HEAD AND NECK

Prognostic factors in head and neck cancer: a 10-year retrospective analysis in a single-institution in Italy

Fattori prognostici del tumore testa-collo: un'analisi retrospettiva monocentrica di 10 anni

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SUMMARY

This study was undertaken to evaluate the association between demographics, lifestyle habits, and clinical data and overall survival (OS), recurrence and second primary cancer (SPC) in patients with first primary head and neck cancer (HNC). We retrospectively reviewed data from 482 patients treated at the "Agostino Gemelli" Teaching Hospital, Rome, between 2002-2012 for primary HNC. Individual parameters were evaluated for association with specific outcomes such as OS, cancer recurrence and second primary cancer (SPC) appearance using hazard ratios (HR) and 95% confidence intervals (CIs). Five-year OS was 60.6% for all HNC cases, 49.0% for oral cavity, 54.8% for oropharynx, 50.0% for hypopharynx and 63.4% for larynx. Predictors of OS were older age (HR = 1.04; 95% CI: 1.02-1.05) and advanced tumour stage (HR = 2.00; 95% CI: 1.41-2.84). The risk of recurrence was associated with drinking 8-14 drinks per week (HR = 1.73; 95% CI: 1.00-2.97). The risk of developing SPC increased with advanced tumour stage (HR = 2.75; 95% CI: 1.39-5.44) and with smoking for more than 40 years (HR = 3.68; 95% CI: 1.10-12.30). OS differed among HNC sites. Increasing age was an unfavourable predictor of HNC OS. Tumour stage was a prognostic factor both for OS and for risk of developing SPC. Alcohol and tobacco consumption were prognostic factors for recurrence and SPC, respectively.

KEY WORDS: Head and neck cancer • Prognostic factors • Epidemiology

RIASSUNTO

È stata condotta un'analisi retrospettiva su 482 pazienti con diagnosi di tumore testa-collo arruolati presso l' ospedale "Agostino Gemelli" di Roma. L'associazione tra fattori demografici, clinici e comportamentali con la overall survival (OS), il rischio di ricorrenza ed il rischio di un secondo tumore primitivo è stata stimata usando gli Hazard Ratio (HR) e gli intervalli di confidenza al 95% (CIs). La OS considerando tutte le sedi tumorali è stata del 60%, mentre considerando le singole sedi tumorali è risultata del 49.0% per il cavo orale, 54.8% per l'orofaringe, 50.0% per l'ipofaringe e 63.4% per la laringe. Un'età avanzata alla diagnosi (HR = 1.04; 95% CI: 1.02-1.05) ed un avanzato stadio del tumore (HR = 2.00; 95% CI: 1.41-2.84) sono risultati fattori significativamente associati con la OS. Il rischio di ricorrenza è risultato associato con il consumo di alcolici (HR = 1.73; 95% CI: 1.00-2.97). Il rischio di sviluppare un secondo tumore primitivo è risultato associato con uno stadio avanzato del tumore primario (HR = 2.75; 95% CI: 1.39-5.44) e con l'aver fumato per più di 40 anni (HR = 3.68; 95% CI: 1.10-12.30). In conclusione abbiamo notato che la OS differisce tra le sedi tumorali del tumore testa-collo. Lo stadio tumorale è risultato essere associato sia con la OS che con il rischio di sviluppare un secondo tumore primitivo. Il consumo di alcol e di tabacco sono risultati essere fattori prognostici, rispettivamente, per la ricorrenza e per l'insorgenza di un secondo tumore primitivo.

PAROLE CHIAVE: *Cancro della testa e del collo • Fattori prognostici • Epidemiologia*

Introduction

Squamous cell carcinoma of the head and neck (HNC) is the sixth common cancer worldwide affecting 600,000 new cases diagnosed each year [1]. In 2009 in Italy there were an estimated 1008 new HNC cases (790 males and 218 females) with a 5-year survival rate of 55% (2000-2004) [2].

Various genetic and environmental factors are related to HNC [3]. The incidence of HNC has a large geographical variability related to different prevalence of lifestyle risk factors, such as alcohol drinking, tobacco smoking and dietary factors [4-12]. Other known risk factors are human papillomavirus (HPV) [13] and Epstein-Barr virus (EBV)

infections [14]. Men have a higher risk having a HNC than women [1].

The most frequent tumour sites of HNC are the larynx, oral cavity and pharynx. Head and neck cancers also include salivary gland tumours as well as nasopharyngeal cancer and paranasal and nasal sinus cancer. These tumours are less frequent and will not be discussed in this report.

The management of HNC is often a clinical challenge, since in more than 60% of patients the disease is locally advanced at diagnosis: a combined modality therapy with surgery, radiotherapy and chemotherapy is generally recommended [15]. When the disease is deemed unresectable or an organ-preservation goal is pursued, the current standard treatment is represented by the combination of radiation and chemotherapy [16].

In head and neck oncology, the lack of well-defined prognostic and predictive factors limits the possibility to tailor the best therapeutic approach on an individual basis.

In this study, we retrospectively evaluated the association of individual parameters with specific outcomes in terms of disease control in a cohort of 482 patients treated at our Italian centre to identify predictive and prognostic factors that could help clinicians in deciding the most appropriate treatment.

Materials and methods

Subjects with histologically confirmed primary squamous cell carcinoma of the head and neck cancer were consecutively recruited at the Gemelli Hospital, from 2002 to 2012. The study was approved by the Ethics Committee of the University. Details of the tumour classification used have been described previously [17].

Data collection

Patients were interviewed face-to-face by trained interviewers or physicians on demographic, alcohol and tobacco consumption, and other relevant lifestyle factors. Interviews were conducted from 15 to 5 days prior to treatment. Questions assessed information at one year before diagnosis. Participant were also followed from the date of diagnosis to the date of death, or loss to follow up, whichever occurred first. Death certificate data were also used for mortality, and the cause of death was coded according to the International Classification of Diseases, Ninth Revision [18]. Cancer recurrence and SPC were collected from medical records and cancer registries. Data on tumour pathology and treatment were obtained from pathology records.

Diagnostic and therapeutic guidelines

Pre-treatment work up included: complete head and neck exam, biopsy, chest imaging, CT with contrast and/or MRI with contrast of primary and neck; FDG-PET /CT

for stage III-IV disease, nutrition, speech and swallowing evaluation, multidisciplinary consultation. Tumour HPV testing was performed in oropharynx primary in the last years.

The therapeutic guidelines used were as follows: oral cavity, early stage T1-T2 N0 surgery; advanced stage (T3N, T1-T3 -N1-N3, T4a any N) surgery or multidisciplinary approach.

Oropharynx: early stage (T1-T2, N0-1) definitive radiotherapy (RT) or surgery; advanced stage (T3, T4a, N0-N1) concurrent systemic therapy/RT or surgery or induction chemotherapy followed by radiotherapy or systemic therapy/RT.

Hypopharynx: early stage (T1-selected T2 N0) definitive RT or surgery; advanced stage (T2-3, any N and t1 N+; T4a any N) induction chemotherapy or surgery or concurrent systemic therapy/RT.

Larynx: early stage (T1-T2 or selected T3) surgery or RT; T3 requiring total laryngectomy any N concurrent systemic therapy/RT or RT if patient not candidate for systemic therapy/RT or surgery or induction chemotherapy; T4 any N surgery.

Outcome definitions

The primary endpoint was overall survival (OS) measured as the time from the date of initial diagnosis of index primary tumours to the date of death from any cause. All observations were censored at loss to follow-up and at the end of the study period. Recurrence was defined as the local, regional or distant return of cancer after that the patient was defined as disease free. By definition, a second primary tumour of the same histologic type as the first had to be separated from it by more than 2 cm of normal epithelium or had to occur at least 3 years after diagnosis of the first primary tumour. Any new tumour of a different histologic type was characterised as a second primary tumour without the requirement of separation of more than 2 cm [19].

Statistical analysis

We used the Kaplan–Meier method to calculate the cumulative proportion surviving and to plot survival curves. We used multivariable Cox's proportional hazards model to determine independent predictors of OS, recurrence and SPC. We formally tested the Cox proportional hazards assumption for each covariate using Schoenfeld residuals [20]. Hazard ratios (HR) for all-cause mortality were adjusted for age, tumour stage and lymph nodes.

Models to predict SPC were adjusted for age, tumour stage, years of smoking and presence of lymph nodes. Models to predict recurrence were adjusted for age, treatment and lymph nodes. With respect to smoking, patients were classified as never, former or current smokers. Cumulative tobacco consumption was calculated as intensity of smoking (never smokers, ≤ 20 cigarettes/day, > 20 ciga-

rettes/day), and smoking duration in years (never smokers, ≤ 20, 21-40, > 40). With respect to alcohol, subjects were classified as never drinkers, former and current, and according to alcohol consumption (none or < 1 drink equivalent/week, 1-7 drinks/week, 8-14 drinks/week, 15-21 drinks/week, 22-28 > 29 drinks/week). The standard definition for one drink equivalent was 14 g ethanol, which approximately corresponds to 150 mL wine, 330 mL beer, and 36 mL spirits [21]. Analysis were performed for overall HNC. Statistical analyses were performed using Stata software, version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

A total of 482 subjects were included in the study. Characteristics of the patients are reported in Table I. Disease location was the oral cavity in 83 (17.2%) patients, oropharynx in 84 (17.4%), hypopharynx in 20 (4.2%), larynx in 290 (60.2%). For 5 patients (1.0%) the disease location was oral cavity or pharynx not otherwise specified. There was a high predominance of male cases (79.1%) and median age at diagnosis was 64 (interquartile range (IQR): 57-70) years old overall. Most patients presented an advanced tumour at the time of diagnosis (Stage III-IV = 54.2%). Lymph nodes are not involved frequently

Table I. Characteristics of head and neck cancer cases by tumour site.

Tumor site	Subjects n (%)	Gender (% male)	Age (median, IQR*)	Stage	n (%)	Lymph node n (%)		Tumour size n (%)
Oral cavity	83 (17.2)	59.0%	64 (51-71)	1-2	29 (34.9)	0 (0)	1	11 (13.9)
							2	29 (36.7)
				3-4	54 (65.1)	26 (51.0)	3	10 (12.7)
							4	29 (36.7)
				Missing	0 (0)	4 (4.8)		4 (4.8)
Oropharynx	84 (17.4)	75.3%	61 (52-68.5)	1-2	31 (36.9)	0 (0)	1	13 (15.5)
							2	32 (38.1)
				3-4	53 (63.1)	41 (77.4)	3	7 (8.3)
							4	32 (38.1)
				Missing	0 (0)	0 (0)		0 (0)
Hypopharynx	20 (4.2)	65.0%	61 (58-66)	1-2	1 (5)	0 (0)	1	1 (5.0)
							2	3 (15.0)
				3-4	19 (95)	14 (73.7)	3	3 (15.0)
							4	13 (65.0)
				Missing	0 (0)	0 (0)		0 (0)
Larynx	290 (60.2)	86.9%	65 (58-71)	1-2	157 (54.1)	0 (0)	1	94 (32.4)
							2	68 (23.5)
				3-4	133 (45.9)	47 (35.3)	3	53 (18.3)
							4	75 (25.9)
				Missing	0 (0)	0 (0)		0 (0)
OC, OP, HP NOS	5 (1.0)	80.0%	64 (51-69)	1-2	3 (60.0)	1 (33.3)	1	1 (20.0)
							2	3 (60.0)
				3-4	2 (40.0)	2 (100.0)	3	-
							4	1 (20.0)
				Missing	0 (0)	0 (0)		0 (0)
Total	482	79.1%	64 (57-70)	1-2	221 (45.9)	0 (0)	1	120 (25.1)
							2	135 (28.2)
				3-4	261 (54.2)	130 (50.4)	3	73 (15.3)
							4	150 (31.4)
				Missing	0 (0)	4 (0.8)		4 (0.8)

*IQR: interquartile range (25°-75° percentile). OC, oral cavity; OP, oropharynx; HP, hypopharynx; NOS, not otherwise specified

Table II. Treatment of head and neck cancer cases according to tumour stage.

Treatment	Stage n (%)	
	1-2	3-4
Radiation	50 (22.7)	4 (1.5)
Surgery	134 (60.9)	52 (20.1)
Chemotherapy and Radiation	16 (7.3)	69 (26.6)
Surgery and Radiation	19 (8.6)	73 (28.2)
Surgery and Chemotherapy	1 (0.5)	7 (2.7)
Surgery and Chemotherapy and Radiation	-	54 (20.9)
Missing	1	2
Total	221 (45.9)	261 (54.1)

in laryngeal cancer (16.2%), unlike oral cavity (31.3%), oropharyngeal (48.9%) and hypopharyngeal (70.0%) cancers. Treatment of HNC cases according to tumour stage is reported in Table II: for patients with an early stage tumour exclusive surgery was the treatment of choice (60.9%), while in the advanced stages (SIII-SIV) the most widely performed treatments were combined surgery with post-operative radiotherapy (Surg/RT, 28.2%) and chemotherapy with radiotherapy (CHT/RT, 26.6%).

Overall survival
Median follow-up time since cancer diagnosis was 49 months (IQR: 19-86) (Table III). During follow-up, 190 of 482 patients (39.4%) died, of which 97 (51.1%) died for HNC cancer, 26 (13.7%) for other cancer and the remaining 67 for other causes (data not shown). Percentages of death for other causes were as follows: oral cavity 10.1%, oropharynx 11.8%, hypopharynx 8.3% and larynx 15.0%. Five-years OS for all HNC sites combined was 60.6%: oral cavity 49.0%, oropharynx 54.8%, hypopharynx 50.0% and larynx 63.4%. Median survival time in months was higher for laryngeal cancer than for the other

tumour sites [(59 vs 23 months, oral cavity $p = 0.002$), 43 (oropharynx $p = 0.023$), 35 (hypopharynx $p = 0.03$)] (Fig. 1). When stratifying the survival time by tumour stages, we did not find significant differences for any cancer sites for early stage tumour sites, while for the advanced tumour stages we observed higher survival for laryngeal cancer than for oral cavity cancer ($p=0.008$) (Figs. 2, 3). Table IV reports the distribution for selected covariates and the HR for all-cause mortality adjusted for age, stage and lymph node status. Reduced survival was associated with increasing age of diagnosis (HR = 1.04; 95% CI: 1.02-1.05), and advanced tumour stage (HR = 2.00; 95% CI: 1.41-2.84).

Cancer recurrence and second primary cancer
Demographic, clinical and lifestyle characteristics and the association with recurrence and SPC are reported in Table V. Among the 482 HNC patients included, disease recurrence was unknown for 26 (5.4%) patients. and 12 (2.5%) patients did not report the date of recurrence. A total of 181 (39.7%) patients developed clinical recurrence. The risk of recurrence was associated with drinking 8-14 drinks per week (HR = 1.73; 95% CI: 1.00-2.97).
Among the 482 HNC patients included, information on SPC were unknown for 17 (3.5%) patients and 17 (3.5%) patients did not report the date of second primary, therefore there were 448 patients with complete information on SPC. A total of 169 (40.0%) patients developed SPC. The risk of developing SPC increased with advanced tumour stage (HR = 2.75; 95% CI: 1.39-5.44) and with smoking for more than 40 years (HR = 3.68; 95% CI: 1.10-12.30).

Discussion

Many therapeutic options are available for patients with HNC, but the appropriate regimen for the individual patient is still a difficult and often controversial choice. Worldwide, HNC is the sixth most common neoplasm, and despite advances in therapy, long-term survival in

Table III. Median survival time and deaths by tumour site.

Follow-up time (months)					Deaths	
	N	Median	1Q	3Q	n	%
Oral cavity (OC)	83	23	10	60	34	41.0%
Oropharynx (OP)	84	43	16	82	38	45.2%
Hypopharynx (HP)	20	35	16	72	10	50.0%
Larynx	290	59	26	94	106	36.6%
OC, OP, HP NOS	5	71	63	82	2	40.0%
Total	482	49	19	86	190	39.4%

1Q: first quartile, 3Q: third quartile. NOS, not otherwise specified
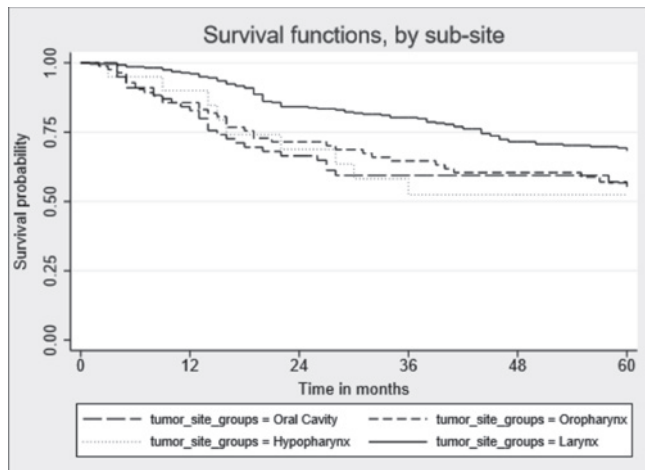
Fig. 1. Kaplan-Meier unadjusted overall 5-year survival by head and neck-cancer site.

Fig. 2 Kaplan-Meier unadjusted overall 5-year survival by head and neck cancer site for early stage tumours.

Fig. 3. Kaplan-Meier unadjusted overall 5-year survival by head and neck cancer site for advanced stage tumours.

HNSCC patients is poor. The prognosis for HNC overall has improved slightly since the 1990s, and is influenced by site, stage, molecular markers and HPV status. Prognostic factors can guide the physician in selecting the best possible treatment for each patient, possibly increasing the therapeutic index [22] [23].
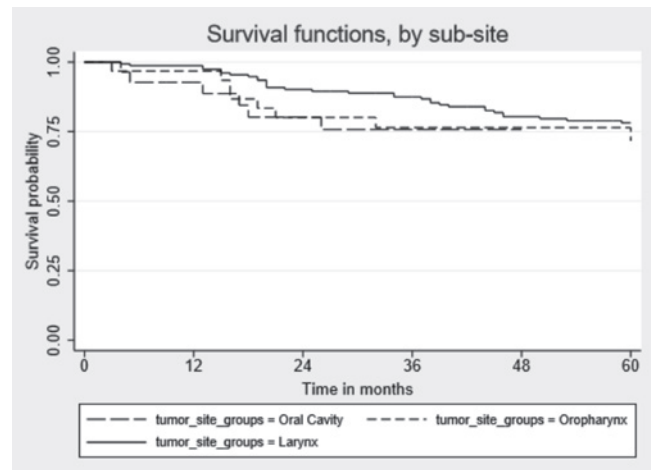
In our analysis, many factors showed an association with one or more of the outcomes. Many are well known in the literature.

For instance, age has a negative impact on the prognosis of patients included in our analysis. Other authors observed that older patients have similar survival outcomes compared with their younger peers; however, they may experience worse toxicity, especially with treatment intensification [24]. As life expectancy increases, surgeons can expect an increasing number of geriatric patients. Management of this subpopulation has become a source of debate because there is a paucity of randomised data regarding the effect of age on treatment response and morbidity associated with the treatment of HNC [25] [26].
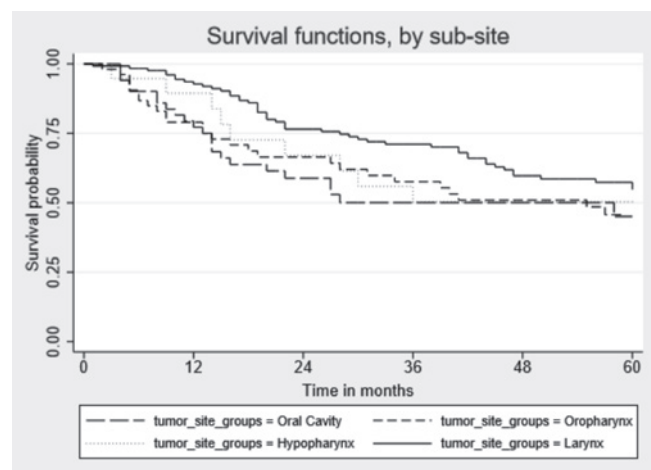
The heterogeneity of HNC creates various difficulties, first of all for tumour site classification. The site of origin is an important prognostic factor, both because of the different stage at diagnosis and because of the different possibilities of surgical treatment. One must pay attention to laryngeal and oropharyngeal classification for suprahyod larynx or oral and oropahryngeal classification for the base of the tongue.

Tumour staging is a well identified prognostic factor for HNC. A large proportion of patients with HNC are often not diagnosed until their disease has reached an advanced stage, requiring aggressive and costly treatment that may not be curative, with relapse occurring in around 50% of cases with locally advanced HNC [27] [28].

We report a significant association between advanced tumour stage (S III-IV) and poor overall and disease-specific survival. The choice of treatment for advanced HNC did not influence time-survival as for other authors [29]. We were unable to find any significant factor that may constitute a contraindication for a combined approach with RT and CHT or surgery/CHT-RT, and identify advanced HNC patients for whom a palliative approach or best supportive care could be preferred.

Smoking and high alcohol consumption habits are not only well-known causative but also prognostic factors in HNC [30]. In our experience, a long history of smoking impacted SPC development. HNC patients have a higher risk of second primary tumours than the general population. The most frequent locations are the head and neck, lung and oesophagus, decreasing long-term survival. The incidence of SPC has increased in the last decade, with a negative effect on survival. Since no specific early diagnostic tool is available, alcohol and tobacco avoidance along with scheduled follow-up are suggested to reduce its incidence [31-33].

In recent years, HPV status was found to play a major role as a prognostic and predictive parameter, especially

Table IV. Predictors of overall survival among head and neck cancer cases by multivariate analysis.

	Subjects		Death from all causes (total/deaths 482/190)
	n	%	HR* (95% CI)
Demographics			
Age at diagnosis (ordinal)	482	100	**1.04 (1.02-1.05)**
Gender			
Men	381	81.2	1.00
Women	88	18.8	0.92 (0.63-1.35)
Tumour characteristics			
Stage			
I/II	221	45.9	1.00
III/IV	261	54.1	**2.00 (1.41-2.84)**
Cigarette smoking and alcohol consumption			
Smoking status			
Never	68	14.6	1.00
Former	259	55.6	1.15 (0.73-1.81)
Current	139	29.8	1.20 (0.73-1.98)
Years of smoking			
Never smokers	68	14.1	1.00
≤ 20	56	11.6	0.93 (0.49-1.75)
21-40	199	41.3	1.16 (0.72-1.86)
> 40	159	33.0	1.22 (0.76-1.97)
Cigarettes per day			
Never smokers	68	14.1	1.00
≤ 20	234	48.5	1.16 (0.74-1.84)
> 20	180	37.3	1.14 (0.71-1.85)
Drinking status			
Never	100	21.4	1.00
Former	19	4.1	0.83 (0.29-2.35)
Current	348	74.5	1.27 (0.86-1.87)
Drinks per week			
Never drinkers or < 1	81	16.8	1.00
1-7	48	10.0	1.33 (0.74-2.39)
8-14	113	23.4	1.36 (0.86-2.16)
15-21	32	6.6	0.98 (0.49-1.98)
22-28	58	12.0	1.15 (0.66-1.99)
> 28	150	31.1	1.52 (0.94-2.45)

*Text in bold indicates statistically significant risk factors. HR: hazard ratio; CI: confidence interval. * HR adjusted by age, stage, lymph nodes.*

in oro-pharyngeal cancer. HPV-positivity is a consistent determinant of superior survival irrespective of the treatment approach used [34-36]. Unfortunately, evaluation of HPV status in HNC entered our clinical practice only a few years ago. For this reason, these data are not available for most patients in our series, making it impossible to obtain a significant analysis.

Apart from HPV, many other biological parameters have been studied as prognostic factors in HNC patients. For instance, a recent meta-analysis on HNC patients confirmed the negative impact of epidermal-growth factor (EGFR) overexpression [37]. In the near future, analysis of these parameters could help physicians in selection of the best treatment approach for each individual patient [38]. Unfortunately, as for HPV, our analysis did not investigate such parameters, because data were missing in a signifi-

Table V. Predictors of recurrence and second primary among head and neck cancer cases by multivariate analysis.

	Recurrence n = 169	Second primary n = 60
	HR (95% CI)[a]	HR (95% CI)[b]
Demographics		
Age at diagnosis (ordinal)	1.00 (0.98-1.02)	1.02 (0.99-1.05)
Gender		
Men	1.00	1.00
Women	0.69 (0.42-1.13)	1.57 (0.76-3.23)
Tumour characteristics		
Stage		
I/II	1.00	1.00
III/IV	0.99 (0.61-1.60)	**2.75 (1.39-5.44)**
Cigarette smoking and alcohol consumption		
Smoking status		
Never	1.00	1.00
Former	0.93 (0.54-1.58)	2.64 (0.80-8.69)
Current	0.61 (0.33-1.14)	3.28 (0.94-11.47)
Years of smoking		
Never smokers	1.00	1.00
≤ 20	0.77 (0.38-1.58)	1.91 (0.42-8.75)
21-40	0.90 (0.51-1.57)	2.34 (0.69-7.93)
> 40	0.71 (0.39-1.30)	**3.68 (1.10-12.30)**
Cigarettes per day		
Never smokers	1.00	1.00
≤ 20	0.81 (0.47-1.39)	2.72 (0.82-8.99)
> 20	0.81 (0.45-1.44)	2.97 (0.87-10.12)
Drinking status		
Never	1.00	1.00
Former	1.21 (0.42-3.48)	0.61 (0.08-4.78)
Current	1.11 (0.71-1.74)	0.73 (0.35-1.51)
Drinks per week		
Never drinkers or < 1	1.00	1.00
1-7	1.33 (0.66-2.67)	0.85 (0.27-2.67)
8-14	**1.73 (1.00-2.97)**	0.99 (0.41-2.39)
15-21	1.07 (0.46-2.51)	0.44 (0.09-2.12)
22-28	0.84 (0.41-1.73)	0.78 (0.27-2.24)
> 28	0.91 (0.51-1.63)	0.83 (0.33-2.11)

Text in bold indicates statistically significant risk factors. HR: Hazard Ratio; CI: Confidence Interval. a HR adjusted by age, treatment, lymph nodes. b HR adjusted by age, stage, years of smoking, lymph nodes.

cant proportion of patients included in this series. Another limitation of the study is represented by not having performed the analysis by HNC subsite and not having available data on comorbidities: due to this latter limitation we could not justify the reason for the elevated number of deaths due to causes other than tumour, although is likely that the advanced age of these patients could be the main reason.

Despite these limitations, we feel that our study contributes in identifying prognostic factors for HNC patients, because the data we considered in this series are easy to collect in any department. The number of patients included in this analysis is small, considering the long-time period studied. However, we preferred a more limited number of patients, but with all the required information available and with sufficient follow-up time.

Conclusions

HNC is the sixth most common neoplasm, and despite advances in therapy, long-term survival in HNC patients is poor. Age and tumour staging are considered the most important prognostic factors for overall survival. Recurrence and second primary tumours are influenced negatively by high alcohol consumption and cigarette smoking. Clinical characteristics remain the best known prognostic factors in HNC. A major effort in HNC prevention and modification of patients' behaviour could lead to early diagnosis and reduction of recurrence and second primary tumours.

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