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Family History of Cancer is associated with poorer prognosis in Oral Squamous Cell Carcinoma

Running title: FHC contributes to poor prognosis in OSCC

Key Words: oral squamous cell carcinoma; family history of cancer; prospective database; prognosis

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Abstract

Objective: The purpose of this study was to investigate the prognostic value of the family history of cancer (FHC) in predicting survival and clinicopathological features in oral squamous cell carcinoma (OSCC) patients.

Materials and Methods: This single-institution study utilized data from 610 patients undergoing surgery from 2014 to 2020 that was prospectively collected and cataloged for research purposes. All patients underwent standard surgery with/without radiotherapy or chemoradiotherapy. We statistically evaluated whether FHC was associated with changes in disease-free survival (DFS) and disease-specific survival (DSS).

Results: Among 610 patients, 141 (23.1%) reported a family history of cancer. The distribution of clinicopathological characteristics was balanced between FHC-positive and FHC-negative OSCC patients. FHC-positive patients had decreased DFS (P=0.005) and DSS (P=0.018) compared to FHC-negative patients.

Conclusions: FHC-positive OSCC patients have a poorer prognosis. FHC positivity is an independent predictor of negative outcomes based on DFS and DSS. FHC should be a consideration in screening, evaluating, counseling, and treating OSCC patients.

1. INTRODUCTION

Oral squamous cell carcinoma (OSCC) is one of the most common cancers. In 2020, there were nearly 370,000 new cases of OSCC worldwide, resulting in 180,000 deaths (Sung et al., 2021). Tobacco/alcohol consumption and betel nut use are the primary risk factors for OSCC (Koyfman et al., 2019). Despite improvements in treatment modalities, the five-year survival rate of OSCC remains 60% - 70% (Nakashima et al., 2018). To improve this poor prognosis, discovering new prognostic factors is urgently required.

Family history of cancer (FHC), especially FHC in first-degree relatives (FDRs) is a recognized risk factor (Fantozzi et al., 2021; Hemminki, Li, & Czene, 2004; Negri et al., 2009; Radoi et al., 2013; Teerlink, Albright, Lins, & Cannon-Albright, 2012). The impact of FHC on prognosis has been discussed controversially in other cancer sites (Chan et al., 2008; Chattopadhyay et al., 2020; Han et al., 2012; Lee, Reilly, Lindstrom, & Czene, 2017; Ouyang et al., 2013; Yuequan, Shifeng, & Bing, 2010). However, high-level evidence for the prognostic value of FHC in OSCC remains lacking. A match-pair study by Cui et al. found that FHC was associated with improved DSS (disease-specific survival) in surgically treated OSCC patients (Cui et al., 2020). Getz et al. found that FHC-positive HNC patients have improved DSS, while this survival advantage was only observed in tobacco and alcohol users (Getz et al., 2017). In contrast, Renkonen et al. found that HNC patients with HNC-FHC had a 1.34-fold increased risk of DSS (Renkonen, Lee, Makitie, Lindstrom, & Czene, 2017). Differences in cancer type, ethnicity, region, and diet could be potential factors to explain this variation in outcomes

(Arnold et al., 2017), as the latter two studies include multiple parts of the head and neck. In addition, these studies above were limited by retrospective nature, and therefore had a high risk of bias.

In this study, we incorporated data from our prospective database and aimed to investigate the prognostic value of FHC in predicting survival and clinicopathological features in OSCC patients.

2. MATERIALS AND METHODS

Patients and data extraction:

To address the research question, this research was conducted in full accordance with the World Medical Association Declaration of Helsinki (2002 version). All patient data were obtained from the IRB-approved Prospective, Observational, Real-world Oral Malignant Tumors Study – POROMS (ClinicalTrials.gov identifier: NCT02395367). POROMS enrolled patients prospectively from December 2014 to December 2020. All patients were newly diagnosed and pathologically confirmed HNSCC treated in the Department of Oral and Maxillofacial-Head and Neck Oncology, Beijing Stomatological Hospital, Capital Medical University. No restrictions on age. Inclusion criteria for the current study were first-time diagnosed OSCC patients (772 patients). Among them, 95 (12.3%) patients who refused or were not offered (due to medical conditions) surgery were excluded. In addition, 56 (7.3%) patients were excluded due to pathologically confirmed carcinoma in situ, and 11 (1.4%) patients were lost to follow-up after surgery. In the end, 610 (79.0%) patients who met the study

criteria were included for analysis. (Figure 1)

Management

The treatment has been described in our previous research (Xu, Wang, Yuan, Feng, & Han, 2017). All included patients underwent surgery to remove the primary tumor. Standard surgery, including radical tumor resection, neck dissection as well as reconstruction of tissue defects (as necessary), was performed. Local excision of the primary site was performed with a minimum margin of 15 mm. Patients who had pT3 and pT4, pN+, perineural invasion, and/or vascular emboli were recommended to receive radiotherapy, whereas patients who presented with extracapsular spread (ECS) and/or positive margins were recommended to receive chemo-radiotherapy.

Variables:

Information on the enrolled patients, including age, gender, sites, clinical features, pT stage, pN stage, tumor stage, depth of invasion (DOI), ECS, histological differentiation, smoking status and alcohol (ethanol) use, personal history of cancer, precancerous lesion, diagnostic delay time and management were extracted and analyzed based on the UICC/AJCC Eighth Edition staging system (Amin et al., 2017). Current smokers/drinkers were defined as those who smoked/drank at the time of diagnosis or had quit tobacco/alcohol for less than one month. Previous smokers/drinkers were defined as those who had quit tobacco/alcohol for at least one month before treatment. Diagnostic delay time was defined as the duration from the first detection of a sign/symptom to seeking health care (Guneri & Epstein, 2014).

Family history assessment:

FHC was determined by questioning the patient and/or family members at the time of initial diagnosis. FHC was considered positive if evidence existed for a malignant tumor in a first or second-degree relative consistent with other studies (Rogoza-Janiszewska et al., 2020). First-degree relatives (FDRs) included parents, siblings, and offspring while second-degree relatives (SDRs) included aunts, uncles, nieces, nephews, and grandparents. (An, Chang, Kim, Song, & Shim, 2019)

Follow-up:

Patients were followed with routine in-person visits or by telephone. The date of the surgery was considered as time zero and the study endpoint was death or loss to follow-up. The last visit date allowable for the study was March 2022.

Our primary outcome variable was disease-free survival (DFS), calculated as the length of time from the first operation until the first documented recurrence, metastasis, second primary cancer, or death. The secondary outcome variable was disease-specific survival (DSS), calculated as the length of time from the first operation to cancer-related death.

Statistical analyses:

Differences in demographic characteristics were tested using the Wilcoxon rank-sum test or the Chi-square test or the two-sided Fisher's exact test, as appropriate. The outcome variables were analyzed with the Kaplan-Meier method using the log-rank test. The hazard ratio (HR) and 95% confidence interval (CI) were used for log-ranking survival analysis, and then the significant factors in the univariate analysis were analyzed by Cox proportional risk model *(enter method)* to determine independent

prognostic factors. The *P*-value was set at 0.05 using a two-tailed approach. All statistical analyses were performed using SPSS 26.0 and GraphPad Prism 8.

3. RESULTS

Patient characteristics:

A total of 610 cases of OSCC were included in this study. Age ranged from 16 to 85 years with a median age of 61 (first quartile to third quartile = 53 to 67). There were 354 males (58.0%) and 256 females (42.0%). Primary tumor location was tongue in 259 patients (42.5%), inferior gingiva in 115 (18.9%), buccal in 112 patients (18.4%), upper gingiva in 58 patients (9.5%), floor of the mouth in 52 patients (8.5%) and hard palate in 14 patients (2.3%). The most frequent clinical stages were stage IV (293 cases, 48.0%), followed by stage II (141 cases, 23.1%), stage III (96 cases, 15.7%), and stage I (80 cases, 13.1%). Among 610 patients, 386 (63.3%) patients received surgery alone, 156 (25.6%) received adjuvant RT and 48 (7.9%) received adjuvant CCRT, details of postoperative treatment in 20 (3.3%) patients were unclear. The distribution of demographic and clinicopathological characteristics was balanced between FHC-positive and negative patients (Table 1).

Fifty-one of 610 patients (8.4%) had a personal history of previous malignancy. Positive FHC was found in 141 (23.1%) patients while 469 patients (76.9%) were FHC-negative. Among FHC-positive patients, the sites of cancer found included the respiratory system (38 cases, 21.1%), liver (25 cases, 13.9%), esophagus (24 cases, 13.3%), other sites including the stomach (17 cases, 9.4%), breast (16 cases, 8.9%),

colon and rectum (10 cases, 5.6%). Seventy-six patients (53.9%) had a family history of upper airway/digestive tract cancer. Most patients (111 cases, 78.7%) had a single relative with cancer. The results are shown in Table 2.

Effect of family history of cancer on survival:

Patient follow-up time ranged from 0.3 to 87 months, with a mean follow-up time of 33.9 ± 21.9 months and a median follow-up time of 30.0 months. As of the last follow-up visit, 132 patients died (Table 3). The leading cause of death in these cases was disease progression (100 cases, 75.8%), including locoregional recurrence and distant metastasis. Death causes also included second primary cancer (6 cases, 4.5%), other cancer-related causes (13 cases, 9.8%), and non-cancer-related causes (13 cases, 9.8%) (One patient died on postoperative day ten due to pulmonary embolism). Among FHC-positive patients, 30 (76.9%) died from disease progression, 3 (7.7%) died from the second primary cancer, 3 (7.7%) died from disease-related causes, and 3 (7.7%) died from intercurrent (noncancer) causes. Among FHC-negative patients, 70 (75.3%) died of disease progression, 3 (3.2%) died of second primary cancer, 10 (10.8%) died of disease-related causes, and 10 (10.8%) died of intercurrent (noncancer) death. However, there was no significant difference in the cause of death between the two groups (P=0.676).

Based on Kaplan-Meier survival analysis, the risk of relapse or metastasis in FHC-positive patients was significantly higher (P=0.005) (Figure 2). This difference remained after adjustment for potential confounders (HR: 1.540; 95% CI: 1.128~2.102; P=0.007). Multivariate analysis revealed tumor stage, histological differentiation, and

FHC as independent prognostic factors for DFS (Table 4). Furthermore, FHC-positive patients demonstrated significantly higher rates of cancer-related death (P=0.018) (Figure 3). Further multivariate analyses indicated that FHC was also an independent prognostic factor for DSS after adjusting for confounders (HR: 1.760; 95%CI: 1.184~2.617; P=0.005), along with age, tumor stage, and histological differentiation (Table 5). However, there was no significant difference in the survival time of patients in terms of the number of cancer relatives or whether there was a family history of upper airway/digestive tract cancer after further stratification.

4. DISCUSSION

This study examined our prospective cohort POROMS data to address the research question of the impact of FHC on OSCC survival outcomes. Our analysis identified that FHC-positive patients had significantly worse DFS and DSS, and as such FHC was an independent negative prognostic factor for OSCC. This result is consistent with those of Renkonen et al. in patients with HNC (Renkonen et al., 2017). The adverse impact of a positive FHC has also been reported in patients with squamous cell skin cancer (Chattopadhyay et al., 2020), esophageal cancer (Yuequan et al., 2010), ovarian cancer, and neurological malignancy (Lee et al., 2017). Lifestyle factors such as tobacco/alcohol (ethanol) use are considered important influencers of survival and such habits may be passed on in families (Giraldi et al., 2017).

Debate exists as to how this impact occurs. In contrast, some previous studies have shown favorable outcomes for FHC-positive patients with the suggestion that those

with positive FHC tend to seek health-related behavioral changes, including regular physical activity and tobacco/alcohol cessation, resulting in improved survival outcomes (Drake, Dias, Teleka, Stocks, & Orho-Melander, 2020; Townsend, Steele, Richardson, & Stewart, 2013). On the other hand, the disease stage at the time of diagnosis has been considered one of the most important factors in prognosis (Guneri & Epstein, 2014). The presence of malignant tumors in relatives may increase family members' awareness of the risk of disease, leading them to seek genetic counseling and cancer screening, making it easier to diagnose the disease early.

Considering that many patients with carcinoma in situ develop from long-term chronic precancerous lesions of the oral mucosa, this study excluded these patients to make the diagnosis more accurate. However, there were neither statistically different distributions related to smoking and drinking in FHC-positive and negative patients nor differences in diagnostic delay (P=0.965), suggesting that at least for patients included in this study, no benefit from lifestyle improvement or early diagnosis was observed. The genetic influence remains a plausible theory. Although currently, only 5-10% of all cancers are due to a known inherited gene defect, it is still possible to assume that much about familial cancer syndromes and cancer susceptibility remains unknown (Cortellini et al., 2018; Garber & Offit, 2005). The proportion of cancers caused by genetic mutations is likely to be underestimated and therefore needs more research. FHC-positive patients may have a unique genetic predisposition, directly or indirectly affecting survival (Chattopadhyay et al., 2019; Chattopadhyay et al., 2020; Wood et al., 2012), regardless of whether they have the same type of cancer as their relatives (Frank,

Sundquist, Yu, Hemminki, & Hemminki, 2017).

In a multicenter retrospective study by Cortellini et al. (Cortellini et al., 2018; Cortellini et al., 2020), FHC-positive patients experienced greater benefit from immune checkpoint inhibitors, suggesting that underlying genetic alterations may lead to changes in immune sensitivity. As incorporating germline genetic testing into medical management has occurred in other tumors, for example, breast, ovarian, and bladder cancer, it may be proved helpful one day in OSCC treatment decisions (Nicolosi et al., 2019).

Although our study has several advantages including data collected prospectively for research and focus on the FHC influence on OSCC, there remain some limitations. First, family history was self-reported and therefore subject to recall bias (Fiederling, Shams, & Haug, 2016; Mai et al., 2011; Ziogas & Anton-Culver, 2003). It has been demonstrated that cancers in certain adjacent sites may be confused by family members (Kerber & Slattery, 1997; Murff, Spigel, & Syngal, 2004), and the narrative reliability of the history of malignant tumors of second-degree or third-degree relatives is low (Chan et al., 2008). In addition, this study was a single-center study with a relatively small sample size rather than other large-sample database studies (Liss et al., 2015; Tian et al., 2021). Finally, according to our previous study, 90% of locoregional, distant recurrences or second primary cancers in OSCC occur in the first two years after surgery (Feng, Niu, Zhang, Gao, & Guo, 2016). This study only observed the short-term effect of FHC on prognosis, its long-term effects need to be further explored. Future studies with larger sample sizes, more detailed patient data, and longer follow-

ups are required to overcome these limitations.

5. CONCLUSION

FHC-positive OSCC patients had a poorer prognosis. FHC positivity is an independent predictor of negative outcomes based on DFS and DSS. FHC should be a consideration in screening, evaluating, counseling, and treating OSCC patients.

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Figure legends

Figure 1. Flowchart outlining 610 OSCC patients included for analysis.

Figure 2. Comparison of disease-free survival between FHC-negative and FHC-positive patients. (*P*=0.005)

Figure 3. Comparison of disease-specific survival between FHC-negative and FHC-positive patients. (*P*=0.018)

Table 1. Comparison of clinical and pathologic variables in patients with or without a family history of cancer (n=610)

Variable	No. (%)	Family History of cancer		*P*
		No (n=469)	Yes (n=141)	
Age, years				0.807
≤60	293(48.0%)	224(47.8%)	69(48.9%)	
>60	317(52.0%)	245(52.2%)	72(51.1%)	
Gender				0.973
Male	354(58.0%)	272(58.0%)	82(58.2%)	
Female	256(42.0%)	197(42.0%)	59(41.8%)	
Sites				0.523
Tongue	259(42.5%)	199(42.4%)	60(42.6%)	
Inferior gingiva	115(18.9%)	95(20.3%)	20(14.2%)	
Buccal	112(18.4%)	85(18.1%)	27(19.1%)	
Floor of the mouth	52(8.5%)	39(8.3%)	13(9.2%)	
Upper gingiva	58(9.5%)	42(9.0%)	16(11.3%)	
Hard palate	14(2.3%)	9(1.9%)	5(3.5%)	
Clinical features				0.745
Exophytic	163(26.7%)	124(26.4%)	39(27.7%)	
Ulcerative	233(38.2%)	183(39.0%)	50(35.5%)	
Infiltrative	214(35.1%)	162(34.5%)	52(36.9%)	
pT stage				0.104
T1+T2	258(42.3%)	190(40.5%)	68(48.2%)	
T3+T4	352(57.7%)	279(59.5%)	73(51.8%)	
pN stage				0.951
N0	395(64.8%)	304(64.8%)	91(64.5%)	
N+	215(35.2%)	165(35.2%)	50(35.5%)	
Tumor stage				0.702
I+II	221(36.2%)	168(35.8%)	53(37.6%)	
III+IV	389(63.8%)	301(64.2%)	88(62.4%)	
Histological differentiation				0.416
Well	94(15.4%)	76(16.2%)	18(12.8%)	
Moderately	407(66.7%)	307(65.5%)	100(70.9%)	
Poor	24(3.9%)	21(4.5%)	3(2.1%)	
Unable to assess	85(13.9%)	65(13.9%)	20(14.2%)	
DOI				0.214
DOI≤5mm	224(36.7%)	168(35.8%)	56(39.7%)	
5mm<DOI≤10mm	171(28.0%)	127(27.1%)	44(31.2%)	
DOI>10mm	215(35.2%)	174(37.1%)	41(29.1%)	
ECS				0.24
No	561(92.0%)	428(91.3%)	133(94.3%)	
Yes	49(8.0%)	41(8.7%)	8(5.7%)	
Smoking status				0.206
Never smoker	342(56.1%)	269(57.4%)	73(51.8%)	

Current smoker	201(33.0%)	146(31.1%)	55(39.0%)	
Former smoker	67(11.0%)	54(11.5%)	13(9.2%)	
Alcohol (ethanol) use				0.588
Never drinker	376(61.6%)	292(62.3%)	84(59.6%)	
Current drinker	197(32.3%)	147(31.3%)	50(35.5%)	
Former drinker	37(6.1%)	30(6.4%)	7(5.0%)	
Personal history of cancer				0.071
No	559(91.6%)	435(92.8%)	124(87.9%)	
Yes	51(8.4%)	34(7.2%)	17(12.1%)	
Precancerous lesion				0.686
No	538(88.2%)	415(88.5%)	123(87.2%)	
Yes	72(11.8%)	54(11.5%)	18(12.8%)	
Diagnostic delay, months				0.965
0≤Delay time<3	389(63.8%)	297(63.3%)	92(65.2%)	
3≤Delay time<6	128(21.0%)	99(21.1%)	29(20.6%)	
6≤Delay time<12	58(9.5%)	46(9.8%)	12(8.5%)	
Delay time≥12	35(5.7%)	27(5.8%)	8(5.7%)	
Management				0.146
Surgery alone	386(63.3%)	303(64.6%)	83(58.9%)	
Surgery + RT	156(25.6%)	110(23.5%)	46(32.6%)	
Surgery + CCRT	48(7.9%)	39(8.3%)	9(6.4%)	
Missing	20(3.3%)	17(3.6%)	3(2.1%)	

Abbreviations. DOI: depth of invasion; ECS: extracapsular spread; RT : radiotherapy; CCRT: concurrent chemoradiotherapy.

Table 2. Distribution of family history of cancer and personal history of cancer

Type	No	%
Cancer Site in Relative (n=180)		
Respiratory system	38	21.1%
Liver	25	13.9%
Esophagus	24	13.3%
Stomach	17	9.4%
Breast	16	8.9%
Cancer of unknown primary	13	7.2%
Colon and rectum	10	5.6%
Oral cavity and pharynx	7	3.9%
Cervix	6	3.3%
Lymphohematopoietic system	6	3.3%
Pancreas	4	2.2%
Thyroid glands	3	1.7%
Prostate	2	1.1%
Ovary	2	1.1%
Brain	2	1.1%
Kidney	2	1.1%
Eye	1	0.6%
Muscular and connective tissues	1	0.6%
Peritoneum	1	0.6%
Upper airway/digestive tract cancer (n=141)		
No	65	46.1%
Yes	76	53.9%
No of relatives with cancer (n=141)		
1	111	78.7%
≥2	30	21.3%
Personal history of cancer (n=51)		
Female reproductive system[a]	12	23.5%
Head and neck[b]	11	21.6%
Lymphohematopoietic system	6	11.8%
Breast	5	9.8%
Stomach	4	7.8%
Esophagus	3	5.9%
Skin	3	5.9%
Colon and rectum	2	3.9%
Cancer of unknown primary	2	3.9%
Liver	1	2.0%
Brain	1	2.0%
Kidney	1	2.0%

[a]:including cervical, endometrial, and ovarian cancer; [b]:including lip, nasopharynx, oropharynx, hypopharynx, and larynx cancer.

Table 3. The details on causes of death*

Cause of death	Patients with negative FHC		Patients with positive FHC		All patients	
	Number (n=93)	%	Number (n=39)	%	Number (n=132)	%
Disease progression	70	75.3%	30	76.9%	100	75.8%
Locoregional progression	47	50.5%	20	51.3%	67	50.8%
Distant metastasis	15	16.1%	6	15.4%	21	15.9%
Locoregional progression+distant metastasis	8	8.6%	4	10.3%	12	9.1%
Second primary cancer[a]	3	3.2%	3	7.7%	6	4.5%
Disease-related	10	10.8%	3	7.7%	13	9.8%
Intercurrent (noncancer) death[b]	10	10.8%	3	7.7%	13	9.8%

*: $P = 0.676$ (*Fisher* exact test); [a]: Three due to esophageal cancer, one due to lung cancer, one due to leukemias, and one due to lymphomas; [b]: Six due to cardiovascular disease, three due to respiratory diseases, two due to accidents, one due to infectious diseases, and one due to autoimmune disease.

Table 4. Univariate analysis and cox model of the prognostic factors for DFS

Variable	Univariate, Log-Rank Test	Cox Model	
		P	HR (95% CI)[a]
Age, years (≤60 vs >60)	0.099		
Gender(male vs female)	0.720		
Sites	0.008	0.136	
Tongue			Ref.
Inferior gingiva		0.721	0.929(0.618~1.395)
Buccal		0.454	1.156(0.791~1.689)
Floor of the mouth		0.181	0.648(0.344~1.223)
Upper gingiva		0.534	1.174(0.707~1.950)
Hard palate		0.035	2.029(1.051~3.919)
Clinical features	0.220		
Exophytic			
Ulcerative			
Infiltrative			
pT stage(T3+T4 vs T1+T2)	0.002		
pN stage(N+ vs N0)	<0.001		
Tumor stage(III+IV vs I+II)	0.003	0.020	1.469(1.062~2.032)
Histological differentiation	0.001	0.007	
Well			Ref.
Moderately		0.015	1.794(1.119~2.876)
Poor		0.003	3.040(1.462~6.323)
Unable to assess		0.614	1.175(0.629~2.194)
DOI	0.002		
DOI≤5mm			
5mm<DOI<10mm			
DOI≥10mm			
ECS	<0.001		
Smoking status	0.693	0.936	
Never smoker			Ref.
Current smoker		0.849	1.039(0.703~1.533)
Former smoker		0.841	0.945(0.543~1.644)
Alcohol (ethanol) use	0.637	0.456	
Never drinker			Ref.
Current drinker		0.828	0.957(0.646~1.418)
Former drinker		0.216	0.612(0.281~1.332)

Personal history of cancer	0.425		
Precancerous lesion	0.867		
Family history	0.005	0.007	1.540(1.128~2.102)
Diagnostic delay, months	0.930		
0≤Delay time<3			
3≤Delay time<6			
6≤Delay time<12			
Delay time≥12			

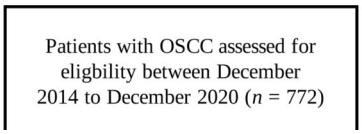
Abbreviations. DOI: depth of invasion; ECS: extracapsular spread; [a]: Multivariate HRs and 95% CIs are adjusted for sites, tumor stage, histological differentiation, smoking status, and alcohol (ethanol) use.

Table 5. Univariate analysis and cox model of the prognostic factors for DSS

Variable	Univariate, Log-Rank Test	Cox Model	
		P	HR (95% CI)[a]
Age, years (≤60 vs >60)	0.014	0.006	1.701(1.162~2.491)
Gender(male vs female)	0.044	0.147	0.690(0.417~1.139)
Sites	0.239		
Tongue			
Inferior gingiva			
Buccal			
Floor of the mouth			
Upper gingiva			
Hard palate			
Clinical features	0.208		
Exophytic			
Ulcerative			
Infiltrative			
pT stage(T3+T4 vs T1+T2)	<0.001		
pN stage(N+ vs N0)	<0.001		
Tumor stage(III+IV vs I+II)	<0.001	<0.001	3.587(2.120~6.068)
Histological differentiation	<0.001	<0.001	
Well			Ref.
Moderately		0.008	2.882(1.323~6.280)
Poor		<0.001	7.399(2.818~19.432)
Unable to assess		0.212	1.842(0.706~4.805)
DOI	<0.001		
DOI≤5mm			
5mm<DOI<10mm			
DOI≥10mm			
ECS	<0.001		
Smoking status	0.268	0.905	
Never smoker			Ref.
Current smoker		0.656	1.131(0.659~1.939)
Former smoker		0.807	1.089(0.550~2.155)
Alcohol (ethanol) use	0.240	0.053	
Never drinker			Ref.
Current drinker		0.120	0.668(0.402~1.111)
Former drinker		0.026	0.252(0.075~0.849)

Personal history of cancer	0.899			
Precancerous lesion	0.055			
Family history	0.018		0.005	1.760(1.184~2.617)
Diagnostic delay, months	0.487			
0≤Delay time<3				
3≤Delay time<6				
6≤Delay time<12				
Delay time≥12				

Abbreviations. DOI: depth of invasion; ECS: extracapsular spread; [a]: Multivariate HRs and 95% CIs are adjusted for age, gender, tumor stage, histological differentiation, smoking status, and alcohol (ethanol) use.



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