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Association between treatment package time and clinical predictors in oropharyngeal cancer

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Abstract

The aim of the present study is to investigate the association of treatment package time with the survival outcomes and clinical parameters in patients with oropharyngeal squamous cell carcinoma.

A total of 49 patients who underwent definitive treatment were enrolled. The treatment package time was calculated in days from the start of any treatment to the completion of all treatments, including postoperative treatment and salvage surgery for residual tumor.

On univariate analyzes, treatment package time ≥118 days, sake index ≥60, Brinkman index ≥450, maximum standardized uptake value ≥42.45, and the presence of synchronous cancer were significantly associated with shorter oropharyngeal squamous cell carcinoma-specific survival. Moreover, a treatment package time of ≥118 days was significantly correlated with shorter overall survival and distant metastasis-free survival. On multivariate analyzes, Brinkman index ≥450 was significantly associated with shorter oropharyngeal squamous cell carcinoma-specific and locoregional recurrence-free survival, and the presence of synchronous cancer was significantly associated with shorter overall and distant metastasis-free survival.

In conclusion, a relatively long treatment package time was a predictor of low survival outcomes in oropharyngeal squamous cell carcinoma by univariate analysis.

Abbreviations: 18F-FDG = 18F-fluorodeoxyglucose, CRT = chemoradiotherapy, DMFS = distant metastasis-free survival, LRRFS = locoregional recurrence-free survival, MTV = metabolic tumor volume, OPSCC = oropharyngeal squamous cell carcinoma, OS = overall survival, PET/CT = positron emission tomography with computed tomography, RT = radiotherapy, SD = standard deviation, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis, TPT = treatment package time, VOI = volumetric region of interest.

Keywords: 18F-fluorodeoxyglucose-uptake, overall survival, positron emission tomography with computed tomography, peak of standardized uptake value, tumor-node-metastasis

1. Introduction

The definitive treatment for oropharyngeal squamous cell carcinoma (OPSCC) includes surgery ± postoperative radiotherapy (RT) with/without chemotherapy or RT with/without chemotherapy such as chemoselection ± salvage surgery for residual tumor.[1,2] Various clinical parameters had been investigated as predictors of the survival outcomes of OPSCC.[1–5] We previously reported several outcome predictors, such as 18F-fluorodeoxyglucose (18F-FDG) uptake, smoking status, and synchronous cancer of head and neck cancer, including OPSCC.[2–4,6,7] Alcohol consumption and smoking were evaluated as life factors.[12] Sake and Brinkman indices were used as methods to evaluate alcohol consumption and smoking, respectively.[11] Standardized uptake value was used as a semiquantitative value on 18F-FDG-uptake for imaging factor.[2]

Prolonged treatment package time (TPT), which is defined as the duration from the start of any treatment to the completion of all treatments,[6,8] has been shown to predict worse survival outcomes in head and neck cancer.[6,8–10] We also reported a significant association between TPT and the survival outcomes of laryngeal cancer in patients who consecutively underwent various treatments, including salvage surgery for residual tumor.[6] However, the association between TPT and clinical predictors such as 18F-FDG uptake in OPSCC is not fully investigated. Therefore, we aimed to investigate the association of TPT with survival outcomes and clinical parameters, including 18F-FDG uptake, in patients with OPSCC.

2. Materials and methods

2.1. Patient selection

From January 2008 to August 2013, 90 patients who were newly diagnosed with oropharyngeal or hypopharyngeal squamous cell carcinoma, had a serum glucose level under 200 mg/mL but were

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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not using insulin, and underwent upper gastrointestinal tract Lugol chromoendoscopy at Aichi Cancer Center Hospital and pretreatment 18F-FDG positron emission tomography with computed tomography (PET/CT) at Nagoya Radiological Diagnosis Foundation were eligible for this study. Of these 90 patients, 49 patients with OPSCC who underwent definitive treatment were enrolled in this retrospective study. All patients provided informed consent for the examinations and treatments. This retrospective study was approved by the institutional review board of Aichi Cancer Center, and conducted according to the Declaration of Helsinki.

2.2. Clinical characteristics

The subsites of the primary tumor were the lateral (N=33), anterior, (n=11), posterior (n=3), and superior (n=2). The clinical tumor-node-metastasis staging for OPSCC was based on the seventh edition of the Union for International Cancer Control were determined by 18F-FDG-PET/CT, enhanced computed tomography or magnetic resonance imaging, routine physical examination, pharyngoscope. Synchronous cancer was defined as the presence of a pathological diagnosis within 6 months after the diagnosis of the index tumor of OPSCC. Ten patients were diagnosed as the presence of synchronous cancer. The sites of the synchronous cancer were esophagus (N=4), stomach (N=2), colon (N=2), lung (N=1), thyroid (N=1). According to a previous report,[11] Brinkman index was calculated by the number of cigarettes consumed per day multiplied by years of smoking. Sake index was computed by the weight (g)/22 of ethanol consumed per day multiplied by years of drinking.

2.3. 18F-FDG-PET/CT

The median duration ± standard deviation (SD) blood sugar level at the time of staging was 104 ± 16.9 mg/dL, and that for the interval between 18F-FDG-PET/CT and the start of any treatment were 16 ± 10.6 days. 18F-FDG PET/CT scanning (Biograph True Point PET/CT/40 with True V: Siemens Health Medical Solutions Inc., Malvern, PA) and semiquantitative assessment of the 18F-FDG uptake parameters (Advantage Workstation 4.6 software program PET VCAR: GE Healthcare, Chalfont, UK) for the volumetric region of interest (VOI) were performed as previously described.[7] In short, a 45% threshold fraction of the maximum standardized uptake value (SUVmax), which was mechanically calculated, from the VOI on 3-dimensional images, was adopted for the metabolic tumor volume (MTV) and the total lesion glycolysis (TLG). The mean standardized uptake value within a 1-cm^3 sphere VOI, which included the maximum pixel, was defined as the peak of standardized uptake value.[7]

2.4. Treatment

According to the initial treatment administered for the primary tumor, the 49 patients were grouped into

(1) induction chemotherapy followed by RT or chemoradiotherapy (CRT) ± salvage surgery for the residual tumor in responders or salvage surgery ± postoperative RT or postoperative CRT in non-responders (chemoselection, n=37),
(2) concurrent CRT ± salvage surgery for the residual tumor (CRT, n=10), 3) operation + postoperative CRT (Ope, n=1), 4) RT alone (RT, n=1).

The selection of initial treatment and the regimens of induction chemotherapy, RT or CRT, and salvage surgery for the residual tumor have been reported elsewhere.[6] In short, patients who refused to undergo operation selected CRT or RT, and those who hoped for maximal organ preservation without reducing treatment efficacy selected chemoselection. In the chemotherapy regimen, 5-fluorouracil and cisplatin for induction chemotherapy or a platinum for CRT were mainly used. Salvage surgery for the residual tumor was performed approximately 1 to 3 months following CRT or RT. As much as possible, salvage surgery was performed for locoregional tumor recurrence.

2.5. Time factor

TPT was calculated in days, from the start to the completion of all treatments, including salvage surgery for residual tumor and postoperative RT.[6] The time to treatment initiation was calculated in days, from the time of pathological diagnosis of OPSCC to the start of any treatment.

2.6. Statistical analysis

All statistical analyzes were performed using the JMP software package (version 9; SAS: Cary, NC). We assessed sake index, MTV, TLG based on the Shapiro–Wilk normality test, in accordance with previous PET parameter study.[13] The Kaplan–Meier method was used for the computation of the survival time, which was defined as the number of days from the start of any treatment to the date of an aim event or the last contact. The aim events were death for overall survival (OS), death from OPSCC for OPSCC-specific survival, local or regional recurrence for locoregional recurrence-free survival (LRRFS), and distant metastasis for distant metastasis-free survival (DMFS). On the basis of a previously reported method,[2,7] various cutoff values for continuous variables (age, Brinkman index, sake index, SUVmax, peak of standardized uptake value, MTV, TLG, time to initiation, and TPT) and for ordinal variables (clinical T and N classification, and clinical stage) were tested in the OPSCC-specific survival analysis by log-rank test. The patients were categorized into 2 groups based on the TPT (<118 vs ≥ 118 days), and differences between the 2 groups were compared by log-rank test, Fisher exact test, and Mann–Whitney U-test. Using Cox proportional hazards model, multivariate survival analyses for OPSCC-specific survival, OS, LRRFS, and DMFS were performed, with adjustments for TPT ($<118/\geq 118$ days), synchronous cancer (absent/present), sake index ($<60/\geq 60$), Brinkman index ($<450/\geq 450$), and SUVmax ($<42.45/\geq 42.45$). A *P*-value less than .05 was considered statistically significant.

3. Results

3.1. Clinical parameters

The clinical parameters in this study are shown in Table 1. Sake index, MTV, and TLG failed the Shapiro–Wilk normality test. The mean ± SD time to initiation and TPT were 23.8 ± 13.1 days and 97.9 ± 39.3 days, respectively. At the end of the study, the median ± SD duration of follow-up was 5.25 ± 2.47 years among all patients, 5.73 ± 1.80 years for the 28 patients who remained

Table 1

Clinical parameters in 49 patients with oropharyngeal squamous cell carcinoma.

Parameter		Number
Age (yr)	Median ± SD	62 ± 11.0
Gender	Male/female	41/8
Clinical T classification (UICC7th)	T1/T2/T3/T4a/T4b	3/24/10/8/4
Clinical N classification (UICC7th)	N0/N1/N2a/N2b/N2c/N3	5/5/9/16/10/4
Clinical stage (UICC7th)	I/II/III/IVA/IVB	1/1/5/38/4
Primary tumor subsite	Tonsils or tonsillar pillars/ Soft palate/Base of tongue/ Posterior pharyngeal wall	33/11/3/2
Synchronous cancer	Absence/presence	39/10
Alcohol consumption	Absence/presence	12/37
Sake index	Median ± SD	40 ± 47
Smoking	Never/Ever	11/38
Brinkman index	Median ± SD	540 ± 521
SUVmax (g/mL)	Median ± SD	42.5 ± 18.5
SUVpeak (g/mL)	Median ± SD	31.0 ± 13.8
MTV (cm^3)	Median ± SD	5.44 ± 13.7
TLG (g)	Median ± SD	162 ± 472
Initial treatment	Chemoselection/CRT/Ope/RT	37/10/1/1
Adjuvant treatment	Absence/presence	33/16
Surgery at initial treatment	Absence/presence	33/16
Radiotherapy at initial treatment	Absence/presence	2/47
Chemotherapy at initial treatment	Absence/presence	1/48
Time to initiation (d)	Median ± SD	22 ± 13.1
Treatment package time (d)	Median ± SD	101 ± 39.3
Follow up days (d)	Median ± SD	1916 ± 900
Recurrence or metastasis	Local/regional/distant	9/7/10
Survival	Alive/ OPSCC death/others death	28/15/6

CRT = chemoradiotherapy, MTV = metabolic tumor volume, RT = radiotherapy, SD = standard deviation, SUVmax = maximum of standardized uptake value, SUVpeak = peak of standardized uptake value, TLG = total lesion glycolysis, UICC7th = the 7th edition of Union for International Cancer Control.

alive, 2.31 ± 2.08 years for the 21 patients who died, and 1.84 ± 1.77 years for the 15 patients who died because of OPSCC. Of all patients, 9 patients (18.4%), 7 patients (14.3%), and 10 patients (20.4%) were diagnosed to have local recurrence, regional recurrence, and distant metastasis, respectively. The 5-year rates for OS, OPSCC-specific survival, LRRFS, and DMFS were 66.9%, 72.7%, 71.3%, and 80.3%, respectively.

3.2. Univariate survival analysis

The results of the univariate OPSCC-specific survival analysis are shown in Table 2. For the analysis of the factors affecting OPSCC-specific survival, continuous variables were categorized based on the cutoff values that had the lowest *P*-values, and these included a sake index of 60 ($P = .01$), Brinkman index of 450 ($P < .01$), SUVmax of 42.45 ($P = .03$), and TPT of 118 ($P < .01$). The results showed that a shorter OPSCC-specific survival was significantly associated with sake index ≥60 ($P = .01$), Brinkman index ≥450 ($P < .01$), SUVmax ≥42.45 ($P = .03$), TPT ≥118 ($P < .01$), and the presence of synchronous cancer ($P < .01$).

3.3. Relationships with TPT

The relationships between the clinical parameters and TPT (<118/≥118) are shown in Table 3. Compared with patients who had TPT <118 (n = 40), those who had TPT ≥118 (n = 9) had significantly higher sake index ($P < .01$) and Brinkman index ($P = .01$) and received more frequent adjuvant treatment ($P < .01$) and surgery as the initial treatment ($P < .01$). On log-rank test, patients with TPT ≥118 had significantly shorter OS ($P = .01$) and DMFS ($P < .01$) compared with those in patients with TPT <118. However, there was no significant difference in the LRRFS ($P = .19$) between TPT ≥118 and TPT <118.

Table 2

Univariate analysis of oropharyngeal squamous cell carcinoma-specific survival.

Parameter		*P*-value
Age (yr)	<47/≥47	.18
Gender	Male/female	.64
Clinical T classification (UICC7th)	T1-T4a/T4b	.21
Clinical N classification (UICC7th)	N0-N2a/N2b-N3	.17
Clinical stage (UICC7th)	I-IVA/IVB	.33
Primary tumor subsite	Tonsils or tonsillar pillars/others	.85
Synchronous cancer	Absence/presence	**<.01**
Sake index	<60/≥60	**.01**
Brinkman index	<450/≥450	**<.01**
SUVmax (g/mL)	<42.45/≥42.45	**.03**
SUVpeak (g/mL)	<27.21/≥27.21	.20
MTV (cm^3)	<3.15/≥3.15	.08
TLG (g)	<399/≥399	.15
Initial treatment	Chemoselection/others	.72
Adjuvant treatment	Absence/presence	.44
Surgery at initial treatment	Absence/presence	.39
Radiotherapy at initial treatment	Absence/presence	.38
Chemotherapy at initial treatment	Absence/presence	.61
Time to initiation (d)	<17/≥17	.12
Treatment package time (d)	<118/≥118	**<.01**

MTV = metabolic tumor volume, SUVmax = maximum of standardized uptake value, SUVpeak = peak of standardized uptake value, TLG = total lesion glycolysis, UICC7th = the 7th edition of Union for International Cancer Control.

3.4. Multivariate survival analysis

The results of the multivariate survival analyzes are shown in Table 4. Compared with patients with Patients with Brinkman index <450, those with Brinkman index ≥450 had significantly shorter OPSCC-specific survival ($P = .03$) and LRRFS ($P = .02$). Compared with patients without synchronous cancer, those with synchronous cancer had significantly shorter OS ($P < .01$) and DMFS ($P = .02$). The cutoff values of different TPT were tested using log-rank test in the univariate OPSCC-specific survival analysis, and TPT of 118 days had the lowest *P*-value of those analyses (Fig. 1A). Patients with TPT of ≥118 days were significantly associated with shorter OPSCC-specific survival (Fig. 1B), OS (Fig. 1C), and DMFS (Fig. 1D) than those with TPT of <118 days by log-rank test. In the log-rank test, patients with Brinkman index of ≥450 were significantly associated with shorter OPSCC-specific survival than those with Brinkman index of <450 (Fig. 1E), whereas patients with the presence of synchronous cancer had shorter OS than those without synchronous cancer (Fig. 1F).

4. Discussion

In the present study on patients with OPSCC, a TPT of ≥118 days was significantly associated with shorter OPSCC-specific survival, OS, and DMFS. A relatively long TPT for several was significantly associated with shorter OPSCC-specific survival, OS, and DMFS by univariate survival analysis.

Table 3

Relationships between clinical parameters and treatment package time (<118/≥118).

Parameter		Treatment package time		
		<118 days (n = 40)	≥118 days (n = 9)	*P*-value
Age	Median ± SD	62.5 ± 11.6	62 ± 8.25	.89*
Gender	Male/female	33/7	8/1	1.00†
Clinical T classification (UICC7th)	T1-T4a/T4b	37/3	8/1	.57†
Clinical N classification (UICC7th)	N0-N2a/N2b-N3	35/5	8/1	1.00†
Clinical stage (UICC7th)	I-IVA/IVB	37/3	8/1	.57†
Primary tumor subsite	Lateral/Others	26/14	7/2	.70†
Synchronous cancer	Absence/Presence	33/7	6/3	.37†
Sake index	Median ± SD	37 ± 37.3	100 ± 58.8	**<.01***
Brinkman index	Median ± SD	490 ± 459	1080 ± 579	**.01***
SUVmax	Median ± SD	42.0 ± 18.2	53.8 ± 18.4	.15*
SUVpeak	Median ± SD	30.5 ± 13.6	37.0 ± 13.4	.15*
MTV	Median ± SD	5.18 ± 14.3	6.54 ± 10.8	.27*
TLG	Median ± SD	137 ± 466	252 ± 519	.13*
Initial treatment	Chemoselection/others	29/11	8/1	.42†
Adjuvant treatment	Absence/presence	33/7	0/9	**<.01†**
Surgery at initial treatment	Absence/presence	32/8	1/8	**<.01†**
Radiotherapy at initial treatment	Absence/presence	2/38	0/9	1.00†
Chemotherapy at initial treatment	Absence/presence	1/39	0/9	1.00†
Time to initiation	Median ± SD	23 ± 13.7	19 ± 9.12	.27*

MTV = metabolic tumor volume, SD = standard deviation, SUVmax = maximum of standardized uptake value, SUVpeak = peak of standardized uptake value, TLG = total lesion glycolysis, UICC7th = the 7th edition of Union for International Cancer Control.

* Mann–Whitney *U* test.

† Fisher exact test.

A relatively long TPT for several treatment modalities such as CRT and surgery with postoperative CRT has been reported to be a predictor of prognosis in head and neck cancer, including OPSCC.[6,8–10] In addition, in 100 patients with laryngeal squamous cell carcinoma that who treated by several treatment modalities including surgical alone, CRT, and chemoselection, we previously reported that a relatively long TPT was significantly associated with shorter cancer-specific survival and DMFS.[6] In the present study, the findings of a significant association between longer TPT and shorter survival outcomes (ie, OPSCC-specific survival, OS, and DMFS) were in agreement with the findings of the previous studies.[6,8–10]

TPT is a posttreatment predictor in head and neck cancer, including OPSCC,[6,8–10] while some parameters have been shown as pretreatment predictors for OPSCC.[1,2,4–6] In our prior reports on pharyngeal cancer, including OPSCC, we also showed

Table 4

Multivariate survival analyses.

Parameter	OPSCC-specific	OS	LRRFS	DMFS
TPT (<118/≥118)				
Hazards ratio	0.62	0.50	0.84	0.39
95% CI	0.16–2.35	0.15–1.69	0.23–3.50	0.08–1.75
P-value	.48	.26	.79	.22
Synchronous cancer (absence/presence)				
Hazards ratio	0.32	0.16	0.83	0.18
95% CI	0.09–1.09	0.05–0.49	0.24–3.32	0.03–0.76
P-value	.07	**<.01**	.78	**.02**
Sake index (<60/≥60)				
Hazards ratio	0.54	0.86	0.77	0.52
95% CI	0.14–2.08	0.28–2.73	0.23–2.87	0.09–2.86
P-value	.37	.79	.69	.45
Brinkman index (<450/≥450)				
Hazards ratio	0.17	0.41	0.20	0.47
95% CI	0.01–0.89	0.09–1.33	0.03–0.79	0.02–3.63
P-value	**.03**	.14	**.02**	.500
SUVmax (<42.45/≥42.45)				
Hazards ratio	0.42	0.60	1.00	0.77
95% CI	0.11–1.28	0.22–1.50	0.35–2.84	0.19–2.75
P-value	.13	.28	.99	.68

95% CI = 95% confidence interval, DMFS = distant metastasis-free survival, LRRFS = locoregional recurrence-free survival, OPSCC = oropharyngeal squamous cell carcinoma, OS = overall survival, SUVmax = maximum of standardized uptake value, TPT = treatment package time.

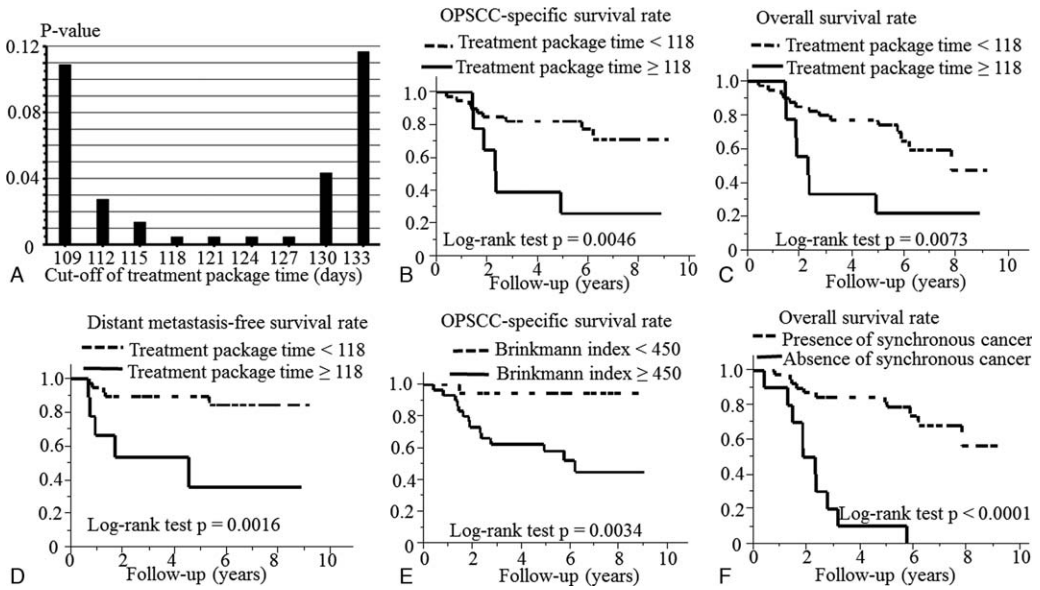

Figure 1. Survival analyzes by log-rank test. (A) The *P*-values for the OPSCC-specific survival analysis using different cutoff levels for treatment package time in 49 patients with OPSCC are shown. Compared with treatment package time <118 days, treatment package time ≥118 days is associated with significantly lower (B) OPSCC-specific survival ($P = .0046$), (C) overall survival ($P = .0073$), and (D) distant metastasis-free survival ($P = .0016$). (E) OPSCC-specific survival is significantly lower with a Brinkman index ≥450 than with a Brinkman index <450 ($P = .0034$). (F) The overall survival is significantly lower with the presence of synchronous cancer than with the absence of synchronous cancer ($P < .0001$). OPSCC = oropharyngeal squamous cell carcinoma.

several pretreatment predictors, such as FDG uptake and social habits (smoking and alcohol consumption).[2,4,5] However, to our best knowledge, the association between TPT and these pretreatment predictors has not been fully examined in OPSCC. Therefore, we thought that there was a need for such an analysis.

In a meta-analysis on RT for head and neck cancer, Lassen P et al reported that smokers may have a prolonged overall treatment time.[5] Likewise, the present study showed a significant association between prolonged TPT and a high Brinkman index. Moreover, our previous studies showed that both alcohol consumption and smoking were significantly associated with shorter disease-free survival in head and neck cancer.[3,4] Similarly, the present study indicated a significant association between worse survival outcomes and the social habit of smoking and alcohol consumption.

In this present study and in our previous study on laryngeal cancer, TPT of ≥118 and ≥68 days, respectively, were significantly associated with shorter DMFS.[6] Therefore, TPT was suggested as a predictor for identifying patients who have a high risk of developing distant metastasis. We considered that the significant association between shorter OPSCC-specific survival and longer TPT was caused by a shorter DMFS. Therefore, we suggested that TPT be made as short as possible in order to improve survival outcomes.

Because a group of patients with TPT of <130 or 133 increased some patients with shorter outcome in comparison with a group of patients with TPT of <118 in the present study, the *P*-value of 2 groups based on cutoff of TPT of 130 or 133 increased in comparison with TPT of 118. When we use cutoff TPT of 130 or 133, our analyses not using lowest *P*-value might change to unclear results.

On the log-rank test in the present study, patients with TPT of ≥118 had significantly shorter OS and DMFS compared with in patients with TPT of <118. However, there was no significant difference in the LRRFS between TPT of ≥118 and TPT of <118. Therefore, we considered that the significant association between shorter OS and TPT of ≥118 was owing to a shorter DMFS.

This study had several limitations, including the retrospective design, small sample size, and unknown p16 immunohistochemistry, which was defined by the eighth Union for International Cancer Control in 2017.[12] Because TPT of ≥118 days in the present study showed significantly higher sake index and Brinkman index, these higher indices in patients with TPT of >118 days may introduce bias in the results. Therefore, a prospective analysis that includes p16 immunohistochemistry would yield more useful results.

In conclusion, among patients with OPSCC treated by several modalities, including CRT and chemoselection, a relatively long TPT was significantly associated with shorter OPSCC-specific survival, OS, and DMFS.

Author contributions

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Design of the work, analysis, drafting: Hidenori Suzuki.

Final approval of the work and review: Hidenori Suzuki, Hidenori Tsuzuki, Tsuneo Tamaki, Masami Nishio, Daisuke Nishikawa, Shintaro Beppu, Nobuhiro Hanai.

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