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Primary Tumor Size Predicts Distant Metastasis of Mucosal Malignant Melanoma in Head and Neck

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Abstract. *Background/Aim: To investigate the possible association between primary tumor size and overall survival and/or distant metastasis-free survival of patients with mucosal malignant melanoma of the head and neck. Patients and Methods: A total of 25 patients that have had primary tumor resection were enrolled in this study. Primary tumor size was assessed as the maximum size of the primary tumor in pathological and surgical reports. Results: Patients with a primary tumor size of ≥43 mm showed a significant association with shorter overall survival (p=0.007) and distant metastasis-free survival (p=0.005) by the log-rank test. Multivariate survival analyses of two Cox's hazards proportional models showed that, in model1, pT4a-4b (p=0.01) and primary tumor size ≥43 mm (p=0.03) were significantly associated with shorter overall survival, and primary tumor size ≥43 mm (p=0.02) was significantly associated with shorter distant metastasis-free survival. In model2, pStage IVA-IVB (p=0.02) and primary tumor size ≥43 mm (p=0.03) were significantly associated with shorter overall survival, and primary tumor size ≥43 mm (p=0.02) was significantly associated with shorter distant metastasis-free survival. Conclusion: Large tumor size (≥43 mm) is a predictor of shorter overall survival and distant metastasis-free survival after primary tumor resection of mucosal malignant melanoma of the head and neck.*

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Mucosal malignant melanoma of the head and neck (MMMHN) is rare, accounting for 0.2-0.8% of all malignant melanoma cases (1). Recent reviews reported that the American Joint Committee Cancer (AJCC) TNM staging system for MMMHN, which was proposed in 2009, is not fully acceptable (1-3). Several studies have researched useful predictors of MMMHN using various approaches such as clinical, pathological and biological methods (4-8).

Distant metastasis (DM) in MMMHN is a major factor that reduces overall survival (OS), which is generally less than 35% (2). The primary tumor size in MMMHN has also been reported to be a predictor of OS by several authors (4, 5). However, the association between the primary tumor size and DM in MMMHN has not been fully investigated.

Therefore, we investigated the possible association between the primary tumor size and OS in MMMHN, and examined whether or not the primary tumor size is associated with distant metastasis-free survival (DMFS).

Patients and Methods

Patients. Primary tumor resection with or without neck dissection was performed in 26 patients who were diagnosed with mucosal malignant melanoma, at the Department of Head and Neck Surgery, Aichi Cancer Center Hospital, between January 2004 and March 2015. After excluding one patient who had been diagnosed with mucosal malignant melanoma in the cervical esophagus, a total of 25 patients with MMMHN were enrolled in this study. This study was approved by the review board, and all patients provided their informed consent for the examinations and treatments.

Clinicopathological parameters. Clinical staging was determined by a routine physical examination, flexible nasopharyngeal endoscopy, enhanced cervical computed tomography or magnetic resonance imaging, and ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography, if possible. The 25 patients underwent *en-bloc* resection with or without free-flap reconstruction surgery. The regimen of chemotherapy was mostly dacarbazine, nimustine hydrochloride, vincristine and interferon-beta. The regimen of biotherapy was

interferon-beta. Postoperative radiotherapy was performed without chemotherapy. After completion of the initial treatment, we tried to perform salvage surgery based on the presence of tumor recurrence. We reviewed the primary tumor sizes of all patients based on the maximum size of the primary tumor in pathological and surgical reports. From both the pathological reports and the records of intraoperative findings, we restaged the pathological T and N classification, pathological stage based on the eighth edition of Union for International Cancer Control TNM classification of Malignant Tumors as described previously (9).

Statistical analysis. Statistical analyses were performed using the JMP software package (version 9; SAS; Cary, NC, USA). The relationships between the primary tumor size and the clinicopathological parameters (age, sex, primary tumor site, pathological T and N classification, pathological stage, positive surgical margin, neck dissection, reconstruction surgery, chemotherapy, biotherapy, radiotherapy) were assessed by Mann–Whitney *U*-test. The survival time, which was calculated as the number of days from the start of any treatment to the specific target event or last contact, was estimated by the Kaplan–Meier method. The target events were death for the OS, local recurrence for the local recurrence-free survival, regional recurrence for the regional recurrence-free survival, and DM for the DMFS. In accordance with a previous report, various cut-off values of the primary tumor size were assessed by univariate analysis of the OS using log-rank test (10). The patients were divided into two groups based on the primary tumor size (<43 mm or ≥43 mm), and differences between the two groups were compared by univariate survival analysis using log-rank test. The associations between the two groups (<43 mm or ≥43 mm) with regard to the clinicopathological parameters were compared by using Fisher's exact test. Multivariate analyses of the factors associated with OS and DMFS used two Cox's proportional hazard models. Model 1 was adjusted with the pathological T classification (pT4a-4b/pT3), and model 2 was adjusted with the pathological stage (pStageIVA-IVB/pStageIII). *p*-Values <0.05 were considered to indicate statistical significance.

Results

Primary tumor size and clinicopathological parameters. The mean±standard deviation (SD) of the primary tumor size in all patients was 27±15 mm (range=1-60 mm). The relationships between the primary tumor size and the clinicopathological parameters are shown in Table I. No significant associations were observed. The association between the pathological T classification and the primary tumor size in all patients is shown in Figure 1.

Survival outcomes. At the end of the study, the mean±SD follow-up period was 1259±1203 days among all patients, 1883±1299 days for the 9 patients who remained alive, and 909±768 days for the 16 patients who died. Local recurrence, regional recurrence and DM were found in 11, 8 and 16 patients, respectively. Salvage surgery was performed on 3 patients with tumor recurrence. The 5-year rates for OS, local recurrence-free survival, regional recurrence-free survival, and DMFS were 45.3%, 50.9%, 63.8%, and 37.9% respectively.

Table I. *The relationships between primary tumor size and clinicopathological parameters (n=25).*

Parameter	Patient number	Primary tumor size (mm) (mean±standard deviation)	*p*-Value*
Age			
<72	12	21.3±16.4	
≥72	13	31.4±12.4	0.08
Gender			
Male	10	31.3±13.6	
Female	15	23.4±15.6	0.12
Primary site			
Oral	12	28.8±13.7	
Sinonasal tract	13	24.5±16.5	0.30
Pathological T classification			
T3	11	21.1±15.4	
T4a-b	14	30.9±13.8	0.12
Pathological N classification			
N0,NX	18	27.3±15.6	
N1	7	24.6±14.5	0.81
Pathological stage			
III	10	22.7±15.3	
IVA-B	15	29.1±14.9	0.33
Positive surgical margin			
Presence	4	31.8±15.1	
Absence	21	25.6±15.2	0.41
Neck dissection			
Presence	12	31.0±14.9	
Absence	13	22.5±14.6	0.10
Reconstruction			
Presence	9	34.0±15.8	
Absence	16	22.4±13.4	0.07
Chemotherapy			
Presence	17	24.9±15.9	
Absence	8	30.1±13.4	0.38
Biotherapy			
Presence	17	26.4±15.1	
Absence	8	27.0±16.1	0.95
Radiotherapy			
Presence	3	31.7±18.7	
Absence	22	25.9±14.9	0.68

*Mann-Whitney *U*-test.

Cut-off values of primary tumor size and univariate analysis. The cut-off values of the primary tumor size and *p*-values in the OS analysis are shown in Figure 2. The primary tumor size of 43 mm allowed for the differentiation of the shorter OS group (primary tumor size ≥43 mm) from the longer OS group (primary tumor size <43 mm) by the log-rank test (p=0.007). Patients with a primary tumor size ≥ 43 mm were significantly associated with shorter DMFS than those with primary tumor size <43 mm (p=0.005). In contrast, the local recurrence-free survival (p=0.09) and regional recurrence-free survival (p=0.06) did not differ significantly in the patients with primary tumor size ≥43 mm. The Kaplan–Meier curves for the OS and

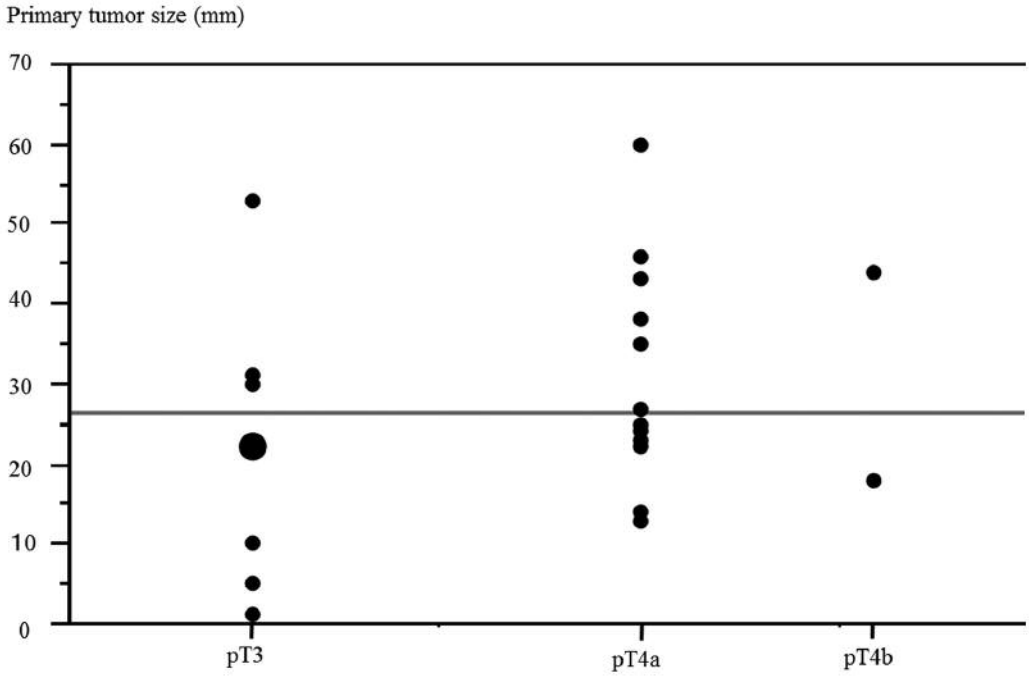

Figure 1. *The association between the pathological T classification and the primary tumor size of 25 patients with mucosal malignant melanoma in the head and neck.*

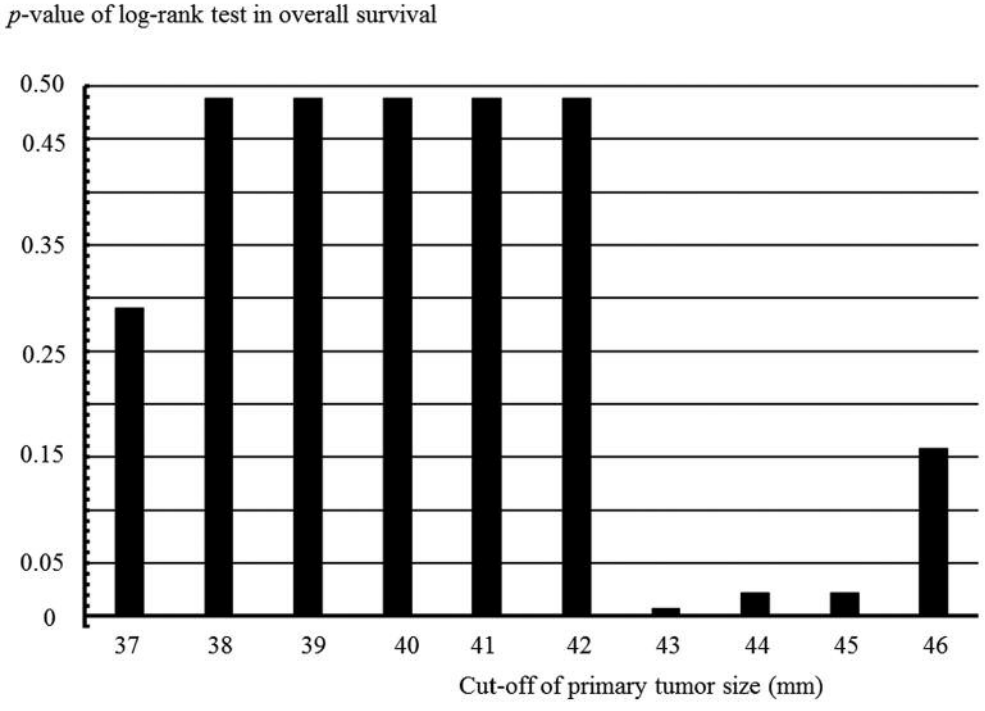

Figure 2. *The p-values of the log-rank test for the overall survival using different cut-off values for the primary tumor size of 25 patients with malignant melanoma in the head and neck.*

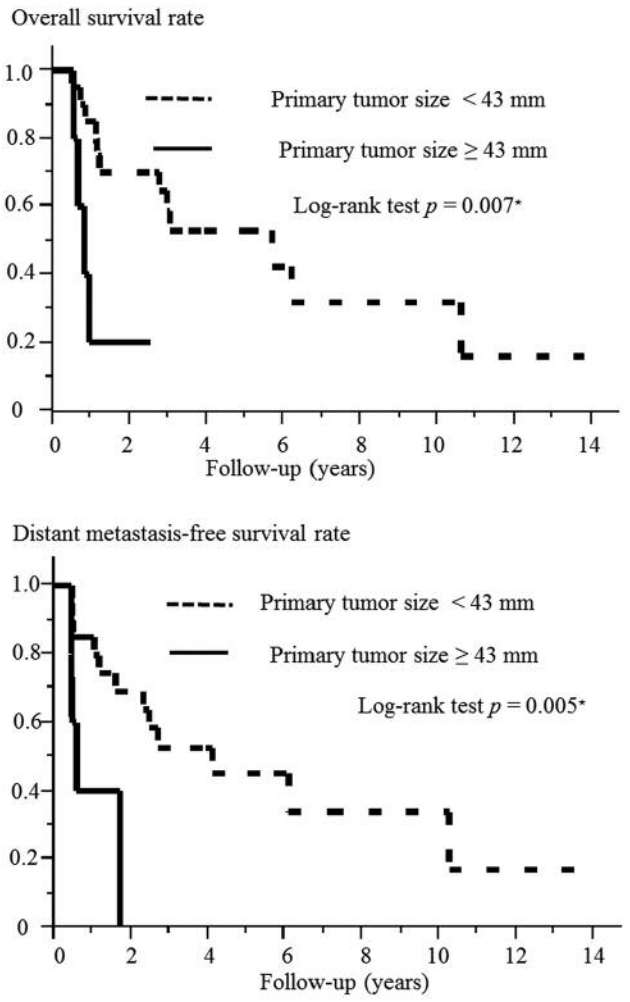

Figure 3. *The association between the primary tumor size and the survival of 25 patients with mucosal malignant melanoma in the head and neck (Kaplan–Meier method). A primary tumor size ≥43 mm was found to be associated with a significantly lower overall survival and distant metastasis-free survival.*

Table II. *Relationships between primary tumor size and clinicopathological parameters (n=25).*

Parameter	Primary tumor size		*p*-Value*
	<43 mm (n=20)	≥43 mm (n=5)	
Age			
<72	11	1	0.32
≥72	9	4	
Gender			
Male	7	3	0.36
Female	13	2	
Primary tumor site			
Oral	9	3	0.65
Sinonasal tract	11	2	
Pathological T classification			
T3	10	1	0.34
T4a-T4b	10	4	
Pathological N classification			
N0-NX	14	4	1.00
N1	6	1	
Pathological stage			
III	9	1	0.61
IVA-IVB	11	4	
Positive surgical margin			
Presence	3	1	1.00
Absence	17	4	
Neck dissection			
Presence	8	4	0.16
Absence	12	1	
Reconstruction surgery			
Presence	5	4	0.04
Absence	15	1	
Chemotherapy			
Presence	14	3	1.00
Absence	6	2	
Biotherapy			
Presence	14	3	1.00
Absence	6	2	
Radiotherapy			
Presence	2	1	0.50
Absence	18	4	

*Fisher's exact test.

DMFS are shown in Figure 3. The associations between the two groups (primary tumor size ≥43 mm/primary tumor size <43 mm) and clinicopathological parameters are shown in Table II. Compared with patients with a primary tumor size of <43 mm, those with a primary tumor size ≥43 mm had underwent reconstruction surgery significantly more frequently (p=0.04).

Multivariate analysis. The results of the multivariate analyses for the OS and DMFS are shown in Table III. In model 1, both pT4a-4b (p=0.01) and primary tumor size ≥43 mm (p=0.03) were significantly associated with shorter OS, and primary tumor size ≥43 mm (p=0.02) was significantly associated with shorter DMFS. In model 2, both pStageIVA-IVB (p=0.02) and primary tumor size ≥43 mm (p=0.03) were significantly associated with shorter OS, and primary tumor size ≥43 mm (p=0.02) was significantly associated with shorter DMFS.

Discussion

In the present study, it was shown for the first time that primary tumor size of ≥43 mm was significantly associated with shorter OS and DMFS in patients with MMMHN.

MMMHN, which accounts for 0.03% of all cancer diagnoses, was an aggressive and rare tumor (3). Regardless

Table III. *The multivariate survival analysis* of mucosal malignant melanoma in head and neck.*

Parameter	Overall survival			Distant metastasis-free survival		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Model-1						
Pathological T classification (pT4a-4b/pT3)	4.17	1.40-15.3	0.01	1.93	0.69-5.63	0.21
Primary tumor size (≥43 mm/<43 mm)	4.95	1.15-20.0	0.03	5.29	1.28-20.0	0.02
Model-2						
Pathological stage (pStageIVA-IVB/pStageIII)	3.51	1.18-12.9	0.02	1.61	0.58-4.70	0.36
Primary tumor size (≥43 mm/<43 mm)	5.26	1.23-21.1	0.03	5.41	1.32-20.3	0.02

*Cox proportional hazard model was used.

of the radical surgery with or without adjuvant treatments for MMMHN, local recurrence, regional recurrence, and DM occurred in up to 81% of patients (6). Although the seventh edition of AJCC Cancer Staging Manual described the TNM classification for MMMHN (11), several prognostic parameters, such as an advanced T category, were shown not to be consistent findings in reports of MMMHN (1). Recent reviews suggested that further accumulation of data regarding predictors of MMMHN is necessary (1-3). Indeed, Houette *et al*. detected a significant association between the staging system and OS in 18 patients with sinonasal mucosal melanoma (7).

Several authors have observed a significant association between primary tumor size and OS (4, 5). For example, tumor size ≥40 mm in 815 patients with MMMHN from the Surveillance, Epidemiology, and End Results Program was found to be a significant predictor of OS in univariate and multivariate analyses (4), and tumor size ≥40 mm in 51 patients with TanyN0M0 of oral mucosal melanoma was associated with a worse OS than patients with a tumor size <40 mm (5). The findings of the present study revealed significant associations between the tumor size and the OS and are in good agreement with these previous studies (4, 5).

Because several reviews on MMMHN have reported that DM is directly associated with a shorter OS (1-4), we hypothesized that the primary tumor size was associated with DM. Indeed, in the present study, we showed that tumor size ≥43 mm was significantly associated with shorter DMFS. The findings of the present study suggested that the tumor size in MMMHN is a predictor of identifying patients that are at high risk of developing DM. Furthermore, we believe that the significant association between primary tumor size of ≥43 mm and shorter OS was caused by the shorter DMFS.

The limitations of the present study were the relatively small number of subjects and its retrospective design. A future prospective study in a larger cohort and in a multi-institutional setting is expected to yield more accurate results.

Conclusion

A large primary tumor size (≥43 mm) is a predictor of shorter OS and DMFS in patients with MMMHN who undergo surgery.

Conflicts of Interest

All of the Authors declare that they have no conflicts of interest.

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