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Which factors affect the long-term survival of patients with oral squamous cell carcinoma with distant metastasis?

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Abstract

Purpose: The development of distant metastases (DM) in patients with oral squamous cell carcinoma (OSCC) leads to dismal prospects for survival. This study aimed to identify risk factors for DM development and long-term survival.

Patients and Methods: This study was a retrospective cohort study of OSCC patients at a single institution. The predictor variables were age, sex, TN classification, histological grade, neck dissection, infiltrative growth pattern (INF), vascular/lymphatic invasion, perineural invasion (PI), extranodal extension, local recurrence, nodal metastasis, DM, the time to diagnosis of DM, surgery for DM. The primary outcome variables were five-year overall survival (5y-OS) and median survival time (MST), which were estimated using the Kaplan-Meier method. Cox hazard models were used to identify risk factors for DM development.

Results: The cohort involved 526 patients, 402 of whom were available for analysis, with 37 of these 402 patients developing DM. On multivariate analysis, cN1-2 (HR: 3.36), moderate/poor differentiation (HR: 2.51), INF c (HR: 3.27), vascular/lymphatic invasion (HR: 2.95), and PI (HR: 2.17) were independent predictors for DM development. The 5y-OS was 84.6% for non-DM patients and 9.7% for DM patients, with a MST of 16.9 months. In DM patients with cN0, the 5y-OS was 18.2%, and the MST was 37.2 months, while in DM patients with cN1-2, the 5y-OS was 4.7%, and the MST was 12.9 months. In patients with time to DM diagnosis ≥10.0 months, the 5y-OS of was 20.0%, and the MST was 38.6 months, while in patients with time to DM diagnosis <10.0 months, the MST of was 11.7 months. The 5y-OS of patients who underwent a pulmonary metastasectomy was 60.0%; the MST of the non-surgery group was 16.0 months.

Conclusion: In DM patients, cN0 and late time to DM diagnosis were associated with long-term survival. Pulmonary metastasectomy may be worth considering to improve survival.

Keywords:

Distant metastasis; oral cancer; prognosis; risk factors; squamous cell carcinoma

Introduction

Oral cancer accounts for 117 384 deaths and 354 864 new diagnoses annually, and lip and oral cancer is the 16th leading cause of cancer deaths worldwide [1]. Oral squamous cell carcinoma (OSCC) is the most common form of oral cancer [2]. The overall and five-year survival rates for OSCC are both approximately 60% but vary from 10% to 82% depending on the clinical stage, age, race, comorbidity, and primary site [3]. Of several prognostic factors, it has been shown that distant metastasis (DM) is one of the strongest for predicting poor survival [4]. DM is found in 8.3-12.1% of primary cases without DM at the initial diagnosis after definitive surgery [4-8]. Although the overall survival rate in oral cancer has improved in the last 20 years thanks to improvements in diagnostic modalities and treatment methods [3, 9], patients with DM development have a poor prognosis, and generally only palliative treatments may be offered [4]. N classification [10], extranodal extension (ENE) [10, 11], and poor differentiation [12] are reportedly independent risk factors for DM development although they are controversial [11, 13]. Therefore, patients with node-negative (N0) disease are considered to have a low risk of DM development; however, some of these patients go on to have DM and a consequently poor prognosis [14].

The aim of the present study was to evaluate the outcomes, including DM development and long-term survival, in patients with OSCC after definitive surgery. The authors hypothesized that node-negative disease would influence long-term survival of OSCC patients with DM. The specific aim of this study was to identify the clinicopathological factors associated with the risk of DM development and the prognosis of patients with DM, including those with clinical N0 (cN0) disease.

Patients and methods

Study design and patients

This study was a retrospective cohort study enrolling patients with OSCC who underwent surgery at Tokyo Dental College Oral Cancer Center between 2007 and 2016. The patients were enrolled according to the reporting recommendations for tumor marker prognostic studies (REMARK) guidelines [15]. To be included in this study sample, patients had to meet the following inclusion criteria: 1) histologically confirmed OSCC; 2) primary definitive surgery at Tokyo Dental College Oral Cancer Center between 2007 and 2016; and 3) availability of clinicopathological information, including age, sex, T classification, stage, primary site, cancer recurrence, nodal metastasis, various pathological features, survival status, survival duration, and cause of death. Patients who did not undergo primary definitive surgery or the lacked information above were excluded. The tumor stages were defined according to the TNM Classification of Malignant Tumors, 7th Edition (UICC) [16]. According to the National Comprehensive Cancer Network guidelines [17], elective neck dissection (END) was considered when the depth of invasion was 4 mm or more, and postoperative adjuvant therapy (tri-weekly cisplatin 100 mg/m2 + radiotherapy) was performed when adverse risk features were found, including the involvement of two or more nodes, positive margins, and ENE in our hospital. The diagnosis of DM was based on computed tomography (CT) or positron emission tomography-CT (PET-CT) findings or histologic evidence. As a rule, at our institution, we perform a monthly follow-up and head and neck CT scan for one year postoperatively; moreover, in advanced cases, a CT scan of the lung area is also performed. At two years postoperatively, CT is performed once every three to four months. A PET-CT is performed if needed, and in advanced cases it is performed at least once every six months. The presence of multiple lung nodules of different sizes on images were considered to indicate pulmonary metastases. A fine needle aspiration biopsy was done if feasible for isolated lung nodules to distinguish it from primary lung cancer. Patients were excluded if their tumor could not be distinguished as a metastasis or primary lung cancer. For patients in our hospital in whom DM developed, depending on their performance status (PS) [18], surgery or radiotherapy was considered when the metastatic lesion was solitary or oligometastatic,

and systemic therapy, including chemotherapy and targeted molecular therapy or best supportive care, was considered for inoperable cases. According to the criteria of Thomford et al. [19], distant metastatic lesions, such as an isolated lung metastasis in patients with good PS, were resected if feasible. This study was approved by the Research Ethics Committee of Tokyo Dental College (I 16-07). Informed consent was provided in compliance with the Helsinki Declaration.

Study variables

The primary predictor variables were demographic characteristics (age, sex), T classification (T1-2/T3-4), cN classification (cN0/cN1-2), histological grade (Well/Moderate, Poor), neck dissection (absent/present), infiltrative growth pattern (INF) (INFa, b/INFc) [20], vascular/lymphatic invasion (absent/present), perineural invasion (PI) (absent/present), ENE (absent/present), local cancer recurrence (absent/present), nodal metastasis (absent/present), DM (absent/present), the time to diagnosis of DM after definitive surgery (< 10.0 months/≥ 10.0 months), surgical treatment for DM (absent/present) and mortality (absent/present).

The primary outcome variables were five-year overall survival (5y-OS) and the median survival time (MST). A receiver operating characteristics (ROC) curve was generated to determine the cut-off value of time to diagnosis of DM to predict a poor prognosis in patients with DM. Additional outcome variables were the development of distant metastasis, the five-year distant metastasis-free survival rate (DMFS) and the DM failure rate.

Statistical analysis

The correlation between the clinicopathological features and DM was examined using the univariate Cox proportional hazards regression model. All the outcome variables were estimated using the Kaplan-Meier method and compared by the log-rank test. Multivariate Cox proportional hazards regression was performed using stepwise selection, with variables not showing a relevant fit

to the model being rejected, to identify the risk factors for DM development. The parameters initially included in the Cox regression analysis were T classification, cN classification, histological grade, neck dissection, INF, vascular/lymphatic invasion, PI, and local cancer recurrence. The proportional hazards assumption was evaluated and satisfied for all variables used. All the tests were two-sided, and all p-values < 0.05 were considered significant. All statistical analyses were performed with EZR ver. 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [21], a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Patient characteristics, clinicopathological features, and primary site related to DM development

This retrospective cohort enrolled 526 patients with OSCC, 402 of whom were available for analysis. Of these, 304 patients had cN0 disease. The mean age of the patients was 67 years (range: 23-95 years). The median duration of follow-up in all 402 cases was 40.3 months (range: 2.6-133.0 months). The median duration of follow-up in cN0 304 cases was 39.9 months (range: 2.6-133.0 months).

Thirty-seven (9.2%) of the 402 patients had DM. Among the 304 patients with cN0 disease, 14 (4.6%) had DM. The median time within which DM was diagnosed after definitive surgery was 8.3 months (1.1 to 36.2 months) in all the patients and 15.8 months (2.2 to 36.2 months) in patients with cN0 disease, and there was a significant difference between the two groups (p = 0.00892, Mann-Whitney U test). Twenty-nine cases were detected by CT, and eight cases were detected by PET-CT. Most of the lung lesions were found by CT, and lesions in other organs were found by PET-CT. The clinicopathological features of the 402 patients are shown in Table 1. Local recurrence occurred in 47 patients (11.7%), 11 (23.4%) of whom had DM development. The primary locations

are shown in Fig. 1. The most frequent primary location was the tongue in 192 patients (47.8%), followed by the lower gingiva in 93 patients (23.1%), upper gingiva in 55 patients (13.7%), floor of the mouth in 28 patients (7.0%), buccal mucosa in 22 patients (5.5%), and other region in 12 patients (2.9%). The incidence of DM was highest in patients with tongue SCC (16 (8.3%) of 192 patients), followed by the lower gingiva (12 (12.9%) of 93 patients). There was no significant difference in the incidence of DM by primary site ($p = 0.541$, Fisher's exact test).

Site of DM

The most frequent metastatic site was the lung, which was found in 33 (89.2%) of 37 cases, followed by bone (18.9%), liver (10.8%), and kidney (8.1%), skin (5.4%), brain (2.7%), heart (2.7%), mediastinum (2.7%), muscle (2.7%), parotid gland (2.7%). In patients with lung metastases, multiple metastases (24 of 33 cases) occurred more frequently than isolated metastases (9 of 33 cases) and tended to be less frequent in patients with cN0 disease. Of all the patients, multiple DM sites were found in 13 patients (35.1%). In patients with cN0 disease, multiple DM sites were found in four patients (28.6%). In patients with cN1-2 disease, multiple DM sites were found in nine patients (39.1%).

Survival analysis

The 5y-OS was 84.6% in patients with no DM and 9.7% in patients with DM. The MST was 16.9 months in patients with DM, who had a significantly worse prognosis than patients with no DM ($p < 0.00001$, Fig. 2A). The 5y-OS was 82.1% in patients with cN0 disease and 61.2% in patients with cN1-2 disease ($p = 0.00011$, Fig. 2B), and the DMFS was 81.1% in patients with cN0 and 60.6% in patients with cN1-2 ($p = 0.00003$, Fig. 2C). In addition, in patients who developed DM, the 5y-OS of patients with cN0 disease at the initial diagnosis was 18.2%, and their MST was 37.2 months, while the 5y-OS of patients with cN1-2 disease was 4.7%, and their MST was 12.9 months

(p = 0.02760, Fig. 2D). The cut-off value of the time to diagnosis of DM after definitive surgery was 10.0 months based on the ROC curve analysis. The 5y-OS of patients with time to diagnosis ≥ 10.0 months was 20.0%, and their MST was 38.6 months while the MST of patients with time to diagnosis < 10.0 months was 11.7 months (p < 0.00001, Fig. 2E). Surgical treatment for distant metastatic lesions was performed in five patients with an isolated lung metastasis; the 5y-OS of the surgery group was 60.0%, and the MST of the non-surgery group was 16.0 months (p = 0.00682, Fig. 2F). The surgical group had significantly longer survival.

Analysis of the DM failure rate

The DM failure rates in patients with cN0 disease and those with cN1-2 disease were compared using Kaplan-Meier analysis and the log-rank test. The DM failure rate in patients with cN0 disease was 5.8% while that in patients with cN1-2 disease was 24.5% (p < 0.00001, Fig. 3A). Next, in patients with cN0 disease, the DM failure rate was 13.0% in patients who underwent END and 3.4% in patients who did not undergo END (p = 0.00444, Fig. 3B). END did not reduce the incidence of DM. In addition, in patients with pathological node-positive disease (pN+), the DM failure rate of patients with ENE was 50.6% while in patients without ENE it was 19.8% (p = 0.00081, Fig. 3C).

Risk factors for developing DM

Based on risk factors identified on univariate analysis, a multivariate stepwise Cox regression analysis was performed. It was found that cN1-2 disease (HR 3.36; 95%CI 1.66-6.80; p = 0.00077), moderate or poor differentiation (HR 2.51; 95%CI 1.18-5.35; p = 0.01669), INF c (HR 3.27; 95%CI 1.49-7.17; p = 0.00314), presence of vascular/lymphatic invasion (HR 2.95; 95%CI 1.36-6.40; p = 0.00634), and presence of perineural invasion (HR 2.17; 95%CI 1.05-6.50; p = 0.03586) were independent predictors of DM development (Table 2).

Discussion

In general, patients with DM development have dismal survival outcomes. Generally, only palliative treatments may be offered to patients with DM, and there is no consensus on the management of these patients. Most patients with head and neck cancer, including oral cancer, who have DM development, will die within about one to 12 months after the diagnosis of DM [13, 22-24]. The MST of patients with DM was reported to be 12 months by Leon et al. [10] In the present study, the 5y-OS of patients with DM was 9.7%, and their MST was 16.9 months, which also underscored the very poor prognosis of patients with DM. However, there were groups with relatively long survival times among patients with DM. Patients with cN0 disease at the initial diagnosis and patients with the diagnosis of DM ≥10 months after surgery had relatively long survival times, and their MST was about three times longer than that of patients with cN1-2 disease or patients with a diagnosis of DM <10 months after surgery.

Furthermore, the 5y-OS of patients who received surgical treatment for a lung metastasis was good, at 60%. The N classification (presence of nodal metastasis) is a strong independent indicator of poor prognosis in patients with OSCC [3, 25]. Therefore, the pathological staging of the nodal status is the gold standard by which risk may be stratified and treatment strategy designed. In the present study as well, patients with pN-positive disease, especially those positive for ENE, were at high risk of DM development. However, pN staging depends on surgical procedures, such as neck dissection or sentinel lymph node biopsy, including elective dissection. Thus, the cN classification, which does not depend on surgical treatment, is useful, and the cN classification is also reportedly a significant predictor of poor prognosis although it is not a pathological classification [14, 26]. The Kaplan-Meier and multivariate analyses in the present study also showed that cN classification is a significant predictor of developing DM. Although positive ENE, moderate or poor differentiation, INF c, vascular/lymphatic invasion, and perineural invasion were significant predictors of DM

development, the cN classification is considered highly useful since it does not depend on surgery. On the other hand, although controlling occult metastases [27] was thought possibly to lead to less DM, END failed to reduce DM. However, since END is usually performed in accordance with the depth of tumor invasion, a selection bias cannot be excluded. Nonetheless, it is possible that END may be found to be significant if an analysis adjusted for confounders, such as a propensity score analysis, were performed; additional investigation is necessary [28]. If DM develops in patients with OSCC, the time to DM detection is usually relatively short. For example, it was reported that the median time to detection was 13 months and 11 months by Lim et al. [12] and Takahashi et al. [29], respectively. In the present study, it was 8.3 months, somewhat short but similar to the findings of previous reports. In addition, cases with a time to diagnosis of DM < 10 months showed a significantly worse prognosis. Since 16 (76.2%) of 21 patients with a time to diagnosis <10 months were cN+, it was suggested that cN+ cases developed DM earlier and had a poor prognosis. In contrast, four (80.0%) of five patients who underwent surgical treatment for DM had a time to diagnosis of DM ≥10 months.

There are some reports that patients who underwent a pulmonary metastasectomy had relatively long-term survival, and Mazer et al. [30] and Wedman et al. [31] reported that the 5y-OS in these patients was 43% and 59%, respectively. In addition, Petrella et al. [32] reported that surgery is a valid curative alternative if the general principles of lung metastasectomy are respected because pulmonary metastatic cancers respond poorly to chemotherapy. Although previous reports have the limitations inherent in small-scale studies, surgical treatment for an isolated lung metastasis may be worth considering to improve survival outcomes. However, while Shiono et al. [33] suggested the efficacy of surgical treatment for pulmonary metastatic lesions, they simultaneously noted that appropriate patient selection is needed because there are cases which respond poorly to surgical treatment. Identifying appropriate criteria for the surgical treatment of patients with DM is necessary going forward.

The most frequently involved organ in OSCC metastases is the lung, followed by bone and liver [10, 13, 34]. In this study, lung metastases were seen in 89.2% of the total patients, followed by bone metastases (18.9%) and liver metastases (10.8%). Therefore, as mentioned above, surgery for pulmonary metastasis is considered to be a valid curative alternative [35]. Furthermore, patients with relatively late DM development may obtain relief, and because the operability and salvage treatment are improved by early detection, postoperative routine surveillance is recommended [36, 37]. However, the incidence of DM in head and neck SCC (HNSCC) cases, including OSCC, is relatively low compared to other tumor types [38]. The guidelines set forth by the NCCN and ASCO suggest that there is no benefit to routine surveillance imaging for all HNSCC cases [17, 39]. On the other hand, it was reported that lung cancer mortality in high-risk patients was reduced by low-dose chest CT screening conducted in the National Lung Screening Trial [40]. Since it is undisputable that DM development has a serious impact on the prognosis of patients with OSCC, follow-up strategies are controversial. Identifying patients with a high risk of DM development and selecting candidates for routine surveillance through additional tests are necessary. Routine surveillance may be required for patients with positive N staging and/or risk factors, such as moderate or poor differentiation, INF c, vascular/lymphatic invasion or perineural invasion on postoperative pathologic examination, because DM occurs in approximately 2.6-9.7% of cases, including patients with cN0 disease [26, 41]. Given the behavior of these pathological factors, it is possible that the ability of cancer cells to migrate to, and invade, the mesenchyma is related to DM development. It may be worthwhile to consider novel candidate markers related to the epithelial-mesenchymal transition, such as tumor budding [42] and the worst pattern of invasion [43], in DM development.

The chief strength of this study was that it included a relatively large number of patients specifically with OSCC alone who underwent definitive surgery. Many previous studies included patients with pharyngeal and laryngeal cancers to increase the case number [5, 6, 10, 24], but these series suffered from the limitation that patterns of DM are different for each primary site [37]. This

study also has several limitations. It was conducted at a single institution, and the number of events, including the incidence of DM, was insufficient. The small number of events may have affected the power of the multivariate analysis. In addition, the tumor stages in this study were defined according to the 7th edition the UICC criteria. Because the 8th edition of the UICC staging criteria includes the depth of invasion [44], different predictors may have been obtained if the 8th edition criteria had been used. Additional research is needed with a larger cohort involving a greater number of events in the future.

In conclusion, although patients with DM development had a poor prognosis, some groups of patients with DM were found to have relatively long-term survival, such as those with cN0 disease at initial diagnosis and/or a long time to diagnosis of DM. Positive N staging, moderate or poor differentiation, INF c, ENE, presence of vascular/lymphatic invasion, and perineural invasion were significant risk factors for DM development.

Table 1. Clinicopathological features of 402 patients with primary OSCC

Variable	No. of patients	Distant Metastasis				
	n = 402; n (%)	Absent	Present	HR	95% CI	p-value
Age, y						
< 67	191 (47.5)	170	21	0.71	0.37-1.35	0.292
≥ 67	211 (52.5)	195	16			
Sex						
Male	177 (44.0)	206	19	1.27	0.67-2.42	0.469
Female	225 (56.0)	159	18			
T classification						
T1-2	236 (58.7)	225	11	3.72	1.84-7.53	< 0.001
T3-4	166 (41.3)	140	26			
cN classification						
cN0	304 (75.6)	290	14	5.68	2.92-11.0	< 0.001
cN1-2	98 (24.4)	75	23			
Stage						
I, II	216 (53.7)	209	7	5.63	2.47-12.8	< 0.001
III, IV	186 (46.3)	156	30			
Neck dissection						
Absent	221 (55.0)	216	5	8.58	3.34-22.0	< 0.001
Present	181 (45.0)	149	32			
Histological grade						
Well	349 (86.8)	325	24	4.32	2.19-8.49	< 0.001

Moderate, Poor	53 (13.2)	40	13			
INF						
a, b	344 (85.6)	327	17	9.10	4.75-17.4	< 0.001
c	58 (14.4)	38	20			
Vascular/lymphatic invasion						
Absent	312 (77.6)	299	13	7.67	3.90-15.1	< 0.001
Present	90 (22.4)	66	24			
Perineural invasion						
Absent	361 (89.8)	337	24	5.74	2.92-11.3	< 0.001
Present	41 (10.2)	28	13			
Local recurrence						
Absent	355 (88.3)	330	25	4.03	2.03-8.03	< 0.001
Present	47 (11.7)	35	12			
Nodal Metastasis						
Absent	259 (66.4)	258	1	72.7	10.0-530.2	< 0.001
Present	143 (35.6)	107	36			
Mortality						
Absent	320 (79.6)	315	5	32.3	12.6-83.1	< 0.001
Present	82 (20.4)	50	32			

HR, hazard ratio; CI, confidence interval; INF, infiltrative growth pattern.

Univariate analysis was done using the Cox proportional hazards regression model

Significance was defined as $p < 0.05$.

Table 2. Hazard ratios for DM development in the multivariate Cox regression model

Variable	HR	95% CI	p-value
cN classification			
cN0	1 (reference)		
cN1-2	3.36	1.66-6.80	0.00077
Histological grade			
Well	1 (reference)		
Moderate or Poor	2.51	1.18-5.35	0.01669
INF			
a, b	1 (reference)		
c	3.27	1.49-7.17	0.00314
Vascular/lymphatic invasion			
Absent	1 (reference)		
Present	2.95	1.36-6.40	0.00634
Perineural invasion			
Absent	1 (reference)		
Present	2.17	1.05-6.40	0.03586

INF, infiltrative growth pattern; HR, hazard ratio; CI, confidence interval

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Figure legends

Figure 1. Primary site of OSCC and the incidence of distant metastases (DM)

The incidence of DM was highest in patients with tongue SCC (16 (8.3%) of 192 patients), followed by the lower gingiva (12 (12.9%) of 93 patients). There was no significant difference in DM by primary site (p=0.541, Fisher's exact test).

Figure 2. Kaplan-Meier survival estimate. (A) 5y-OS of patients with DM and non-DM ($p < 0.00001$, log-rank test). (B) 5y-OS of patients with cN0 disease and cN1-2 disease ($p = 0.00011$). (C) DMFS of patients with cN0 disease and cN1-2 disease ($p = 0.00003$). (D) 5y-OS of patients with cN0 disease and cN1-2 disease at the initial diagnosis among patients with DM development ($p = 0.02760$). (E) 5y-OS of patients whose time to diagnosis of DM $\geq$ 10.0 months and < 10.0 months ($p < 0.00001$). (F) 5y-OS of the surgery group and the non-surgery group ($p = 0.00682$).

DM, distant metastasis; MST, median survival time.

Figure 3. DM failure rate after definitive surgery. (A) DM failure rates in patients with cN0 disease and cN1-2 disease ($p < 0.00001$). (B) DM failure rates in patients who underwent END and did not undergo END among patients with cN0 disease. (C) DM failure rates of patients with and without ENE among patients with pathological node-positive disease.

END, elective neck dissection; ENE, extranodal extension.

Fig.1

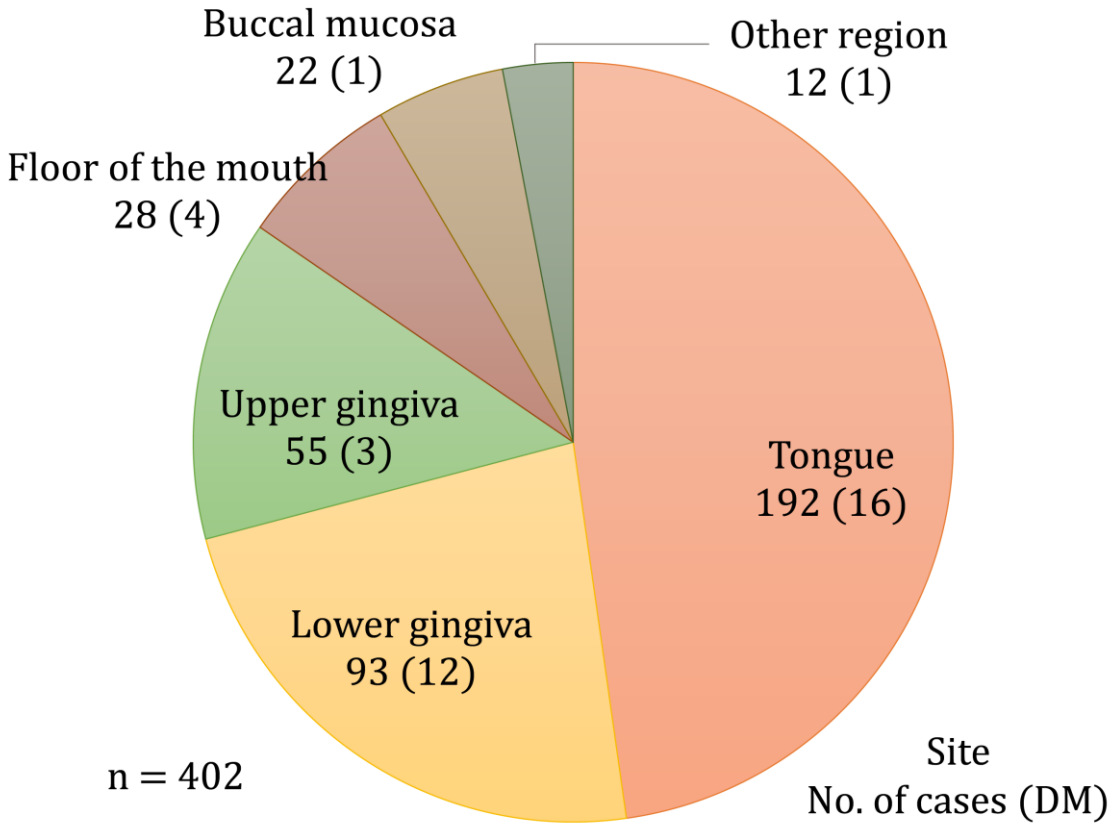

Buccal mucosa
22 (1)
Other region
12 (1)
Floor of the mouth
28 (4)
Upper gingiva
55 (3)
Tongue
192 (16)
Lower gingiva
93 (12)
n = 402
Site
No. of cases (DM)

Fig.2A

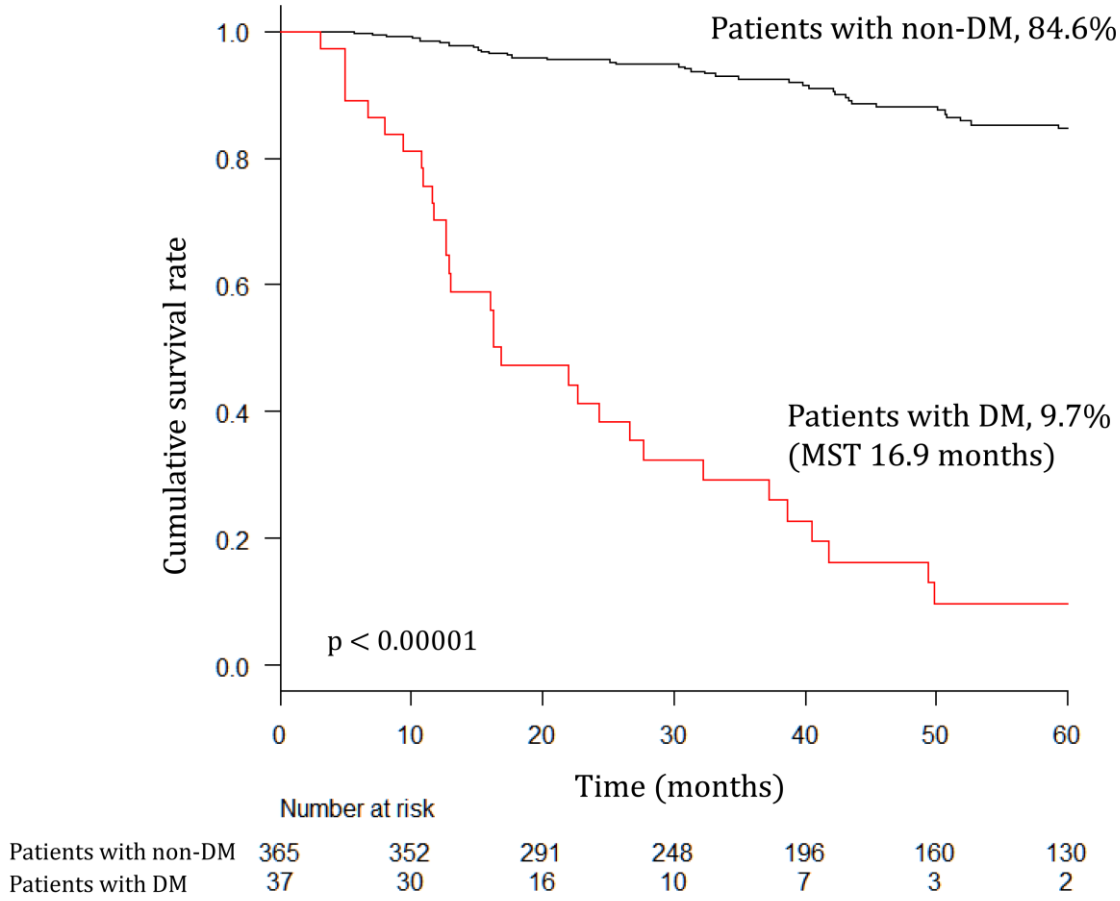

Patients with non-DM, 84.6%
Patients with DM, 9.7%
(MST 16.9 months)
p < 0.00001
Cumulative survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
Time (months)
Number at risk
Patients with non-DM 365 352 291 248 196 160 130
Patients with DM 37 30 16 10 7 3 2

Fig.2B

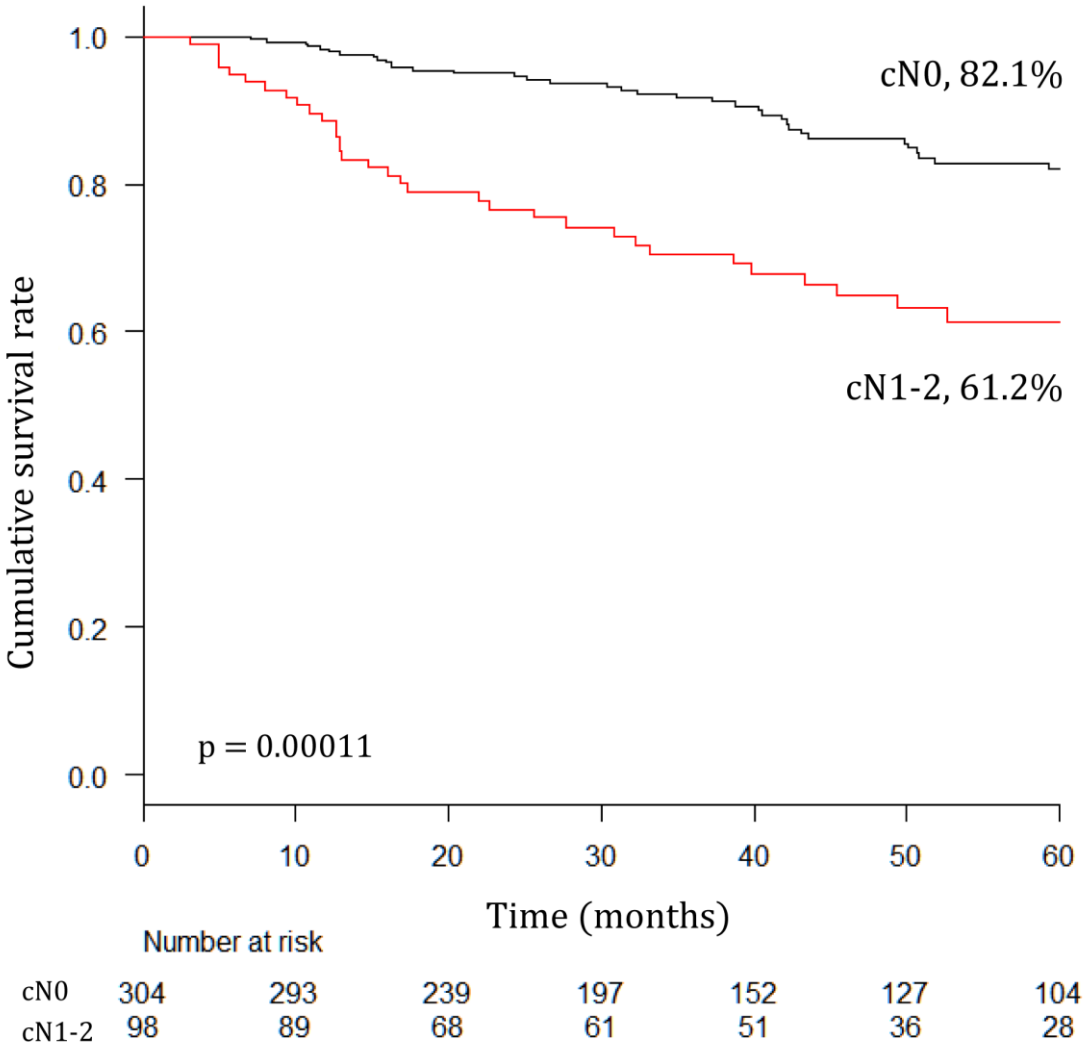

1.0
0.8
0.6
0.4
0.2
0.0
Cumulative survival rate
cN0, 82.1%
cN1-2, 61.2%
p = 0.00011
0
10
20
30
40
50
60
Time (months)
Number at risk
cN0 304 293 239 197 152 127 104
cN1-2 98 89 68 61 51 36 28

Fig.2C

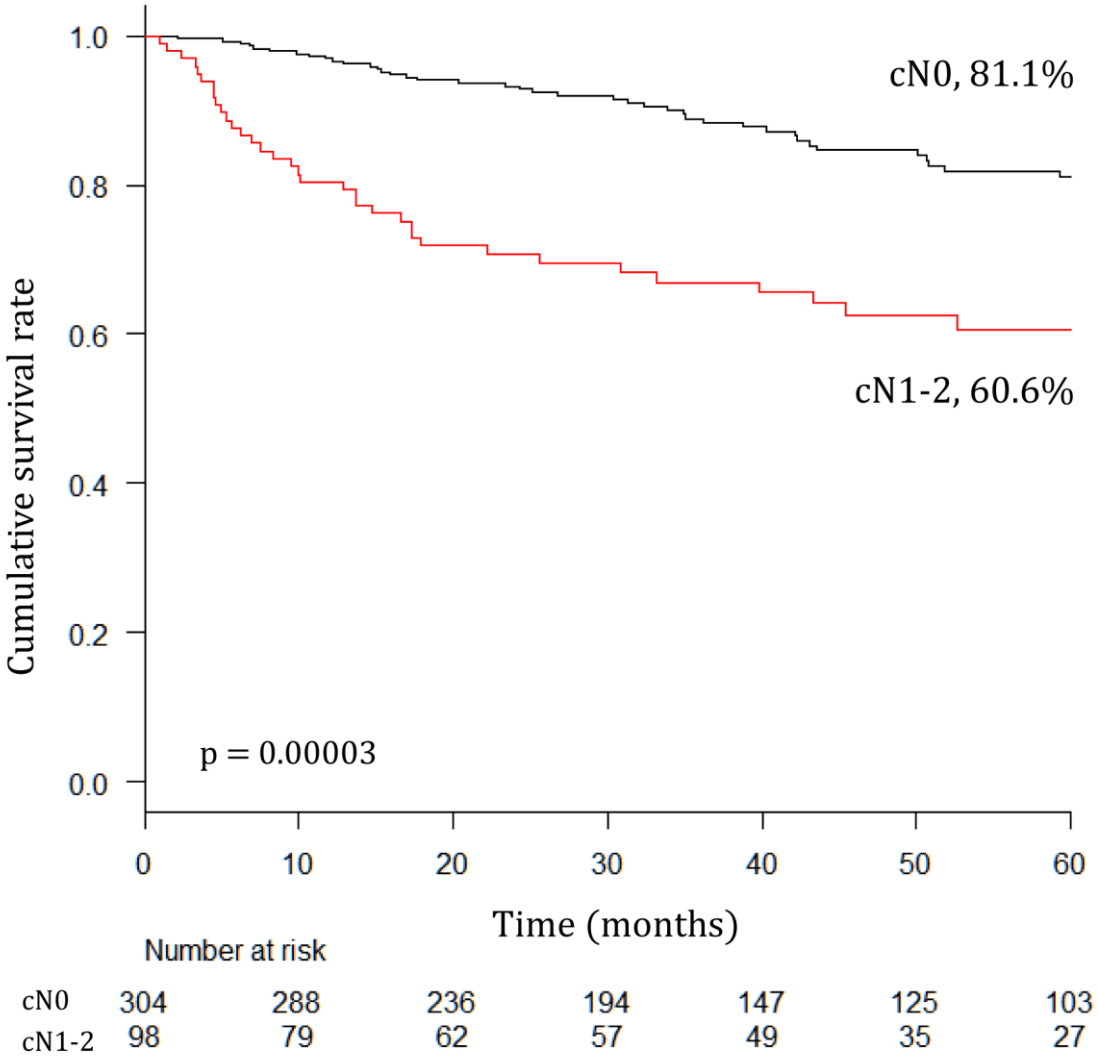

1.0
0.8
0.6
0.4
0.2
0.0
Cumulative survival rate
cN0, 81.1%
cN1-2, 60.6%
p = 0.00003
0
10
20
30
40
50
60
Time (months)
Number at risk
cN0 304 288 236 194 147 125 103
cN1-2 98 79 62 57 49 35 27

Fig.2D

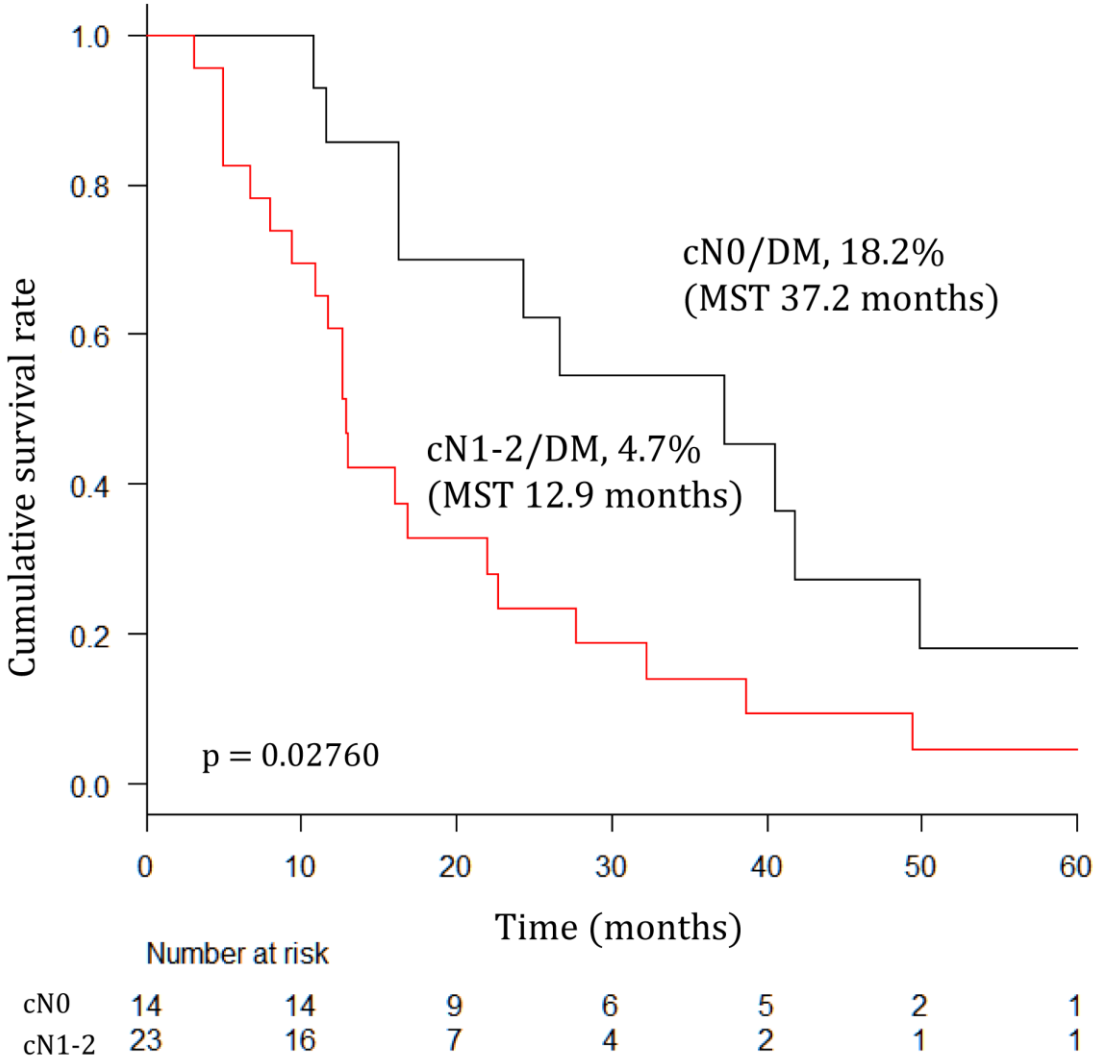

1.0
0.8
0.6
0.4
0.2
0.0
Cumulative survival rate
cN0/DM, 18.2%
(MST 37.2 months)
cN1-2/DM, 4.7%
(MST 12.9 months)
p = 0.02760
0
10
20
30
40
50
60
Time (months)
Number at risk
cN0 14 14 9 6 5 2 1
cN1-2 23 16 7 4 2 1 1

Fig.2E

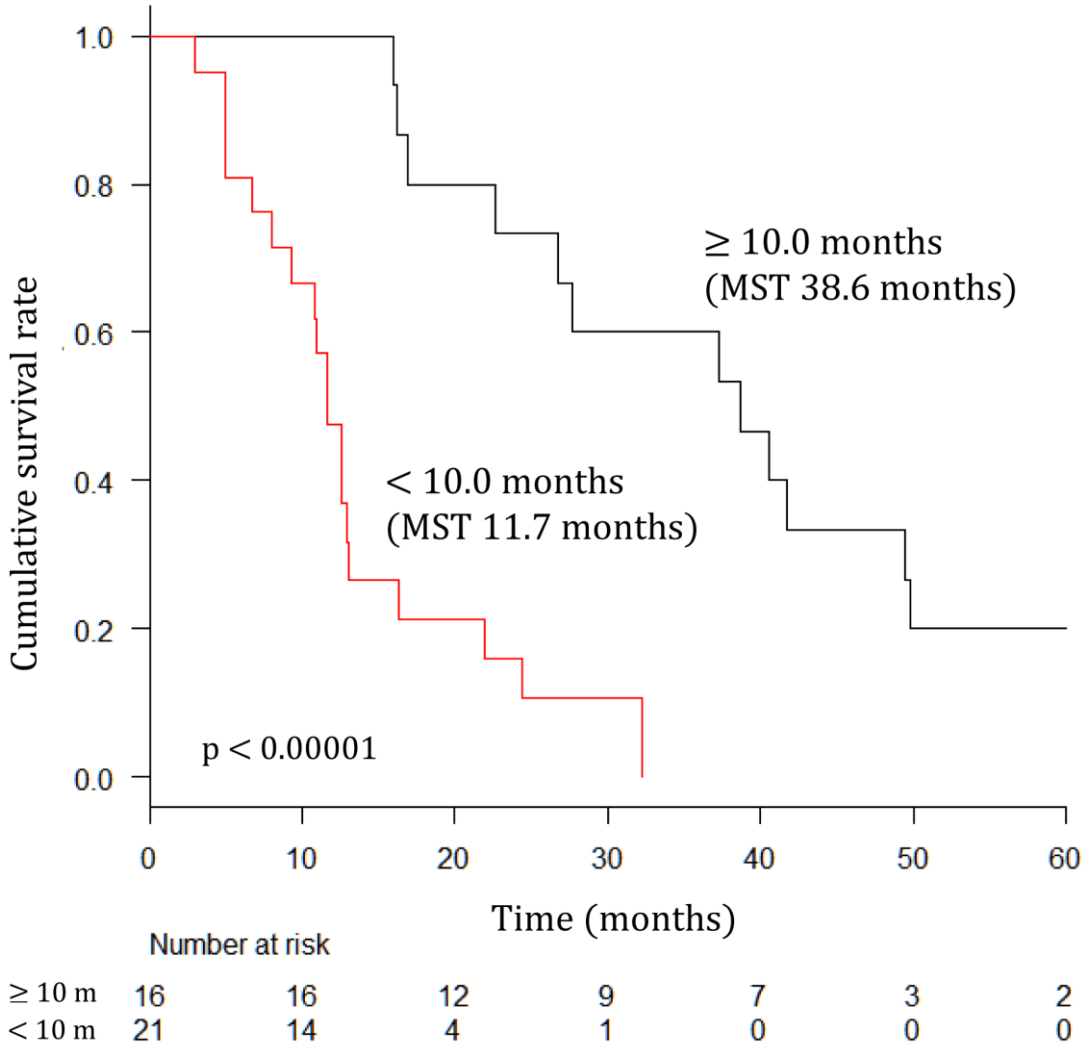

1.0
0.8
0.6
0.4
0.2
0.0
Cumulative survival rate
≥ 10.0 months
(MST 38.6 months)
< 10.0 months
(MST 11.7 months)
p < 0.00001
0
10
20
30
40
50
60
Time (months)
Number at risk
≥ 10 m 16 16 12 9 7 3 2
< 10 m 21 14 4 1 0 0 0

Fig.2F

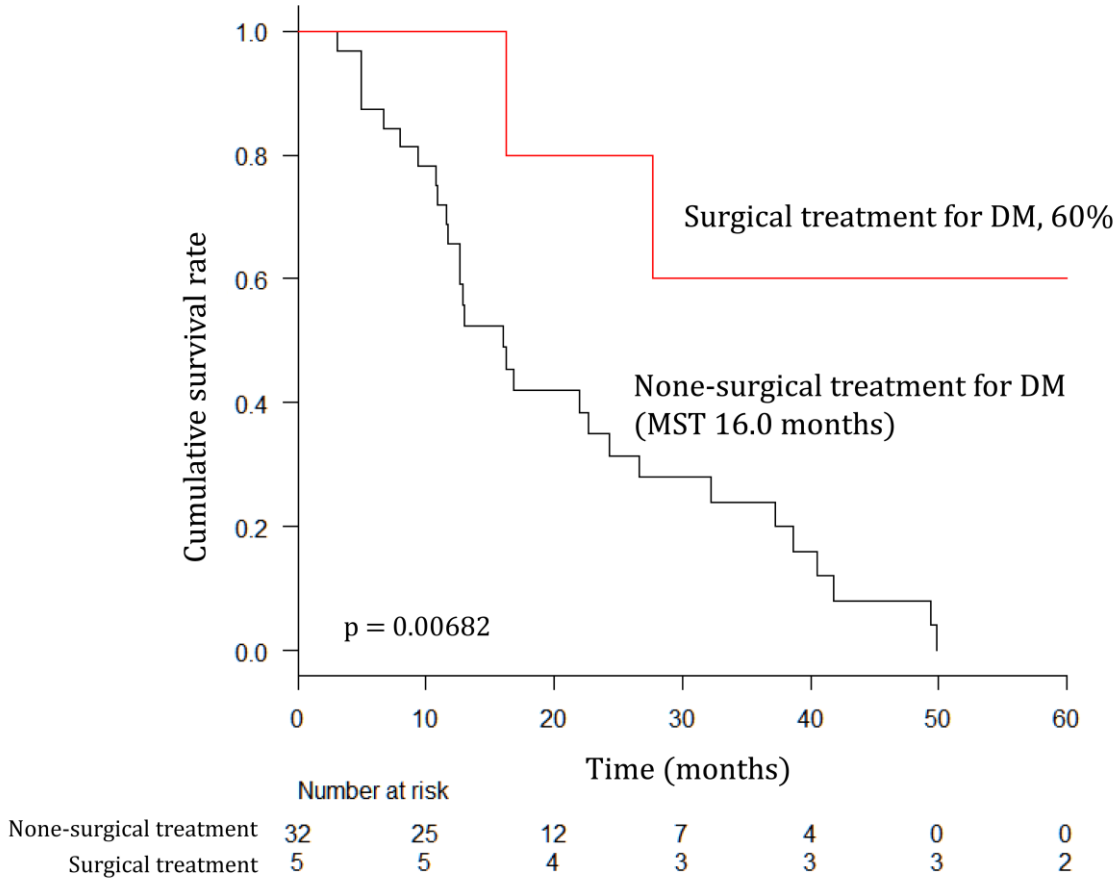

Cumulative survival rate
1.0
0.8
0.6
0.4
0.2
0.0
Surgical treatment for DM, 60%
None-surgical treatment for DM
(MST 16.0 months)
p = 0.00682
0
10
20
30
40
50
60
Time (months)
Number at risk
None-surgical treatment 32 25 12 7 4 0 0
Surgical treatment 5 5 4 3 3 3 2

Fig.3A

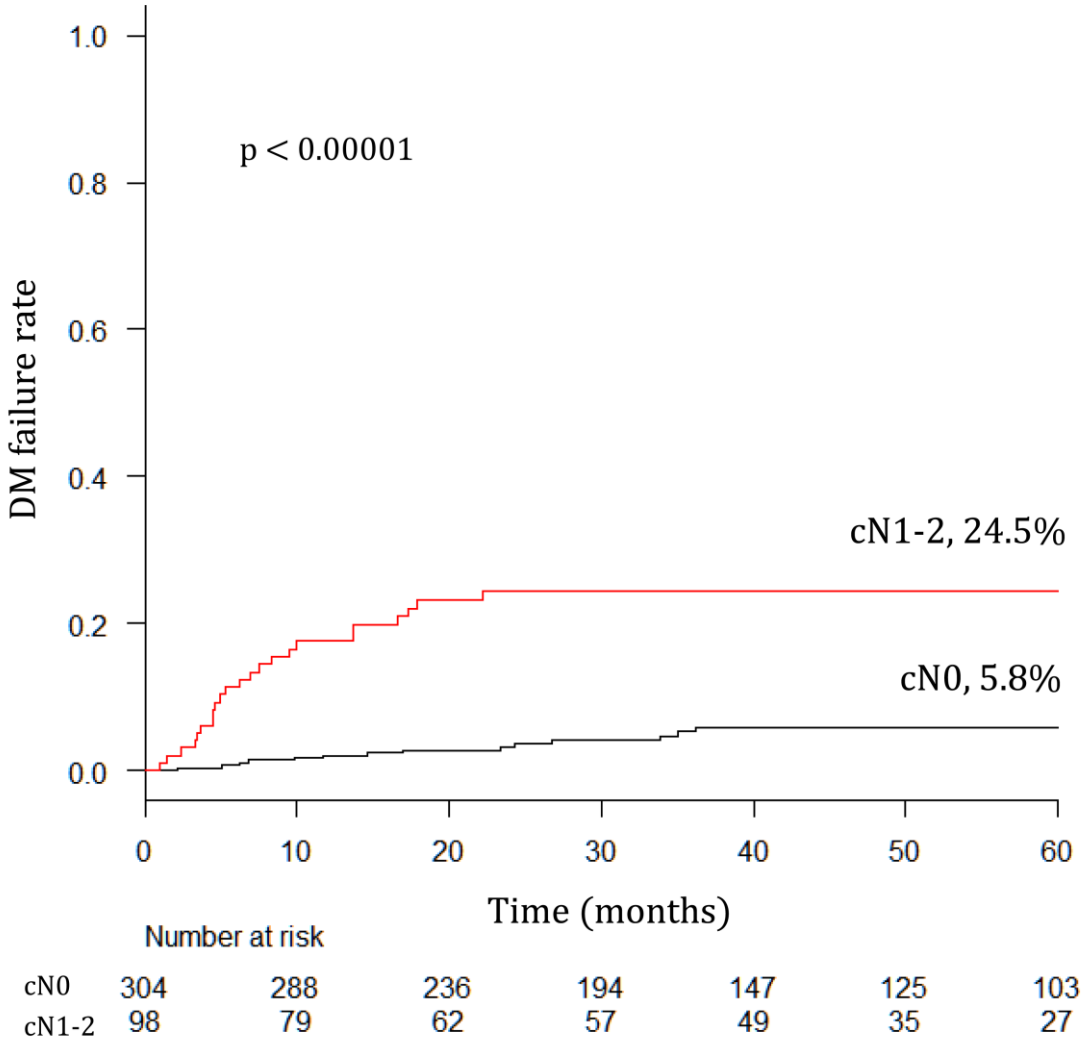

1.0
0.8
0.6
0.4
0.2
0.0
DM failure rate
p < 0.00001
cN1-2, 24.5%
cN0, 5.8%
0
10
20
30
40
50
60
Time (months)
Number at risk
cN0 304 288 236 194 147 125 103
cN1-2 98 79 62 57 49 35 27

Fig.3B

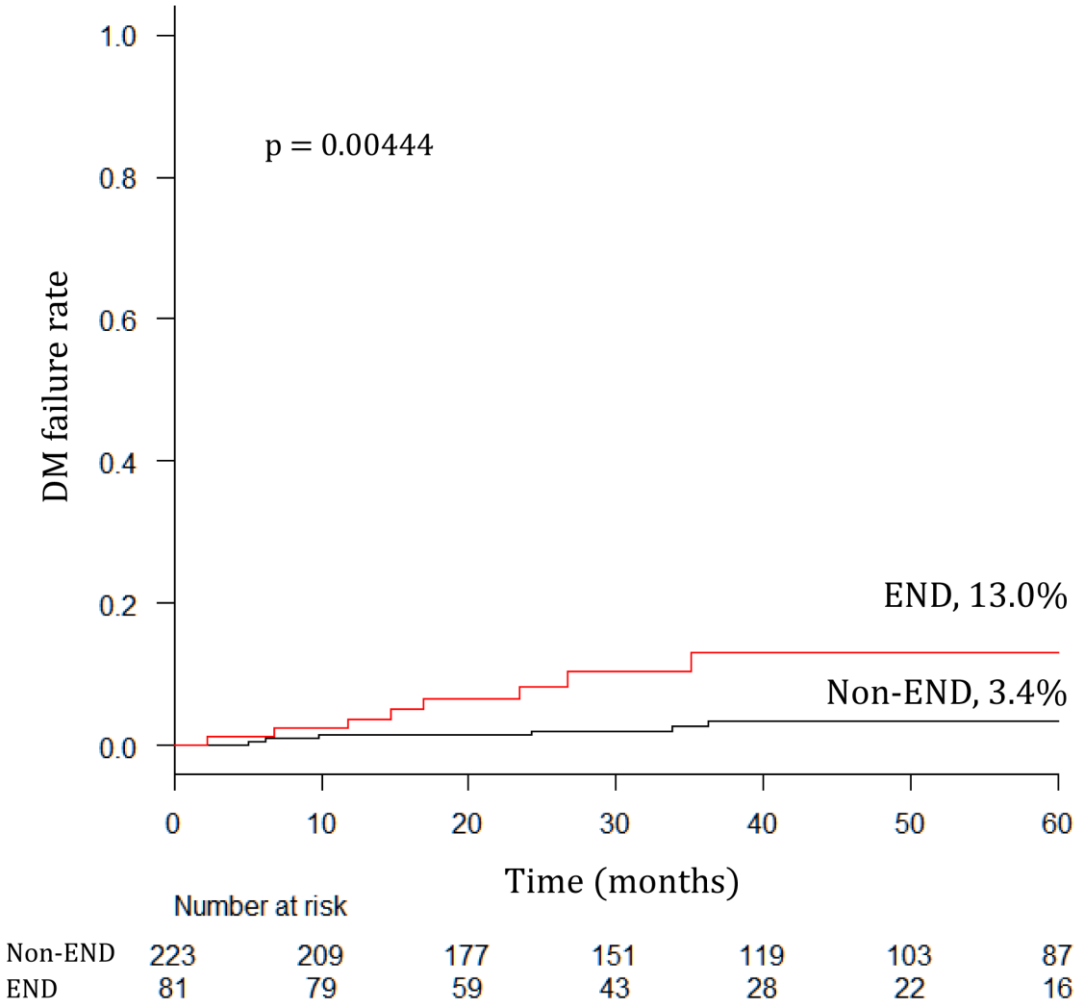
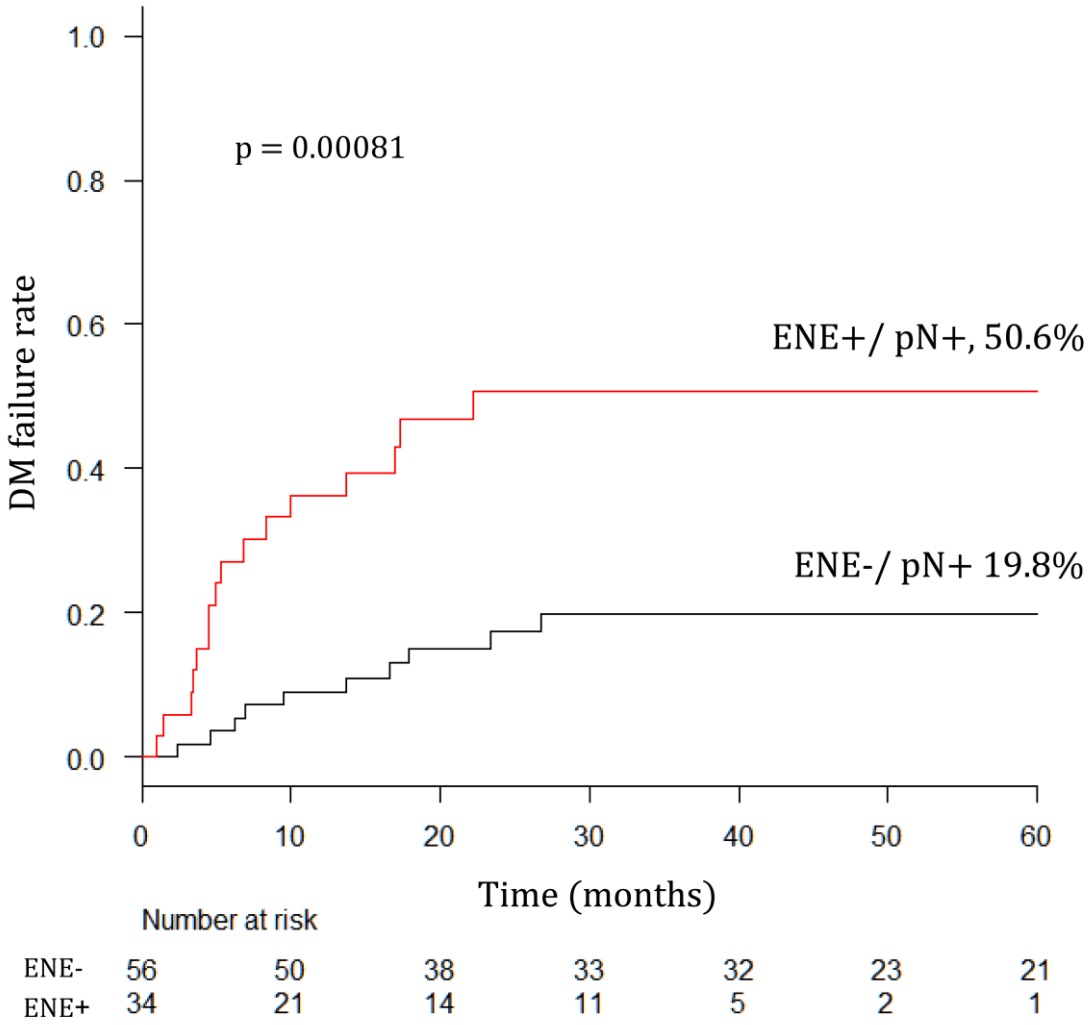

1.0
0.8
0.6
0.4
0.2
0.0
DM failure rate
p = 0.00444
END, 13.0%
Non-END, 3.4%
0
10
20
30
40
50
60
Time (months)
Number at risk
Non-END 223 209 177 151 119 103 87
END 81 79 59 43 28 22 16

Fig.3C


1.0
0.8
0.6
0.4
0.2
0.0
DM failure rate
p = 0.00081
ENE+/ pN+, 50.6%
ENE-/ pN+ 19.8%
0
10
20
30
40
50
60
Time (months)
Number at risk
ENE- 56 50 38 33 32 23 21
ENE+ 34 21 14 11 5 2 1