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Impact of smoking cessation on clinical outcomes in patients with head and neck squamous cell carcinoma receiving curative chemoradiotherapy: A prospective study

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Abstract

Background: We hypothesized that patients with head and neck squamous cell carcinoma (HNSCC) with smoking cessation during curative chemoradiotherapy (CRT) had fewer complications and lower tumor progression risks.

Methods: Sixty-three patients with nonmetastatic HNSCC who were smokers at diagnosis (carbon monoxide [CO] breath concentrations ≥3 ppm) and underwent curative CRT were prospectively enrolled. Successful smoking cessation throughout CRT was confirmed by CO breath concentrations <3 ppm at CRT completion.

Results: Forty-one patients (65%) successfully discontinued smoking throughout CRT. With a median 33-month follow-up, patients with successful smoking cessation during CRT had significantly fewer, greater, and lower probabilities of grade ≥3 acute toxicities ($P = .01$), progression-free survival ($P = .03$), and permanent gastrostomy or tracheostomy ($P = .04$), respectively, than those continuing smoking throughout CRT. In multivariate analysis, successful smoking cessation during CRT significantly reduced tumor progression risks (hazard ratio: 0.4, $P = .05$).

Conclusion: Smoking cessation during curative CRT reduced treatment-related toxicities and tumor progression risks in patients with HNSCC.

KEYWORDS
chemoradiotherapy, head and neck squamous cell carcinoma, smoking cessation, survival outcomes, toxicities

1 | INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is a highly aggressive solid tumor involving nasal and oral cavity, pharynx, larynx, and paranasal sinuses. Curative treatments include surgery or concurrent chemoradiotherapy (CRT).[1] Despite modern treatment approaches, the survival is poor and more than a third of patients with advanced disease experience relapse, and retreatment is challenging.[2] The toxicity and morbidity resulting from current therapies can severely impair the quality of life, and prognosis for these patients remains poor. Modern CRT, for curative intent and organ preservation, has been increasingly used in treating HNSCC.[3]

Smoking influences hemoglobin by the binding of carbon monoxide (CO) to hemoglobin, leading to the formation of carboxyhemoglobin.[4] Hemoglobin's affinity for CO is 200-280

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times higher than its affinity for oxygen, and low concentrations of CO can lead to a significant level of carboxyhemoglobin. The formation of carboxyhemoglobin causes a left shift to the hemoglobin-oxygen dissociation curve, resulting in low oxygen partial pressure and inadequate release of oxygen to the tissues, leading to an increase in the fraction of hypoxic cells.[5] The amount of carboxyhemoglobin is correlated with increasing smoking status.[6] Smoking during curative CRT causes increasing carboxyhemoglobin concentrations and reduced oxygen supply to radiotherapy sites.

Few studies have prospectively examined the effect of smoking cessation on the clinical outcomes of radiotherapy.[7] We hypothesized that patients with HNSCC who achieved smoking cessation during curative CRT would have fewer complications and lower risks of tumor progression.

2 | METHODS

2.1 | Patients

This prospective study was approved by the Institutional Review Board of our institute (201406075RINC) and was performed in accordance with the Declaration of Helsinki, including all relevant details. The study is prospectively registered with ClinicalTrials.gov (number NCT02251730). Patients with nonmetastatic HNSCC (age 20-70 years) who were smokers at the time of diagnosis (confirmed by CO breath test concentrations of ≥3 ppm[8]) undergoing curative CRT between August 2014 and May 2015 were prospectively enrolled. Written informed consent was obtained from all patients. Tobacco exposure (in pack-years) was registered at enrollment for each patient, and the number of pack-years = (packs smoked per day) × (years as a smoker).[9] The curative CRT would either be of definitive setting, with gross tumor or lymphadenopathy, or of adjuvant setting, with major risk factors including positive margins or extracapsular extension. The tumors were staged according to the American Joint Commission on Cancer classification system, seventh edition.[10] The staging evaluations included MRI of the head and neck, chest radiography, liver ultrasonography, and bone scintigraphy, as well as positron emission tomography/CT, if clinically required. Histopathological grading was performed by an experienced pathologist. Nasopharynx tumors were excluded due to their unique characteristics differing from other HNSCCs. For patients with oropharyngeal cancer, immunohistochemistry was carried out for p16 on representative 4-μm sections cut from formalin-fixed paraffin-embedded tissue blocks. p16 overexpression was defined as ≥70% cytoplasmic and nuclear staining.[9] The measurement of exhaled CO level provided an accurate immediate noninvasive method of assessing smoking status, and had been incorporated into our national smoking cessation program.[11]

2.2 | Treatments

The radiotherapy treatment technique used in this study has been previously described.[12,13] Briefly, after the immobilization of the head using a thermoplastic mask, CT was performed with a 3 to 5-mm slice thickness of the head and neck region. The clinical target volumes (CTVs) were CTV-66/70 (70 Gy to the gross tumor and lymphadenopathy in definitive setting, or 66 Gy to the operative bed for positive margins and areas of extracapsular extension in adjuvant setting); CTV-60 (60 Gy to the subclinical disease and high-risk lymphatic regions and the entire operative bed in adjuvant setting); and CTV-54 (54 Gy to the low-risk regions, including the low neck and supraclavicular fossa regions). The planning target volumes (PTVs) were evenly expanded using a 4-mm margin. Several dose fractionations (60 Gy in 30 fractions or 66-70 Gy in 33-35 fractions) were used, at the discretion of the attending physician. The treatment goals were as follows: 100% of the radiation dose should cover 95% of the PTV and the maximum dose should not exceed 110%. To avoid imminent overdose to critical structures, this goal could be modified to 95% of the radiation dose, and should cover 95% of PTV; the maximum dose should be less than 115%. The maximum doses to the brain stem, optic nerves/chiasm, eyes, and spinal cord were set at 54, 54, 50, and 45 Gy, respectively. At least one side of the parotid glands received a mean dose of 26 Gy, or the volume receiving 30 Gy radiation was <50%. Pinnacle planning software version 8.0 m (Philips Medical Systems, Milpitas, California) was used for all patients. The plans were optimized using the inverse planning algorithm (direct machine parameter optimization) and heterogeneity corrections. All patients underwent intensity-modulated radiotherapy (IMRT), delivered by an Elekta Synergy accelerator (Elekta, Stockholm, Sweden) with a step-and-shoot technique. The treatment position was verified weekly using cone-beam CT X-ray volume imaging. In most patients, the CRT regimen included 30 mg/m^2 cisplatin every week during radiotherapy.

2.3 | Smoking cessation throughout CRT

Patients were referred for smoking cessation program before CRT.[14] The program provided individualized counseling and incentives to help patients reach the goals of smoking cessation during CRT by well-trained (on smoking cessation techniques) full-time research assistants. The stepped-care approach, initiated with strong physician advice and individualized counseling to quit smoking, was followed by more intensive treatment suggestion (pharmacologic treatment) for those having difficulty quitting or remaining abstinent. Successful smoking cessation throughout CRT was confirmed by CO breath test concentrations of <3 ppm at the end of CRT.[15]

2.4 | Follow-up assessment

Acute toxicities were rated according to the Common Terminology Criteria for Adverse Events version 4.0.[16] Late toxicities were assessed according to the late morbidity scoring criteria of Radiation Therapy Oncology Group.[17] Follow-up analyses were conducted based on a comprehensive protocol using the relevant data available on January 31, 2018. Follow-up visits were conducted at 1, 2, 3, 6, 9, and 12 months, post-CRT, and every 3 months thereafter. Treatment response after CRT was assessed every 3 months using endoscopy or head and neck MRI as well as biopsy of suspicious lesions. Chest radiographs were taken every 6 months, whereas CT, MRI, bone scanning, or other investigations were performed when there was clinical suspicion of tumor progression. Tumor progression analysis included locoregional recurrence (LRR) and distant metastasis (DM), determined by physicians and radiologists via a panel discussion. LRR was defined as recurrence at the head and neck region or cervical nodal sites; and DM, as metastasis beyond the locoregional sites based on pathologic, cytologic, or radiologic evidence. Histological confirmation was not mandatory for LRR or DM. Patients who had no tumor progression at the time of analysis were censored at the date of last contact. Progression-free survival (PFS) was defined as the time (months) from the date of completion of treatment to that of tumor progression or censoring. Overall survival (OS) was defined as the time (months) from the date of completion of treatment to that of death or censoring.

2.5 | Statistical analysis

Statistical comparisons between patients who successfully achieved smoking cessation and patients who continued smoking during CRT were performed using the Mann-Whitney *U* test to compare parameters for age and tobacco exposure, and Pearson's chi-square test for all others including sex, tumor site, stage, histologic grade, hemoglobin concentration before CRT, radiotherapy setting (definitive vs adjuvant), radiotherapy total dose, or concurrent systemic therapy. Statistical comparisons between CO breath concentrations before and after CRT were performed using the nonparametric Wilcoxon signed-rank test. Associations between smoking during CRT and grade ≥3 acute or late toxicities, permanent gastrostomy or tracheostomy, or hospitalization rate were evaluated by Pearson's chi-squared test. Associations between smoking during CRT and hospitalization durations were evaluated by the Mann-Whitney *U* test. The analysis was conducted using follow-up data available on January 31, 2018. A Kaplan-Meier life table analysis and the log-rank test were used to assess survival times and to compare survival according to prognostic factors. A *P*-value of <.05 was considered statistically significant. All prognostic variables found to be potentially significant ($P < .15$) in the univariate analysis were included in the multivariate analysis based on the Cox proportional hazards regression model. Statistical analyses were performed using SPSS for Windows, version 17.0 (SPSS, Chicago, Illinois).

3 | RESULTS

3.1 | Patient characteristics

Sixty-three patients with nonmetastatic HNSCC (stage IV disease, 68%) scheduled to undergo curative CRT were prospectively included in this study (median age, 56 years; range, 30-70 years) (Table 1). Among all patients, a median of 6 pack-years of tobacco exposure history was observed, ranging from 2 to 80 pack-years. The primary sites were oropharynx (42%), oral cavity (25%), hypopharynx (21%), larynx (6%), and others (6%). Among 26 patients with oropharyngeal cancer, p16 overexpression was demonstrated in 16 patients. The mean pre-CRT hemoglobin concentration was 12.4 g/dL (range, 7.4-17.0 g/dL). The median radiotherapy dose was 70 Gy in 33 fractions. Most patients (86%) received weekly cisplatin with a median of 6 cycles during curative CRT. Four patients received taxane-based chemotherapies and five received tegafur-uracil, at the discretion of the attending physician. One patient (2%) did not reach the CRT total dose of 70 Gy, as he developed life-threatening sepsis at 30 Gy.

The mean initial concentration of breath CO before curative CRT was 7 ppm (range, 1-29 ppm) for the 63 patients. Forty-one patients (65%) successfully achieved smoking cessation throughout CRT, confirmed by CO breath test concentrations of <3 ppm at the end of CRT. The mean concentrations on CO breath test after curative CRT was 2 ppm (range, 1-3 ppm) among patients who reached successful smoking cessation, and 9 ppm (range, 4-22 ppm) among patients who continued smoking during CRT. As shown in Figure 1, post-CRT CO breath concentrations were significantly lower in patients who achieved successful smoking cessation ($P = .003$) than in those who continued smoking during CRT ($P = .13$). As shown in Table 1, there was no significant difference in distributions of age, sex, tumor site, stage, histological grade, pre-CRT hemoglobin, radiotherapy setting (definitive vs adjuvant), radiotherapy total dose, or concurrent systemic therapy between patients who reached successful smoking cessation and who continued smoking during CRT. Heavier tobacco exposure was seen in patients who continued smoking during CRT, compared with patients who reached successful smoking cessation (median, 25 vs 5 pack-years, $P = .001$, Figure 2).

The median follow-up time was 33 months (range, 3-47 months). At the time of analysis, 4 of the 41 patients who reached successful smoking cessation throughout CRT relapsed to smoking, and these 4 patients were consistently counseled, under the smoking cessation program.

TABLE 1 Patient with HNSCC clinical characteristics and treatment parameters (n = 63)

		Successful smoking cessation throughout CRT[d]		
	Total, no. of patients (%)	Yes, No. of patients (%)	No, No. of patients (%)	*P* value[e]
No. of patients	63	41	22	
Age (y)				.06
Median (range)	56 (30-70)	61 (36-70)	50 (32-69)	
Sex				.67
Male/female	59/4	38/3	21/1	
Tobacco exposure (pack-years)				.001
Median (range)	6 (2-80)	5 (2-80)	25 (5-80)	
Tumor site				.33
Oral cavity	16 (25)	14 (34)	2 (9)	
Oropharynx with p16 overexpression	16 (25)	12 (30)	4 (18)	
Oropharynx without p16 overexpression	10 (17)	3 (7)	7 (32)	
Hypopharynx	13 (21)	7 (17)	6 (27)	
Larynx	4 (6)	2 (5)	2 (9)	
Others	4 (6)	3 (7)	1 (5)	
Stage groupings[a]				.80
I	3 (5)	1 (2)	2 (9)	
II	6 (10)	4 (10)	2 (9)	
III	11 (17)	8 (20)	3 (14)	
IV	43 (68)	28 (68)	15 (68)	
Histologic grade				.48
Low (well differentiated)	13 (21)	7 (17)	6 (27)	
Intermediate (moderately differentiated)	32 (50)	23 (56)	9 (41)	
High (poorly differentiated, undifferentiated)	18 (29)	11 (27)	7 (32)	
Hb before CRT				.95
<9 g/dL	3 (5)	2 (5)	1 (5)	
≥9 g/dL	60 (95)	39 (95)	21 (95)	
Radiotherapy setting				.19
Definitive	42 (67)	25 (61)	17 (77)	
Adjuvant[b]	21 (33)	16 (39)	5 (23)	
Radiotherapy total dose				.22
≥66 Gy	56 (89)	35 (85)	21 (95)	
<66 Gy	7 (11)	6 (15)	1 (5)	
Concurrent systemic therapy				.56
Weekly cisplatin	54 (86)	35 (85)	19 (86)	
Other regimens[c]	9 (14)	6 (15)	3 (14)	

Abbreviations: CRT, chemoradiotherapy; Hb, hemoglobin; HNSCC, head and neck squamous cell carcinoma.

[a]Stage is classified by the American Joint Committee on Cancer 7th edition.

[b]The adjuvant radiotherapy setting enrolled patients with major risk factors including positive margins or extracapsular extension.

[c]Other regimens include taxane-based chemotherapies (n = 4) and tegafur-uracil (n = 5).

[d]Successful smoking cessation throughout CRT was confirmed by carbon monoxide breath test concentrations of <3 ppm at the end of CRT.

[e]Significance tested using Mann-Whitney *U* test to compare parameters for age and tobacco exposure, and Pearson's chi-square test for all others.

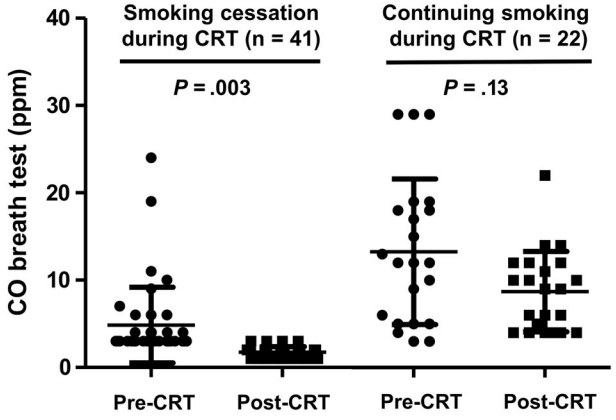

FIGURE 1 Carbon monoxide (CO) breath concentrations pre-chemoradiotherapy (CRT) and post-CRT in 63 patients with head and neck squamous cell carcinoma. Mean and SD of pre-CRT and post-CRT CO breath concentrations in patients who achieved successful smoking cessation and in those who did not. *P* values for statistical comparisons between CO breath concentrations before and after CRT were performed using the nonparametric Wilcoxon signed-rank test. The post-CRT CO breath concentration was significantly lower in patients who achieved successful smoking cessation ($P = .003$) than in those who continued smoking during CRT ($P = .13$)

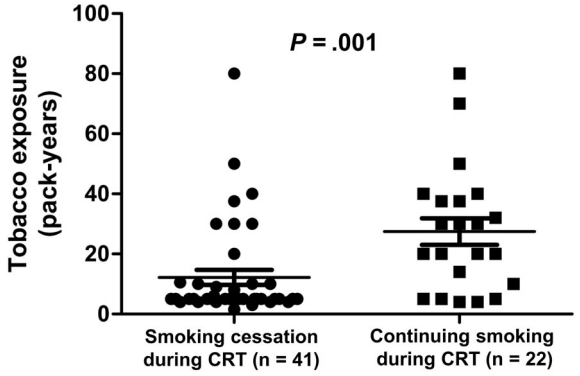

FIGURE 2 Tobacco exposure (pack-years) in 63 patients with head and neck squamous cell carcinoma. Mean and SD of tobacco exposure (pack-years) in patients who achieved successful smoking cessation and in those who did not. *P* values for statistical comparisons of tobacco exposure (pack-years) between patients who attained successful smoking cessation and patients who continued smoking during CRT were performed using the Mann-Whitney *U* test. Heavier tobacco exposure was seen in patients who continued smoking during CRT, compared with patients who attained successful smoking cessation (median 25 vs 5 pack-years, $P = .001$)

3.2 | Association of successful smoking cessation with treatment-related toxicities

With respect to acute CRT toxicities among all the patients, grades 3, 4, or 5 acute toxicities of any kind developed in 19, 1, and 1 patient, respectively. The grades 4 and 5 acute toxicity was leukopenia. A quarter of patients (25%) experienced grade 3 acute mucositis whereas 13% experienced grade 3 acute dermatitis (Table 2). Patients who achieved successful smoking cessation during CRT had significantly lesser probability of grade ≥3 acute toxicities (22% vs 55%, $P = .01$), compared to patients who continued smoking throughout CRT. A total of 38 patients (60%) were hospitalized during CRT, with a median hospitalization duration of 47 days (range, 3-96 days), and there was no difference in hospitalization rate (61% vs 59%, $P = .88$) or hospitalization durations (median, 48 days vs 46 days, $P = .63$) irrespective of whether patients achieved successful smoking cessation or not. A nasogastric feeding tube was inserted in 18 patients (29%) during CRT, with a median duration of 29 days (range, 3-51 days). There was no difference in nasogastric feeding tube insertion rate irrespective of whether patients achieved successful smoking cessation or not ($P = .87$).

With regard to late CRT toxicities overall, grade 3 late toxicities of any kinds developed in 10 patients (16%), but no patient had grade 4 or 5 late toxicities (Table 2). Five patients (8%) experienced grade 3 osteonecrosis necessitating hyperbaric oxygen or operative intervention. Five patients (8%) had soft tissue toxicities with severe induration and loss of subcutaneous tissue, needing aggressive rehabilitation; or severe infection, needing

TABLE 2 CRT acute and late toxicities in patients with HNSCC

	Successful smoking cessation throughout CRT[a]		
	Yes, No. of patients (%)	No, No. of patients (%)	*P* value[b]
Grade ≥3 acute toxicities			
Mucositis	7 (17)	9 (41)	.07
Dermatitis	3 (7)	5 (23)	.12
Leukocytes (total whole blood cells)	4 (10)	5 (23)	.26
Hemoglobin	2 (5)	0 (0)	.54
Platelets	1 (2)	2 (9)	.28
Any acute toxicities	9 (22)	12 (55)	.01
Grade ≥3 late toxicities			
Soft tissue toxicities (fibrosis, infection, etc)	4 (10)	1 (5)	.65
Osteoradionecrosis	4 (10)	1 (5)	.65
Trismus	3 (7)	0 (0)	.19
Any late toxicities	8 (20)	2 (9)	.47
Permanent gastrostomy or tracheostomy	2 (5)	5 (23)	.04

Abbreviations: CRT, chemoradiotherapy; HNSCC, head and neck squamous cell carcinoma.

[a]Successful smoking cessation throughout CRT was confirmed by carbon monoxide breath test concentrations of <3 ppm at the end of CRT.

[b]Significance tested using the Pearson's chi-square test.

hospitalization. Three patients (5%) had trismus with joints stiffness and pain, with severe limitation of mouth opening. No difference occurred in any grade 3 late toxicities irrespective of whether patients achieved successful smoking cessation throughout CRT or not ($P = .47$).

At the time of analysis, three patients had secondary primary cancer, two with hepatocellular carcinoma, and one with esophageal cancer. There was no difference in incident rate of secondary malignancy irrespective of whether patients achieved successful smoking cessation throughout CRT (2%) or not (9%, $P = .24$). At the time of analysis, seven patients (11%) had permanent gastrostomy or tracheostomy (Table 2), at a median of 10 months (range, 2-21 months) after CRT completion. Patients who reached successful smoking cessation throughout CRT had significantly lower rate of permanent gastrostomy or tracheostomy (5% vs 23%, $P = .04$) compared to patients who continued smoking during CRT.

3.3 | Association of successful smoking cessation with clinical outcomes

With a median follow-up of 33 months (range, 3-47 months), among the 63 patients, 29 (46%) had progression at one or more sites, and 20 (32%) died of any cause. With regard to the initial progression sites, LRR occurred in 14 patients, distant recurrence in 13, whereas synchronous locoregional and distant recurrence occurred in 2 patients. Patients who reached successful smoking cessation throughout CRT had a significantly greater probability of PFS (Figure 3A, 3-year PFS 61% vs 34%, $P = .03$), compared to patients who continued smoking during CRT. No significant differences occurred in OS (Figure 3B, $P = .42$), locoregional control (Figure 3C, $P = .54$), or distant metastases-free survival (Figure 3D, $P = .07$). Univariate analysis (Table 3) revealed that advanced stages (≥IV), heavier tobacco exposure (≥6 pack-years), and continued smoking during CRT were associated with higher risks of tumor progression. However, age, histological grade, pre-CRT hemoglobin, radiotherapy setting (definitive vs adjuvant), radiotherapy total dose, or tumor site (oropharyngeal cancer with p16 overexpression) did not reach significance level with progression risk.

In order to analyze the influence of smoking cessation during CRT on tumor progression, patients were stratified by stages (<IV vs ≥IV) and tobacco exposure (<6 vs ≥6 pack-years). As shown in Figure 4, patients who attained successful smoking cessation throughout CRT had significantly lower risk of tumor progression compared to patients who continued smoking during CRT, in either stratification

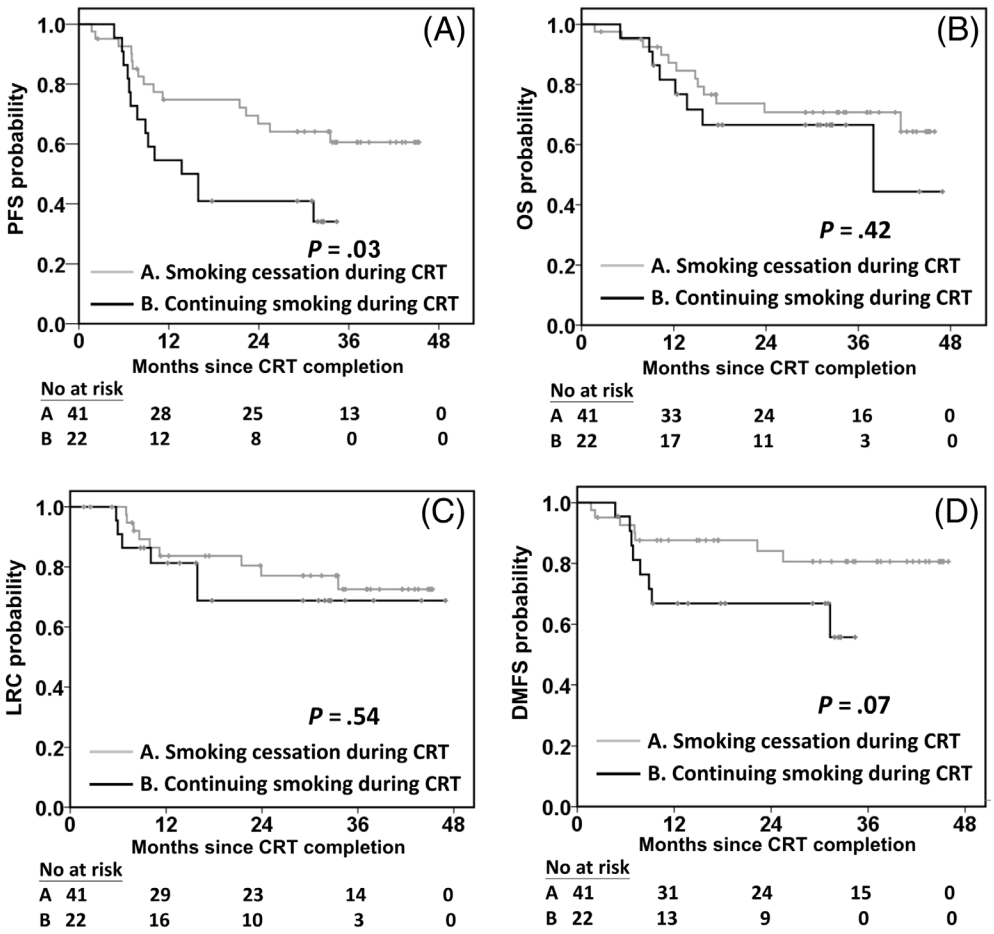

FIGURE 3 Clinical outcomes of 63 patients with head and neck squamous cell carcinoma receiving curative chemoradiotherapy (CRT). The patients were grouped according to whether they reached successful smoking cessation throughout CRT, confirmed by carbon monoxide breath test concentrations of <3 ppm at the end of CRT. The groups were then compared with respect to A, progression-free survival (PFS); B, overall survival (OS); C, locoregional control (LRC); and D, distant metastasis-free survival (DMFS). *P* values were determined using Kaplan-Meier log-rank tests, describing the overall comparison between the two groups. Patients who attained successful smoking cessation throughout CRT had significantly greater probability of PFS ($P = .03$), compared to patients who continued smoking during CRT

TABLE 3 Univariate analysis of potential prognostic factors for survivals among patients with HNSCC

	3-year PFS (%)	*P* value[b]	3-year OS (%)	*P* value[b]
Age (y)		.78		.89
<65	51.0		69.9	
≥65	50.1		67.5	
Stage		.003		.07
<IV	68.6		88.4	
≥IV	42.2		61.2	
Tobacco exposure		.14		.13
<6 pack-years	60.0		75.2	
≥6 pack-years	39.6		63.9	
Histologic grade		.48		.84
Low and intermediate (well and moderately differentiated)	53.1		69.9	
High (poorly differentiated, undifferentiated)	44.4		68.9	
Pre-CRT Hb		.19		.64
≥9 g/dL	52.2		69.8	
<9 g/dL	0.0		50.0	
Radiotherapy setting		.31		.28
Adjuvant	61.9		74.7	
Definitive	44.7		66.2	
Radiotherapy total dose		.49		.49
≥66 Gy	51.6		70.6	
<66 Gy	42.9		57.1	
Site		.28		.53
Oropharynx with p16 overexpression	58.9		73.7	
Others	47.8		62.7	
Smoking status		.03		.42
Successful smoking cessation throughout CRT[a]	60.5		70.7	
Continued smoking during CRT	34.1		66.5	

Abbreviations: CRT, chemoradiotherapy; Hb, hemoglobin; HNSCC, head and neck squamous cell carcinoma; OS, overall survival; PFS, progression-free survival.

[a]Successful smoking cessation throughout CRT was confirmed by carbon monoxide breath test concentrations of <3 ppm at the end of CRT.

[b]Significance tested using Kaplan-Meier life table analysis and the log-rank test.

by tobacco exposure (Figure 4A, $P = .05$) or advanced stages (Figure 4B, $P = .04$). In the multivariate analysis (Table 4), despite advanced stages (≥IV) or heavier tobacco exposure (≥6 pack-years), successful smoking cessation during CRT significantly reduced the risk of tumor progression (hazard ratio: 0.4, 95% confidence interval [CI]: 0.2-0.9, $P = .05$).

4 | DISCUSSION

The current study was a prospective single-institutional series, reporting on both toxicities and clinical outcomes of patients with HNSCC receiving curative CRT, emphasizing the influence of smoking cessation during CRT.

The study showed that continued smoking during curative CRT increased the risks of treatment-related toxicities and tumor progression in patients with HNSCC. This negative effect of smoking on radiotherapy outcome is consistent with findings of other studies. Browman et al retrospectively demonstrated that smoking during CRT led to a lower rate of tumor response and poor survivals, although no significant difference occurred in the acute CRT side effects (stomatitis or dermatitis).[18] Al-Mamgani et al retrospectively demonstrated that patients with early stage glottis cancer who continued smoking after radiotherapy had significantly poor local control and low voice quality; however, the acute adverse effects during radiotherapy were not addressed.[19] Peppone et al retrospectively demonstrated association between smoking and increased symptom burden, during and following the treatments for cancer.[20] Hoff et al prospectively showed that heavy smokers had significantly reduced probability of locoregional control, disease-specific survival, and OS, compared to non-smoking patients, while not addressing the acute adverse effects during radiotherapy.[7] Our study was a consecutive series reporting on the adverse influence of continued smoking during CRT, on both toxicities and clinical outcomes, in patients with HNSCC receiving curative CRT.

Heavy tobacco exposure had been established as a poor prognostic factor in patients with head and neck cancer receiving curative CRT.[9] Ang et al demonstrated that in patients with oropharyngeal cancer receiving curative CRT, the risk of death increased significantly with each additional pack-year of tobacco smoking, and human papillomavirus infection status, pack-years of tobacco smoking, and tumor and nodal classification estimated the risk of death.[9] Our study further established the importance of smoking cessation during CRT, showing that patients who attained successful smoking cessation throughout CRT had significantly lower risk of tumor progression compared to patients who continued smoking during CRT, in either stratification by tobacco exposure or advanced stages, with a hazard ratio of 0.4. This hazard ratio reduction was in accordance with the study conducted by Browman et al, in which continuing smoking during CRT led to death, with a relative risk of 2.5 (95% CI: 1.4-4.4).[18]

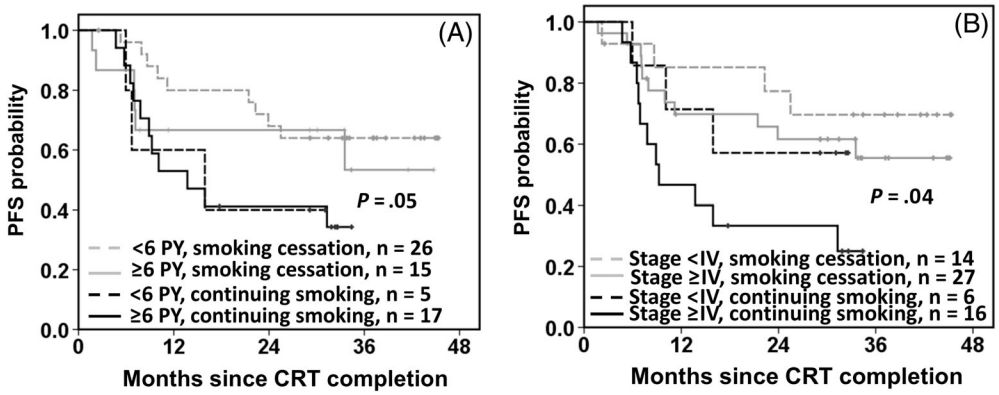

FIGURE 4 Clinical outcomes of 63 patients with head and neck squamous cell carcinoma receiving curative chemoradiotherapy (CRT). The patients were grouped according to whether they attained successful smoking cessation throughout CRT, confirmed by carbon monoxide breath test concentrations of <3 ppm at the end of CRT, and stratified by A, tobacco exposure (<6 pack-years [PY] vs ≥6 PY) and B, advanced stage (stage <IV vs stage ≥IV). *P* values on progression-free survival (PFS) were determined using Kaplan-Meier log-rank tests, describing the overall comparison between either stratification

TABLE 4 Multivariate analysis of potential prognostic factors for survivals in patients with HNSCC

	Progression-free survival	
	HR (95% CI)	***P* value[b]**
Tobacco exposure ≥6 pack-years	1.1 (0.5-2.6)	.84
Stage IV disease	1.9 (0.8-4.5)	.16
Successful smoking cessation throughout CRT[a]	0.4 (0.2-0.9)	.05

Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; HNSCC, head and neck squamous cell carcinoma.

[a]Successful smoking cessation throughout CRT was confirmed by carbon monoxide breath test concentrations of <3 ppm at the end of CRT.

[b]Significance tested using multivariate analysis based on the Cox proportional hazards regression model.

Evidence showed that tumor hypoxia, a reduction in the tissue oxygen tension, adversely affected locoregional tumor control and survival, in head and neck cancer. There are several approaches, or biomarkers, for assessing tumor hypoxia.[21] Direct oxygen measurements in tissues could be achieved by needle electrode or by blood oxygen level-dependent MRI.[22] The indirect approach consists of the measurement of endogenous molecular markers including hypoxia inducible factor-1, or immunohistochemical staining of 2-nitroimidazole compounds on tissue sections[23] or the secreted hypoxia markers, including vascular endothelial growth factor and osteopontin.[24] In this study, we chose CO breath test concentrations of <3 ppm as the definition of successful smoking cessation throughout CRT.[15] Smoking during curative CRT causes the formation of CO, and the binding of CO to hemoglobin causes carboxyhemoglobin formation. The resulting low oxygen partial pressure and inadequate release of oxygen in tissues is thus an indirect indicator of hypoxia.

The measurement of exhaled CO level provided an immediate noninvasive method of assessing smoking status, and had been incorporated into our national smoking cessation program.[11] Cotinine was the major metabolite of nicotine, and cotinine levels in blood, urine, and saliva had also been recognized as biomarkers of smoking status; nevertheless, the cotinine level might have been affected when patients took nicotine formulations (eg, nicotine patch, gum, and lozenge) for smoking cessation. The cotinine level and CO breath test both had good reliability and accuracy in examining smoking status.[25] Moreover, in the smoking cessation clinical trials literature, the majority of studies used CO as the method for biochemical verification for smoking cessation.[26,27] Therefore, we measured CO level as the means of confirming smoking cessation status in our study.

We did not observe a difference in locoregional control between the two groups (patients who reached or did not reach successful smoking cessation throughout CRT). The relatively high locoregional control rate achieved in our study could have resulted from the modern and precise radiotherapy technique employed. IMRT achieves better dose differentiation between tumorous and normal tissues and facilitates simultaneous delivery of different fractional doses to different targets, allowing for dose painting and dose escalation, leading to better tumor coverage.[3,12]

In the present study, more than half of the patients were hospitalized during CRT, with a median hospitalization duration of 47 days. At our institution, all patients were managed by the multidisciplinary head-and-neck team, comprising otolaryngologists, medical oncologists, radiation oncologists, pathologists, rehabilitation physicians, psychologists, clinical nurse specialists, dietitian, and other health care professionals.[28] Our multidisciplinary team aimed to improve patients' outcomes and applied relaxed

criteria for hospitalization during radiotherapy, including underlying comorbidities, nutrition support, treatment side effects requiring medical care, systemic or chemotherapy infusion, or patient preferences.[29] Also, our National Health Insurance implemented the global budget program policy which tolerated the increase in length of hospital stays[30]; thus, long admissions had been the standard treatment for patients with HNSCC receiving curative CCRT in our institution. Nevertheless, there was no difference in hospitalization rate irrespective of whether patients achieved successful smoking cessation or not.

This study had few limitations. The number of enrolled patients was relatively small, and the follow-up duration was short. The concurrent chemotherapy and radiotherapy regimens were not in concordance. Despite these limitations, smoking cessation during curative CRT reduced treatment-related toxicities and risks of tumor progression in patients with HNSCC. Efforts should be made to reach smoking cessation during curative CRT, in order to improve the therapeutic efficacy of curative CRT.

In conclusion, this study showed that smoking cessation during curative CRT reduced treatment-related toxicities and risks of tumor progression in patients with HNSCC. Efforts should be made to ensure smoking cessation during curative CRT, in order to improve the therapeutic efficacy of curative CRT.

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CONFLICT OF INTEREST

The authors indicate no potential conflict of interest.

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