Time to Recurrence Associated With Poor Prognosis in Japanese Oral Squamous Cell Carcinoma Patients

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Time to recurrence associated with poor prognosis in Japanese oral squamous cell carcinoma patients

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Running head: Time to recurrence and prognosis in OSCC
Key words: oral squamous cell carcinoma, time to recurrence, disease-specific survival, prognosis, salvage surgery

ABSTRACT

Purpose: Recurrence in oral squamous cell carcinoma (OSCC) is not rare. Due to lack of studies assessing characteristics of recurrent OSCC, including time to recurrence and outcomes, we sought to investigate its characteristics, time to recurrence, and outcomes in Japanese OSCC patients.

Methods: This study was a non-randomized retrospective cohort study in a tertiary referral center. It included 208 (117 men and 91 women) patients with recurrent oral cancer who underwent major curative surgery in the Department of Oral and Maxillofacial Surgery at Kobe University Hospital between January 1999 and April 2017. The outcomes were disease-specific survival (DSS) and overall survival (OS).

Results: In multivariable Cox proportional hazards analysis, the time to recurrence (hazard ratio [HR] 3.55, 95% confidence interval [CI] 1.69-6.63; P = 0.001), extranodal extension (ENE, HR 2.72, 95% CI 1.51-4.89; P = 0.001), and high T stage (HR 2.00, 95% CI 1.01-3.97; P = 0.046) were independent predictors of DSS. The time to recurrence (HR 3.29, 95% CI 1.82-5.96; P < 0.001) and ENE (HR 2.64, 95% CI 1.52-4.56; P = 0.001) were independent predictors of OS.

Conclusion: Time to recurrence, extranodal extension, and higher T stage were independent prognosis predictors in OSCC.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most common tumor of the head and neck region. It occurs mostly (> 90%) in the oral cavity [1]. Though there have been recent improvements in the treatment of advanced OSCC, the survival of oral cancer patients has not dramatically improved [2]. The reported recurrence rate ranges from 7 to 47.4% in patients who received curative therapy [3]. Particularly, the prognosis is worse in patients with recurrent tumors [4-6]. Therefore, improvement in the diagnosis and management of recurrence tumors remains important. Almost all recurrent tumors develop within 2 years after initial treatment [7, 8]. The patients with early recurrences have worse prognosis than those with late recurrences [9-11].

Local and regional control are important for the treatment of recurrent tumors. Previously, we reported that locoregional failure was a risk factor for distant metastasis and poor survival [12]. Salvage surgery is critical for locoregional control in patients with recurrent tumors. However, recurrence occurs in about 60% of patients who underwent salvage surgery [7, 13]. Since salvage surgery needs wide resections and flap reconstructions, clinicians should carefully select the patients to undergo this.

Due to the lack of studies assessing the characteristics of recurrent OSCC including the time to recurrence and outcomes, we investigated these in Japanese patients with OSCC.

MATERIALS AND METHODS

This nonrandomized study retrospectively evaluated a cohort of 208 patients with a first recurrence of oral cancer and who underwent a major curative surgery in the Department of Oral and Maxillofacial Surgery at the Kobe University Hospital between January 1999 and April 2017. The institutional review board of the Kobe University Graduate School of Medicine approved the study and it was carried out in accordance with the Helsinki Declaration of 1975, as revised in 1983. All patients underwent a wide excision of the primary tumor and/or neck dissection with either modified radical neck dissection or selective neck dissection and with or without postoperative adjuvant chemoradiation. Patients carried out preoperative examinations including chest X-ray, computed tomography (CT), and magnetic resonance imaging (MRI). Patients with other cancers before the diagnosis of OSCC, inadequate information on clinicopathological parameters, simultaneous second primary cancer, or previous radiotherapy or chemotherapy for head and neck cancer or other diseases were excluded. For the follow-up after the initial treatment, we performed a one-to-three-months follow-up for the first year, two-to-four-months follow-up for the second year, four-to-six-months follow-up for year the third to fifth year, and every 6–12 months thereafter. Chest x-ray, computed tomography (CT), or positron emission tomography (PET) was performed during the follow-up sessions. Before 2005, CT and chest x-ray screenings were done at 3 and 6 months of follow-up, respectively. After 2006, CT and PET-CT were done at 3 months and 1 year of follow-up, respectively.

The data assessed for each patient included the sex, age, smoking history, alcohol consumption, performance status, subsite, clinical T classification (Union Internationale Contre le Cancer/American Joint Committee on Cancer [UICC/AJCC] staging system 8th edition) [14], clinical N classification, histological grade (well differentiated, moderately differentiated, or poorly differentiated), surgical margins, number of pathologically metastatic lymph nodes, presence of pathological extranodal extension (ENE), the time to

recurrence, the type of treatment after tumor recurrence, and treatment outcome. The time to recurrence was defined as the time from the curative surgery in the cases that underwent only surgery or finished postoperative radiotherapy or chemoradiotherapy to recurrence. The endpoints evaluated were the disease-specific survival (DSS) as the primary outcome and overall survival (OS) as the secondary outcome. Survival times were calculated from the date of surgery.

All of the variables were introduced into a multivariate Cox proportional hazard model, in which patients were divided by age ($\leq$ 64 years vs. $\geq$ 65 years), performance status (PS, 0 or 1 vs. 2 or 3), subsite (tongue vs. others), T stage (1 or 2 vs. 3 or 4), N stage (0 vs. others), histological grade (well vs. moderately or poorly differentiated), surgical margins (negative vs. close or positive), number of pathologically metastatic lymph nodes (0 or 1 vs. $\geq$ 2), and time to recurrence [$\leq$ 6 months (early time) vs. $\geq$ 7 months (late time)]. Because the type of treatment after tumor recurrence is a factor after recurrence, the factor was excluded from the multivariate analysis.

The discriminatory ability of the time to recurrence as an indicator of possible DSS was evaluated with a receiver operating characteristic (ROC) curve. This ROC curve was used to determine the cutoff values for clinical tests. The area under the resulting curve (AUC) measured the accuracy of this discrimination, and ranged from 0.5 to 1. The cutoff value was chosen to minimize the number of false-positive and false-negative results.

Statistical analysis

SPSS 22.0 (SPSS, Chicago, IL) and Ekuseru-Toukei 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan) were used for the statistical analyses. Cumulative DSS and OS were calculated using the Kaplan–Meier product limit method. Significance among the curves was determined using the log-rank test. Probabilities of less than 0.05 were accepted as significant. All of the variables associated with the DSS or OS

were introduced into multivariate Cox proportional hazard models. Hazard ratio (HR) and 95% confidence intervals (CIs) were also calculated.

RESULTS

The mean follow-up time was 43.0 (range, 1-211) months. During the follow-up period, the 3-year OS and DSS were 51.0% and 54.3%, respectively. Recurrence occurred in 166 (79.8%) patients and 192 (92.3%) patients within one year and two years after curative treatment, respectively (Table 1). Salvage surgery was performed in 125 (60.1%) patients with recurrence while 54 (26.0%) patients with recurrence received palliative therapy or supportive therapy because they had inoperable recurrences with no history of curative radiotherapy or chemoradiotherapy, incurable distant metastasis, or they refused further treatment. Death occurred in 101 (48.6%) patients (Table 1).

The mean of the time to recurrence was 8.76 ± 11.5 months and the optimal cutoff value was 6 months in this study. The AUC of the ROC curve for the time to recurrence was 0.60. The resulting sensitivity was 0.76, and the specificity was 0.41.

Univariate analysis showed that high T stage ($P < 0.001$), high N stage ($P < 0.001$), ENE ($P < 0.001$), pathological multiple lymph node metastases ($P = 0.001$), moderate or poor differentiation ($P < 0.001$), postoperative adjuvant therapy ($P < 0.001$), early time of recurrence ($P < 0.001$), and no salvage surgery ± radiotherapy and/or chemotherapy ($P < 0.001$) were associated with a poor 3-year DSS and 3-year OS (Table 2). The DSS of each time to recurrence and each treatment modality is shown in Figure 1 and 2.

In multivariable Cox proportional hazards analysis, the time to recurrence [hazard ratio (HR) 3.55, 95% confidence interval (CI) 1.69-6.63; P = 0.001], ENE (HR 2.72, 95% CI 1.51-4.89; P = 0.001), and high T stage (HR 2.00, 95% CI 1.01-3.97; P = 0.046) were independent predictors of DSS (Table 3). The time to recurrence (HR 3.29, 95% CI 1.82-5.96; P < 0.001) and ENE (HR 2.64, 95% CI 1.52-4.56; P = 0.001) were independent predictors of OS (Table 4).

The 3-year DSS of patients with and without ENE were 55.1% and 15.1%, respectively (Figure 3). The 3-year DSS of patients with T1/2 stage and T3/4 stage were 67.9% and 42.1%, respectively (Figure 4).

DISCUSSION

We successfully investigated the clinicopathologic characteristics, the time to recurrence, and treatment modalities for survival in Japanese patients with recurrent OSCC. Early time to recurrence was associated with a poor prognosis.

More than 75% of OSCC patients develop recurrence within 2 years after initial treatment [15]. Other studies reported 68-80% of recurrent tumors within 2 years [7, 8]. Schwartz et al. reported that 92% of recurrent cases developed within 3 years after the first treatment [16]. In this study, 92.3% patients developed recurrence within 2 years after initial treatment.

It has been well known that the status of the cervical lymph nodes and local metastases are the most important factors affecting survival and locoregional recurrence [12, 14, 15, 17-19]. Particularly, ENE was associated with poor prognosis due to regional failure and distant metastasis [12, 17-19]. In patients with recurrent OSCC in this study, ENE and higher T stage were significant independent predictors of DSS in the multivariable Cox proportional hazards analysis. The results are consistent with other reports [12, 14, 15, 17-19]. The relationships between the histologic grading and prognosis were controversial [20, 21]. Several investigators reported that the poorly differentiated tumors had worse metastases, recurrence, and prognosis compared to the well-differentiated tumors [18, 19, 22-24]. However, in multivariate analysis in this study, histologic differentiation was not a significant risk factor for poor prognosis, although the difference was significant in univariate analysis.

The patients with early recurrences had worse prognoses than those with late recurrences [7, 9, 11, 13, 25]. Schwarz et al. reported that oral cancer patients with recurrence within 6 months had poor prognoses than those with recurrence after 6 months [16]. Some investigators demonstrated that patients with recurrent disease development in less than 12 months had poor prognoses than those with recurrence development after 12 months among patients who received salvage surgery [7, 13, 25]. Other researchers set the

cut-off time to recurrence at 18 months [9, 26]. In this study, the cutoff value of the time to recurrence that speculated poor prognosis was 6 months based on the result of the ROC curve, although the result had a low accuracy. These results are consistent with Schwarz et al.'s report [16]. In this study, the shorter the time to recurrence, the poorer the prognosis. In multivariable Cox proportional hazards analysis, the time to recurrence was a significant independent predictor of DSS and OS. The poor prognosis in patients with earlier recurrences may be more aggressive biologically [27].

Salvage surgery is critical for locoregional control in patients with recurrent tumors. Some investigators reported that the performance of a salvage treatment was a prognostic factor for overall survival [3, 22]. Haque et al. reported that the patients who underwent salvage surgery with recurrence within 6 months after initial treatment had worse prognosis [28]. Liao et al. demonstrated that late relapse (> 10 months after definitive treatment) was associated with a better survival than early relapse (< 10 months) in patients with recurrent OSCC [29]. In this study, patients who received salvage surgery had a better survival than those who received other treatment modalities. The 3-year DSS of patients with salvage surgery was 75.2%. However, salvage surgery needs wide resections and flap reconstructions which can result to laryngeal dysfunction and dysphagia. There is also a possibility that the patients with better conditions were selected for salvage surgery, and the patients with worse conditions or inoperable advanced tumors were selected for palliative therapy. Therefore, the clinician must carefully select patients with early recurrent tumors for salvage surgery.

This study had several limitations. First, the present study was retrospective and nonrandomized. Therefore, bias could not be completely excluded, although multivariate analysis was performed to decrease the effect of confounding factors as much as possible. We cannot deny the possibility that there was a selection bias in the choice of patients for salvage surgery which affected our results. Future research should involve large-scale, prospective cohort studies to evaluate predictors of prognosis and treatment modalities.

In conclusion, we successfully demonstrated the clinicopathologic characteristics, the time to recurrence, and treatment modalities for survival in Japanese patients with recurrent OSCC. In particular, an early time to recurrence was associated with poor prognosis. The time to recurrence, ENE, and higher T stage were independent predictors of DSS. The time to recurrence and ENE were independent predictors of OS. We propose that clinicians consider these risk factors and pay close attention to the management of patients with recurrent OSCC. Salvage surgery may be useful as a treatment modality.

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Figure captions

Figure legends

Figure 1. Early time of recurrence were associated with a poor 3-year DSS ($P < 0.001$).

Figure 2. No salvage surgery ± radiotherapy and/or chemotherapy were associated with a poor 3-year DSS ($P < 0.001$).

Figure 3. The 3-year DSS of patients with and without ENE were 55.1% and 15.1%, respectively ($P < 0.001$).

Figure 4. The 3-year DSS of patients with T1/2 stage and T3/4 stage were 67.9% and 42.1%, respectively ($P < 0.001$).

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Conflict of interest: Takumi Hasegawa, Erina Kobayashi, Rika Amano, Izumi Saito, Daisuke Takeda, Yasumasa Kakei, Akira Kimoto, Akiko Sakakibara, Masaya Akashi declare that they have no conflict of interest.

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Contribution: All authors contributed equally to this work.

Compliance with Ethical Standards

Due to the retrospective nature of this study, informed consent is not required. Instead, we published the information of this study and granted the occasions of refusing to participate in this study. This retrospective study has been conducted in full accordance with the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board of Kobe University Graduate School of Medicine.

AUTHOR CONTRIBUTIONS

Study design: T Hasegawa, A Kimoto, A Sakakibara, M Akashi

Acquisition of data: T Hasegawa, E Kobayashi, R Amano, I Saito

Analysis and interpretation of data: T Hasegawa, D Takeda, Y Kakei

Manuscript preparation: T Hasegawa, A Kimoto, A Sakakibara, M Akashi

Manuscript editing: T Hasegawa, A Matsuda, R Amano, I Saito, D Takeda, Y Kakei, A Kimoto, A Sakakibara, M Akashi

Manuscript review: T Hasegawa, A Matsuda, R Amano, I Saito, D Takeda, Y Kakei, A Kimoto, A Sakakibara, M Akashi

Statistical analysis: T Hasegawa

Table 1. Characteristics of patients with recurrence tumor

Variables	Number of patients (%)
Number of patients	208 (100.0)
Sex	
Male	117 (56.3)
Female	91 (43.7)
Age	
Range (Years)	15–97
Mean ± SD	66.8 ± 14.4
≥ 64	81 (58.9)
≤ 65	127 (61.1)
Smoking history	
No	103 (49.5)
Yes	35 (16.8)
Unknown	70 (33.7)
Alcohol drinking	
No	84 (40.4)
Yes	51 (24.5)
Unknown	73 (35.1)
Performance status	
0, 1	189 (90.9)
≥ 2	19 (9.1)
Subsite	
Tongue	98 (47.1)
Other	110 (52.9)
T classification	
1, 2	94 (45.2)
3, 4a/b	114 (54.8)
N classification	
0, 1	150 (72.1)
≥ 2	58 (27.9)

Pathological status	
Status of positive lymph metastasis	
ENE -	105 (50.5)
ENE +	44 (21.2)
Nonexcuted neck dissection on first surgery	59 (28.4)
Number of pathological lymph node metastases	
0, 1	81 (38.9)
More than 2	68 (32.7)
Nonexcuted neck dissection on first surgery	59 (28.4)
Surgical margins	
Negative	143 (68.8)
Involved margins	65 (31.2)
Histological differentiation	
Well differentiated	100 (48.1)
Moderately or poorly differentiated	104 (50.0)
Unknown	4 (1.9)
Postoperative adjuvant therapy	
No	156 (75.0)
Yes	47 (22.6)
Unknown	5 (2.4)
The site of recurrence (overlapping distribution)	
Local recurrence	
No	118 (56.7)
Yes	90 (43.3)
Regional recurrence (including metachronous metastasis)	
No	81 (38.9)
Yes	127 (61.1)
Distant metastasis	
No	134 (64.4)
Yes	74 (35.6)
Timing of recurrence	
1-4 months	95 (45.7)
5-8 months	53 (25.5)
9-12 months	18 (8.7)
13-24 months	26 (12.5)
25-36 months	16 (7.7)
Salvage treatment	
Surgery ± radiotherapy and/or chemotherapy	125 (60.1)
Curative radiotherapy or chemoradiotherapy	16 (7.7)

Chemotherapy alone	13 (6.2)
Palliative therapy or Supportive therapy	54 (26.0)
Treatment outcome	
Survival	68 (32.7)
Death of local failure	40 (19.2)
Death of regional failure	29 (13.9)
Death of distant metastasis	32 (15.4)
Death of other disease	16 (7.7)
Tumor-bearing survival	23 (11.1)

Table 2. Characteristics of patients according to DSS and OS

Variables	n (%)	3 year DSS (%)	*P* value	3 year OS (%)	*P* value
Number of patients	208 (100.0)				
Sex					
Male	117 (56.3)	51.5	0.287 *	49.3	0.546 *
Female	91 (43.7)	58.0		53.2	
Age					
≥ 64	81 (58.9)	43.9	0.086 *	43.0	0.435 *
≤ 65	127 (61.1)	61.8		56.5	
Smoking history					
No	103 (74.6)	59.6	0.485 *	55.6	0.814 *
Yes	35 (25.4)	55.5		52.1	
Alcohol drinking					
No	84 (62.2)	56.8	0.616 *	51.4	0.440 *
Yes	51 (37.8)	58.2		56.8	
Performance status					
0, 1	189 (90.9)	53.8	0.475 *	51.3	0.997 *
≥ 2	19 (9.1)	60.1		49.1	
Subsite					
Tongue	98 (47.1)	51.7	0.849 *	47.9	0.891 *
Other	110 (52.9)	56.7		53.9	
T classification					
1, 2	94 (45.2)	67.9	< 0.001 *	64.0	0.001 *
3, 4a/b	114 (54.8)	42.1		39.4	
N classification					
0, 1	150 (72.1)	64.8	< 0.001 *	61.2	< 0.001 *
≥ 2	58 (27.9)	26.5		24.5	
Pathological status					
Status of positive lymph metastasis					
ENE -	105 (70.5)	55.1	< 0.001 *	52.4	< 0.001 *
ENE +	44 (29.5)	15.1		12.9	
Number of pathological lymph node metastases					
0, 1	81 (54.4)	53.0	0.001 *	50.2	< 0.001 *

More than 2	68 (45.6)	31.6		29.6	
Surgical margins					
Negative	143 (68.8)	54.4	0.941 *	51.3	0.832 *
Involved margins	65 (31.2)	53.7		50.2	
Histological differentiation					
Well differentiated	100 (49.0)	68.1	< 0.001 *	62.7	0.001 *
Moderately or poorly differentiated	104 (51.0)	40.3		38.6	
Postoperative adjuvant therapy					
No	156 (76.8)	63.8	< 0.001 *	59.6	< 0.001 *
Yes	47 (23.4)	26.7		26.0	
Timing of recurrence					
1-4 months	95 (45.7)	39.7	< 0.001 *	36.7	< 0.001 *
5-8 months	53 (25.5)	52.1		44.4	
9-12 months	18 (8.7)	65.2		65.2	
13-24 months	26 (12.5)	76.0		76.0	
25-36 months	16 (7.7)	93.8		93.8	
Salvage treatment					
Surgery ± radiotherapy and/or chemotherapy	125 (60.1)	75.2	< 0.001 *	71.2	< 0.001 *
Curative radiotherapy or chemoradiotherapy	16 (7.7)	46.0		46.0	
Chemotherapy alone	13 (6.2)	28.9		28.8	
Palliative therapy or Supportive therapy	54 (26.0)	10.1		8.9	

*: Log-rank test.

Table 3. Results of multivariate Cox proportional hazards analysis of predictors of disease specific survival (DSS)

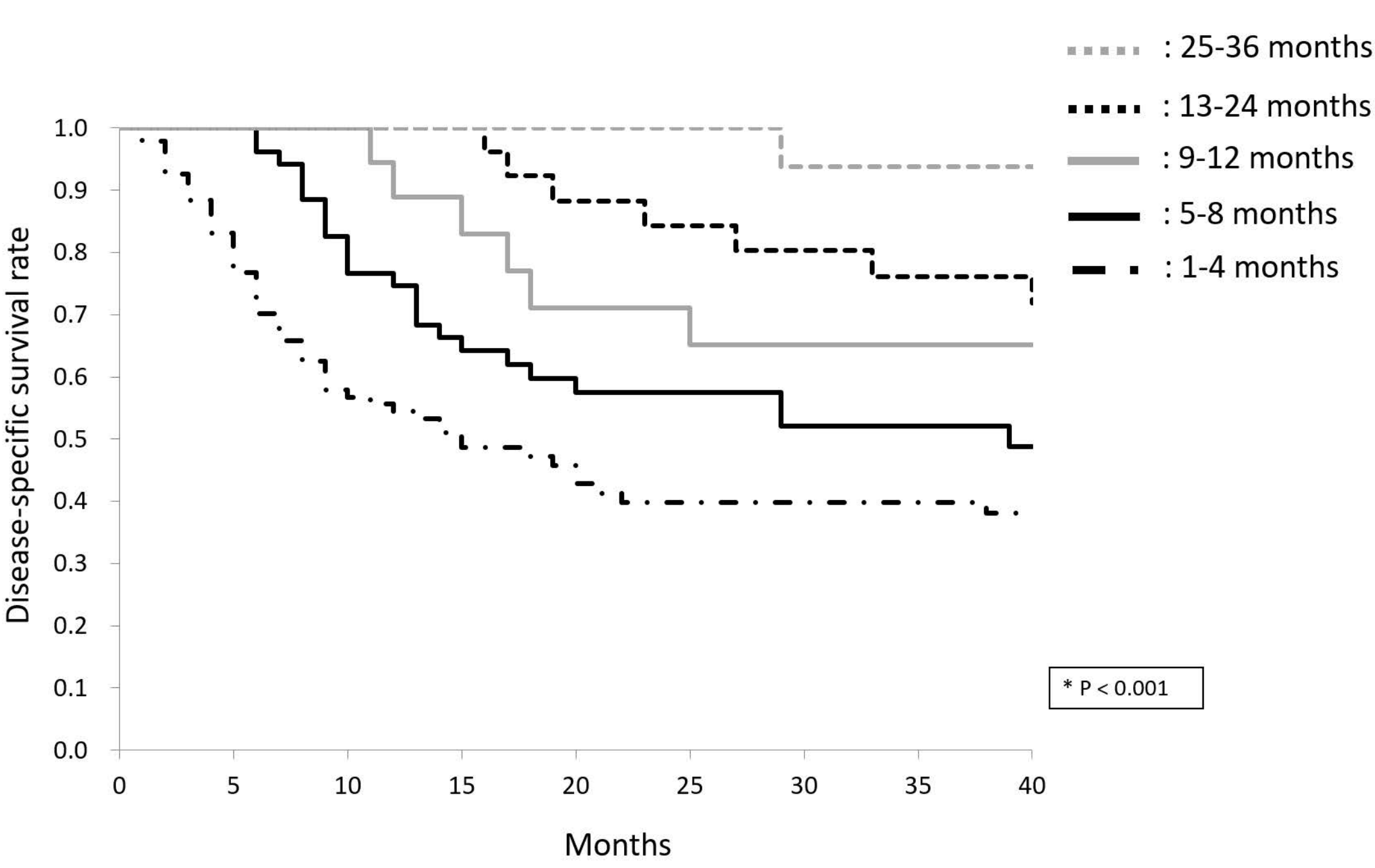
Variable	P value	Hazards ratio	95 % CI	
			Lower	Upper
The timing of recurrence (≤ 6 months)	0.001	3.35	1.69	6.63
Extra nodal extension	0.001	2.72	1.51	4.89
Higher T stage (T3 and 4)	0.046	2.00	1.01	3.97

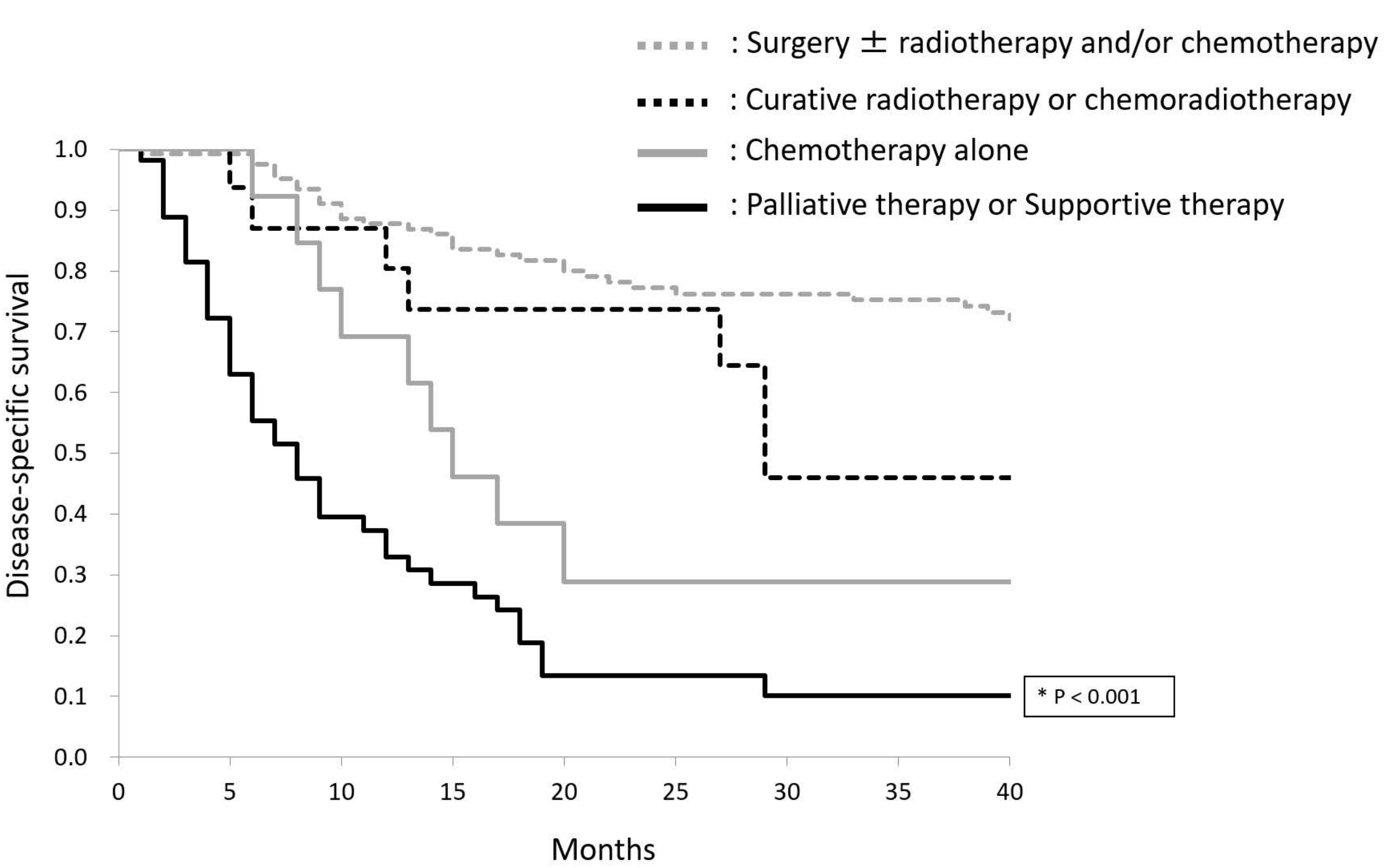
CI: Confidence interval

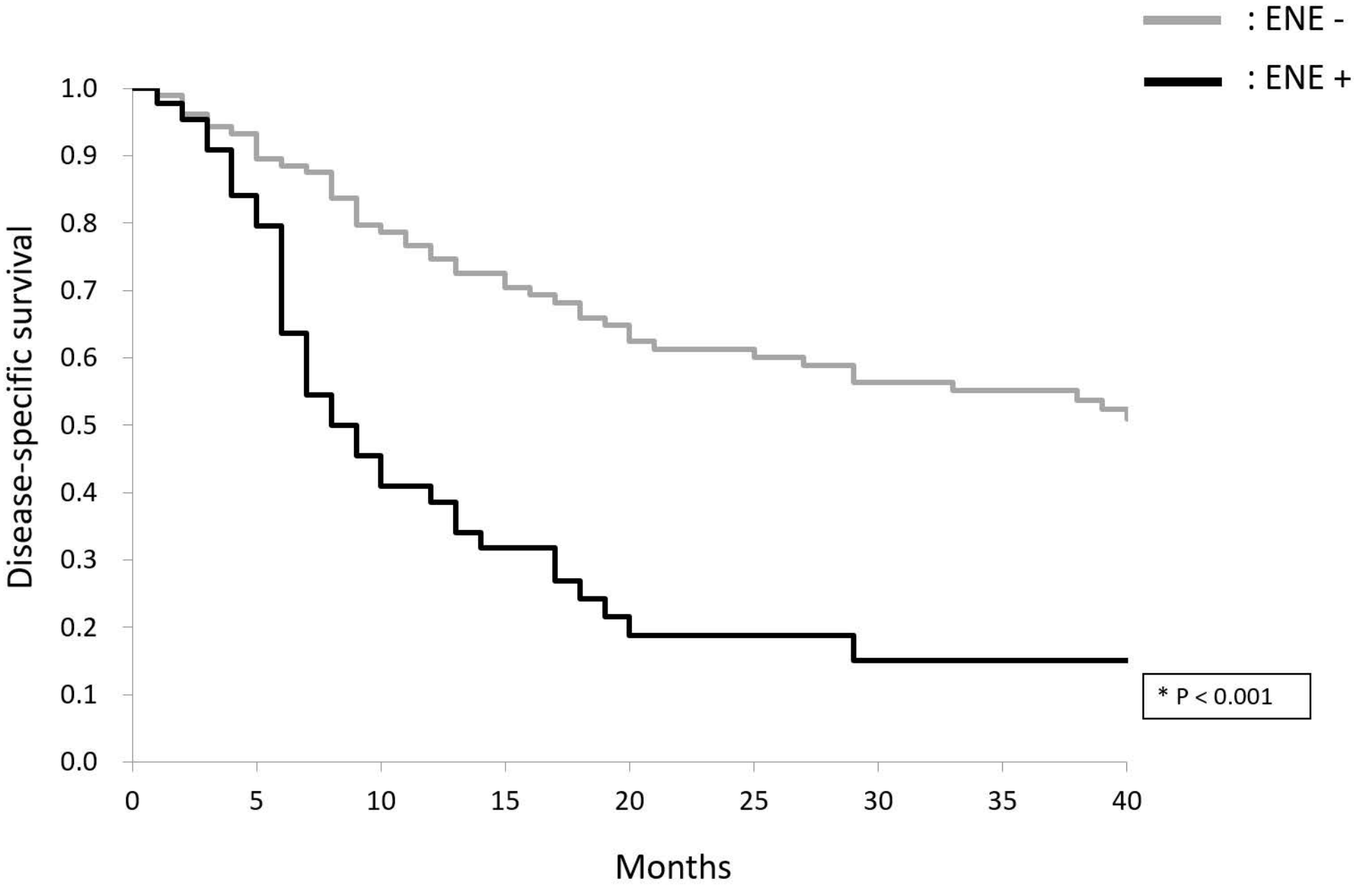
Table 4. Results of multivariate Cox proportional hazards analysis of predictors of overall survival (OS)

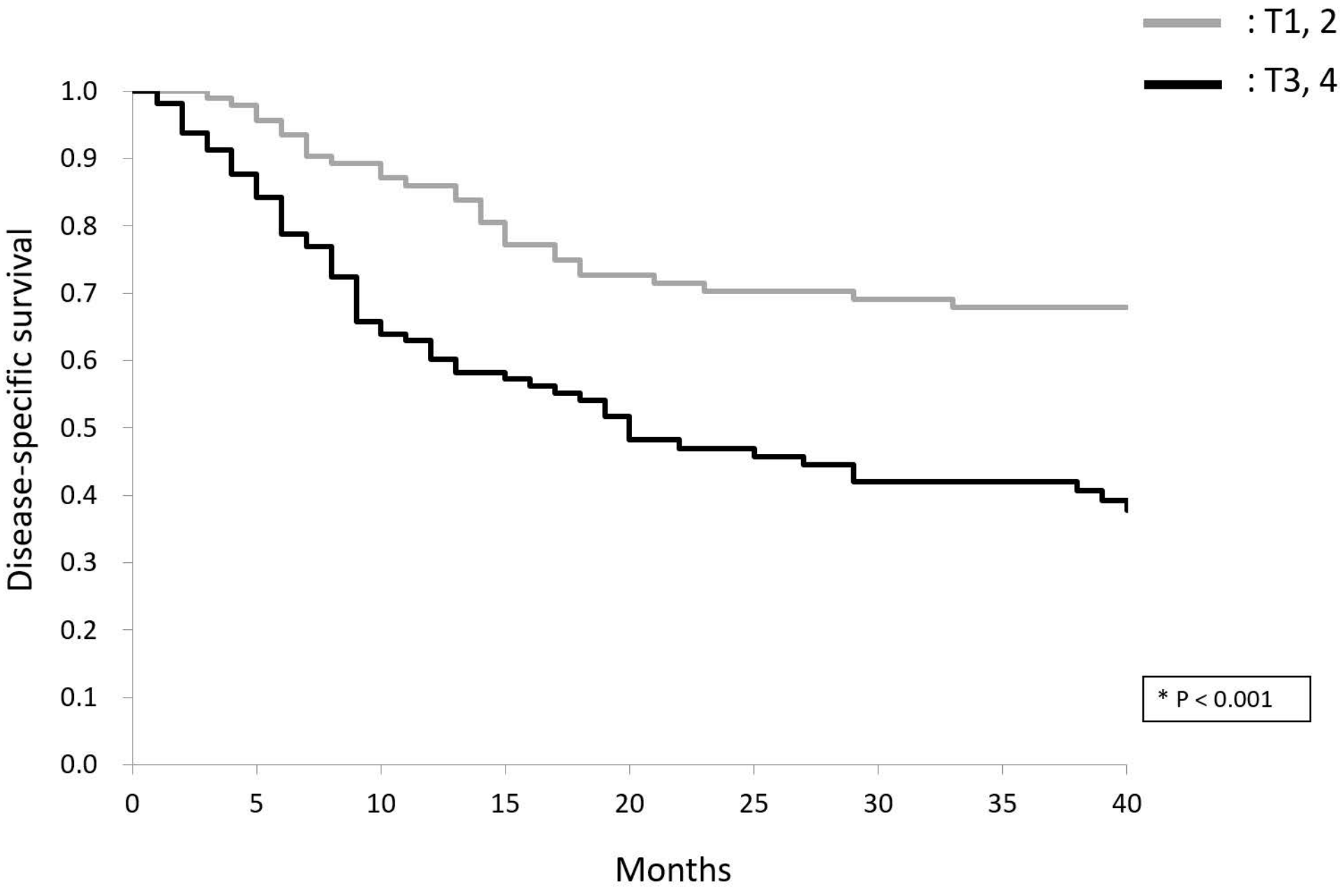
Variable	P value	Hazards ratio	95 % CI	
			Lower	Upper
The timing of recurrence (≤ 6 months)	< 0.001	3.29	1.82	5.96
Extra nodal extension	0.001	2.64	1.52	4.56

CI: Confidence interval


: 25-36 months
: 13-24 months
: 9-12 months
: 5-8 months
: 1-4 months
Disease-specific survival rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
15
20
25
30
35
40
Months
* P < 0.001


: Surgery ± radiotherapy and/or chemotherapy
: Curative radiotherapy or chemoradiotherapy
: Chemotherapy alone
: Palliative therapy or Supportive therapy
Disease-specific survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
15
20
25
30
35
40
Months
* P < 0.001


: ENE -
: ENE +
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Disease-specific survival
0
5
10
15
20
25
30
35
40
Months
* P < 0.001


: T1, 2
: T3, 4
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Disease-specific survival
0
5
10
15
20
25
30
35
40
Months
* P < 0.001