

Treatment package time predicts cancer-specific survival and distant metastasis in laryngeal cancer

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Received July 12, 2018; Accepted October 26, 2018

DOI: 10.3892/ol.2018.9664

Abstract. We investigated whether treatment package time was significantly associated with survival outcomes of resectable locally-advanced laryngeal squamous cell carcinoma in patients who consecutively underwent various treatments, including surgery alone and salvage surgery for residual tumor. A total of 100 patients with clinical T3-T4 resectable laryngeal squamous cell carcinoma were enrolled in this study. The treatment package time was calculated in days between the start of any treatment and the end of all treatments, including postoperative radiotherapy and salvage surgery for residual tumors. Using a log-rank test, a treatment package time of ≥ 68 days showed significantly shorter cancer-specific ($P=0.0013$) and distant metastasis-free survival ($P=0.0017$), compared with a treatment package time of <68 days. Multivariate survival analyses of two Cox's hazards proportional models was conducted. In both model-1, which adjusted for cT3/cT4, cN0-1/cN2-3 and total laryngectomy/non-total laryngectomy, and model-2, which adjusted for cT3/cT4, cN0-1/cN2-3 and induction therapy/non-induction therapy, the cancer-specific survival and distant metastasis-free survival, according to treatment package time, were significantly longer with <68 days compared with ≥ 68 days ($P<0.01$). The present study demonstrated that a prolonged treatment package time is a prognostic factor for shorter cancer-specific and distant

metastasis-free survival after various treatments for resectable locally-advanced laryngeal cancer.

Introduction

Total laryngectomy (TL) \pm radiotherapy (RT) had been the classical treatment for resectable locally-advanced laryngeal squamous cell carcinoma (LALSCC), which is classified as clinical T3-T4a disease (1). Various organ-preserving treatment modalities, including partial laryngectomy (PL), concurrent chemoradiotherapy (CRT), chemoselection from induction chemotherapy have been performed for resectable LALSCC (1-5). We have also showed the efficacy of alternating chemoradiotherapy (ACRT) with early assessment following induction of CRT and salvage surgery for residual tumors in resectable LALSCC (6). Although the tumor-node metastasis (TNM) classification of resectable LALSCC is globally used as the prognostic factor of survival outcomes, such as cancer-specific survival (CSS), after various treatments, the same TNM classification is unable to predict survival outcomes (2-4). Recently, the prognostic factors for resectable LALSCC have been investigated by various approaches (2-4,7-10).

Treatment package time (TPT), which is similar to overall treatment time, is calculated from the start of any treatment to the end of all treatments and had been shown as a prognostic factor in several cancers (3,4,7-10). Prolonged TPT of several modalities, including RT alone and surgery with postoperative RT, has been reported to be a predictor of worse CSS for head and neck cancer (3).

To the best of our knowledge, the association between survival outcomes and TPT in patients with resectable LALSCC, who consecutively underwent various treatments, including surgery alone and salvage surgery for residual tumor, has not been previously investigated. In the present study, we investigated whether TPT was significantly associated with survival outcomes of resectable LALSCC in patients who consecutively underwent various treatments, including surgery alone and salvage surgery for residual tumor.

Materials and methods

Patients. Between 2004 June and 2016 October, 101 patients who were newly diagnosed as clinical T3-T4a laryngeal

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Abbreviations: ACRT, alternating chemoradiotherapy; CRT, concurrent chemoradiotherapy; CSS, cancer-specific survival; DMFS, distant metastasis-free survival; LALSCC, locally-advanced laryngeal squamous cell carcinoma; LRRFS, locoregional recurrence-free survival; OS, overall survival; PL, partial laryngectomy; RT, radiotherapy; TL, total laryngectomy; TNM, tumor-node metastasis; TPT, treatment package time

Key words: LALSCC, TPT, CSS, DMFS, prognostic factor

squamous cell carcinoma consecutively underwent definitive treatment at the Aichi Cancer Center Hospital. After excluding one patient who diagnosed as cN3 with unresectable disease, a total of 100 patients with resectable LALSCC were enrolled in this study. This study was approved by the review board of Aichi Cancer Center Hospital, and informed consent for the examinations and treatments was obtained from all of the patients. The subsites of the primary tumor were the supraglottis (n=64), glottis (n=32), and subglottis (n=4). Clinical staging based on the TNM classification of the seventh edition of the International Union Against was determined from routine physical examination, flexible laryngeal endoscope, enhanced cervical computed tomography, and 18F-FDG-PET/CT, if possible. The Charlson comorbidity index, which was a weighted index, was calculated from 19 comorbid conditions.

Initial treatment. The 100 patients were classified based on initial treatment of the primary tumor: TL ± RT with or without chemotherapy (TL, n=27); PL (PL, n=5); concurrent CRT ± salvage surgery for residual tumor (CRT, n=11); induction CRT followed by CRT ± salvage surgery for residual tumor to responders or TL ± RT with or without chemotherapy to non-responders (ACRT, n=27); induction chemotherapy following concurrent RT with or without chemotherapy ± salvage surgery for residual tumor to responders or TL ± RT with or without chemotherapy to non-responders (chemoselection, n=27); and RT alone ± salvage surgery for residual tumor (RT alone, n=3). We recommended postoperative RT with or without chemotherapy to patients with multiple lymph node metastasis, extranodal extension, and positive resection margin. Salvage surgery was performed for residual tumor found on pathological and imaging examination at 1-2 months after the completion of RT with or without chemotherapy, as described previously (11). After completion of the initial treatments, including salvage surgery for residual tumor, we made an effort to perform salvage surgery based on the presence of tumor recurrence.

Selection of initial treatment. The recommended treatment of choice was TL, but for patients who wished not to undergo surgery, we initially selected concurrent CRT or RT alone in those with advanced age or who refused chemotherapy. For patients who required maximal organ preservation without a reduction in treatment efficacy, ACRT was selected from January 2004 to January 2011 if consistent with the protocol; after February 2011, most patients underwent chemoselection. Patients who wished organ preservation and refused RT underwent PL. The details of the *en bloc* dissection, RT procedures, chemotherapy regimens, and the selection of primary treatment have been reported elsewhere (6,11-14). In brief, definitive RT was given at a total dose of 66-70 Gy with 2 Gy per fraction; induction chemotherapy was given mostly by intravenous infusion of 5-fluorouracil and cisplatin, the regimens of concurrent CRT were triweekly or weekly cisplatin, and weekly cetuximab.

Time to treatment initiation and TPT. According to previous reports (9,14), the time to treatment initiation was calculated in days from the time of pathological diagnosis of LALSCC to

the start of any treatment; TPT was likewise calculated in days from the start of any treatment to the end of all treatments, including postoperative RT and salvage surgery for residual tumor.

Statistical analysis. Statistical analyses were carried out using the JMP software package (version 9; SAS Institute, Inc., Cary, NC, USA). The best cut-off values for time to treatment initiation or TPT for death due to LALSCC were assessed by receiver-operating characteristic curve (ROC) analysis, as described previously (12). ROC analysis in the present study was performed by using TPT or the time to treatment initiation, as continuous variables. Survival time, which was calculated as the number of days from the start of any treatment to a target event or last contact, was analyzed by the Kaplan-Meier method. The target events were death for overall survival (OS), death due to LALSCC for CSS, local or regional recurrence for locoregional recurrence-free survival (LRRFS), and distant metastasis for distant metastasis-free survival (DMFS). The patients were categorized into two groups based on their TPT (<68 days vs. ≥68 days); differences between the two groups were compared by univariate survival analysis using a log-rank test. Another grouping, using two models, was based on the initial treatment of the primary tumor; model 1 was TL (n=27) and the non-TL (n=73) groups, whereas model 2 compared the induction group, which included ACRT and chemoselection (n=54), and the non-induction group (n=46). The associations between the two groups (TPT <68 days or TPT ≥68 days) with regard to the clinical characteristics (cT and cN classification, cStage, subsite, vocal cord fixation, charlson comorbidity index, gender, age, adjuvant treatment, initial treatment, treatment group) were compared by using chi-squared test or Fisher's exact test. Multivariate analyses for the factors associated with CSS and DMFS used two Cox's proportional hazards models. Model-1 was adjusted with the cT (cT3/cT4), cN (cN0-1/cN2-3), TPT (<68 days/≥68 days), and treatment group (TL/non-TL). Model-2 was adjusted with the cT (cT3/cT4), cN (cN0-1/cN2-3), TPT (<68 days/≥68 days), and treatment group (induction/non-induction). P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical characteristics. The clinical characteristics of the population are shown in Table I. At the end of the study, the mean ± SD follow-up period was 1317±930 days among all patients, 1,478±961 days for the 68 patients who remained alive, 976±768 days for the 32 patients who died, and 1,000±716 days for the 20 patients who died due to LALSCC. The mean ± SD of the time to treatment initiation and TPT were 26.0±13.1 days and 58.3±51.4 days, respectively. The association between TPT and number of patients were shown in Fig. 1. Locoregional recurrence and distant metastasis were found in 25 and 17 patients, respectively. TL on initial treatment, including salvage surgery, was performed on 46 patients with residual tumor and on nine patients with recurrence tumor. The overall five-year rates for OS, CSS, LRRFS, and DMFS were 68.9, 78.0, 70.9, and 76.3%, respectively.

Table I. Characteristics of initial treatment in 100 patients with laryngeal squamous cell carcinoma.

Characteristics	Total	Initial treatment					
		TL	PL	Concurrent RT	ACRT	Chemo-selection	RT alone
cT, cT3/cT4	100	27	5	11	27	27	3
cN	72/28	19/8	4/1	11/0	20/7	16/11	2/1
cN0/cN1	59/13	17/4	5/0	8/0	14/5	12/4	3/0
cN2/cN3	26/2	5/1	0/0	3/0	8/0	10/1	0/0
cStage, cStageIII/cStageIV	57/43	17/10	4/1	8/3	15/12	11/16	2/1
Charlson comorbidity index, 0/≥1	37/63	10/17	1/4	1/10	15/12	8/19	1/2
Sex, male/female	94/6	24/3	5/0	11/0	25/2	26/1	3/0
Subsite, supraglottis/glottis/subglottis	64/32/4	18/8/1	1/4/0	8/3/0	16/10/1	19/6/2	2/1/0
Vocal cord fixation, presence/absence	44/56	18/9	0/5	3/8	16/11	19/8	1/2
Age	67.4±8.1	72.9±8.6	69.2±6.7	69.7±6.9	63.1±7.3	65.9±5.4	61.7±9.0
Treatment package time, days	58.3±51.4	8.8±24.0	1±0	65.3±32.6	77.9±41.2	92.6±46.4	87.3±61.2
Time to initiation	26.0±13.1	31.4±18.7	33.2±3.0	29.3±7.3	20.3±8.9	24.0±8.4	21.7±14.2
Adjuvant treatment, PORT(POCRT)/salvage surgery/no	6/10/84	3/0/24	0/0/5	0/3/8	0/3/24	3/3/23	0/1/2
Outcomes							
Follow-up, days	1317±930	1012±727	524±262	846±680	2123±1031	1189±663	1016±882
Laryngectomy, initial/salvage for recurrence/no	46/9/45	27/0/0	0/0/5	0/2/9	5/5/17	12/2/13	2/0/1
Recurrence or metastasis, locoregional/distant/none	25/17/58	5/4/18	1/0/4	4/1/6	5/3/19	9/8/10	1/1/1
Survival, alive/cancer death/others death	68/20/12	16/5/6	5/0/0	6/2/3	20/4/3	20/7/0	1/2/0

Data for age, treatment package time and follow-up days are presented as the mean ± standard deviation. TL, total laryngectomy; PL, partial laryngectomy; RT, radiotherapy; ACRT, alternating chemoradiotherapy; Chemo, chemotherapy; PORT, postoperative radiotherapy; POCRT, postoperative chemoradiotherapy.

ROC analysis. From the ROC analyses, the best cut-off values for time to treatment initiation and TPT to detection of death from LALSCC were 15 days (AUC=0.50, P=0.81) and 68 days (AUC=0.73, P<0.01), respectively. The ROC, AUC of the ROC, sensitivity, and 1-specificity of TPT for death from LALSCC are shown in Fig. 2; the time to treatment initiation for death from LALSCC was additionally determined (data not shown).

Univariate survival analysis. Compared with patients with TPT <68 days, those with TPT ≥68 days had significantly shorter CSS (P=0.0013) and DMFS (P=0.0017). On the other hand, the two groups of TPT had no difference in the OS (P=0.08) and LRRFS (P=0.16). The Kaplan-Meier curves for CSS and DMFS are shown in Figs. 3 and 4, respectively.

TPT and clinical characteristics. The associations between the TPT and clinical characteristics are shown in Table II. Compared with patients with TPT <68 days, those with TPT ≥68 days had significantly higher number of patients of cN2-3 disease (P=0.02), who received adjuvant treatment (P<0.01), initial treatment (P<0.01), in the TL group (P<0.01) and the induction therapy group (P<0.01).

Multivariate survival analysis. The results of the multivariate analyses for CSS and DMFS are shown in Table III. In model 1, cN0-1 (P=0.02), TPT <68 days (P<0.01), and the non-TL group (P=0.02) were significantly associated with a longer CSS, and cN0-1 (P<0.01), TPT <68 days (P<0.01), and the non-TL group (P=0.03) were significantly associated with a longer DMFS. In mode 2, cN0-1 (P=0.01), TPT <68 days (P<0.01), and the induction therapy group (P<0.01) were significantly associated with longer CSS, and cN0-1 (P<0.01), TPT <68 days (P<0.01), and the induction therapy group (P=0.02) were significantly associated with longer DMFS.

Discussion

In the present study, we showed for the first time that a TPT of ≥68 days was significantly associated with shorter CSS and DMFS in patients with resectable LALSCC who consecutively underwent various treatments, including surgery alone and salvage surgery for residual tumor.

Various organ-preserving treatments modalities are being offered in clinical practice, and several trials have reported on

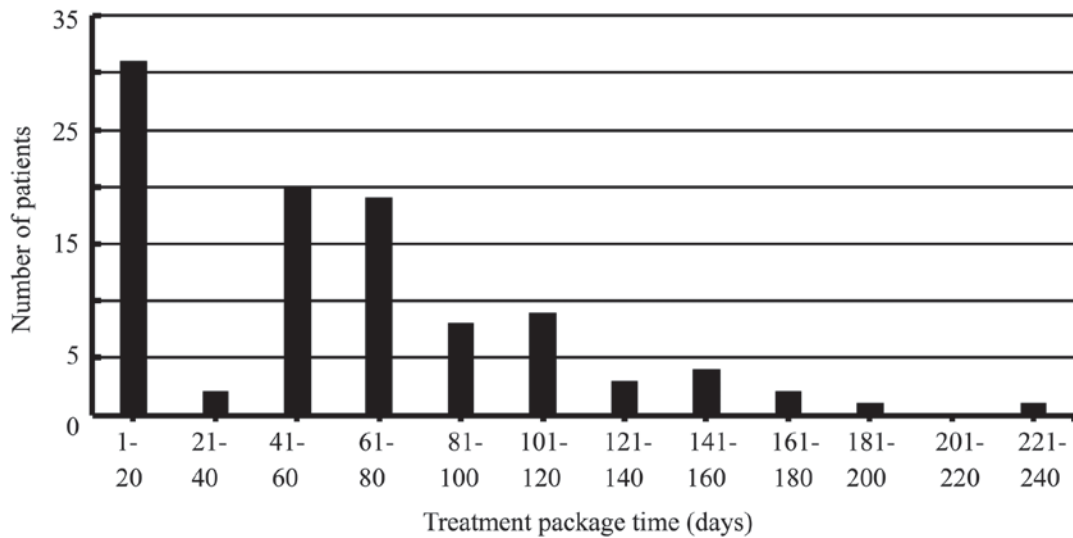


Figure 1. Association between the treatment package time and the number of patients with resectable locally-advanced laryngeal squamous cell carcinoma (n=100).

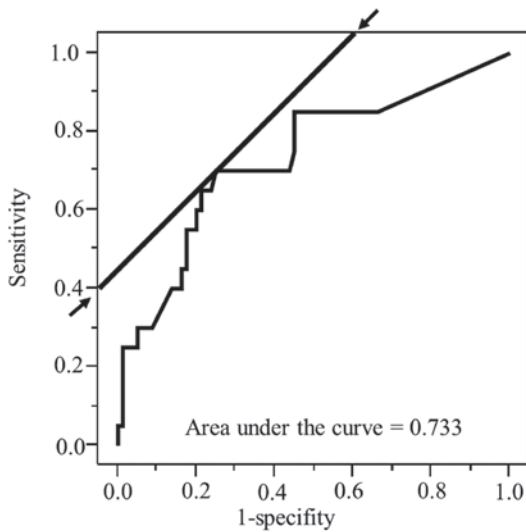


Figure 2. Receiver-operating characteristic curves on the best cut-off value of treatment package time for death from resectable locally-advanced laryngeal squamous cell carcinoma. The straight line between arrows within the plot was drawn at a 45 degree angle tangent to the Receiver-operating characteristic curves.

concurrent CRT vs. induction following CRT (1-5). We have also shown the efficacy of ACRT with early assessment for laryngeal squamous cell carcinoma and that of chemoselection for several cancer sites, including the hypopharynx and cervical esophagus (6,11-13).

The TPT as time factor of several treatment modalities, including RT alone, concurrent CRT, and surgery with post-operative CRT, has been shown to be a prognostic factor in several types of cancer, including laryngeal cancer (3,7-10). We also investigated the association between survival outcomes and the time factors of several treatments, including ACRT, in hypopharyngeal cancer (11). To the best of our knowledge, the association between survival outcomes and TPT of various treatments, including surgery alone, chemoselection, and ACRT with salvage surgery for residual tumor, has not

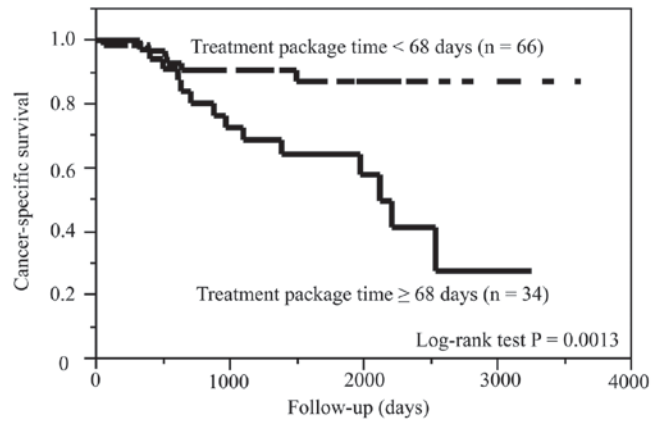


Figure 3. Association between the treatment package time and cancer-specific survival in 100 patients with resectable locally-advanced laryngeal squamous cell carcinoma. Log-rank test of Kaplan-Meier survival curves shows that the cancer-specific survival was significantly shorter for a treatment package time of ≥ 68 days than for a treatment package time of < 68 days.

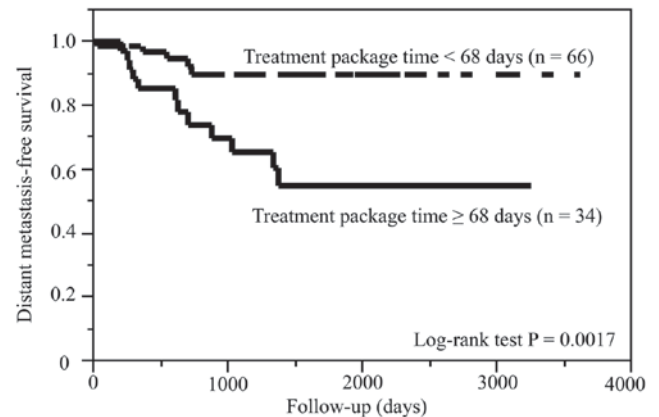


Figure 4. Association between treatment package time and distant metastasis-free survival in 100 patients with resectable locally-advanced laryngeal squamous cell carcinoma. Log-rank test of Kaplan-Meier survival curves shows that distant metastasis-free survival was significantly shorter for a treatment package time of ≥ 68 days than for a treatment package time of < 68 days.

Table II. Association between treatment package time (<68 days/≥68 days) and clinical characteristics in laryngeal squamous cell carcinoma.

Clinical characteristics	Total, n=100	Treatment package time		P-value
		<68 days, n=66	≥68 days, n=34	
cT, cT3/cT4	72/28	47/19	25/9	1.00
cN, cN0-1/cN2-3	72/28	53/13	19/15	0.02
cStage, cStageIII/cStageIV	57/43	41/25	16/18	0.20
Subsite, glottis/others	32/68	25/41	7/27	0.11
Vocal cord fixation, presence/absence	44/56	30/36	14/20	0.83
Charlson comorbidity index, 0/≥1	37/63	25/41	12/22	0.83
Gender, male/female	94/6	62/4	32/2	1.00
Age, <68/≥68	49/51	28/38	21/13	0.09
Adjuvant treatment, presence/absence	16/84	3/63	13/21	<0.01 ^a
Treatment group				
Total laryngectomy/non-total laryngectomy	27/73	26/40	1/33	<0.01 ^a
Induction therapy/non-induction therapy	54/46	24/42	30/4	<0.01 ^a

^aP<0.05.

Table III. Multivariate analysis for CSS and DMFS in laryngeal squamous cell carcinoma.

A, Model-1						
Clinical characteristics	CSS			DMFS		
	HR	95% CI	P-value	HR	95% CI	P-value
cT, cT3/cT4	0.89	0.34-2.47	0.81	0.96	0.35-2.74	0.93
cN, cN0-1/cN2-3	0.33	0.12-0.86	0.02 ^a	0.11	0.03-0.36	<0.01 ^a
Treatment package time, <68 days/≥68 days	0.14	0.03-0.45	<0.01 ^a	0.15	0.03-0.59	<0.01 ^a
Treatment group, TL/non-TL	5.50	1.31-23.0	0.02 ^a	5.94	1.16-32.2	0.03 ^a

B, Model-2						
Clinical characteristics	CSS			DMFS		
	HR	95% CI	P-value	HR	95% CI	P-value
cT, cT3/cT4	0.64	0.23-1.86	0.40	0.77	0.27-2.28	0.63
cN, cN0-1/cN2-3	0.30	0.11-0.79	0.01 ^a	0.11	0.03-0.36	<0.01 ^a
Treatment package time, <68 days/≥68 days	0.08	0.02-0.28	<0.01 ^a	0.16	0.04-0.56	<0.01 ^a
Treatment group, induction/non-induction	0.09	0.02-0.30	<0.01 ^a	0.19	0.05-0.72	0.02 ^a

^aP<0.05. CSS, cancer-specific survival; DMFS, distant metastasis-free survival; TL, total laryngectomy; HR, hazards ratio; 95% CI, 95% confidence interval.

been previously investigated in resectable LALSCC. Thus, we considered that there was a need for such an analysis.

Overall treatment time, which is calculated the same as the TPT, had been shown by several authors to be a significant prognostic factor in various types of cancer (3,4,7,8,10). For example, an overall treatment time of <80 days for

chemoselection was significantly correlated with longer CSS in patients with squamous cell carcinomas of pharynx and larynx (3). The findings of the present study revealed significant associations between prolonged TPT and shorter CSS and are in good agreement with the results of the previous study (3).

Although the present study for patients with consecutively various treatments investigated in comparison with previous study for head and neck cancer with adjuvant chemoradiotherapy following surgery, both present and previous studies showed similar findings of the significant association between better survival outcomes and shorter TPT (15).

Soyfer *et al* (8), reported that the duration of postoperative RT in days was significantly correlated with distant recurrence in gastric cancer. The findings of the present study revealed significant associations between prolonged TPT and shorter DMFS and are in good agreement with the results of the previous study (8).

Because distant metastasis is directly correlated with CSS in LALSCC (2), we hypothesized that TPT is correlated with DMFS. Indeed, in the present study, we showed that prolonged TPT was significantly associated with shorter DMFS. The findings from the present study suggested that the TPT in LALSCC is a prognostic factor for identifying groups that are at a high-risk of developing distant metastasis. Moreover, we thought that the significant association between a TPT of ≥ 68 days and a shorter CSS was caused by a shorter rate of DMFS.

In the present study, the TPT < 68 days with good prognosis shows that definitive treatment with shorter TPT is important. We considered that the cut off at 68 days is an important day, because this contained not only surgery but also surgery and RT or CRT. We considered that TPT $68 \geq$ days results in a shorter prognosis in the present study, because the patients with TPT $68 \geq$ days was significantly associated with more frequent cN2-3 and adjuvant treatment. From the significant association between TPT and survival outcomes in the present study, we suggest that it is essential to perform definitive treatment with shorter TPT as the true meaning in the head and neck treatment. In the present study, the cut-off date (68 days) was experimentally determined by ROC analysis using TPT as continuous variables.

The present study is examined whether the TPT predicts CSS and distant metastasis in laryngeal cancer. A limitation of this study is that the backgrounds of patients in the compared groups are very different. Patients with advanced cancer may have cancer specific-deaths and metastases at a higher rate than those with less advanced cancer. The limitations of this study were the retrospective design and the relatively small number of subjects. A future prospective study on a large cohort in a multi-institutional setting would yield more accurate results. In a future study regarding the effect of TPT, the background factors of patients in the study should be matched.

In conclusion, the present study demonstrated that a prolonged TPT was a prognostic factor of shorter CSS and DMFS in patients with resectable LALSCC who consecutively underwent various treatments modalities, including surgery alone and salvage surgery for residual tumor.

Acknowledgements

Not applicable.

Funding

The present study was by the JSPS KAKENHI (grant no. 16K11253).

Availability of data and materials

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

Authors' contributions

HS designed the study, acquired and analyzed the data, drafted the manuscript, and is accountable for all aspects of the study. HTe, NH, DN, YusK, SB, TK, HTac, YutK and HTan acquired the data and critically revised the manuscript. YH designed the study and acquired the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the review board of Aichi Cancer Center Hospital (Nagoya, Japan), and informed consent for the examinations and treatments was obtained from all of the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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