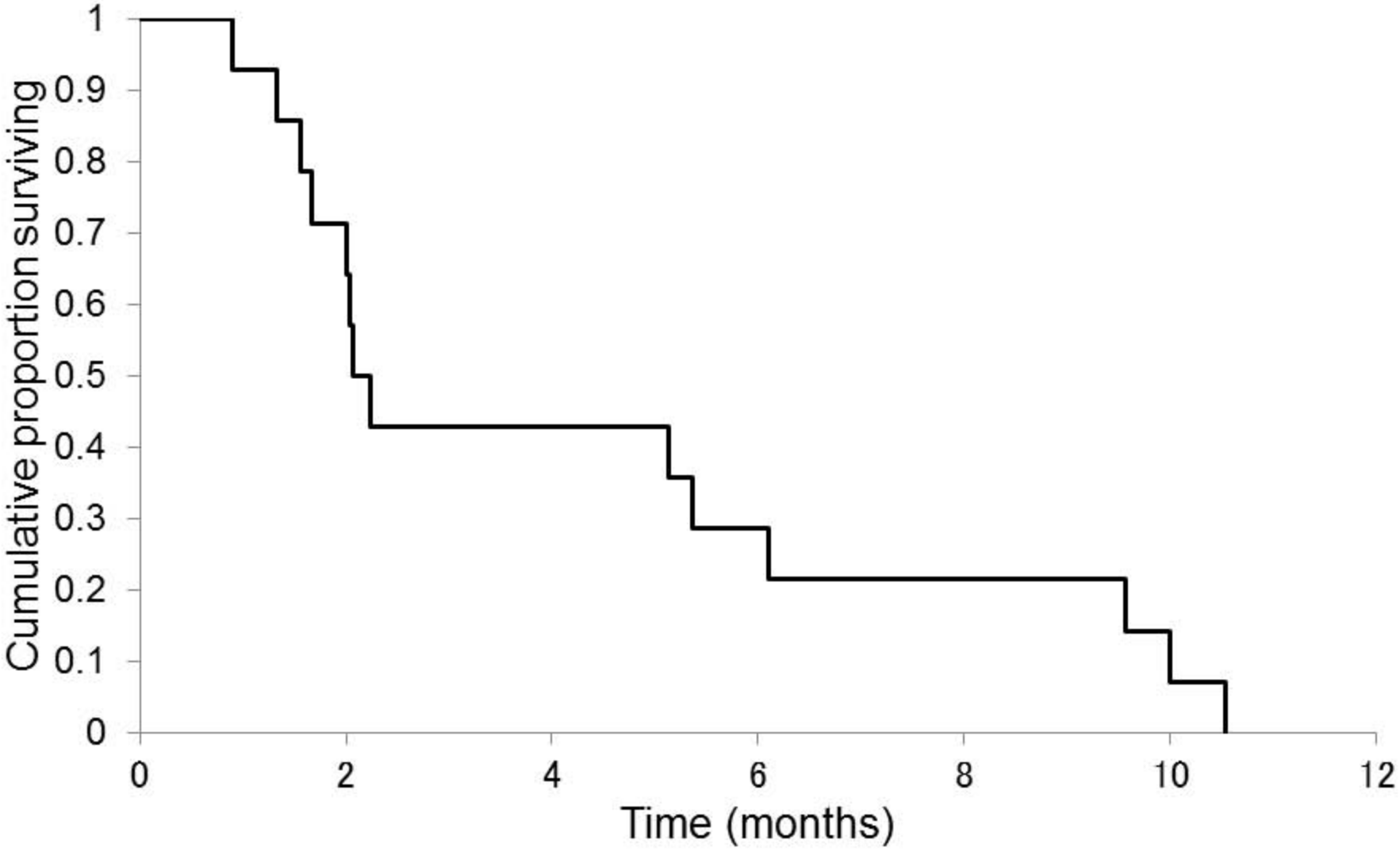
Cumulative proportion surviving
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
Time (months)

Figure 2

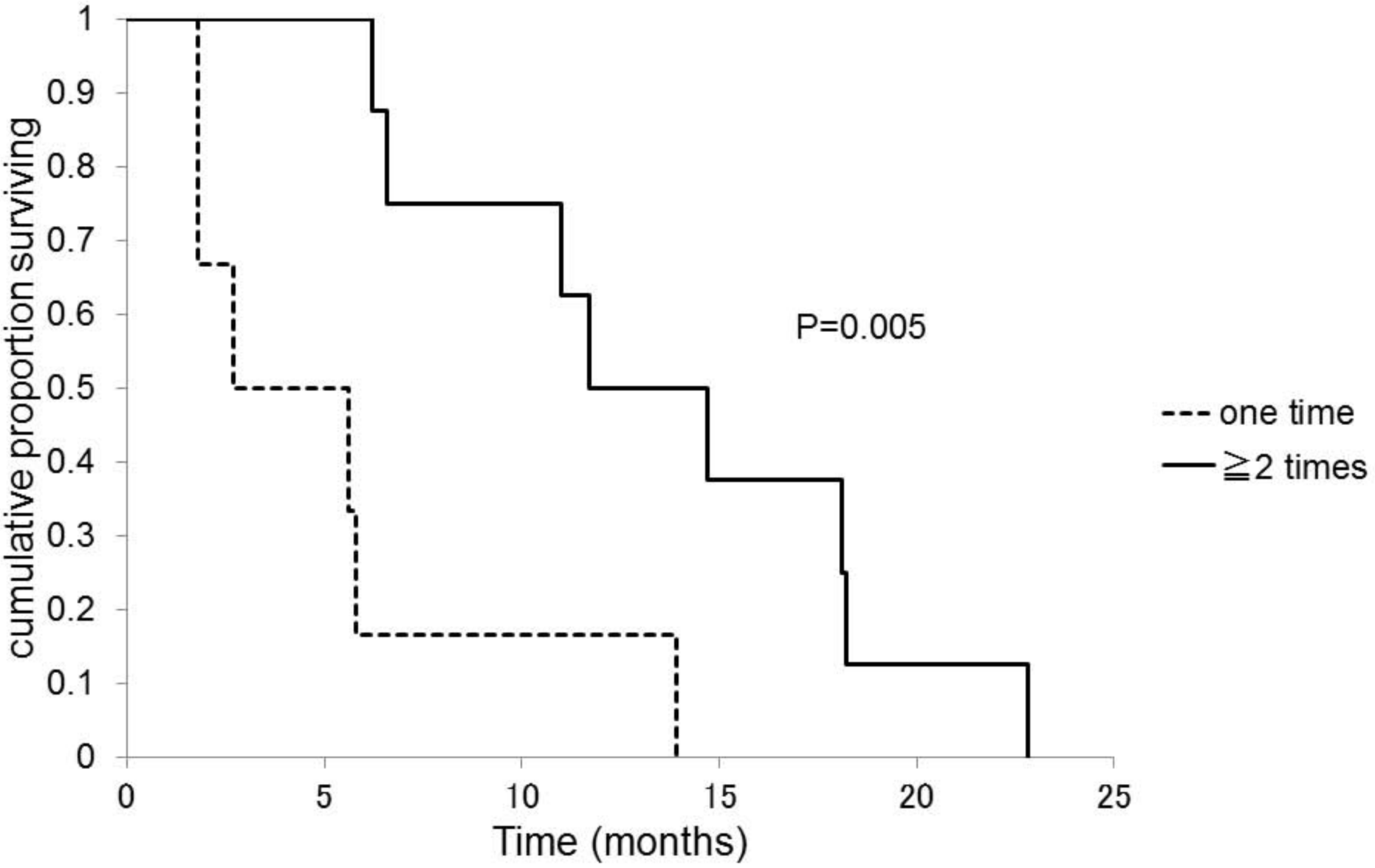
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
cumulative proportion surviving
0
5
10
15
20
25
Time (months)
P=0.005
one time
≧2 times

Figure 3

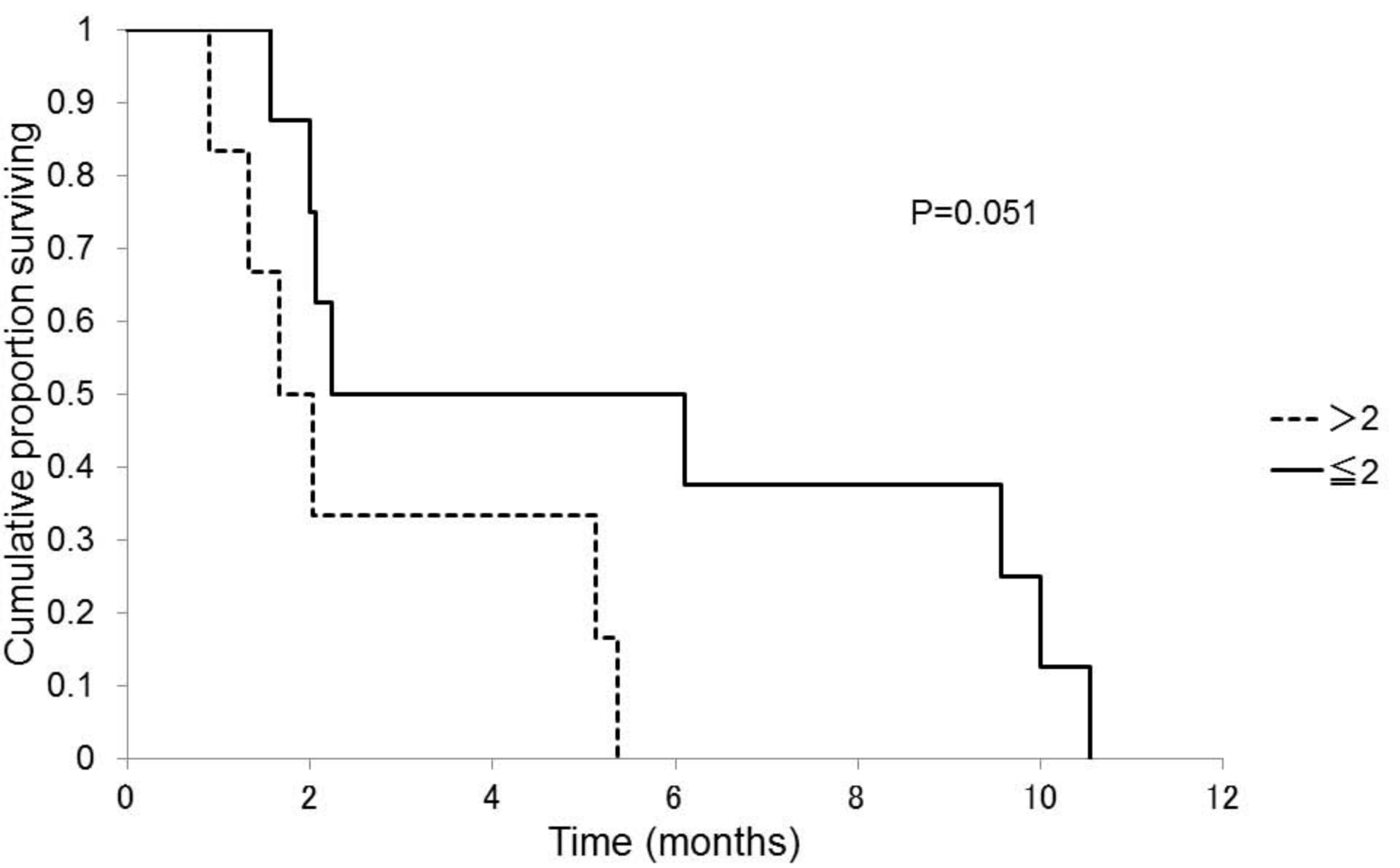
Cumulative proportion surviving
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
Time (months)
P=0.051
>2
≦2

Figure 4

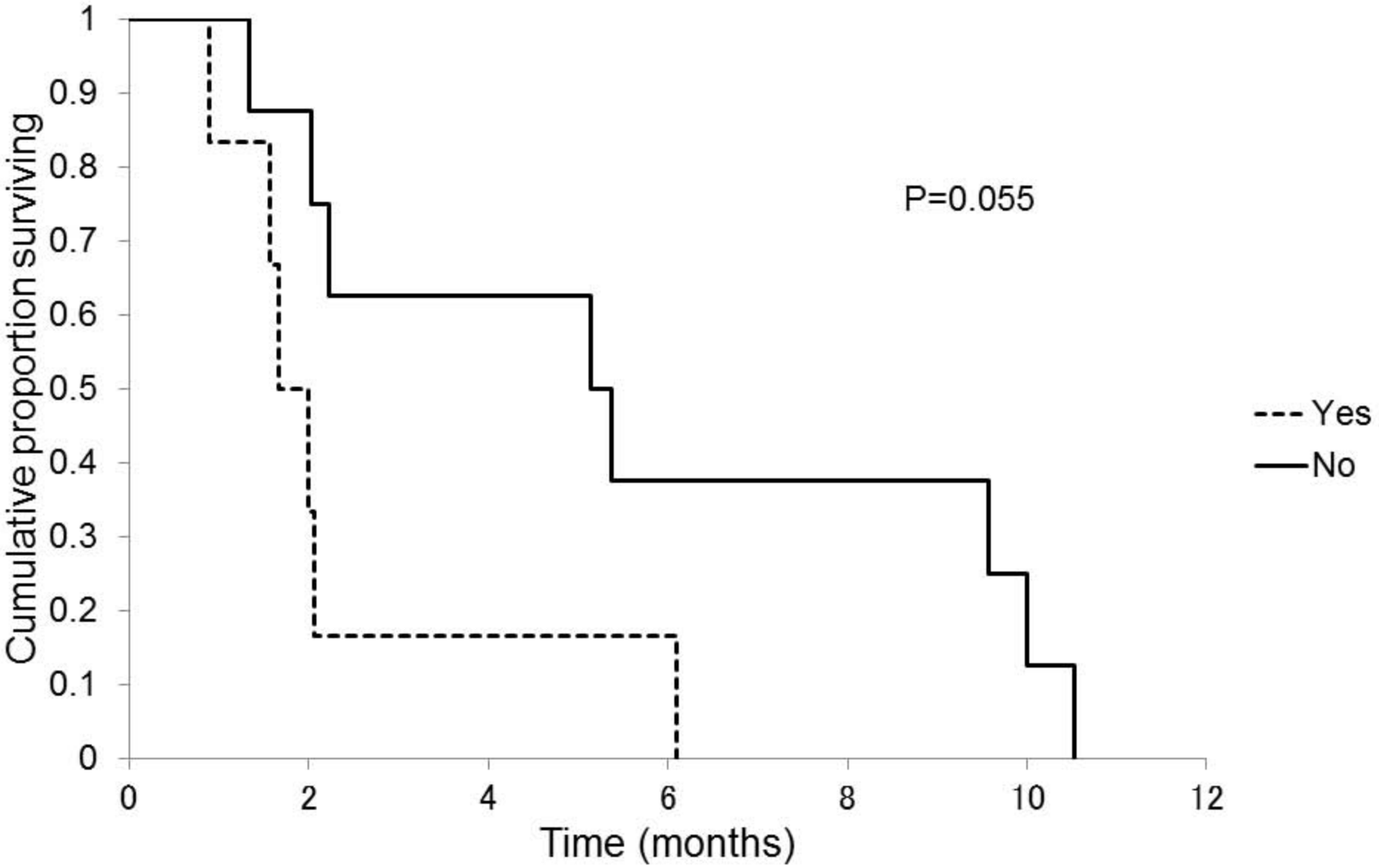
Cumulative proportion surviving
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
Time (months)
P=0.055
Yes
No

Figure 5