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Multi-center retrospective study of the prognosis and treatment outcomes of Japanese oral squamous cell carcinoma patients with single lymph node metastasis and extra nodal extension

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Key words: oral cancer, single neck metastasis, extracapsular spread, postoperative adjuvant therapy, overall survival

A short title: Outcome of single lymph node metastasis for oral cancer

Conflict of interest: None declared.

Contribution: All authors contributed equally to this work.

Synopsis:

We investigated and compared the prognosis among postoperative therapies in pN1 OSCC patients with ENE.

The prognosis of ENE+pN1 was not as poor as that of ENE+MLM.

Adjuvant therapy (RT/CCRT) after surgery is recommend for ENE+pN1 cases.

ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) containing single lymph node metastasis (pN1) with extra nodal extension (ENE) is a rare clinical situation. Therefore, it is unclear whether pN1 with ENE is at high risk of recurrence among the OSCC population, or whether postoperative radiotherapy (RT) / concomitant chemoradiotherapy (CCRT) is effective in these cases.

Objectives: The purpose of this retrospective study was to investigate the prognosis and compare between no postoperative therapy and postoperative RT/CCRT in pN1 with ENE OSCC patients.

Methods: Clinicopathological data and treatment modalities were investigated. The evaluated endpoints were overall survival (OS) and type of recurrence.

Results: The 3-year cumulative OS rates for the pN1 only, multiple lymph node metastasis (MLM) only, ENE+MLM, and ENE+pN1 groups were 77.2%, 66.8%, 43.3% and 66.6%, respectively. In the ENE+pN1 group, the most common cause of death in the surgery only group was from regional failure. The surgery+RT/CCRT group was associated with better disease-specific survival and OS rates than the surgery only groups ($P<0.05$).

Conclusions: The prognosis of ENE+pN1 was not as poor as that of ENE+MLM, although both these groups feature ENE. Adjuvant therapy (RT/CCRT) after surgery is recommend for cases of ENE+pN1.

INTRODUCTION

There have been recent improvements in the treatment of advanced oral squamous cell carcinoma (OSCC). Surgical treatment for resectable advanced OSCC is the most common approach [1-3], and postoperative radiotherapy (RT) and chemotherapy have become important adjuvant treatments for advanced OSCC. One of the OSCC treatment principles is based on the two randomized trials for head and neck squamous cell carcinoma (HNSCC) with high risk of recurrence [4, 5]. The collaborative comparative analysis of these two randomized trials indicated that the addition of concomitant cisplatin (CDDP) to postoperative RT improved outcomes including overall survival (OS) in HNSCC patients with one or the combination of two major prognostic factors [6]. The two primary prognostic factors associated with a high risk of recurrence were microscopically involved section margins (incomplete resection (ICR)) and extra nodal extension (ENE) of neck lymph nodes. However, the other high-risk factors of recurrence differed between the two trials [4, 5]. In one randomized trial (the Radiation Therapy Oncology Group (RTOG) 9501 trial), the involvement of two or more regional lymph nodes was defined as a high-risk factor of recurrence, similar to ICR and ENE [5]. Furthermore, several retrospective studies have demonstrated a relationship between multiple lymph node metastases (MLM) and a high risk of recurrence [7-10]. One report also demonstrated that patients with pathologic N2 disease had poor prognoses regardless of the presence of ENE [11]. In contrast, in another randomized trial (the European Organization for Research and Treatment of Cancer (EORTC) 22931 trial), MLM was not defined as a risk factor for recurrence [4]. Because of these different definitions of high-risk factors, cases with only MLM, and without ENE, are not universally recommended postoperative concomitant chemoradiotherapy (CCRT) with high-dose CDDP. Clinically, most patients with pathological ENE status may simultaneously have MLM in regional lymph nodes. Therefore, OSCC with single lymph node metastasis (pN1) and ENE is too rare for a single-institution study. Therefore, it is unclear whether pN1 with ENE is really at a high

risk of recurrence among the OSCC population, or whether postoperative RT/CCRT is effective in these cases. In this study, we retrospectively investigated the prognosis of pN1 OSCC patients with ENE and compared outcomes between patients who received no postoperative therapy and those who underwent postoperative RT/CCRT.

PATIENTS & METHODS

This was a nonrandomized, multicenter retrospective cohort study. The institutional review board of Kobe University Graduate School of Medicine approved this study. This validation study included pooled individual patient data from seven institutions. Between January 2001 and December 2013, 2042 OSCC cases were investigated at the following institutes: Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine; Department of Clinical Oral Oncology, Unit of Translational Medicine, Nagasaki University Graduate School of Biomedical Sciences; Department of Oral and Maxillofacial Surgery, Division of Surgery, Tokai University School of Medicine; The First Department of Oral and Maxillofacial Surgery, Graduate School of Dentistry; Department of Oral and Maxillofacial Surgery, School of Medicine, Nara Medical University; Department of Dentistry and Oral Surgery, Shinshu University School of Medicine. Patients who had undergone neoadjuvant RT or chemotherapy or had inadequate clinical information were excluded. Among the remaining 1973 patients, 669 patients with pathologically positive lymph nodes (pN+) were eligible for inclusion. Due to the retrospective nature of this study, informed consent was not required. Instead, we published the information regarding this study and granted occasions of refusing to participate in this study. A total of 401 male and 268 female patients were investigated. Mean patient age was 65.9 ± 13.3 years (range: 22–96 years). Treatment selection was based on institutional policy or patient preference. Initially, the 669 pN+ patients were divided into four groups: pN1 without ENE (pN1 only group), MLM without ENE (MLM only group), MLM with ENE (ENE+MLM group), and pN1 with ENE (ENE+pN1 group). For each group, clinicopathological data, including sex, age, performance status (PS), subsite, clinical T classification (UICC/AJCC staging system 7th edition), clinical N classification, histologic grade (high, moderate or poor), surgical margin, timing of neck dissection, and treatment outcome were investigated. The evaluated endpoints were overall survival (OS) rate and type of recurrence. In the ENE+pN1 group, treatment modalities (surgery only [S only],

with postoperative RT/CCRT [S + RT/CCRT]) and the level of neck metastasis were investigated. The OS and disease specific survival (DSS) rates of the ENE+pN1 group were compared between S only and S + RT/CCRT. Postoperative RT alone was performed using a total of 50–70 Gy. Conventional RT was administered at 2 Gy/day for 5 days/week. A large volume encompassing the primary site and areas of at-risk lymph nodes received up to 50–60 Gy in 25–30 fractions. High-risk regions for malignant dissemination or ICR margins received a 6–10 Gy boost. Chemotherapy primarily consisted of cisplatin or tegafur-gimeracil-oteracil (S-1). Cisplatin chemotherapy doses were 80 or 100 mg/m^2 of body surface area and were given on days 1, 22 and 43 during the RT course. The major exclusion criteria of postoperative CCRT with CDDP were older age, a past history of renal failure or hepatitis, and poor performance status. S-1 chemotherapy consisted of one cycle of S-1 given at a dose of 80–120 mg/day (80 mg/day for body surface area (BSA; m^2) <1.25, 100 mg/day for 1.25 < BSA < 1.5, and 120 mg/day for BSA >1.5) for 2 weeks, followed by 1 week of rest. This regimen was also performed during the RT course. Postponements, dose reductions, discontinuation of chemotherapy were considered when severe hematological toxicities, including neutropenia and thrombocytopenia, renal dysfunction, febrile neutropenia, sever mucositis and dermatitis, and severe diarrhea, were observed.

Statistical analysis

Data collection and statistical analyses were carried out with SPSS 15.0 (SPSS, Chicago, IL) and and Ekuseru-Toukei 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan). The association of each variable was tested by using the Mann-Whitney U nonparametric test for ordinal variables and the Fisher's exact test or Chi-squared test for categorical variables. Cumulative DSS and OS were calculated using the Kaplan-Meier product-limit method. The significant levels among the curves were determined using the log-rank test. Probabilities of less than 0.05 were accepted as significant.

RESULTS

Clinicopathological patient characteristics and the status of lymph node metastasis in each group are summarized in Table 1. There were more men than women. The most common tumor subsite was oral tongue, followed by lower gingiva. The most common histological differentiation was well differentiated. In the ENE+MLM group, moderately differentiated SCC was more common than in the other groups. The most common among the timing of neck dissection was initial treatment. However, in the ENE+pN1 group, neck dissection at metachronous metastasis was most common, which was different from the other groups. The mean follow-up time among the 669 patients was 51.6 months (range: 1–178 months). A total of 116 (62.4%), 114 (53.5%), 73 (36.1 %) and 38 (55.9%) patients survived in the pN1 only, MLM only, ENE+MLM, and ENE+pN1 groups, respectively. A total of 21 (11.3%), 22 (10.3%), 32 (15.8 %) and 11 (16.2%) patients died of regional failure in each of the groups, respectively. A total of 11 (5.9%), 19 (8.9%), 46 (22.8 %) and 7 (10.3%) patients died of distant metastasis in each of the groups, respectively (Table 1). The major cause of death in the ENE+MLM group was from distant metastasis (22.8 %), and that in the ENE+pN1 group was regional failure (31.7%) (Table 1).

The 3-year cumulative OS rates for the pN1 only, MLM only, ENE+MLM, and ENE+pN1 groups were 77.2%, 66.8%, 43.3% and 66.6%, respectively (Figure 1). The pN1 only group was associated with a better OS rate than the MLM only groups ($P < 0.05$). The ENE+MLM group was associated with a worse OS rate than the other groups ($P < 0.05$).

Clinicopathological patient characteristics and treatment modalities of the ENE+pN1 group are summarized in Table 2. Patients in the S+RT/CCRT group were younger and had a lower PS than those in the S only group; however, there was no significant difference between the two groups. Neck dissection at metachronous neck metastasis or recurrence in the S+RT/CCRT group was more than in the S only group; however, there was no significant difference between the two. The most common level of lymph node metastasis was IB, followed by IIA. Single lymph node metastasis at Level IV

or V was only found in three cases (4.4%). The major cause of death in the S only group was from regional failure (33.3%) (Table 2).

The 3-year cumulative OS rates for the S only and S+RT/CCRT groups were 38.9% and 76.9%, respectively (Figure 3). The S+RT/CCRT group was associated with a better OS rate than the S only group ($P < 0.05$). The 3-year cumulative DSS rates for the S only and S+RT/CCRT groups were 42.4% and 73.4%, respectively (Figure 4). The S+RT/CCRT group was associated with a better DSS rate than the S only group ($P < 0.05$).

DISCUSSION

In this study, we investigated the prognosis of pN1 with ENE OSCC patients and retrospectively compared them between no postoperative therapy and postoperative RT/CCRT. Several investigators have indicated a correlation between MLM and poor prognosis [7-10]. Greenberg et al. demonstrated oral tongue cancer patients with MLM had a poor prognosis regardless of the presence of ENE [11]. However, in this study, the ENE+MLM group was associated with a lower OS rate than the MLM only group. Moreover, ENE was associated with poor prognosis due to regional failure and distant metastasis. These results correspond with numerous other studies that have reported a poor prognosis for ENE [4, 5, 9, 12-17].

Clinically, most patients with pathological ENE status simultaneously have MLM in regional lymph nodes. Thus, almost all other studies have combined the cases of ENE+pN1 and ENE+MLM and analyzed them together as the ENE group. The reason for this may be that ENE+pN1 cases among OSCC patients are not prevalent enough for single-institution studies. For instance, in one single-institution study there were only 12 cases (9.8 %) among 122 pN+ cases [11]. Wreesmann et al. also reported only 12 cases (4.9 %) among 245 pN+ cases [16]. Shibuya et al. reported only 2 cases (4.3 %) among 47 pN+ cases [17]. Therefore, it was unclear whether ENE+pN1 really had a poor prognosis among the OSCC population. In this study, we report 68 cases (10.2 %) of ENE+pN1 in a multi-center study. The rate of ENE+pN1 cases was similar to the study by Greenberg et al. [11]. The 3-year cumulative OS rate for ENE+pN1 was 66.6%, similar to the MLM only group (without ENE). Therefore, the prognosis of ENE+pN1 was not as poor as that of ENE+MLM, although both groups have the feature of ENE. However, half of the cases in the ENE+pN1 group were metachronous metastasis, which was different from the other groups. More attention should be paid to this point, because patients with metachronous metastasis may have a poor prognosis if postoperative observation cannot be adequately performed [18, 19].

Generally, metastasis of lower neck level (Level IV/V) is a risk factor of poor prognosis in the N+ group [13, 17]. Recently, we demonstrated that oral tongue cancer, high N staging, and neck dissection upon the occurrence of metachronous neck metastasis or recurrence were significantly associated with the development of level IV/V metastases [17]. Therefore, almost all patients with metastasis of lower neck level have MLM in regional lymph nodes. In this study, metastasis of lower neck level was only seen in three cases (4.4 %) in the ENE+pN1 group. These three cases did not have poor prognoses (2 patients: survival, 1 patient: death of other disease), although these cases were oral tongue cancer and metachronous metastasis. However, the correlation between prognosis and metastasis of lower neck level in the ENE+pN1 group should be investigated in future work because of the small population in this study.

A collaborative analysis of two randomized controlled trials indicated that the addition of concomitant CDDP to postoperative RT improved the outcome of HNSCC patients with ICR and/or ENE [6]. However, OSCC patients were only 25% of all HNSCC subjects in the two trials. Recently, we compared the prognosis of postoperative RT alone and postoperative CCRT in Japanese OSCC patients with a high risk of recurrence [20]. The results suggested that the addition of concomitant CDDP to postoperative RT improved locoregional control. However, our data failed to show a benefit for distant metastasis and OS rates [20]. Yanamoto et al. also demonstrated that the addition of cytotoxic chemotherapy to RT does not provide additional survival benefit (OS and DSS) in OSCC patients with pN+ disease [14]. Additionally, according to the long-term follow-up in one randomized controlled trial, there was no long term (10-year) benefit in OS from the addition of concurrent CDDP to postoperative RT in patients with a high risk of recurrence (ENE and/or ICR) [21]. That study also demonstrated that MLM patients did not benefit from the addition of CDDP to postoperative RT [21]. Conversely, Fan et al. reported that the addition of concomitant CDDP to postoperative RT improved outcomes for OSCC patients with MLM without ENE and/or ICR, although in a retrospective study [22]. Our

data failed to show a benefit of adding concomitant chemotherapy to postoperative RT for the ENE+pN1 group (data not shown). However, this result should be carefully considered because of the small population size. Finally, adjuvant therapy (RT alone or CCRT) after surgery is recommend for ENE+pN1 cases because the S+RT/CCRT group was associated with better DSS and OS rates than the S only group in this study.

This study had several limitations. First, ENE+pN1 cases in this study might actually be MLM cases because of the pathological oversight of micrometastasis. The presence of lymph node metastasis is diagnosed by light microscopy. Therefore, micrometastases smaller than 2 mm can easily escape identification, resulting in down-staging the N stage. Some investigators have reported that through thin sectioning lymph nodes they can identify a 25%–28% rate of occult lymph node disease [23, 24]. Second, the level of ENE progression was not investigated in this study. The pathological level of ENE progression may be an important factor for predicting prognoses and the application of adjuvant therapy, although it is controversial [11, 16, 25, 26]. Previously, we demonstrated that DSS and RFS rates were significantly lower in patients with type C level of ENE progression, which was defined as microscopic tumor invasion into the perinodal fat or muscle tissue, than in patients with the other two types [25]. Especially among the pN1+ENE cases, in which 11 (72.7%) patients of Type C survived, and 16 (88.9%) patients of the other types survived. Third, the treatment protocols for RT/CCRT were not standardized because this was a retrospective study. Future research should involve a prospective cohort study with standardized treatment protocols and other factors.

In conclusion, we analyzed the prognosis of pN1 with ENE OSCC patients and retrospectively compared them between no postoperative therapy and postoperative RT/CCRT. The prognosis of ENE+pN1 was not as poor as that of ENE+MLM, although both group have the feature of ENE. In the ENE+pN1 group, the S+RT/CCRT group was associated with better DSS and OS rates than the S only group. Therefore, adjuvant therapy (RT/CCRT) after surgery is recommend for ENE+pN1 cases.

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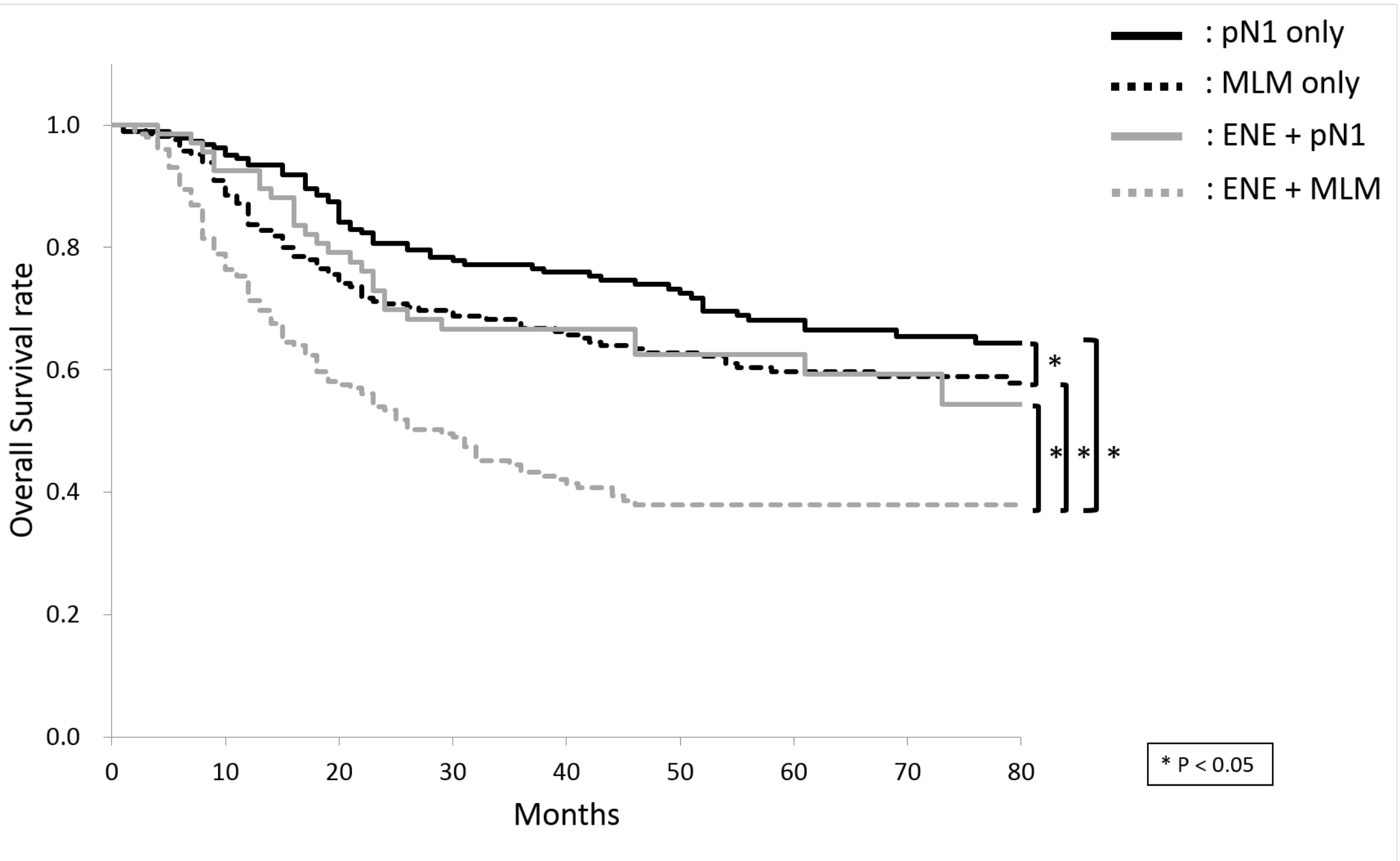
FIGURE CAPTIONS

FIGURE LEGENDS

Figure 1. The 3-year cumulative OS rates for the pN1 only, MLM only, ENE+MLM, and ENE+pN1 groups were 77.2%, 66.8%, 43.3% and 66.6%, respectively. The pN1 only group was associated with a better OS rate than the MLM only group ($P < 0.05$). The ENE+MLM group was associated with a worse OS rate than the other groups ($P < 0.05$).

Figure 2. The 3-year cumulative OS rates for the S only and S+RT/CCRT groups were 38.9% and 76.9%, respectively. The S+RT/CCRT group was associated with a better OS rate than the S only group ($P < 0.05$).

Figure 3. The 3-year cumulative DSS rates for the S only and S+RT/CCRT groups were 42.4% and 73.4%, respectively. The S+RT/CCRT group was associated with a better DSS rate than the S only group ($P < 0.05$).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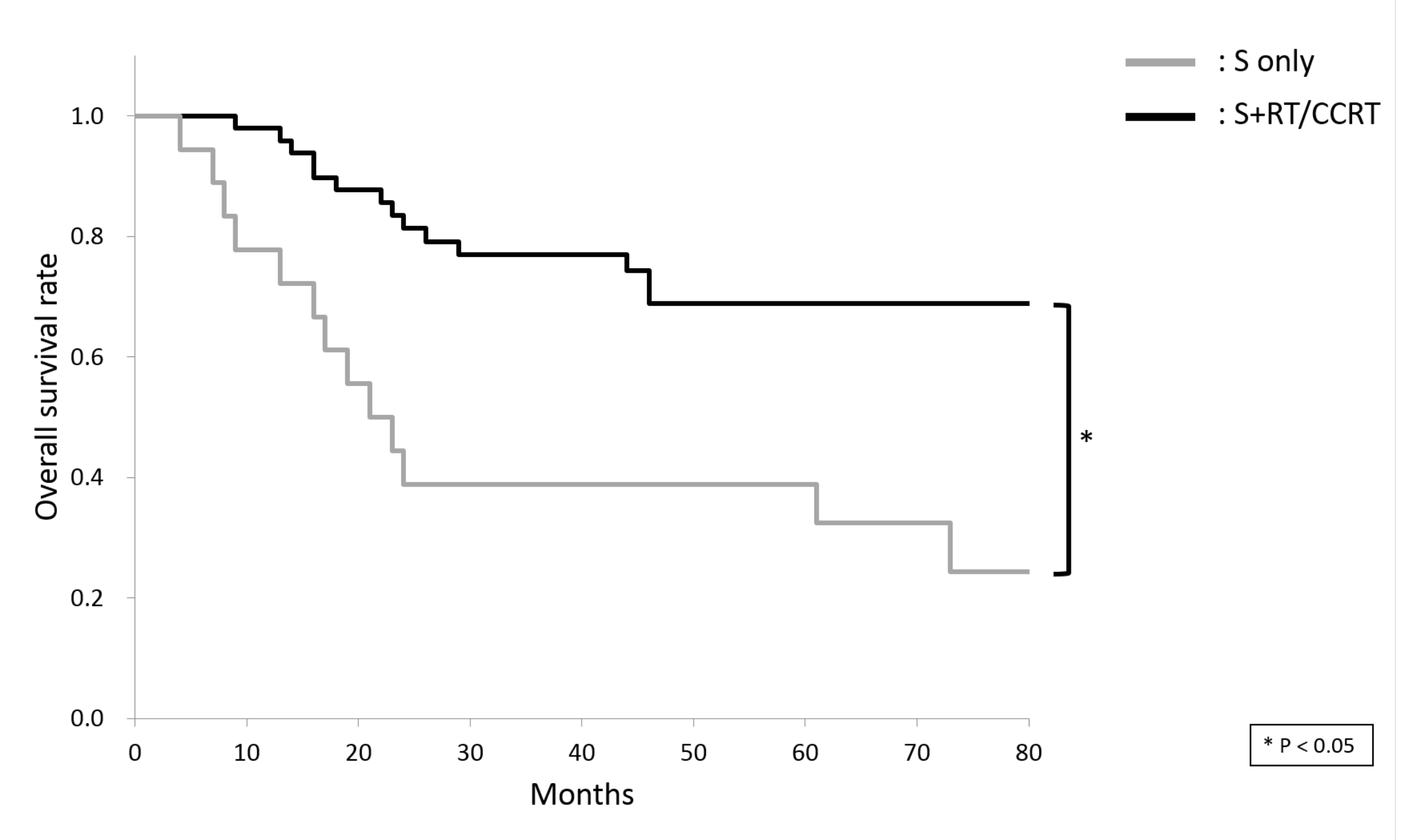
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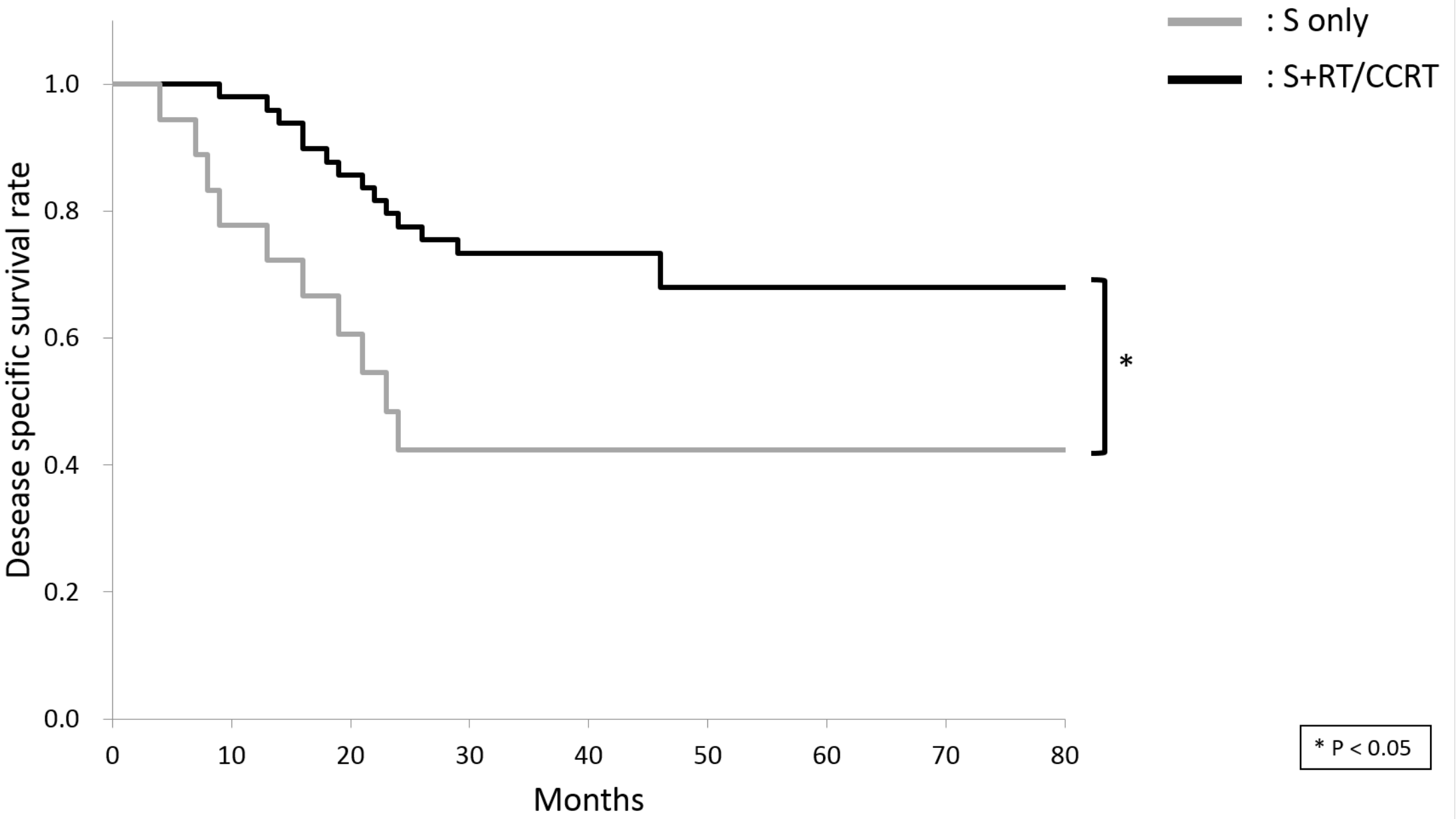
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Table 1. The characteristics and status of lymph node metastases (n =669)

Variables	Groups			
	pN1 only (n; %)	MLM only (n; %)	ENE +MLM (n; %)	ENE + pN1 (n; %)
Sample size	186 (27.8)	213 (31.8)	202 (30.2)	68 (10.2)
Gender				
Male	111 (59.7)	122 (57.3)	129 (63.9)	39 (59.9)
Female	75 (40.3)	91 (42.7)	73 (36.1)	29 (40.1)
Age				
Range	22-96	31-92	26-90	30-96
Mean ± SD	64.6 ± 14.5	67.4 ± 12.0	65.3 ± 13.6	66.9 ± 12.8
Performance status (PS)				
0	135 (72.6)	159 (74.6)	148 (73.3)	51 (75.0)
1	28 (15.1)	31 (14.6)	25 (12.4)	9 (13.2)
2	9 (4.8)	14 (6.6)	13 (6.4)	4 (5.9)
3	2 (1.1)	2 (0.9)	5 (2.5)	0 (0)
unknown	12 (6.5)	7 (3.3)	11 (5.5)	4 (5.9)
Subsite				
Oral tongue	94 (50.5)	92 (43.2)	103 (51.0)	37 (54.4)
Upper gingiva	16 (8.6)	31 (14.6)	20 (9.9)	6 (8.8)
Lower gingiva	41 (22.0)	59 (27.7)	35 (17.3)	11 (16.2)
The floor of the mouth	18 (9.7)	16 (7.5)	25 (12.4)	5 (7.4)
Buccal mucosa	12 (6.5)	12 (5.6)	16 (7.9)	8 (11.8)
Others	5 (2.7)	3 (1.4)	3 (1.5)	1 (1.5)
Clinical T stage at initial visiting				
1	35 (18.8)	17 (8.0)	27 (13.4)	9 (13.2)
2	87 (46.8)	93 (43.7)	82 (40.6)	35 (51.5)
3	15 (8.1)	30 (14.1)	24 (11.9)	7 (10.3)
4a	40 (21.5)	61 (28.6)	57 (28.2)	13 (19.1)
4b	9 (4.8)	12 (5.6)	12 (5.9)	4 (5.9)
Clinical N stage at initial visiting				
0	96 (51.6)	76 (35.7)	75 (37.1)	45 (66.2)
1	64 (34.4)	40 (18.8)	22 (10.9)	14 (20.6)
2a	0 (0)	2 (0.9)	0 (0)	1 (1.5)
2b	22 (11.8)	73 (34.3)	71 (35.1)	7 (10.3)
2c	4 (2.2)	20 (9.4)	31 (15.3)	1 (1.5)

3	0 (0)	2 (0.9)	3 (1.5)	0 (0)
Pathological status				
Surgical margin				
Negative (ICR -)	156 (83.9)	175 (82.2)	167 (82.7)	53 (77.9)
Involved margins (ICR +)	30 (16.1)	38 (17.8)	35 (17.3)	15 (22.1)
Histological differentiation				
Well	111 (59.7)	119 (55.9)	100 (49.5)	41 (60.3)
Moderate	69 (37.1)	78 (36.6)	94 (46.5)	25 (36.8)
Poor	4 (2.2)	10 (4.7)	5 (2.5)	2 (2.9)
Others	2 (1.1)	6 (2.8)	3 (1.5)	0 (0)
The timing of neck dissection				
Initial treatment	126 (67.8)	159 (74.6)	142 (70.3)	26 (38.2)
Metachronous neck metastasis	49 (26.3)	46 (21.6)	55 (27.2)	37 (54.4)
Recurrence	11 (5.9)	8 (3.8)	5 (2.5)	5 (7.4)
Treatment outcome				
Survival	116 (62.4)	114 (53.5)	73 (36.1)	38 (55.9)
Tumor-bearing survival	4 (2.2)	6 (2.8)	6 (3.0)	2 (2.9)
Death of local failure	13 (7.0)	28 (13.1)	27 (13.4)	5 (7.4)
Death of regional failure	21 (11.3)	22 (10.3)	32 (15.8)	11 (16.2)
Death of distant metastasis	11 (5.9)	19 (8.9)	46 (22.8)	7 (10.3)
Death of operative complication	1 (0.5)	2 (0.9)	2 (1.0)	0 (0)
Death of other disease	20 (10.8)	22 (10.3)	16 (7.9)	5 (7.4)

Table 2. The characteristics and treatment modalities for the ENE + pN1 cases (n =68)

Variables	S only	S + RT/CCRT	P value
Sample size	18 (26.5)	50 (73.5)	
Gender			
Male	11 (61.1)	28 (56.0)	0.786 *
Female	7 (38.9)	22 (44.0)	
Age			
Range	46–96	30–85	
Mean ± SD	71.2 ± 13.1	65.4 ± 12.5	0.050 **
< 65	7 (38.9)	24 (48.0)	
≥ 65	11 (61.1)	26 (52.0)	
Performance status (PS)			
0 or 1	14 (77.8)	44 (88.0)	0.059 *
> 2	3 (16.7)	1 (2.0)	
Unknown	1 (5.6)	5 (10.0)	
Subsite			
Oral tongue	11 (61.1)	26 (52.0)	0.587 *
Others	7 (38.9)	24 (48.0)	
Pathological status			
Surgical margin			
Negative (ICR -)	13 (72.2)	42 (84.0)	0.306 *
Involved margins (ICR +)	5 (27.8)	8 (16.0)	
Histological differentiation			
Well	11 (61.1)	28 (56.0)	0.786 *
Moderate or Poor	7 (38.9)	22 (44.0)	
The timing of neck dissection			
Initial treatment	9 (50.0)	17 (34.0)	0.487 ***
Metachronous neck metastasis	8 (44.4)	29 (58.0)	
Recurrence	1 (5.6)	4 (8.0)	
The level of lymph node metastasis			
IA	1 (5.6)	1 (2.0)	
IB	8 (44.4)	29 (58.0)	
IIA	3 (16.7)	13 (26.0)	
IIB	0 (0)	2 (4.0)	
III	5 (27.8)	3 (6.0)	

IV	1 (5.6)	1 (2.0)
V	0 (0)	1 (2.0)
Cumulative radiation dose (Gy)		
Range	-	50-70
Mean ± SD	-	60.9 ± 6.0
The concomitant chemotherapy to postoperative RT		
Cisplatin	-	13
Tegafur-gimeracil-oteracil	-	9
None (RT alone)	-	28
Treatment outcome		
Survival	5 (27.8)	33 (66.0)
Tumor-bearing survival	0 (0)	2 (4.0)
Death of local failure	2 (11.1)	3 (6.0)
Death of regional failure	6 (33.3)	5 (10.0)
Death of distant metastasis	2 (11.1)	5 (10.0)
Death of other disease	3 (16.7)	2 (4.0)

*: Fisher`s exact test. **: Mann-Whitney U test. ***: Chi-squared test.