



Mucosal melanoma of the head and neck: a retrospective analysis of 34 cases in Japan

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Abstract: Background: Mucosal melanoma of the head and neck (MMHN) is a rare condition. Aims/Objectives: This study aimed to investigate oncological outcomes of surgical intervention in patients with MMHN. Material and Methods: The study included 34 patients with MMHN who underwent surgical resection as initial treatment at 10 institutions in Japan between July 2005 and June 2015. Results: The 5-year overall survival (OS), local control rate (LCR), disease-free survival (DFS), and disease-specific survival (DSS) rates were 48.7%, 53.4%, 32.4%, and 55.1%, respectively. Based on multivariate analysis, no independent prognostic factors for the 5-year OS and DSS were found. Based on univariate analysis, the 5-year LCR was worse in patients with lesions in nasal cavity and paranasal sinuses than in oral cavity and pharynx. However, no differences in oncological outcomes were identified in relation to primary sites, and postoperative radiotherapy (PORT) and adjuvant systemic therapy did not contribute to improvements in the 5-year OS. Conclusions and Significance: No independent prognostic factors for the 5-year OS or DSS were identified. Regional or distant recurrences are often identified, regardless of local control with surgical resection. Difficult control of MMHN with conventional therapeutic strategies, such as surgical intervention, PORT, and systemic therapy, has been suggested.

Keywords: Mucosal melanoma of the head and neck, retrospective study, prognostic factor, surgical resection

Introduction: Mucosal melanoma of the head and neck (MMHN) is a rare disease comprising less than 1% of all melanomas and has a poor prognosis in western countries [1,2]. The most common sites of origin are the nasal cavity and paranasal sinuses, followed by the oral cavity [3]. In Japan, MMHN accounts for 8% of all melanomas [3], and according to the head and neck cancer registry in Japan, 101 of 119 MMHN patients (84.9%) had lesions in the nasal cavity or paranasal sinuses in 2019 [4]. Radical surgical resection is the mainstay treatment for this rare pathology. However, it is difficult to secure sufficient margins in some cases, and radiotherapy is occasionally selected as the initial treatment [5]. Multimodal treatment is usually administered, and adjuvant radiotherapy and/or systemic therapy is often started after surgical resection. However, the 5-year overall survival (OS) rate of MMHN remains at 14%–47%, and the prognosis is not satisfactory [5]. Recently, immune checkpoint inhibitors (ICIs)

have attracted attention as a fourth option for the treatment of malignancies. In Japan, nivolumab (anti-programmed death 1 agent) and ipilimumab (anti-cytotoxic T-lymphocyte-associated antigen 4 monoclonal antibody) were approved for the treatment of malignant melanoma in 2014 and 2015, respectively. In CheckMate 067 Clinical Trials, these ICIs extended the prognosis of advanced melanomas [6]; thus, an improvement in the prognosis of MMHN is expected with these drugs. Before discussing the contribution of ICIs to the treatment of MMHN, it is necessary to investigate the outcomes and limitations of conventional treatments. Therefore, in this multi-institutional retrospective study, we performed a chart review of 34 patients with surgically treated MMHN and investigated their clinical outcomes and prognostic factors.

Patients and methods:

Patients: This retrospective study was conducted at Kyoto University Hospital and Affiliated Facilities Head and Neck Clinical Oncology Group (KYOTO-HNOG), which includes 12 medical centers in Japan. This study was approved by the Institutional Review Board of each facility. From July 2005 to June 2015, 48 patients with MMHN were treated in these facilities and 34 of 48 patients with MMHN underwent surgical resection as the initial treatment. Of the 48 patients, three underwent palliative treatment and 11 underwent radiotherapy as the initial treatment (Fig. 1). The patient characteristics, treatment modalities, and clinical outcomes were retrospectively reviewed. All patients were staged according to the American Joint Committee on Cancer (AJCC), 8th edition guidelines.

Outcomes of patients: The follow-up period was defined as the period from the date of surgery to the date of death or the final follow-up. Clinical results, including OS, local control rate (LCR), disease-free survival (DFS), and disease-specific survival (DSS), were estimated using the Kaplan–Meier method. Candidate factors including primary tumor site, margin status, complications, postoperative radiotherapy (PORT), and adjuvant systemic therapy were examined.

Statistical analyses: Statistical analyses were performed using EZR version 1.55 (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing) [7]. The log-rank test was used for univariate analysis. Multivariate Cox regression analysis was performed for each variable identified as statistically significant by univariate analysis. Fisher's exact test was used to compare two groups. A p-value <0.05 was considered to be statistically significant.

Results:

Patient and lesion characteristics: Patient and lesion characteristics are summarized in Table 1. This study included 34 patients (15 males and 19 females) with MMHN. The median age was 74.5 years (30–85 years), and the median observation period was 55 months (5–154 months).

Treatments: Surgical resection was safely performed in 34 patients, with no severe complications. However, positive/unclear margins were identified in eight patients in the nasal cavity and paranasal sinuses. All patients who underwent curative surgical resection of the oral cavity and pharynx achieved negative margins, and Fisher's exact test revealed significant differences in the margin status between the nasal cavity and paranasal sinus lesions and oral cavity and pharynx lesions ($p = 0.0339$). Of the 34 patients who underwent surgical resection, only three had stage IVB. However, positive or unclear margins were identified in all three cases. After surgical resection, 5 patients received PORT and 20 patients received adjuvant systemic therapy. Systemic therapy includes interferon therapy, chemotherapy, and a combination of both.

Clinical outcomes: Of the 34 patients who underwent surgical resection, 16 died due to MMHN and four died due to other causes. The 5-year OS, LCR, DFS, and DSS rates were also estimated (Table 2). The 5-year LCR was worse in patients with MMHN in the nasal cavity and paranasal sinuses than in those with MMHN in the oral cavity and pharynx ($p = 0.00645$) (Fig. 2-b). However, between the nasal cavity and paranasal sinus groups and the oral cavity and pharynx groups, no significant difference was found in the 5-year OS ($p = 0.57$) (Fig. 2-a). Between the margin-positive/unclear and margin-negative groups, no significant differences were found in the 5-year LCR ($p = 0.151$) and DFS ($p = 0.0879$) (Fig. 3-b and 3-c), but a significant difference was found in the 5-year OS ($p = 0.00919$) and DSS ($p = 0.0169$) (Fig. 3-a and 3-d). Significant differences between stage III and IVA–IVB were found in the 5-year OS ($p = 0.00846$), DFS ($p = 0.0379$), and DSS ($p = 0.0478$) (Fig. 4-a, 4-c, and 4-d). Regarding additional treatments, no significant improvement was found in the 5-year OS in relation to PORT and adjuvant systemic therapy (Fig. 5-a and 5-b). However, multivariate analysis showed that TNM classification (stage III vs. stage IVA–IVB) and margin status were not independent prognostic factors for the 5-year OS and DSS (Table 3).

Recurrence: Of the 34 patients, 24 experienced tumor recurrence during the observation period. The

median time to recurrence was 9 months (2–84 months). Of the 24 patients, 13 underwent salvage surgery; of which, 4 survived and 9 died. Of the four patients who survived without cancer after salvage surgery, local recurrence was resected in two patients and cervical recurrence was dissected in one patient. Remaining one patient experienced lung metastases and pneumonectomy was performed. Of the nine patients who died after receiving salvage surgery, seven patients experienced local recurrence (six patients at the nasal cavity or paranasal sinuses and one patient in the larynx), one patient had cervical recurrence, and the remaining one patient had recurrences in the cervical lymph node, lung, and small intestine. All the lesions were surgically resected; however, lesion control was not achieved. Of the 11 patients who did not undergo salvage surgery, 9 died and 2 survived with the disease. Of the two patients who survived the disease, one patient had recurrences in local lesions, cervical lymph nodes, and lungs and received palliative radiotherapy to the local lesion. The other patient experienced local recurrence and received radiotherapy, local injection of interferon, and administration of nivolumab. The primary tumor and tumor recurrence sites are summarized in Table 4. Fisher's exact test was performed on the primary tumor sites and a significant difference was found between the sites ($p = 0.00686$). Regarding the primary tumor sites and cervical or distant recurrence, no significant differences were found ($p = 0.0608$). Patients with tumors in the nasal cavity and paranasal sinuses tended to experience local recurrence, but cervical or distant recurrence was equally observed regardless of the primary site of the tumor.

Discussion: We performed a multi-institutional retrospective study of MMHN and investigated its prognostic factors. In our study, no independent prognostic factors for 5-year OS and DSS were found in multivariate analysis. Regarding the primary tumor sites, the 5-year LCR was worse in patients with lesions in the nasal cavity and paranasal sinuses than in those with lesions in the oral cavity and pharynx. However, there was no significant difference in cervical or distant recurrence between the two groups, and the 5-year OS rates were equivalent. PORT and adjuvant systemic therapy did not extend the 5-year OS, and difficulty in controlling MMHN with conventional surgical interventions has been suggested. Sun et al. reported that the surgical margin was an independent prognostic factor for OS in a retrospective review of 161 MMHN cases [8]. Sahovaler et al. also reported that negative or close margins compared to positive margins were associated with a higher 3-year OS, and a significant

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difference was found in a retrospective review of 76 patients with MMHN [9]. In contrast, Sayed et al. reported no association between the margin status and OS in a multivariate analysis of 72 patients with sinonasal mucosal melanoma [10]. In addition, Omura et al. investigated Japanese patients with MMHN and reported no significant association between margin status and OS/DSS [11]. Our results indicated that a positive/unclear surgical margin was not an independent prognostic factor, which is consistent with the results of the latter studies. Sahovaler et al. reported that clearance of surgical margins is usually less challenging in patients with oral cavity involvement than in those with sinonasal tract [9]. In a single-center study of 47 patients with MMHN in Japan, Omura et al. reported that sinonasal mucosal melanoma was an independent significant adverse prognostic factor for OS and DSS [11]. By contrast, McLean et al. reported no significant difference in OS between sinonasal and oral cavity melanomas [12]. In our study, the 5-year OS was equivalent between the nasal cavity and paranasal sinus groups and the oral cavity and pharynx groups, despite differences in the 5-year LCR. Based on previous studies and our data, the relationship between the primary site and prognosis remains inconclusive. However, a high recurrence rate was confirmed in other studies [8,11], and difficult regional/distant lesion control of MMHN was suggested regardless of local control with surgical intervention. Unfortunately, adjuvant treatment does not contribute to lesion control in patients with MMHN. In an in vitro study, Strojanc reported that melanoma cells have a high intrinsic capacity for the repair of sublethal DNA damage caused by photon beam radiotherapy [13]. Patel et al. reported that PORT was more likely to be used in sinonasal lesions than in oral lesions because of the inherent difficulty in obtaining satisfactory surgical clearance in sinonasal tumors; however, there was no evidence of the efficacy of PORT in patients with MMHN [14]. In our study, we also found no significant difference in the 5-year OS in relation to PORT, and its therapeutic effects were not confirmed. Regarding cutaneous melanoma, a prospective randomized controlled trial reported that adjuvant interferon increased relapse-free survival and OS [15]. However, no systemic therapy regimen has been recognized as effective for the treatment of mucosal melanoma [5]. Bartell et al. reported that biochemotherapy, which included at least one chemotherapeutic agent (cisplatin, vinblastine, or dacarbazine) and at least one biologic agent (interferon-a or interleukin-2), for advanced MMHN should be considered as a systemic treatment option in retrospective review of 15 patients [16]. In contrast, Lee et al. reported that adjuvant systemic

therapy (chemotherapy and interferon) after surgery did not increase the disease control rate [17]. In this study, 58.8% of patients received adjuvant systemic therapies, but they did not extend the 5-year OS, and no contribution of adjuvant systemic therapies after surgery was suggested. Adjuvant ICI have attracted attention as new therapeutic options for mucosal melanomas [6]. However, in previous studies, a limited number of MMHN cases were included; thus, future studies on adjuvant ICI for MMHN are warranted.

Limitations: This study had some limitations. One of the limitations of our study was its retrospective design. In addition, the sample size was small (34 patients). There would be a selection bias because the indications for surgical or adjuvant treatment could vary among facilities. Further studies with larger sample sizes are needed to elucidate the clinical characteristics of surgically resected MMHN.

Conclusion: We performed a retrospective study based on multi-institutional data to determine the treatment outcomes in surgically resected cases. In this study, multivariate analysis revealed no independent prognostic factors for 5-year OS and DSS in MMHN cases. Better margin clearance was achieved in MMHN in the oral cavity or pharynx than in those in the nasal cavity or paranasal sinuses, and better local control was confirmed in the oral cavity or pharynx. However, the regional and/or distant recurrences were equivalent in both groups, and no intergroup differences were observed in survival. PORT and adjuvant systemic therapy did not extend the 5-year OS, and difficult disease control of MMHN with conventional surgical intervention has been suggested.

Declaration of Interest statement: There are no conflicts of interest to declare. (2294 words)

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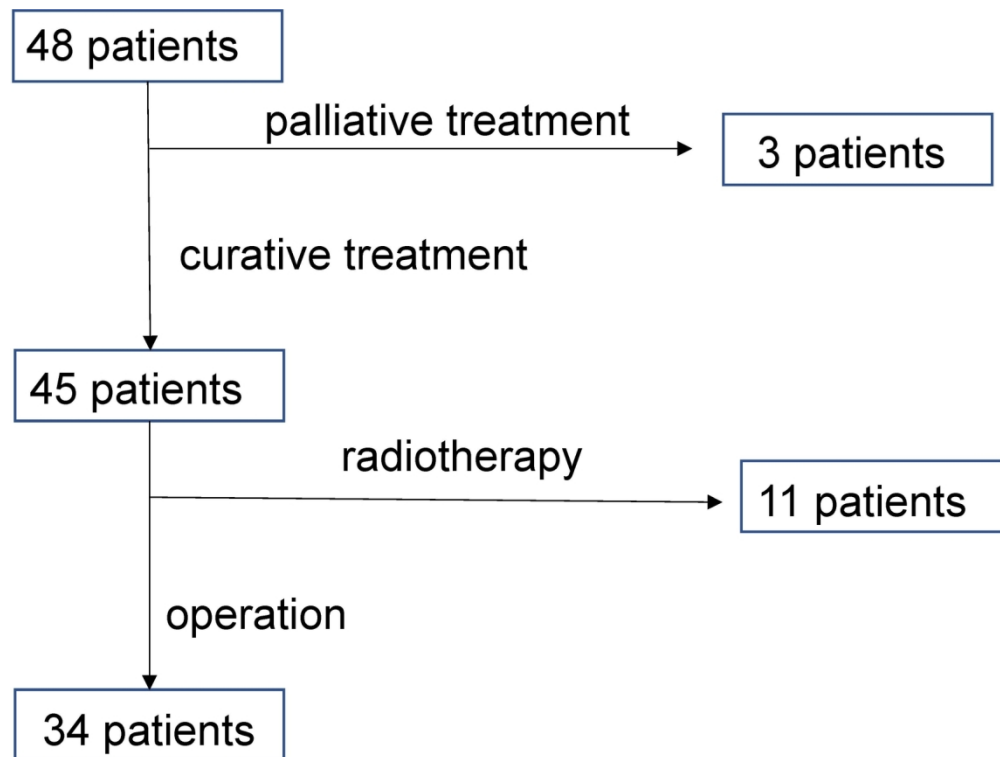


Fig. 1. Treatment courses of patients

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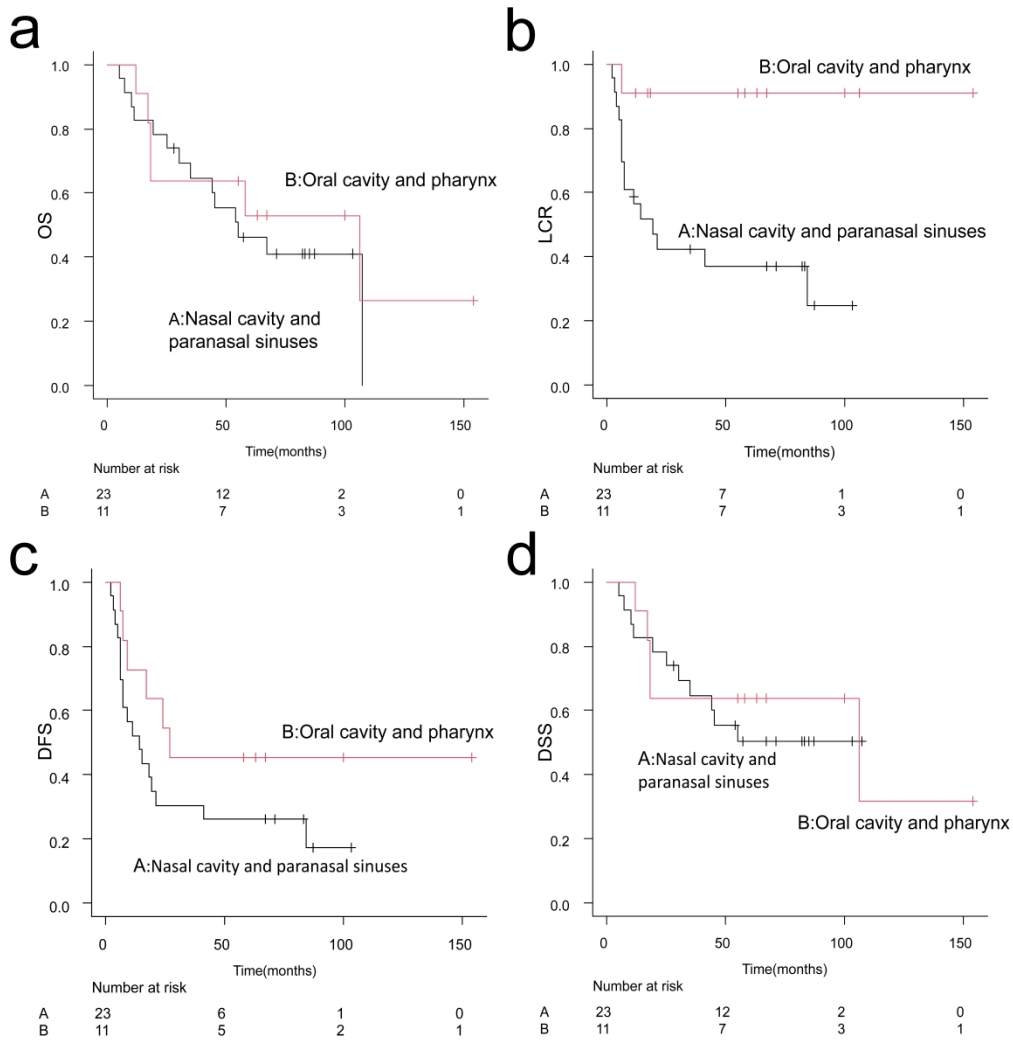


Fig. 2. 5-year OS (a), LCR (b), DFS(c), DSS(d) were compared according to the primary sites. Significant differences were observed about 5-year LCR, but not observed about 5-year OS, DFS, and DSS.

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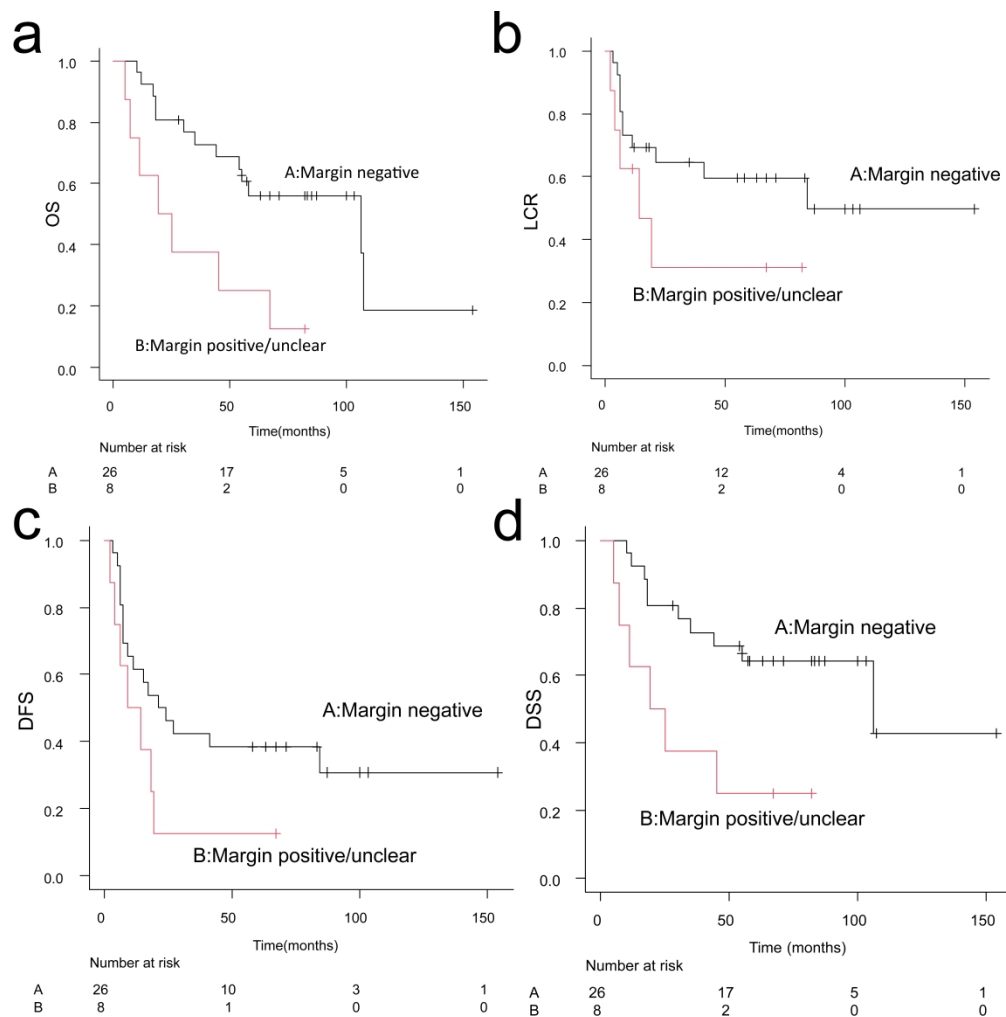


Fig. 3. 5-year OS (a), LCR (b), DFS (c), DSS (d) were compared according to the margin status. Significant differences were not observed for 5-year LCR and DFS, but observed for 5-year OS and DSS.

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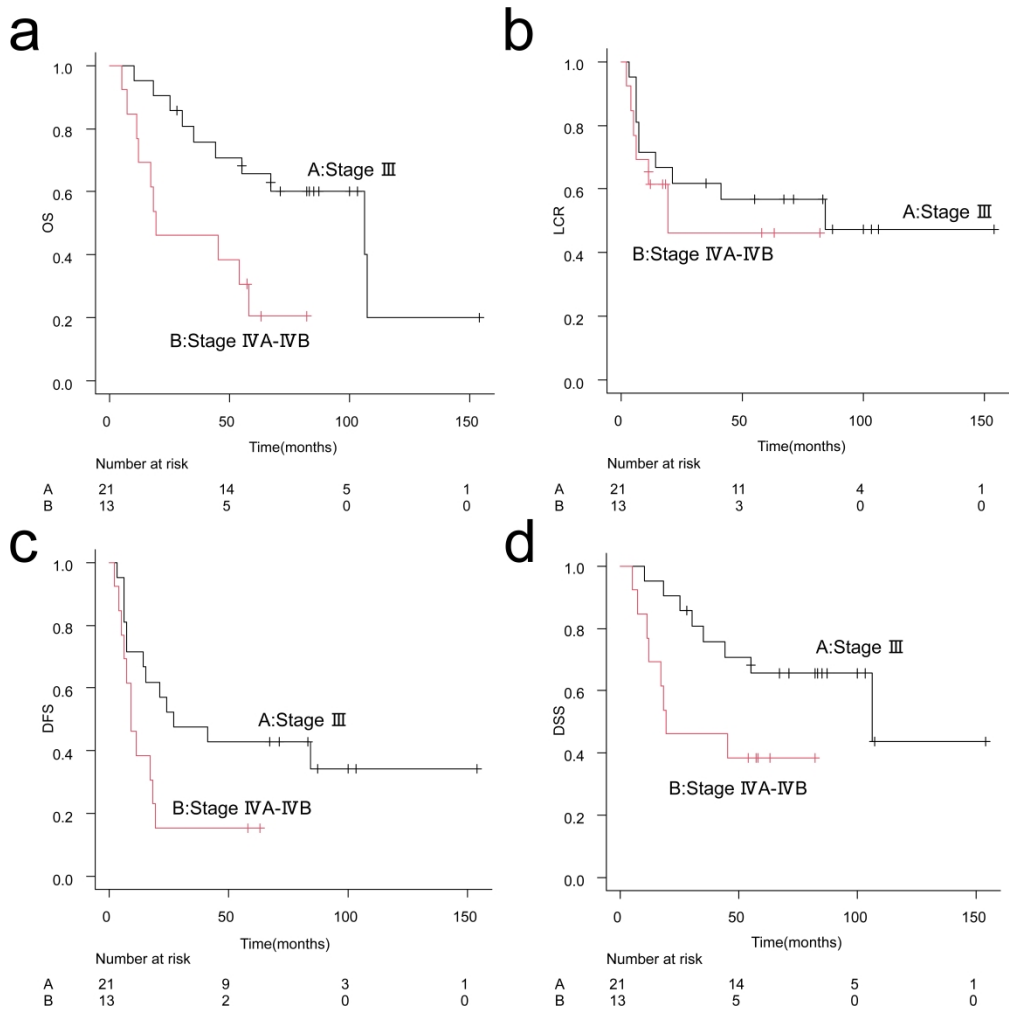


Fig. 4. 5-year OS (a), LCR (b), DFS(c), DSS(d) were compared according to the TNM classification (stage III vs stage IVA-IVB). Significant differences were not observed for 5-year LCR, but observed for 5-year OS, DFS, and DSS.

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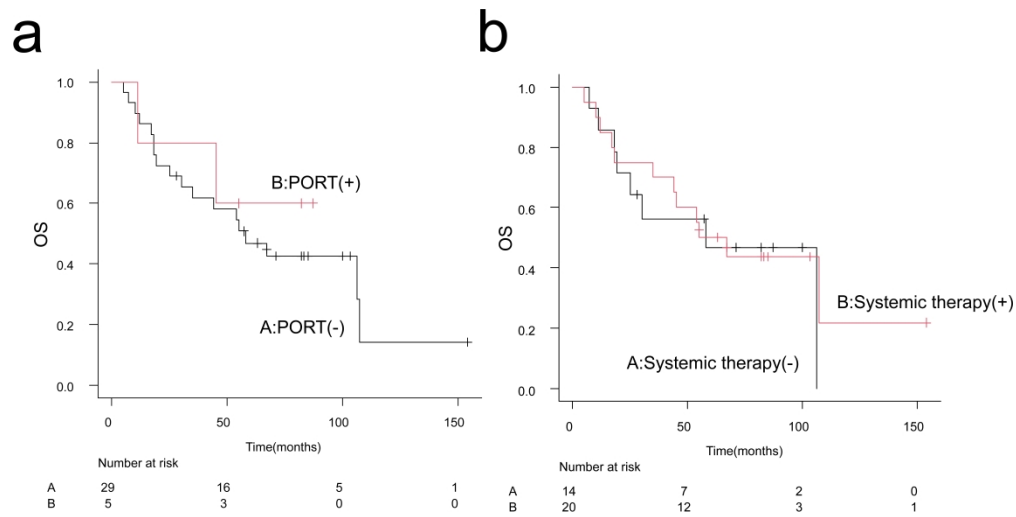


Fig. 5. 5-year OS was compared according to the PORT (a) and adjuvant systemic therapy (b). Significant differences were not observed for these two factors.

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Table1. Patient characteristics.

Characteristic	No. of patients
Sex	
Males	15
Females	19
Age(years)	
Median(range)	74.5 (30-85)
Observation period(months)	
Median(range)	55 (5-154)
Primary sites	
Nasal cavity and paranasal sinuses	23
Oral cavity	9
Pharynx	2
T classification	
T3	24
T4a	7
T4b	3
N classification	
N0	31
N1	3
M classification	
M0	34
M1	0
TNM classification(AJCC 8th)	
Stage III	21
Stage IVA	10
Stage IVB	3
Margin status	
Negative	26
Positive or unclear	8
Postoperative radiotherapy	
Yes	5
No	29
Adjuvant systemic therapy	
Yes	20
No	14

Table 2. Univariate analysis of prognostic factors for 5-year OS, LCR, DFS, and DSS.

	No. of patients	OS(5-year)	p	LCR(5-year)	p	DFS(5-year)	p	DSS(5-year)	p
All cases	34	48.7		53.4		32.4		55.1	
Primary sites									
Nasal cavity and paranasal sinuses	23	46.2		37.1		26.1		50.4	
Oral cavity and pharynx	11	53	0.57	90.9	0.00645	45.5	0.136	63.6	0.741
T stage									
T3	24	56.8		60.8		41.7		61.6	
T4a	7	42.9		57.1		14.3		57.1	
T4b	3	NA		NA		NA		NA	
N stage									
N0	31	54		50.1		32.3		57.1	
N1	3	NA	0.0648	NA	0.204	NA	0.929	NA	0.299
TNM classification(AJCC 8th)									
Stage III	21	65.5		56.7		42.9		65.5	
Stage IVA	10	26.7		70		20		50	
Stage IVB	3	NA		NA		NA		NA	
Stage III	21	65.5		56.7		42.9		65.5	
Stage IVA+IVB	13	20.5	0.00846	46.2	0.48	15.4	0.0379	38.5	0.0478
Margin status									
Negative	26	55.9		59.6		38.5		64.4	
Positive or unclear	8	25	0.00919	31.2	0.151	12.5	0.0879	25	0.0169
Postoperative radiotherapy									
Yes	5	60		75		20		60	
No	29	46.9	0.584	49.7	0.222	34.5	0.89	54.2	0.777
Adjuvant systemic therapy									
Yes	20	50		58.3		35		54.5	
No	14	46.9	0.769	46.9	0.757	28.6	0.84	56.2	0.69

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Table3. Multivariate analyses for 5-year OS and DSS.

Variable	Category	Hazard ratio	95% CI	p value
OS(5-year)				
TNM classification	Stage III vs Stage IVA-IVB	2.525	0.9057-7.042	0.07662
Margin status	Positive or unclear vs negative	2.27	0.8044-6.405	0.1214
DSS(5-year)				
TNM classification	Stage III vs Stage IVA-IVB	1.988	0.6569-6.024	0.2246
Margin status	Positive or unclear vs negative	2.498	0.8083-7.723	0.1118

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Table 4. Primary sites and recurrence sites.

Primary sites	Recurrence sites						Total No. of patients
	T	N	M	T+M	N+M	T+N+M	
Nasal cavity and paranasal sinuses	12	0	2	2	1	1	18
Oral cavity and pharynx	1	2	2	0	1	0	6
Total No. of patients	13	2	4	2	2	1	24

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