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A cause-specific Cox model for second primary tumors in patients with head and neck cancer: A RONCDOC study

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Abstract

Background: The aim of this study was to identify risk factors for the development of second primary tumors (SPTs) in the head and neck region, lungs, and esophagus in patients with head and neck cancer.

Methods: We collected data from 1581 patients. A cause-specific Cox model for the development of an SPT was fitted, accounting for the competing risks residual/recurrent tumor and mortality.

Results: Of all patients, 246 (15.6%) developed SPTs. Analysis showed that tobacco and alcohol use, comorbidity, and the oral cavity subsite were risk factors for SPTs. The C-index, the discriminative accuracy, of the model for SPT was 0.65 (95% confidence interval, 0.61–0.68).

Conclusions: Our results show that there is potential to identify patients who have an increased risk to develop an SPT. This might increase their survival chances and quality of life. More research is needed to provide head and neck clinicians with definitive recommendations.

KEYWORDS

head and neck cancer, prediction model, risk factor, second primary tumor, upper aerodigestive tract

1 | INTRODUCTION

Each year in the Netherlands, approximately 2500 patients are diagnosed with head and neck squamous cell carcinoma (HNSCC) of the oral cavity, pharynx, and larynx.[1] At present, these patients have a low to moderate 5-year survival rate of 45%–69% depending on the subsite of the tumor.[1] Low survival rates can be explained by the high incidence of tumor recurrence, advanced tumor stages at diagnosis, and patient delay.[2-4] However, part of the mortalities are not caused by the index tumor, but by the occurrence of a second primary tumor (SPT).[2] Addressing, diagnosing, and treating more SPTs might be of substantial benefit for HNSCC patients.

SPTs in patients with HNSCC occur most frequently in the head and neck (HN) region, the lungs, and the esophagus.[2] They can develop alongside the index tumor or during follow-up and are not the same as a residual/

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recurrent tumors or metastases.[5,6] The frequent occurrence of SPTs in HNSCC patients can be explained by the concept of field cancerization.[7] This concept implies that tumors occur in a field of preneoplastic squamous cells that have an anaplastic tendency. This tendency could give rise to multifocal development of primary tumors at various rates within the field.

At present, there is limited evidence available on factors that increase the risk of SPT development in patients with an HNSCC index tumor. Some studies have suggested old age, tobacco and alcohol use, and the subsite of the index tumor to be independent risk factors for SPTs.[8,9] A tendency for SPTs to develop along the respiratory axis (lungs) in patients with an index laryngeal tumor and along the digestive axis (esophagus) for patients with hypopharyngeal index tumors has also been noted.[10] Consequently, tobacco use is associated with increased risk for lung SPTs and alcohol use for SPTs in the esophagus.[11] However, most data are derived from small studies performed in Asia. It is unclear if these results can be extrapolated to a Western population. Also, most studies do not account for competing risks (e.g., a patient that dies shortly after treatment will not develop an SPT).

The objective of the present study is to identify risk factors and develop a prediction model for the development of SPTs in the HN region, lungs, and esophagus in a large cohort of patients with HNSCC. If risk factors are identified, they may help to personalize follow-up strategies with regard to screening for SPTs. Possibly, subgroups of patients with HN cancer can be identified that are more prone to the development of an SPT. This approach the potential to diagnose more SPTs in early stage of development and thereby potentially increase the overall survival rate and quality of life of HNSCC patients.

2 | MATERIALS AND METHODS

This study was approved by the medical ethics committee of the Erasmus MC (MEC-2016-751). The manuscript was written according to the STROBE guidelines for reporting observational studies.[12]

2.1 | Subjects

Patients were selected from the Rotterdam Oncology Documentary (RONCDOC). The RONCDOC is a database that compromises patients with HN cancer treated at the Erasmus MC Cancer Institute. We analyzed 1774 patients who had been diagnosed with a HNSCC (oral cavity, naso-, oro-, and hypopharynx, and larynx) between January 1, 2006 and December 31, 2011. The end date was chosen to allow long-term follow-up of all patients. The patients included were divided into two groups: patients who developed an SPT and a control group with only one HNSCC. The SPT group was further subdivided in three groups: patients with a HN, lung, or esophagus SPT. We excluded patients with prior malignancies in the HN region, lungs, or esophagus and patients who were treated with palliative intent (most often because of distance metastases).

2.2 | Data collection

Patient, tumor, and therapy data were acquired from both the Netherlands Comprehensive Cancer Organization and from the electronic patient records of the Erasmus MC Cancer Institute.[13] Subsequently, the data of each included patient were manually checked for inconsistencies between the two sources and missing data. Data were revised or supplemented when needed. In the case of doubt about the validity of the patient data, the specific patient was discussed by the research staff until a consensus was reached. A log was kept in which the inclusion of patients was recorded. This led to a high degree of classification accuracy and low risk of selection bias. The following patient data were collected: date of birth and death, last follow-up date, comorbidity, prior malignancies, tobacco and alcohol consumption, anemia, and weight loss. The following tumor and therapy data were collected for the index tumor and the SPT: subsite, date of diagnosis, clinical and histopathologic TNM-classification, tumor stage, and type and intention of therapy. Data on patient follow-up were obtained using the electronic patient records and the Dutch Civil Registry. Final date of follow-up was defined as the final date the patient was confirmed to be alive. The minimum follow-up was 5 years.

2.3 | Definitions

SPTs were defined according to the Warren & Gates and the updated Hong et al. criteria, which state that: the SPT (a) must be diagnosed as malignant, (b) must be histologically distinct from the index tumor, and (c) has to be at least 2 cm from site of the index tumor or has to occur >3 years after the diagnoses of the index tumor.[5,6] These criteria were used to distinguish SPTs from metastases and residual/recurrent tumors. The latter occur at the same site and share the same histopathology as the index tumor. Residual tumors develop <6 months after the

index tumor and recurrent tumors between 6 months and 3 years. A tumor that developed at the same site as but ≥3 years after the index tumor was considered to be an SPT. An SPT was defined as synchronous if the tumor developed <6 months after the diagnosis of the index tumor and as metachronous if it developed after ≥6 months. Comorbidities were scored with the Adult Comorbidity Evaluation-27 (ACE-27).[14] The ACE-27 is a validated evaluation form which can be used to identify important medical comorbidities and grade their severity. The intention of therapy was scored as curative or palliative based on the Dutch guidelines for the treatment of HNSCC, lung carcinoma, and esophagus carcinoma.[15] Tobacco and alcohol use was registered as never, past, and current smoker/drinker. For tobacco use the number of pack years (PY) was registered and for alcohol use the number of units per week. Anemia was defined as hemoglobin levels <8.5 mmol/L for males and <7.5 mmol/L for females.

TABLE 1 Baseline patient characteristics and univariable analysis between control and SPT group ($n = 1581$)

Variable	Control group	SPT + group All	*p*-value	SPT + sub-groups HN	*p*-value	Lungs	*p*-value	Esoph.	*p*- value	Missing *N* (%)
N total	1335	246		141		82		23		-
Male sex, *n* (%)	986 (74)	174 (70)	0.308	92 (65)	0.028*	64 (78)	0.400	18 (78)	0.633	-
Age year, mean (SD)	64 (11)	63 (9)	0.099	62 (9)	0.065	63 (9)	0.638	63 (8)	0.834	-
Tobacco use, *n* (%)			0.011*		0.238		0.028*		0.190	9 (1)
Never	167 (13)	19 (8)		15 (11)		4 (45)		0 (0)		
Past	370 (28)	56 (23)		31 (22)		18 (22)		7 (30)		
Current	791 (60)	169 (69)		93 (67)		60 (73)		16 (70)		
PY, mean (SD)	33 (27)	41 (34)	0.001*	32 (22)	0.635	53 (46)	<0.0001*	48 (23)	0.023*	338 (21)
Alcohol use, *n* (%)			0.001*		0.061		0.047*		0.008*	14 (0.9)
Never	271 (21)	25 (10)		17 (12)		8 (10)		0 (0)		
Past	111 (8)	24 (10)		13 (9)		6 (7)		5 (22)		
Current	940 (71)	196 (80)		110 (79)		68 (83)		18 (78)		
U/W, mean (SD)	20 (26)	30 (39)	<0.0001*	27 (29)	0.004*	34 (55)	<0.0001*	32 (15)	0.002*	167 (11)
Comorbidity, *n* (%)			0.089		0.764		0.016*		0.009*	3 (0.2)
None	438 (33)	61 (25)		44 (31)		13 (16)		4 (17)		
Mild	462 (35)	98 (40)		52 (38)		34 (42)		11 (48)		
Moderate	309 (23)	59 (24)		34 (24)		23 (28)		2 (9)		
Severe	124 (9)	27 (11)		10 (7)		11 (14)		6 (26)		
Anemia, *n* (%)	195 (15)	30 (13)	0.327	20 (15)	0.948	7 (9)	0.125	3 (13)	0.759	79 (5)
Weight loss, *n* (%)			0.942		0.899		0.925		0.682	332 (21)
<5%	794 (75)	136 (74)		77 (78)		44 (73)		15 (79)		
≥5% and <10%	146 (14)	27 (15)		16 (15)		8 (13)		3 (16)		
≥10%	124 (12)	22 (12)		13 (12)		8 (13)		1 (5)		

Note: Comorbidity was scored by the ACE-27. *p*-Values compared to the control group were calculated with Student *t*-test (continuous data) and χ^2-test (categorical data), *p-value <0.05.

Abbreviations: HN, head and neck; PY, pack year; SPT, second primary tumor; U/W, alcohol units per week.

TABLE 2 Baseline index tumor characteristics and univariable analysis of control and SPT group ($n = 1581$)

Variable	Control group	SPT + group		SPT + subgroups						
		All	*p*-value	HN	*p*-value	Lungs	*p*-value	Esoph.	*p*-value	Missing
N total	1335	246	-	141	-	82	-	23	-	-
Subsite, *n* (%)			0.002*		<0.0001*		0.286		0.386	0 (0)
Oral cavity	381 (29)	87 (35)		60 (43)		23 (28)		4 (17)		
Nasopharynx	29 (2)	1 (0)		0 (0)		1 (1)		0 (0)		
Oropharynx	294 (22)	70 (29)		38 (27)		26 (32)		6 (26)		
Hypopharynx	106 (8)	18 (7)		10 (7)		4 (5)		4 (17)		
Larynx	525 (39)	70 (29)		33 (23)		28 (34)		9 (39)		
cT, *n* (%)			0.394		0.015*		0.433		0.733	5 (0)
CIS	15 (1)	6 (2)		6 (4)		0 (0)		0 (0)		
1	378 (29)	66 (27)		45 (32)		17 (21)		4 (17)		
2	400 (30)	82 (33)		46 (33)		29 (35)		7 (30)		
3	274 (21)	48 (20)		22 (16)		20 (24)		6 (26)		
4	263 (20)	6 (18)		22 (16)		16 (20)		6 (26)		
cN, *n* (%)			0.568		0.502				0.967	11 (1)
0	869 (66)	165 (67)		99 (70)		51 (62)	0.723	15 (65)		
1	155 (12)	34 (14)		18 (13)		13 (16)		3 (13)		
2	287 (22)	45 (18)		23 (16)		17 (21)		5 (22)		
3	13 (1)	2 (1)		1 (1)		1 (1)		0 (0)		
Tumor stage, *n* (%)			0.399		0.022*		0.440		0.885	17 (1)
0	15 (1)	6 (2)		6 (4)		0 (0)		0 (0)		
I	310 (24)	57 (23)		39 (28)		14 (17)		4 (17)		
II	277 (21)	55 (22)		30 (21)		20 (24)		5 (22)		
III	255 (19)	51 (21)		25 (18)		20 (24)		6 (26)		
IV	462 (35)	76 (31)		40 (29)		28 (34)		8 (35)		
Therapy, *n* (%)			0.653		0.157		0.626		0.268	15 (1)
Radiotherapy	426 (32)	73 (30)		38 (27)		30 (37)		5 (22)		
Surgery + RT	401 (30)	68 (28)		39 (28)		21 (26)		8 (35)		
Surgery	258 (20)	54 (22)		40 (29)		12 (15)		2 (9)		
RT + CT	191 (15)	43 (18)		21 (15)		16 (20)		6 (26)		
Surgery + RT + CT	43 (3)	7 (3)		2 (1)		3 (4)		2 (9)		
Chemotherapy	2 (0)	0 (0)		0 (0)		0 (0)		0 (0)		
Radiotherapy, *n* (%)	1061 (80)	191 (78)	0.397	100 (71)	0.013*	70 (85)	0.262	21 (91)	0.187	15 (1)

Note: *p*-values compared to the control group were calculated with χ^2-test (categorical data), *p-value <0.05.
Abbreviations: CT, chemotherapy; HN, head and neck; PY, pack year; RT, radiotherapy; SPT, second primary tumor.

Weight loss was defined as the percentage of weight patients lost within 6 months prior to diagnosis of the index tumor. It was categorized as mild (<5%), moderate (≥5 and <10%), and severe (≥10%). The candidate predictors for our model were age, sex, tobacco use (in PY), alcohol use (in U/W), cT, cN, comorbidity (ACE-27), subsite of the index tumor, and therapy of the index tumor.

TABLE 3 Hazard ratios from the cause-specific Cox regression analysis of risk factors for the development of SPTs

Variable	HR	(95% CI)	*p*-value	Missing (%)
Tobacco (PY)	1.007	(1.004–1.011)	$0.097 \cdot 10^{-3}$*	21.4
Alcohol (U/W)	1.006	(1.004–1.009)	$0.005 \cdot 10^{-3}$*	10.5
Comorbidity				<0.1
None	1.000	Reference		
Mild	1.568	(1.138–2.159)	0.006*	
Moderate	1.435	(0.998–2.062)	0.051	
Severe	1.854	(1.165–2.950)	0.009*	
Subsite				0.0
Oral cavity	1.000	Reference		
Nasopharynx	0.190	(0.026–1.368)	0.099	
Oropharynx	1.018	(0.739–1.402)	0.915	
Hypopharynx	0.740	(0.437–1.252)	0.261	
Larynx	0.707	(0.441–0.835)	0.002*	

Note: Comorbidity was scored by the ACE-27.
Abbreviations: CI, confidence interval; HR, hazard ratio; PY, pack year; U/W, units per week.
*p-value <0.05.

TABLE 4 Patient characteristics and absolute risk for a second primary tumor in 10 randomly selected patients

Patient	PY	U/W	ACE-27	Location	cT	cN	Age	Therapy	AbsRisk
1	24	2	None	Nasoph.	2	2	56	Surg + CRT	0.050
2	40	35	Moderate	Larynx	1	0	89	RT	0.080
3	75	2	None	Larynx	0	0	83	RT	0.083
4	0	28	None	Oral	1	1	44	Surgery	0.095
5	20	0	Mild	Hypoph.	3	1	73	RT	0.095
6	50	63	None	Hypoph.	3	2	49	Surg + CRT	0.101
7	25	42	Mild	Hypoph.	3	2	62	Surg + CRT	0.111
8	50	84	Moderate	Oral	1	3	57	Surg + CRT	0.112
9	40	42	Moderate	Hypoph.	2	0	63	RT	0.173
10	60	112	Mild	Hypoph.	3	1	49	Surg + CRT	0.293

Abbreviations: AbsRisk, absolute risk; ACE-27, comorbidity score; CRT, chemoradiotherapy; PY, pack years; RT, radiotherapy; Surg, surgery; U/W, alcohol units per week.

2.4 | Statistical analysis

Statistical analyses were performed using IBM SPSS (version 21.0) and R Statistical Software (version 3.6.2). Continuous data were expressed as mean values and standard deviation (SD). Categorical data were presented as frequencies and percentages. Differences between groups were analyzed using the χ^2-test or the Fisher's exact-test (categorical data) and the independent Student's *t*-test (continuous data). Data were missing for the variables related to tobacco and alcohol use, anemia, weight loss, TNM-classification, tumor stage, and therapy. To handle the missing data, multiple imputation was performed five times using package *mice* in R.[16] Cause-specific Cox regression analysis was used to estimate the hazard ratios (HRs) of the candidate predictors to develop an SPT. Competing risks are present when an individual is at risk for more than one event and the occurrence of one of these competing events will prevent the event of interest from ever happening. In the present study, mortality and the occurrence of a residual/recurrent tumor were identified as competing events with the occurrence of an SPT. We performed three separate Cox models, one for our primary outcome (SPT), one for the competing risk mortality, and one for the compering risk the occurrence of a residual/recurrent tumor. Consequently, these three models were combined in one cause-specific Cox model. This final model can be used to

calculate the absolute risk for the development of SPTs taking into account the two competing risks. The absolute risk for the development of an STP, accounting for mortality and a recurrent tumor, for a few example patients was calculated.[17] Backward stepwise selection was used in the multivariable analysis to define the final Cox models, using Akaike Information Criterion ($p < 0.157$) as a cutoff score. The concordance probability (C-index) was assessed to evaluate the model's discriminative performance. In survival analysis, a pair of patients is called concordant if the risk of the event predicted by a model is lower for the patient who experiences the event at a later time point. The C-index is the frequency of concordant pairs among all pairs of subjects.

3 | RESULTS

Of the initial 1774 HNSCC patients, 193 patients were excluded because of prior malignancies in the HN region, lungs or esophagus, or because they were not treated with curative intent. The remaining 1581 patients were included in this study. Of them, 246 (15.6%) developed an SPT. The SPTs developed in the HN region in 141 cases (8.9%), in the lungs in 82 cases (5.2%) and in the esophagus in 23 cases (1.4%). The median follow-up was 4.96 years (IQR 2.05–6.90).

Patient and tumor characteristics of the SPT and control group are presented in Tables 1 and 2. After univariable analysis, the following variables were significantly different between the SPT group and controls: tobacco use (status and PY), alcohol use (status and U/W), and the subsite of the index tumor. For patients with HN SPTs, the baseline characteristics differed on the variables sex, alcohol use (U/W), the subsite, cT-classification, and tumor stage of the index tumor, and surprisingly whether patient had received radiotherapy (RT) as part of their treatment ($p = 0.013$). For lung SPT patients, tobacco use (status and PY), alcohol use (status and U/W), and comorbidity were significantly different between patient with lung SPTs and non-SPT controls. The group of patients with esophageal SPTs was too small to make reliable conclusions.

The mean amount of PYs was higher in the SPT group (41 [SD 34]) than in the controls (33 [SD 27], $p < 0.001$). Alcohol use was also significantly higher in the group of patients that developed an SPT. Patients with SPTs were more often current smokers ($p < 0.001$) and used more units of alcohol per week (30 [SD 39] vs. 20 [SD 26], $p < 0.001$).

Multivariable Cox regression analysis was performed for the primary outcome SPT and competing risks mortality and the occurrence of a residual/recurrent tumor, after establishing the univariable relationship between the tumor- and patient-specific variables as mentioned above (Table 3; Appendix 1). Data on tobacco use and the amount of PY were missing in 338 cases (21.4%). Alcohol consumption was unknown in 167 cases (10.5%) and for three patients (0.002%) there was not enough data to calculate the comorbidity index.

Patients that developed SPTs smoked more tobacco. The HR per pack year was 1.007 (95% CI 1.004–1.011, $p = 0.097 \cdot 10^{-3}$). A similar result showed for alcohol use: the HR per unit per week was 1.006 (95% CI 1.004–1.09, $p = 0.005 \cdot 10^{-3}$). Patients with no comorbidity on the ACE-27 index were less likely to develop an SPT. The HRs for mild, moderate, and severe comorbidity were 1.568, 1.435, and 1.854 respectively. Finally, the results showed that patients with laryngeal tumors developed less SPTs than patients with oral cavity tumors ($p = 0.002$). The cT and cN classification, age, and therapy of the index tumor did not significantly contribute to the model for SPT.

The C-index of the overall prediction model for SPTs was 0.65 (95% CI 0.61–0.68). The absolute risks for the development of an SPT based on the cause specific Cox model, accounting for competing risks of 10 randomly selected patients was presented in Table 4.

4 | DISCUSSION

In this study, we developed a model for the development of SPTs in a large population of consecutive HNSCC patients. A total of 246 (15.6%) patients of our population developed an SPT. The majority occurred in the HN region, followed by the lungs and esophagus. These values are in accordance with the findings from previous studies.[2] Our prediction model showed that tobacco and alcohol use, comorbidity, and the location of the index tumor predicted the occurrence of an SPT. A better understanding of which subpopulation of HNSCC patients have an increased SPT risk, could guide clinicians in their decisions regarding length of follow-up and active SPT screening.

4.1 | SPT risk factors

Our results showed a strong association between the use of tobacco and alcohol and the occurrence of SPTs. The SPT risk significantly increased with every consumed pack year or unit alcohol per week at the moment of diagnosis of the index tumor. Some studies did not find this association.[18,19] Although others only found an increased risk for severe alcohol users (>3 units/day).[8] It

is thought that the continuation of tobacco and alcohol after treatment increases the risk for the occurrence of an SPT. Although our study did not address the continuation of tobacco and alcohol use, Do et al. showed an increased risk for the development of SPT in patients who continued these habits.[20] Hence, it could be wise to counsel and help patients to break these patterns of behavior.

Our study suggests that patients with comorbidity have a higher risk to develop an SPT than patients without a systemic disease. Although comorbidity is a known prognostic factor for the overall survival of a patient with HN cancer, there is, to our knowledge, no literature that evaluates the association between comorbidity and the development of SPTs.[21] It is not understood why the presence of comorbidity at the time of diagnosis of the index tumor, is associated with the risk to develop an SPT in the follow-up period.

Some researchers found a higher risk for the development of SPTs in patients with regional lymph node metastases (N+ status) of the index tumor.[18,19] In this study, univariate analysis showed a significant difference in the cT-classification and tumor stage of patients a SPT in the HN region compared to the control group. However, multivariate analysis showed no association between the cT- or cN-classification or tumor stage of the index tumor and the development of an SPT. This could be explained by the fact that an SPT is looked upon as an individual malignant entity, which is not related to the index tumor.[5]

A potentially interesting finding in our univariable analysis is that patients that developed a HN SPT more frequently received RT as (a part of the) therapy of their index tumor. This group includes patients that received only RT and patients received RT in combination with surgery and/or chemotherapy. This might be because RT treatment is often given to patients with more developed tumors. However, cT and cN classification did not prove to be predictive factors for SPT development. It could also suggest that RT increases the risk of developing an SPT within the RT field, as has been suggested by other researchers. Gao et al. reported that RT carried a 68% excess risk of developing an SPT in the HN region in patients who survived more than 5 years after laryngeal cancer.[22] A large retrospective study of more than 30 000 oral cavity HNSCC also showed that patients treated with radiation only or radiation with surgery had higher risks of developing an SPT, than patients treated with surgery only.[23] According to Rennemo et al., RT does seem to delay the occurrence of an SPT within the mucosa exposed to irradiation, with many SPTs occurring late during follow-up.[24]

4.2 | Screening and follow-up

The incidence of esophageal SPTs in the present study (1.5%) falls in the incidence range of 1%–6%, which were reported in other retrospective nonscreening studies.[25] This study also showed an incidence of 15% in studies that actively screen for esophageal SPTs with Lugol chromoendoscopy. Lugol is a stain that is sprayed on the esophageal mucosa. Mucosal areas that are void of Lugols stain are associated with dysplasia. The discrepancy between incidences of retrospective studies and screening studies could partially be explained by the differences between Western and Asian populations, as the majority of screening studies are performed in Asian populations. However, it is also possible that the stated incidence in nonscreening studies underestimates the true incidence of esophageal SPTs in HNSCC patients. In that case, it might be useful to screen HNSCC patients with Lugol chromoendoscopy to diagnose more esophageal SPTs.

Crippen et al. showed an average time to diagnosis of lung SPT of 6.7 years, with only 18% of the cases diagnosed in the first 5 years.[26] They also concluded that patients with HN cancer in all subsites had a significantly higher relative risk of a lung SPT than the standard population. Additionally, Pagedar et al. reported that patients with low stage lung SPTs (after an index HN tumor) had a worse survival rate than patients with an index lung tumor and no SPT.[27] Combining the long time to occurrence and low survival rate of affected patients, screening for lung SPTs in patients treated for HNSCC does not seem to have a positive effect on their overall survival. Defining a subpopulation in which lung SPT screening is advantageous based on the subsite of the index HNSCC tumor proved to be difficult. A study by Lee et al. found that patients with index laryngeal tumors were most prone to develop SPTs.[8] These findings are in conflict with our results. We found a significant lower risk for patients with a laryngeal tumor to develop an SPT in the HN-region, lungs, or esophagus compared to patients with an index tumor in the oral cavity. Cloos et al. discussed the difference between tumors in different HN subsites.[28] They argue that this difference might be explained by the different embryogenetic development of the subsites and their different mucosal exposure to tobacco and alcohol.

Our cause-specific Cox regression analysis showed a moderate capability to predict the development of SPTs. Tobacco and alcohol use, comorbidity, and subsite in the oral cavity are the highest risk factors. Another study by Brands et al. concluded in their review that patients with oral squamous cell carcinoma have a lifelong risk for a SPT.[29] They discuss the benefit of routine follow-up and weigh the extra anxiety patients without new disease will experience against the possible gain of quality of life and survival of patients with an SPT. The risk model we have developed here might aid in a stricter selection of HNSCC patients who need to undergo long-term follow-

up of SPTs. We believe an increased awareness of the occurrence of lung and esophageal SPTs in patients with HN cancer could lead to earlier SPT diagnosis. For example, a patient that experiences dysphagia after RT treatment for a HN tumor could suffer from (long-term) postradiation complication, but their symptoms might also be caused by a esophageal SPT. In this case, an endoscopy might be warranted. Our results also show that, for example, patients with oral or oropharyngeal tumors are more prone to develop SPTs than patients with laryngeal tumors. Clinicians should be extra aware of possible SPTs in these subgroups of patients. Diagnosing SPTs at an earlier stage of development will of course increase the quality of life of patients compared to diagnosis at a later stage.

4.3 | Limitations

Our study has some limitations that may have influenced our results. First, the number of patients with a lung or esophagus SPT was limited in this study. As a result, it was not possible to determine the risk factors for SPTs in these subsites. Second, it remained challenging to determine whether a lung malignancy is an SPT or a metastasis from the index HN tumor. Ideally, the genetics of both tumors should be determined. In this study, loss of heterozygosity analysis was performed in most squamous cell carcinoma in the lungs. However, exceptions were made for patients with lung carcinoma which developed more than 5 years after the index tumor and for patients who were treated with a palliative intent. Finally, we might not have analyzed all possible risk factors that include the human papilloma and Epstein–Barr virus, which are known to be related to tumor development. Since we collected all our data at the moment of diagnosis of the index tumor, we were also not able to determine the risk of continuation of tobacco and alcohol use within our population. Despite these possible limitations, we managed to conduct a study with high quality data and data analysis that produced reliable and clinically useful results.

5 | CONCLUSION

In this work, we identified that tobacco and alcohol use, comorbidity, and the oral cavity subsite were the most pronounced risk factors for the development of an SPT for HNSCC patients. Despite our high-quality data and correction for competing risks in our prediction model for the development of SPTs, it should be further developed to allow clinical use. More research with larger groups per SPT subsite (HN region, lungs, or esophagus) is needed to provide HN clinicians with definitive recommendations regarding the follow-up of their patients and potential SPT screening regimes.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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