Prognostic impact of cigarette smoking on the survival of patients with established esophageal squamous cell carcinoma receiving radiotherapy: A retrospective study from southern China

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Abstract. Cigarette smoking is associated with the development of esophageal squamous cell carcinoma (ESCC); however, the influence of smoking on survival of patients with ESCC receiving radiotherapy, with or without chemotherapy, has remained elusive. The present study retrospectively analyzed 479 patients with ESCC from southern China who were categorized based on their smoking history (never, previous or current). To consider the cumulative effect of smoking, the number of pack years (PYs) was used as a representative variable. Associations between cigarette smoking and survival were evaluated using the Kaplan-Meier analysis and Cox proportional hazards model. Among the 497 patients, 308 (64.3%) had reported a history of cigarette smoking. The 5-year overall survival for patients void of a smoking history, former smokers and current smokers was 50.9, 27.0 and 34.3%, respectively. The adjusted hazard ratios (HRs) for previous and current smoking vs. no smoking history were 1.57 [95% confidence interval (CI), 1.06-2.32] and 3.01 (95% CI, 1.15-7.86), respectively. Heavy smokers with a high number of PYs had a HR for death of 1.75 (95% CI, 1.28-2.41) compared with light smokers. In the cohort of 407 patients treated with intensity-modulated radiotherapy/three-dimensional conformal radiotherapy, similarly significant results were obtained. In conclusion, cigarette smoking is an independent and poor prognostic factor for patients with ESCC treated with radiotherapy and/or chemotherapy. It is associated with an increased risk of death, and the risk increases with the increase in PYs. This result may help to manage tobacco use among patients with ESCC. The smoking status should be taken into consideration in prospective studies on ESCC. More frequent follow-ups are recommended for those patients with ESCC with a history of smoking.

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Abbreviations: EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; EA, esophageal adenocarcinoma; OS, overall survival; HR, hazard ratio; CI, confidence interval; DFS, disease-free survival; RT, radiotherapy; UICC, Union for International Cancer Control; AJCC, American Joint Committee on Cancer; 2DRT, two-dimensional RT; 3DCRT, three-dimensional conformal RT; IMRT, intensity modulated RT; PY, pack year

Introduction

Esophageal cancer (EC) is one of the most common cancer types of the digestive tract worldwide and remains one of the fourth leading causes of cancer-associated mortality in China (1,2). Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA) are the two major histological subtypes of EC. In China, ESCC accounts for ~90% of all cases of EC, whereas EA is the predominant subtype in Western countries (3-5). Surgery is considered to be the standard treatment for this localized disease and is the best single-modality therapy for potentially this resectable disease (2). However, most patients with EC already have locally advanced or metastatic disease at the time of diagnosis. Radiotherapy (RT) combined with chemotherapy, with or without surgery, has become the major treatment (2).

Cigarette smoking is well known to promote the development of EC, irrespective of the pathological type (6,7). Most studies on the subject have revealed that smoking is a risk factor for the occurrence of ESCC (8-12). A review indicated that cigarette smoking induces a more malignant tumor phenotype by increasing the cell proliferation, migration and invasion, as well as angiogenesis, and by activating cellular pro-survival pathways (13). However, few studies have focused on the effect of smoking on EC patient survival outcomes. In

a study by Wang *et al* (14), the patients underwent esophagectomy without any pre-operative therapy, and smoking was identified to be an independent prognostic factor for overall survival (OS) [hazard ratio (HR)=2.186; 95% confidence interval (CI), 1.309-3.650; P=0.003] and disease-free survival (DFS) (HR=2.471; 95% CI, 1.467-4.163; P=0.001). However, another study from Southern China indicated that smoking history only affected treatment outcomes in those ESCC patients receiving surgery plus chemotherapy, and not in those receiving surgery alone (15). Furthermore, one study from Shandong province reported a negative result, namely that neither smoking nor drinking affected the 2-year OS or DFS of ESCC patients (16). Considering these inconsistent results, the impact of smoking on the survival of ESCC remains elusive and the patients mainly received surgery in previous studies (14-16).

Smoking was reported as an independent predictor of a pathological complete response to neoadjuvant chemoradiotherapy in patients with ESCC (17). That study performed no further analysis of the impact of smoking on long-term survival. A recent study identified cigarette smoking as a significant and independent poor prognostic risk factor for OS among those patients with ESCC receiving definitive RT or concurrent chemoradiotherapy, with or without esophagectomy (18). In addition, smoking was demonstrated to have an unfavorable impact on tumor control by irradiation in animal models, by exacerbating tissue hypoxia (19,20). Tumor hypoxia is well known to influence the reaction to radiation and chemotherapy (21,22). In the present study, it was speculated that smoking not only induces malignant transformation of normal cells, but may also change tumor-associated genes or associated metabolic activity, thus making tumor cells more aggressive and less sensitive to RT and chemotherapy. Therefore, RT with or without chemotherapy, as the major treatment for those patients with local advanced ESCC, is probably affected by smoking to a greater extent than by surgery. Therefore, the aim of the present study was to elucidate the effect of a history of cigarette smoking on the survival of patients with ESCC receiving RT, with or without chemotherapy.

Patients and methods

Patients. The medical records of the eligible patients, who were hospitalized at the Sun Yat-sen University Cancer Center (Guangzhou, China) between January 2007 and December 2013, were retrospectively reviewed. Patients were eligible if their biopsy specimens were histologically confirmed as ESCC and if they had no distant metastasis, were previously untreated and received RT with or without chemotherapy after diagnosis. Essential pre-treatment assessments were the review of the complete patient history, including a family history of cancer and lifestyle behavior; physical examination; hematology and biochemistry profiles; computed tomography of the neck, chest and upper abdomen; and endoscopic ultrasound. Patients who had distant metastasis, received surgery or had incomplete data were excluded.

The information retrieved from the medical records included age, sex, pathological type, smoking status at diagnosis (never/current/former smoker), number of cigarettes smoked per day, number of years of smoking and alcohol drinking status at diagnosis (yes vs. no). The patients' smoking status was defined as follows: Never smokers, patients who had never smoked prior to treatment; current smokers, patients who smoked prior to treatment or had stopped for <1 year; former smokers, patients who had stopped smoking for at least 1 year prior to treatment. The tumor locations included cervical, upper third of thoracic esophagus, middle third of thoracic esophagus and lower third of thoracic esophagus. All patients were re-staged according to the sixth edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging system for ESCC (23).

Treatment. The treatment strategy for the patients with ESCC was discussed by a multidisciplinary team, which included surgeons, a physician, a radiation specialist, a radiologist and a pathologist. The final treatment choice was made according to the National Comprehensive Cancer Network (NCCN) guidelines and the overall condition of the patient, which included the physical performance and the economic status (2). All of the patients included received RT. The radiation techniques and dose prescriptions were in accordance with those described previously (24,25). The chemotherapy consisted of fluoropyrimidine- or taxane-based regimens [cisplatin combined with 5-fluorouracil (5-FU) or cisplatin combined with docetaxel] every 3 weeks or weekly (26,27). A total of 423 out of 479 (88.3%) patients received RT plus chemotherapy. Among the patients who received chemotherapy, 110 received chemotherapy containing 5-FU, while 323 received chemotherapy containing docetaxel.

Follow-up. Patients were followed up at regular intervals after completing their treatment. The specific follow-up intervals were one month after completion of treatment, then every 2 months during the first 6 months, every 3 months for the next 6 months, every 4 months during the second year and every 6 months thereafter.

Study endpoints. The endpoint of the present study was the OS, defined as the time from treatment to death resulting from any cause. First, the association between survival and the smoking status at diagnosis (never smokers, former smokers and current smokers) was assessed. Second, the cumulative effects of smoking in terms of pack-years (PYs) were assessed. The PYs were calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the patient had smoked.

Statistical analysis. Survivals rates were estimated using the Kaplan-Meier method and compared between subgroups using the log-rank test. Univariate analyses were performed to determine variables associated with OS. Multivariate analyses were performed using the Cox proportional hazards model. Comparisons of demographic, clinical and pathological variables between subgroups were performed using χ^2 statistics, Fisher's exact test or the Kruskal-Wallis test. Continuous variables were assessed using restricted cubic splines (RCS) nested with Cox models using the RCS macro of the SAS software 9.1 (SAS Institute, Cary, NC, USA) and the cutoff scores of the continuous variables were subsequently selected based on receiver operating characteristic curve analyses. A

two-sided P<0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA) and SAS software 9.1.

Results

Patient characteristics, treatment and outcomes. A total of 479 patients with ESCC were included. The clinical stage distribution according to the sixth edition of the UICC/AJCC staging system for the 479 patients was as follows: Stage II, n=75 (15.6%); stage III, n=227 (47.4%); and stage IV, n=177 (37.0%). Overall, 56/479 patients (11.7%) were treated with RT alone and 423/479 (88.3%) received RT plus chemotherapy. Of these 423 patients, 336 (70.1%) received concurrent chemotherapy, 52 (10.9%) received a combination of induction and concurrent chemotherapy, and 35 patients (7.3%) received a combination of concurrent and adjuvant chemotherapy. With respect to RT, 72 patients (15.0%) were treated with two-dimensional RT (2DRT), 298 patients (62.2%) with three-dimensional conformal RT (3DCRT) and 109 patients (22.8%) with intensity-modulated RT (IMRT).

Within a median follow-up duration of 27.89 months (range, 0.8-116.3 months), 286 patients died. The 1-, 2-, 3- and 5-year survival rates were 73.3, 56.0, 47.4 and 39.5%, respectively.

Patient characteristics. The percentage of never smokers, former smokers and current smokers in the entire cohort was 35.7% (171/479), 9.0% (43/479) and 55.3% (265/479), respectively. When the entire population was stratified by the smoking status, no significant differences were identified in terms of the T-stage, N-stage, M-stage, clinical stage and RT techniques between the different groups. However, significant differences were observed in terms of age, sex, drinking status, tumor grade, tumor location and chemotherapy approach. Male patients were more frequent among the former and current smokers (Table I).

Kaplan-Meier analysis of the impact of smoking on survival. Former and current smokers had a poorer OS than never smokers in the entire population (Fig. 1A). The 5-year OS was 27.0% for former smokers vs. 34.3% for current smokers (P<0.001), and vs. 50.9% for never smokers (P<0.001). No significant difference in OS was identified between the former and current smokers (P=0.129). The small sample and no significant difference in survival (P=0.129) prompted us to combine the former and current smokers into a single group, whose 5-year survival rate was 32.3%, which was significantly poorer than that of the never smokers (P<0.001; Fig. 1B).

The cumulative effect of smoking also had a significant effect on the survival of patients with ESCC. In patients with a history of smoking, 47.5 PYs was identified as the cutoff value for heavy and light smokers associated with OS. Heavy smokers had a poorer 5-year OS of 16.3% compared with that of light smokers, with a 5-year OS of 38.4% (log-rank test, P<0.001; Fig. 1C).

Among the patients treated with IMRT/3DCRT, current smokers or former smokers also had a poorer OS than never smokers [5-year OS, 56.4% for never smokers vs. 38.4% for current smokers (P<0.001) and vs. 30.3% for former smokers (P<0.001); Fig. 1D]. The significant difference compared with

the never smokers still remained when current smokers and former smokers were combined (5-year OS, 36.1 vs. 58.2%; log-rank test, P<0.001; Fig. 1E). No significant difference was observed between the former and current smokers (P=0.101). Among those patients with a smoking history, heavy smokers with >42.5 PYs of cigarettes had a poorer 5-year OS of 22.1% compared with light smokers, with a 5-year OS of 43.4% (P=0.006; Fig. 1F).

Univariate analysis of the impact of cigarette smoking on survival. Among the patients with ESCC, univariate analyses identified drinking history (HR 1.57; 95% CI 1.25-1.98; P<0.001), advanced T stage (HR 1.40; 95% CI 1.17-1.67; P<0.001), advanced M stage (HR 1.54; 95% CI 1.21-1.95; P<0.001), advanced clinical stage (HR 1.62; 95%CI 1.28-2.05; P<0.001) and smoking history (HR 1.86; 95% CI 1.42-2.44; P<0.001) as significant risk factors for shorter OS (Table II). Female patients had a longer OS than male patients (HR 0.57; 95% CI 0.41-0.79; P<0.001). Restricted to those patients with a smoking history, Higher PYs (>47.5) was a significant risk factor for shorter OS comparing to low PYs (≤47.5) (HR 1.70; 95% CI 1.26-2.30; P=0.001). Similar results were found in those patients receiving 3DRT/IMRT.

Multivariate analysis of the impact of cigarette smoking on survival. The number of PYs had linear effects on OS in most cases, which was proven by the analysis using RCS nested within Cox modes (data not shown). In the multivariate analysis, the smoking status (former and current smokers vs. never smokers), T-stage and M-stage were identified as significant and independent prognostic factors for OS for the entire population and the patients treated with IMRT/3DCRT (Table III). PYs (heavy vs. light smokers) were had similar results (Table III).

In addition, the authors of the current study also assessed the association between smoking history and OS across strata of other potential predictors of patient outcome in the entire population (Table IV). The impact of the age, drinking status, tumor location or chemotherapy on the risk of death was not significantly affected by the smoking history. The effect of a history of smoking to increase the risk of death was restricted to male patients (adjusted HR=1.63; 95% CI, 1.08-2.45; P=0.020), as well as patients with a low degree of differentiation (adjusted HR=3.47; 95% CI, 1.08-11.19; P=0.037), a clinical stage of II/III (adjusted HR=1.44; 95% CI, 1.02-2.04; P=0.039) and treatment by 3DCRT/IMRT (adjusted HR=1.74; 95% CI, 1.12-2.68; P=0.013). No significant impact was observed among female patients, possibly due to small sample sizes. Of note, a different result was obtained for patients with 2DRT: A smoking history had a positive impact on OS (HR=0.34; 95% CI 0.12-0.91; P=0.033). This result is unexpected as it was hypothesized that a history of smoking would negatively impact OS; this notable result may be due to the small sample size, as only 72 patients received 2DRT, and among them, 17 were never smokers, 7 were former smokers and 48 were current smokers.

The impact of smoking on survival was then further assessed in detail (Table V). A smoking history (HR=1.57; 95% CI, 1.06-2.32; P=0.025) and current smoking (HR=3.01; 95% CI, 1.15-7.86; P=0.025) as opposed to a never-smoking

Table I. Demographic and clinicopathological characteristics of patients with esophageal squamous cell carcinoma by status of smoking.

Characteristics	All (n=479)	Never smoker (n=171)	Former smoker (n=43)	Current smoker (n=265)	P-value
Age (years)					0.002
<60	234 (48.9)	79 (46.2)	11 (25.6)	144 (54.3)	
≥60	245 (51.1)	92 (53.8)	32 (74.4)	121 (45.7)	
Sex					<0.001
Male	379 (79.1)	75 (43.9)	42 (97.7)	262 (98.9)	
Female	100 (20.9)	96 (56.1)	1 (2.3)	3 (1.1)	
Drinking					<0.001
No	294 (61.4)	156 (91.2)	22 (51.2)	116 (43.8)	
Yes	185 (38.6)	15 (8.8)	21 (48.8)	149 (56.2)	
Tumor grade					0.020
High	124 (25.9)	59 (34.5)	11 (25.6)	54 (20.4)	
Intermediate	278 (58.0)	86 (50.3)	27 (62.8)	165 (62.3)	
Low	77 (16.1)	26 (15.2)	5 (11.6)	46 (17.3)	
Tumor location					0.040
Cervical	63 (13.2)	27 (15.8)	4 (9.3)	32 (12.1)	
Upper[a]	140 (29.2)	55 (32.2)	12 (27.9)	73 (27.5)	
Middle[b]	242 (50.5)	80 (46.7)	18 (41.9)	144 (54.4)	
Lower[c]	34 (7.1)	9 (5.3)	9 (20.9)	16 (6.0)	
T-stage					0.768
T2	82 (17.1)	31 (18.1)	6 (14.0)	45 (17.0)	
T3	263 (54.9)	95 (55.6)	27 (62.8)	141 (53.2)	
T4	134 (28.0)	45 (26.3)	10 (23.2)	79 (29.8)	
N-stage					0.162
N0	53 (11.1)	25 (14.6)	3 (7.0)	25 (9.4)	
N1	426 (88.9)	146 (85.4)	40 (93.0)	240 (90.6)	
M-stage					0.797
M0	303 (63.3)	109 (63.7)	29 (67.4)	165 (62.3)	
M1a	176 (36.7)	62 (36.3)	14 (32.6)	100 (37.7)	
Clinical stage					0.629
II	75 (15.6)	32 (18.7)	7 (16.3)	36 (13.6)	
III	227 (47.4)	79 (46.2)	22 (51.2)	126 (47.5)	
IV	177 (37.0)	60 (35.1)	14 (32.5)	103 (38.9)	
Treatment					0.007
RT alone	56 (11.7)	27 (15.8)	11 (25.6)	18 (6.8)	
CCRT	336 (70.1)	114 (66.7)	27 (62.8)	195 (73.6)	
IC+CCRT	52 (10.9)	19 (11.1)	3 (7.0)	30 (11.3)	
CCRT+AC	35 (7.3)	11 (6.4)	2 (4.6)	22 (8.3)	
RT technique					0.151
2D RT	72 (15.0)	17 (9.9)	7 (16.3)	48 (18.1)	
3DCRT	298 (62.2)	108 (63.2)	27 (62.8)	163 (61.5)	
IMRT	109 (22.8)	46 (26.9)	9 (20.9)	54 (20.4)	

Values are expressed as n (%). [a]Upper, [b]middle and [c]lower third of thoracic esophagus based on the UICC stage system. CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; AC, adjuvant chemotherapy; RT, radiation therapy; 2DRT, two-dimensional RT; 3DCRT, three-dimensional conformal RT; IMRT, intensity-modulated RT.

status, was associated with a higher of risk of death. The risk of death for heavy smokers was higher than that for light smokers, with an HR of 1.75 (95% CI, 1.28-2.41; P<0.001). When the PYs were evaluated as a continuous variable, the
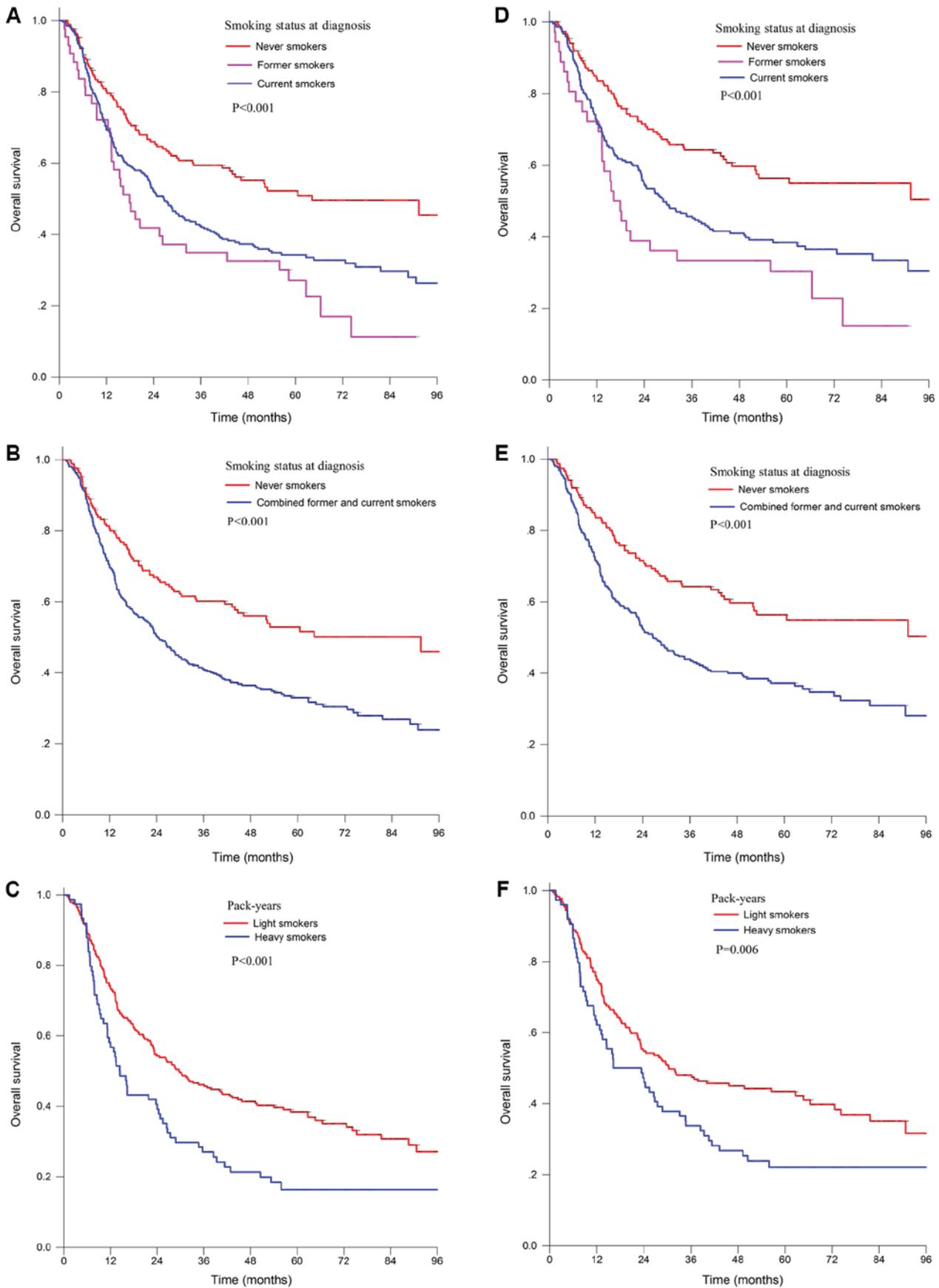
Figure 1. Kaplan-Meier curves for overall survival (A-C) in the entire study population and (D-F) the cohort subjected to IMRT or 3DRT according to smoking status at diagnosis. Patients were stratified according to (A and D) the smoking status (never, former and current), (B and E) the smoking history (no and yes) and (C and F) PYs (light and heavy). A former smoker was defined as an individual who had not smoked for 12 months or more prior to treatment A PY was defined as the equivalent of smoking one pack of cigarettes per day for 1 year. The cutoff value was 47.5 pack-years in the entire study population and 42.5 pack-years in the cohort subjected to IMRT/3DRT. PY, pack year. IMRT, intensity-modulated radiation therapy; 3DRT, three-dimensional conformal radiation therapy.

Table II. Univariate analysis in patients with esophageal squamous cell carcinoma.

Variable	Entire population		IMRT/3DRT cohort	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (≥60 vs. <60 years)	1.12 (0.88-1.41)	0.360	1.21 (0.93-1.57)	0.165
Sex (female vs. male)	0.57 (0.41-0.79)	0.001	0.49 (0.34-0.72)	<0.001
Drinking (yes vs. no)	1.57 (1.25-1.98)	<0.001	1.56 (1.20-2.03)	0.001
Tumor grade (high/intermediate vs. low)	1.02 (0.75-1.39)	0.895	0.96 (0.67-1.39)	0.847
Tumor location (cervical/upper vs. middle/lower)	1.16 (0.92-1.47)	0.216	1.15 (0.88-1.51)	0.289
T-stage (T4 vs. T3 /T2)	1.40 (1.17-1.67)	<0.001	1.31 (1.07-1.59)	0.009
N-stage (N1 vs. N0)	1.48 (0.98-2.24)	0.060	2.10 (1.22-3.61)	0.008
M-stage (M1a vs. M0)	1.54 (1.21-1.95)	<0.001	1.55 (1.18-2.02)	0.001
Clinical stage (IV vs. II/III)	1.62 (1.28-2.05)	<0.001	1.62 (1.24-2.12)	<0.001
Chemotherapy (yes vs. no)	0.64 (0.45-0.89)	0.009	0.69 (0.47-1.02)	0.065
RT technology (IMRT/3DRT vs. 2DRT)	0.46 (0.35-0.62)	<0.001	-	-
Smoking history	1.86 (1.42-2.44)	<0.001	2.07 (1.53-2.82)	<0.001
PYs	1.70 (1.26-2.30)[a]	0.001	1.56 (1.13-2.16)[b]	0.007

[a]≤ vs. >47.5; [b]≤ vs. >42.5. HR, hazard ratio; CI, confidence interval; RT, radiation therapy; 2DRT, two-dimensional RT; 3DCRT, three-dimensional conformal RT; IMRT, intensity-modulated RT.

HR for death increased by 1% per pack-year (HR=1.01; 95% CI, 1.003-1.011; P=0.004).

In the subgroup of patients treated with IMRT/3DCRT, the HR for death was 1.53 (95% CI, 1.02-2.30; P=0.039) for former smokers and 3.00 (95% CI, 1.14-7.86; P=0.025) for current smokers, compared with that for never smokers. Heavy smokers had a higher risk of death than light smokers, with an HR of 1.55 (95% CI, 1.11-2.16; P=0.011). Similarly, when the pack-years was evaluated as a continuous variable, the HR for death increased by 1% per pack-year (HR=1.01; 95% CI, 1.004-1.012; P=0.016).

Discussion

The present study on 479 patients with ESCC receiving RT with or without chemotherapy indicated that smoking was an independent prognostic factor for poor survival after adjustment for other known prognostic factors, including age, sex, drinking status, degree of differentiation, tumor location, T-stage, N-Stage, M-stage, clinical stage, chemotherapy administration and radiation technique. The risk of death was also identified to be increased depending on the PYs of cigarettes. A specific analysis of the cohort of 407 patients treated with 3DCRT/IMRT was also performed to account for the heterogeneity of RT techniques. Considering that virtually all current smoking patients were male, an analysis based on sex was also performed revealing that smoking had a significant impact on death among male patients (adjusted HR=1.63; 95% CI, 1.08-2.45; P=0.020) but in not female patients (adjusted HR=0.40; 95% CI, 0.04-3.63; P=0.400), possibly due to small sample sizes. Finally, the impact of long-term smoking on OS was assessed by treating the number of PYs as a continuous variable. The resulting HRs for death increased by a small but significant value between 0.003 and 0.011. A previous study

reported a similar result, namely that smoking decreased the OS of patients with oropharyngeal cancer by 1% per PY of smoking (28). The small sample size may be one of the reasons for the unsatisfactory interval between 0.003 and 0.011 obtained in the present study.

According to the 2014 Surgeon General's Report on smoking and tobacco use, there is sufficient evidence to infer a causal association between cigarette smoking and increased all-cause mortality and cancer-specific mortality, but is not sufficient to infer a causal association between cigarette smoking and the risk of recurrence, poorer response to treatment and increased treatment-associated toxicity (29). A review discussing the known biological effects of smoking on cancer cell biology emphasized the clinical effects of continued smoking in patients with cancer treated with chemotherapy or RT (30). Smoking causes adverse outcomes in patients with cancer, leading to complications associated with cancer treatment and continued development of comorbid disease (30). The two aforementioned studies considered lung cancer, prostate cancer, head and neck cancer, breast cancer, cervical cancer, Hodgkin's disease, colon cancer and male cancer patients (29,30). However, few studies focused on patients with ESCC receiving RT with or without chemotherapy. The study by Shitara *et al* (31) indicated that heavy cigarette smoking (cumulative smoking of >20 PYs) was a poor prognostic factor in patients with ESCC who had been treated by chemoradiotherapy. However, in their analysis, non-smokers and light smokers were combined into a group of non-heavy smokers (cumulative smoking of up to 20 PY), which may have introduced bias and only provides limited information on the effect of smoking behavior (31). An analysis of 1,084 patients with ESCC revealed a significant association between OS and smoking history in the group treated with chemotherapy plus surgery, but not in that treated with surgery alone (15). That

Table III. Multivariate regression analysis in patients with esophageal squamous cell carcinoma using the Cox proportional hazards model for overall survival in terms of smoking history (smoking history vs. no smoking history) and PYs (heavy vs. light smokers).

| | Entire population | | | | IMRT/3DRT cohort | | | |
| | Smoking history (n=479) | | PYs[a,c] (n=308) | | Smoking history (n=407) | | PYs[b,c] (n=253) | |
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (≥60 vs. <60 years)	1.27 (0.99-1.62)	0.06	1.05 (0.78-1.41)	0.766	1.29 (0.98-1.69)	0.07	1.11 (0.81-1.53)	0.52
Sex (female vs. male)	0.92 (0.59-1.44)	0.71	1.05 (0.32-3.45)	0.933	0.84 (0.511.41)	0.52	1.17 (0.28-4.94)	0.82
Drinking (yes vs. no)	1.17 (0.89-1.53)	0.24	1.05 (0.79-1.41)	0.725	1.13 (0.84-1.52)	0.42	1.02 (0.74-1.41)	0.78
Tumor grade (high/intermediate vs. low)	1.00 (0.83-1.20)	0.99	1.05 (0.84-1.31)	0.657	0.98 (0.79-1.21)	0.83	1.02 (0.78-1.32)	0.92
Tumor location (cervical/upper vs. middle/lower)	1.09 (0.93-1.26)	0.28	1.09 (0.91-1.31)	0.333	1.08 (0.91-1.28)	0.35	1.04 (0.85-1.27)	0.74
T-stage (T4 vs. T3 /T2)	1.45 (1.21-1.75)	<0.001	1.59 (1.28-1.99)	<0.001	1.34 (1.09-1.65)	0.01	1.41 (1.11-1.81)	0.01
N-stage (N1 vs. N0)	1.18 (0.78-1.80)	0.43	0.95 (0.59-1.55)	0.854	1.54 (0.89-2.69)	0.13	1.34 (0.67-2.66)	0.40
M-stage (M1a vs. M0)	1.69 (1.32-2.16)	<0.001	1.75 (1.31-2.34)	<0.001	1.53 (1.17-2.02)	0.01	1.69 (1.23-2.34)	0.001
Chemotherapy (yes vs. no)	0.92 (0.83-1.03)	0.14	0.89 (0.78-1.01)	0.069	0.97 (0.86-1.09)	0.62	0.93 (0.81-1.07)	0.32
RT technology (IMRT/3DRT vs. 2DRT)	0.76 (0.61-0.93)	0.01	0.86 (0.68-1.09)	0.220	-	-	-	-
Smoking history	1.57 (1.06-2.31)	0.02	-	-	1.74 (1.12-2.68)	0.01	-	-
PYs	-	-	1.75 (1.28-2.41)[a]	<0.001	-	-	1.55 (1.11-2.16)[b]	0.01

[a] ≤ vs. >47.5; [b] ≤ vs. >42.5. [c] Analysis for those patients having a smoking history. PY, pack year; RT, radiation therapy; HR, hazard ratio; CI, confidence interval.

Table IV. Impact of clinicopathological characteristics on 5-year OS in the entire population and effect of the smoking history on the survival of patients with esophageal squamous cell carcinoma in subgroups by clinicopathological characteristics.

Factor	5-year OS (%)	P-value[a]	No. of deaths/total no. of patients in the group		Adjusted HR of mortality (95%CI)	P-value[b]
			No smoking history	Smoking history		
Total	39.5		68/164	218/315	1.57 (1.06-2.31)	0.025
Age (years)		0.359				
<60	41.6		30/77	107/157	1.54 (0.86-2.75)	0.139
≥60	37.5		38/87	111/158	1.57 (0.91-2.70)	0.102
Sex		0.001				
Male	35.7		29/68	215/311	1.63 (1.08-2.45)	0.020
Female	55.0		39/96	3/4	0.40 (0.04-3.63)	0.400
Drinking		<0.001				
No	47.1		61/152	91/142	1.56 (1.00-2.43)	0.052
Yes	28.2		7/12	127/173	1.19 (0.54-2.64)	0.663
Degree of differentiation		0.895				
High/intermediate	39.6		59/140	179/261	1.38 (0.90-2.09)	0.136
Low	38.9		24/96	53/97	3.47 (1.08-11.19)	0.037
Tumor location		0.215				
Cervical/upper[c]	42.0		32/79	86/123	1.70 (0.94-3.07)	0.077
Middle[d]/lower[e]	37.7		35/84	132/192	1.61 (0.93-1.79)	0.090
Clinical stage		<0.001				
II+III	46.0		39/108	123/194	1.44 (1.02-2.04)	0.039
IV	28.1		29/56	95/121	1.57 (0.85-2.87)	0.146
Chemotherapy		0.008				
No	21.3		14/26	25/30	2.04 (0.69-6.05)	0.197
Yes	41.7		54/138	193/285	1.44 (0.95-2.20)	0.090
Radiation technique		<0.001				
2DRT	15.0		14/17	48/55	0.34 (0.12-0.91)	0.033
3DCRT/IMRT	44.1		54/147	170/260	1.74 (1.12-2.68)	0.013

Adjusted HR was adjusted for age, sex, drinking status, degree of differentiation, tumor location, clinical stage, chemotherapy and radiation technique. [a]P for OS by each factor; [b]P for patients with a smoking history vs. no smoking history. RT, radiation therapy; HR, hazard ratio; CI, confidence interval; 2DRT, two-dimensional RT; 3DCRT, three-dimensional conformal RT; IMRT, intensity-modulated RT; OS, overall survival. [c]Upper, [d]middle and [e]lower third of thoracic esophagus based on the UICC stage system.

study indicated that smoking affected the outcome of chemotherapy. In a recent study, which focused on patients receiving definitive RT or concurrent chemoradiotherapy, cigarette smoking was identified as a significant and independent poor prognostic risk factor for OS by a multivariate Cox regression analysis (18). Two groups of patients received esophagectomy after chemoradiotherapy, which may have caused bias. The study by Zhang *et al* (16) reported a negative result, namely that smoking was not a prognostic factor for survival of patients with ESCC who received definitive RT. However, the cohort comprised only 79 patients. In the present study, all of the patients received RT and 70.1% of patients received chemotherapy. Therefore, the present results more strongly support the view that smoking is an independent predictor of poorer survival for patients with ESCC who received RT with or without chemotherapy.

In the present study, smoking had a significant impact on the risk of death among male but not female patients, possibly due to small sample sizes. No impact of smoking on survival was observed in breast cancer patients (32,33). In addition, no significant impact of smoking on OS was obtained in female patients with nasopharyngeal carcinoma (34). The reason may be that smoking in quantity and intensity is less frequent among women than among men. However, with the amount of women actively and passively smoking increasing, this association may change (35). In the present study, 100 female patients were included, of which only four of had a history of smoking. Thus, more samples of female patients are required

Table V. Effect of smoking history on overall survival in patients with esophageal squamous cell carcinoma after adjustment for potential prognostic factors.[a]

Variable	Entire population		IMRT/3DCRT cohort	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Smoking status at diagnosis				
Former vs. never	1.57 (1.06-2.32)	0.025	1.53 (1.02-2.30)	0.039
Current vs. never	3.01 (1.15-7.86)	0.025	3.00 (1.14-7.86)	0.025
PYs				
Heavy vs. light	1.75 (1.28-2.41)[b]	<0.001	1.55 (1.11-2.16)[c]	0.011
Continuous PYs	1.01 (1.003-1.011)	0.004	1.01 (1.004-1.012)	0.016

[a]Adjusted for age (<60 vs. >60 years), sex, drinking (no vs. yes), tumor location, tumor grade, T-stage, N-stage, M-stage (M0 vs. M1a) treatment and radiation technology. [b]PYs: ≤ vs. >47.5. [c]PYs: ≤ vs. >42.5. HR, hazard ratio; CI, confidence interval; 3DCRT, 3-dimensional conformal RT; IMRT, intensity-modulated RT; RT, radiation therapy; PYs, pack years.

to evaluate the impact of smoking on survival of patients with ESCC receiving RT with or without chemotherapy.

No significant difference of OS was identified between former and current smokers, and the two groups had a similarly poor survival compared with never smokers (P<0.001). The relatively poor survival for smokers with a higher number of PYs compared with those with a low number of PYs demonstrated the unfavorable cumulative effects of long-term, heavy smoking. The negative influence of smoking on survival was still maintained in the former smokers. Despite the cessation of smoking for >1 year, the possible impact of smoking on exacerbating tissue hypoxia, which induces the expression of a variety of genes associated with an aggressive malignant phenotype, and promoting chemoradioresistance and tumor progression may have already occurred and remains in these former smokers (21,36,37). Furthermore, continued smoking after diagnosis may reduce the efficacy of anti-cancer treatment and increase the proportion of cancer stem-like cells, resulting in a poor outcome; in addition, increased higher rates of treatment complications and side effects, such as higher treatment-associated weight loss, lead to a poorer quality of life (38-43). A study reported that 60% of patients smoked during the week prior to surgery and 13% who were abstinent prior to surgery had resumed smoking (44). Their relapse of smoking was probably associated with a higher perceived difficulty in quitting, higher tendency toward depression, greater fears regarding cancer recurrence, a lower quitting self-efficacy and a lower perception regarding their cancer-associated risk. In addition, cessation of smoking after a cancer diagnosis was reported to significantly reduce the risk of death compared with persistent smoking (29). For the cohort of the present study, data on the smoking status during treatment or follow-up are lacking; therefore, the possibility that certain former smokers resumed smoking during treatment or follow-up cannot be excluded. Evidence-supported measures that increase chances of cessation include direct physician advice, approved pharmacotherapy, structured counseling and a follow-up plan (45). Individual behavioral counseling, a combination of pharmacological and behavioral interventions for smoking cessation, are effective in assisting smokers to quit (46).

Of note, the present study has certain limitations. First, there was an inherent bias owing to the study's retrospective design. The smoking and drinking status at diagnosis were based on the medical records, rather than standardized questionnaires at enrollment. Furthermore, in the present cohort, males accounted for the majority and few female patients had a smoking history (four smokers among 100 female patients), indicating that the present results may only apply to males. The patients included were all from Southern China, and the applicability of the present results to patients from other geographical areas remains elusive. In addition, the patients were re-staged using the sixth AJCC/UICC staging system and not the most recent staging system according to which the N-stage is based on the number of positive lymph nodes. In the sixth AJCC/UICC staging system, N-stage was defined as with or without regional lymph node. The difference in N-stage may change the treatment strategies. Furthermore, there was heterogeneity in the chemotherapy regimens, administration schedules and prescription doses, which ranged from 50.4 to 66.0 Gy or even higher doses (7 patients received >66.0 Gy; the maximum dose received by any one patients was 70 Gy).

Finally, the treatment strategies were not entirely consistent with the latest NCCN guidelines. For instance, the T2 patients did not receive surgery due to rejection or intolerance of surgery, a group for whom surgery is the primary treatment, and some T3-T4 patients did not receive induction chemoradiotherapy followed by surgery. There were various reasons why those patients did not receive surgery. The patients with a location of the tumor in the lower esophagus, for whom surgery is the preferred treatment, only accounted for 7.1%. Certain patients had comorbidities based on which they were not able to tolerate surgery. Certain patients refused surgery considering the associated complications and cost. The cohort was restricted to those subjects who received RT, with or without chemotherapy, not those who received surgery. Furthermore, induction chemotherapy followed by surgery is the standard treatment for EC according to the NCCN guidelines. The evidence that these guidelines are based on mostly comes from Western countries, in which EA is the pre-dominant subtype; however, in China, the most prevalent subtype is ESCC.

The most common location of the tumor in Western countries is the lower esophagus, for which surgery is the preferred choice. In China, the tumor is located in the cervical and upper esophagus for most cases, for which surgery is more difficult. At our institution, the treatment strategies for the patients with ESCC were discussed by a multidisciplinary team, according to the NCCN guidelines and the status of the patients. The final treatment plan was based on the NCCN guidelines, the specific situation and the choice of each patient. Among the T2 patients in the present study, 44% (36/82) had a tumor located in the cervical and upper esophagus, and 81.7% of cases (67/82) were N1. To reduce the bias caused by the treatment strategy and selection, sub-group analyses were performed to evaluate the association between the smoking history and OS. In addition to an analysis of the entire population, those patients who received 3DCRT/IMRT were also assessed separately, and similarly significant results were obtained. It is important to validate the present results in a prospective study with an independent cohort.

In conclusion, the present study indicated that a smoking history at diagnosis was an independent prognostic factor for poor survival among patients with ESCC. This result may help to manage the tobacco use among patients with ESCC. The smoking status should be taken into consideration in prospective studies on ESCC. The present results require to be validated in future studies and the molecular/genetic mechanism of the effect of smoking on ESCC should be further elucidated and interpreted.

Acknowledgements

Availability of data and materials

All data generated or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

All the authors were involved in conceiving and designing the study. GRZ, ZS and JYL collected the data. GRZ performed the statistical analysis. GRZ and ZS drafted and wrote the manuscript. FYX and QL gave advice on the study design, interpreted the results and critically revised the manuscript. All authors have read and approved the final version of the manuscript.

Ethical approval and consent to participate

This study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center (Guangzhou, China) and Panyu Central Hospital (Guangzhou, China). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Patient records were anonymized and de-identified prior to analysis. Written informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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