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HEAD AND NECK

Oral tongue squamous cell carcinomas in young patients according to their smoking status: a GETTEC study

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Abstract

Background Incidence of oral tongue squamous cell carcinoma (OTSCC) is increasing, especially in young adults, despite decreasing tobacco and alcohol consumption.

Methods This multicentric retrospective study of 185 young adults with OTSCC (median follow-up 43 months), investigated risk factors, tumour characteristics and oncological outcomes according to the smoking status.

Results Overall, 38% of patients were smokers (S). Non-smokers (NS) were significantly younger than S. Sex ratios were 1.1 for N and 1.8 for S. NS patients were less frequently cannabis or alcohol users than S, but were more likely to have a history of leukoplakia. Second primaries were observed in NS (4.4%) and in S (12.7%). Despite more frequent local relapse in NS ($p = 0.018$), there was no difference in diagnostic stage and overall survival between groups.

Conclusion OTSCC affects differently young S and NS patients suggesting the existence of a specific clinical entity of OTSCC in non-smoking young adults.

Keywords Oral tongue · Squamous cell carcinoma · Young patients · Non-smoker · Risk factors

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Introduction

Oral tongue squamous cell carcinoma (OTSCC) represents the most common malignancy of the oral cavity with 53,260 cases in 2020 according to the SEER [1]. They are part of the head and neck squamous cell carcinomas (HNSCC) originating from the epithelial lining of the upper aerodigestive tract. HNSCC are presumed to be mainly due to tobacco and alcohol use, which are their main risk factors. In the last 20 years, probably thanks to tobacco prevention campaigns, an important reduction in cigarette consumption has been observed, in particular in men, resulting in the decrease of smoking-related cancers such as lung cancers [2]. Similarly, the overall incidence of HNSCC has been decreasing slowly [3], the incidence of oral, pharyngeal, and laryngeal cancers dropping from 18.3/100,000 in 1980 to 14.2/100,000 in 2017 according to the SEER [1]. Yet, a distinct evolution of some HNSCC sites has been observed, including cancers of the oral cavity for which the number of new cases in the United States increased from 19,600 (13,000 men, 6000 women) in 2012 to 32,000 cases in 2016 [1, 4]. Among SCC of the oral cavity, OTSCC in particular have been described as rising [5] with an average incidence increase of 2.42 per decade according to the SEER [1]. OTSCC is reported to be especially increasing among young adults [6] and more particularly among White women [5, 7]. The observed diverging trends suggest a different aetiology for these cancers as well as changes in the distribution of underlying exposures. While Human Papilloma Virus (HPV) is an independent risk factor in the rise of oropharyngeal squamous cell carcinomas (OPSCC) [8], no consistent link could be established by several studies between HPV [8–12], HSV [13] or EBV [13] and OTSCC. Therefore, unlike OPSCC, it is unlikely that viruses may be responsible for the observed incidence increase of OTSCC, for which underlying factors remaining largely unknown.

While the observed increase in the incidence of OTSCC [5] may suggest the emergence of a new oral tongue cancer unrelated to tobacco, formal demonstration is still lacking, and it remains unclear whether OTSCC in NS patients should be considered as a specific disease.

The available literature on OTSCC in non-smokers (NS) remains sparse and inconclusive. Published epidemiological studies are rarely designed to investigate cancer risk factors according to oral cavity subsites, and oral and pharyngeal cancers are often analysed together. Moreover, the relative rarity of OTSCC among the overall HNSCC population and the current lack of specific aetiological hypotheses make the conduct of specific and sufficiently powered studies difficult. Most studies focusing on young patients compare their outcomes to those of aged patients, and do not distinguish patients by risk factors [14, 15]. Other assumed risk factors for OTSCC, such as personal history of oral leukoplakia [16, 17], alcohol or cannabis use [18], are poorly investigated. Finally, the stage at diagnosis, and oncological outcomes of OTSCC in young non-smoking adults have rarely been investigated.

The purpose of this study was thus to describe the clinical characteristics and outcome of young adults diagnosed with OTSCC, according to their smoking status.

Materials and methods

This is a national multicentre retrospective study based upon the review of the medical files of all patients aged 40 years or less, newly diagnosed with an OTSCC, and treated between 1/01/2005 and 31/12/2015 in one of the 12 French university hospitals and three comprehensive cancer centres, members of the GETTEC (Groupe d'Etude des Tumeurs de la Tête et du Cou—French collaborative group). The study satisfied the European rules for data protection and was registered in the GDPR file of the Leon Bérard Comprehensive cancer center (N°R201-004-014) on behalf of the GETTEC.

Patient records were eligible for inclusion in the study for patients aged 15 to 40 years, diagnosed with a histologically confirmed OTSCC (coded according to the International Classification of Disease ICD-10-CM: C02.0, C02.1 C02.2 C02.3). In line with previous studies focussing on young adults, we defined 40 years as the upper age limit for this study. Patients with missing data regarding their tobacco consumption were not eligible, as well as patients with terminal illness due to other cancer or comorbidities.

Data collected from the patients' medical records included the following variables: date of birth, date of OTSCC diagnosis, tumour location on the tongue, histological characteristics, TNM stage assessed clinically and radiologically according to the 7th edition of the classification, past medical history including previous cancer, medical history of leukoplakia, cancer treatments, surgical margins, date and type of recurrence, existence of second HNSCC primaries, date and status at last medical examination, vital status, cause of death, alcohol consumption, tobacco smoking. Non-drinkers were those answering "no" to the following question regarding their drinking status: "are you nowadays or have you formerly been drinking an alcoholic beverage more than two times a week". Non-smokers (NS) were defined as patients having smoked less than 100 cigarettes in their lifetime. Cannabis smokers were defined as those with current or former, regular or acute, cannabis consumption.

Survival was calculated from the end of treatment. A SCC located on the mobile tongue and appearing on the scar of the previous tumour was considered as a local recurrence regardless of the delay in relation to the primary tumour. A SCC appearing on any area of the mobile tongue which had no contact with the primary location (example: T1 of the left mobile tongue and then T1 of the right mobile tongue) was considered a second primary, as well as a SCC located elsewhere in the upper aerodigestive tract, including in the oral cavity.

Participants' characteristics, according to their smoking status, were described using means and standard deviation (SD), as well as median and interquartile range (IQR) for quantitative data and using their frequencies and percentages for qualitative data. The number of missing values was specified, but they were not considered in the analyses. Pseudonymised data were analysed using descriptive statistics, Chi-square and Fisher exact tests for comparisons of qualitative data, and Welch two-sample *t* test for quantitative data. Overall and local recurrence-free survival was estimated by the Kaplan–Meier method. Univariate analyses of survival distributions between groups were done by the log rank (Mantel–Cox) test. Multivariate analysis was done by linear regression adjusting for other known risk factors of local relapse (resection margins and tumour differentiation). The threshold of statistical significance was set at 0.05. All analyses were performed using PRISM® software.

Results

Population

Between January 2005 and December 2015, 188 patients newly diagnosed with OTSCC were identified in 12 university hospitals and three comprehensive cancer centres, members of the GETTEC (Groupe Etude des Tumeurs de la Tête et du Cou- Comprehensive group for studying head and neck cancer). Three patients did not meet eligibility criteria: two patients with missing smoking status, and one patient who died prematurely from synchronous T4b stage hypopharyngeal tumour. One hundred and eighty five patients were included in the analysis.

Median follow-up time between diagnosis and last follow-up visit or death was 43 months (IQR 2–188 months). Seventy-one patients were chronic current or former smokers (S) (38%), the 114 (62%) remaining patients were NS. Median tobacco consumption of S was 11 pack-year (range 3—40). Overall, the mean age was 32 years (IQR 17–40) and 43.21% was female. NS were significantly younger than S and the proportion of females tended to be larger among NS (sex ratio 1.07) than among S (1.84) (Table 1).

Risk factors according to the smoking status

All baseline characteristics are reported in Table 1. Information on alcohol consumption was missing for two patients, as well as data on previous or concomitant oral leukoplakia for one patient.

Overall, 13 patients (7%) had been treated for a previous malignancy without any significant difference between NS and S in terms of prevalence and previous treatment received (Table 1). Compared to S patients, NS exhibited a lower prevalence of regular or acute cannabis use and alcohol consumption. Conversely, NS had a significantly more frequent past medical history of leukoplakia than S.

OTSCC characteristics

The T and N staging of these tumours according to the TNM 7th edition is shown in Table 2. Overall, most patients (143 patients; 77.3%) presented with early stage tumours (T1/T2 and N0/N1), and no patient had distant metastases at the time of diagnosis. No statistically significant difference was observed for the T stage (χ^2, $p=0.985$) and the N stage (χ^2 $p=0.208$) at baseline between NS and S.

Treatment of the OTSCC

One hundred sixty-four patients (88.5%) underwent surgical resection as primary treatment; seven (3.8%) of them had a reconstruction with a pedicle flap and 20 (12.2%) had a free flap. Among patients receiving surgery, 85 patients (45.9%) had exclusive resections, 32 (17.3%) received postoperative radiotherapy, 40 (21.6%) postoperative concomitant radio–chemotherapy, 6 (3.2%) postoperative brachytherapy and one patient refused postoperative brachytherapy.

Sixteen patients (9.6%) received neo-adjuvant chemotherapy, ten because of a rapidly growing tumour, and the remaining six patients for an unresectable tumour. Fifteen patients received chemotherapy combining docetaxel, cisplatin and 5-fluorouracil (TPF) as an induction protocol, and one patient 5FU and cisplatin. Among the 16 patients treated with neo-adjuvant chemotherapy, ten subsequently underwent surgery followed by concomitant radio–chemotherapy, three underwent surgery followed by radiotherapy and one patient received concomitant radio–chemotherapy; two patients died prematurely because of tumour evolution before any further treatment. Five patients (2.7%) were treated with concomitant definitive radio–chemotherapy.

Table 1 Past medical history and habitus of studied young patients

Risk factor	Non-smokers	Current or former smoker	Total	*p* value (test)
Age	30 ± 6 years old	33 ± 6.4 years old	32 ± 6.3	**0.002** Welch two-sample t test
Sex				
Male	59 (51.8%)	46 (64.8%)	105 (56.8%)	**0.082** Pearson's Chi-squared test
Female	55 (48.2%)	25 (35.2%)	80 (43.2%)	
Total	114 (100%)	71 (100%)	185 (100%)	
Alcohol				
No	111 (97.4%)	45 (63.4%)	156 (84.3%)	**< 0.001** Pearson's Chi-squared test
Yes	3 (2.6%)	24 (33.8%)	27 (14.6%)	
Total (*missing data*)	114 (100%)	69 (97.2%) (*2*)	183 (98.9%)	
Cannabis				
No	114 (100%)	65 (91.5%)	179 (96.8%)	**0.003** Fisher's exact test for count data
Yes	0 (0%)	6 (8.5%)	6 (3.2%)	
Total	114 (100%)	71 (100%)	185 (100%)	
Leukoplakia				
No	84 (73.7%)	66 (93%)	150 (81%)	**0.002** Pearson's Chi-squared test
Yes	29 (25.4%)	5 (7%)	34 (18.4%)	
Total (*missing data*)	113 (99.1%) (*1*)	71 (100%)	183 (99.4%)	
Other cancer				
No	107 (93.8%)	65 (91.6%)	172 (93%)	0.570 Fisher's exact test for count data
Yes	7 (6.2%)	6 (8.4%)	13 (7%)	
Total	114 (100%)	71 (100%)	185 (100%)	
Personal history of chemotherapy for another reason				
No	109 (96%)	69 (97%)	178 (96.2%)	0.710 Fisher's exact test for count data
Yes	5 (4.4%)	2 (2.8%)	7 (3.7%)	
Total	114 (100%)	71 (100%)	185 (100%)	
Personal history of radiotherapy for another reason				
No	109 (96%)	68 (96%)	177 (95.7%)	1 Fisher's exact test for count data
Yes	5 (4.4%)	3 (4.2%)	8 (4.3%)	
Total	114 (100%)	71 (100%)	185 (100%)	

Significant *p*-values are in bold

Histological findings

Most patients (72%) presented with a well-differentiated squamous cell carcinoma at diagnosis, without any difference in tumour differentiation between NS and S (Table 2). HPV status was missing in 136 patients (73.7%). Among the 49 patients (29.9%) with p16 immunohistochemistry (IHC) performed on tumour tissue, nine patients were positive (18.4%). Resection margins were negative (sufficient, R0) in 129 of 177 patients (72.9%) who underwent surgery, and positive (insufficient < 5 mm, R1) in 48 patients (27.1%) on the final histological examination, without statistically significant difference between NS and S.

Relapses, second primaries and metastases

Occurrence of relapses, second primaries and metastases in NS and S are presented on Table 2.

Overall, median time to local recurrence was 11 months (range 4–44) with no difference in time to recurrence between the two groups (10.5 and 11 months in NS and S, respectively), without any difference between the two groups. Kaplan–Meier analysis of local recurrence-free time is presented in Fig. 1, and showed no significant difference between NS and S. However, the prevalence of local tumour relapse was more frequent in NS (23.7%) compared to S (9.9%) (Pearson's Chi-squared test, $p = 0.018$). After

Table 2 Oncological outcomes: stage at diagnosis, histological examination of operative specimen margins, relapses, second primaries and metastases occurrences

Outcome	Non-smokers	Current or former smoker	Total	*p* value (test)
T stage				
T1	43 (38%)	27 (38%)	70 (38%)	0.985 Pearson's Chi-squared test
T2	47 (41%)	28 (39%)	75 (41%)	
T3	13 (11%)	8 (12%)	21 (11%)	
T4	11 (10%)	8 (11%)	19 (10%)	
Total	114	71	185	
N stage				
N0	79 (69%)	50 (71%)	129 (70%)	$p=0.208$ Pearson's Chi-squared test
N1	11 (10%)	9 (13%)	20 (11%)	
N2a	5 (4%)	3 (4%)	8 (4%)	
N2b	8 (7%)	8 (11%)	16 (9%)	
N2c	11 (10%)	1 (1%)	12 (6%)	
N3	0 (0%)	0 (0%)	0 (0%)	
Total	114	71	185	
Differentiation degree				
Well	83 (44.8%)	51 (27.6%)	134 (72%)	0.236 Pearson's Chi-squared test
Moderate	24 (13%)	19 (10.3%)	43 (23%)	
Poor	7 (3.8%)	1 (0.5%)	8 (4%)	
Total	114	71	185	
Histological margins				
Clear (> 5 mm)	75 (70.8%)	54 (76%)	129 (72.9%)	0.721 Pearson's Chi-squared test
Close (< 5 mm)	28 (26.4%)	15 (21.1%)	43 (24.3%)	
Positive (< 1 mm)	3 (2.8%)	2 (2.8%)	5 (2.8%)	
Total	106 (100%)	71 (100%)	177 (100%)	
Second primaries				
No	109 (95.6%)	62 (87.3%)	171 (92.4%)	**0.038** Pearson's Chi-squared test
Yes	5 (4.4%)	9 (12.7%)	14 (7.6%)	
Total	114 (100%)	71 (100%)	185 (100%)	
Local recurrence				
No	87 (76.3%)	64 (90.1%)	151 (81.6%)	**0.018** Pearson's Chi-squared test
Yes	27 (23.7%)	7 (9.9%)	34 (18.4%)	
Total	114 (100%)	71 (100%)	(185 (100%)	
Lymph node recurrence				
No	100 (87.7%)	64 (90.1%)	164 (88.6%)	0.610 Pearson's Chi-squared test
Yes	14 (12.3%)	7 (9.9%)	21 (11.4%)	
Total	114 (100%)	71 (100%)	185 (100%)	
Metastatic recurrence				
No	107 (93.9%)	64 (90.1%)	171 (92.4%)	0.350 Pearson's Chi-squared test
Yes	7 (6.1%)	(9.9%)	14 (7.6%)	
Total	114 (100%)	71 (100%)	185 (100%)	

Significant *p*-values are in bold

adjusting for resection margins and tumour differentiation, the association between local tumour relapse and smoking status remained significant (OR = 0.368; [0.127; 0.609] $p=0.031$), NS being at greater risk of local tumour recurrence compared to *S*. Overall, 14 patients (7.5%) experienced metastatic evolution, without difference between NS and S.

NS patients presented significantly less frequent second primaries than S, $n=5$ (4.4%) and 9 (12.7%), respectively ($p=0.038$). Second primaries of NS were located exclusively in the oropharynx (2) and oral cavity (3); second primaries of S were located in the oral cavity (3), oropharynx (3), larynx (2), and hypopharynx (1).

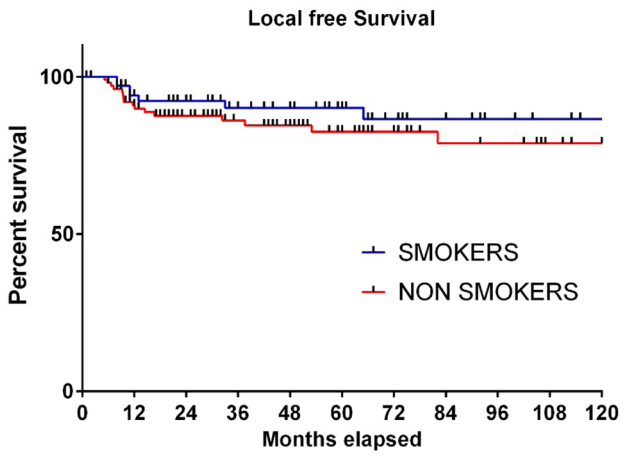

Fig. 1 Kaplan–Meier analysis of local free survival

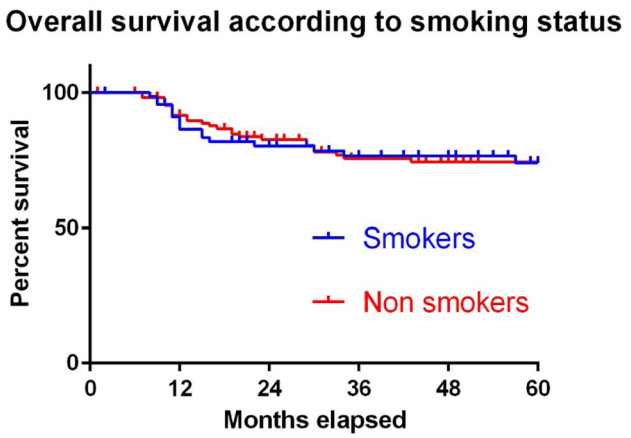

Fig. 2 Kaplan–Meier analysis of overall survival, according to patients smoking status

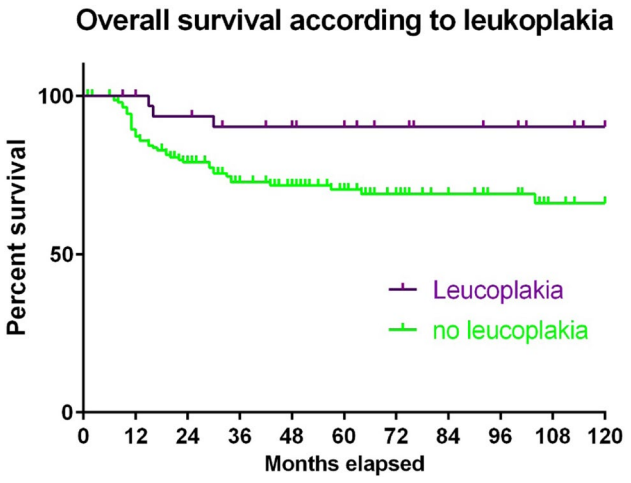

Fig. 3 Kaplan–Meier analysis of overall survival of according to patient's personal history of leukoplakia

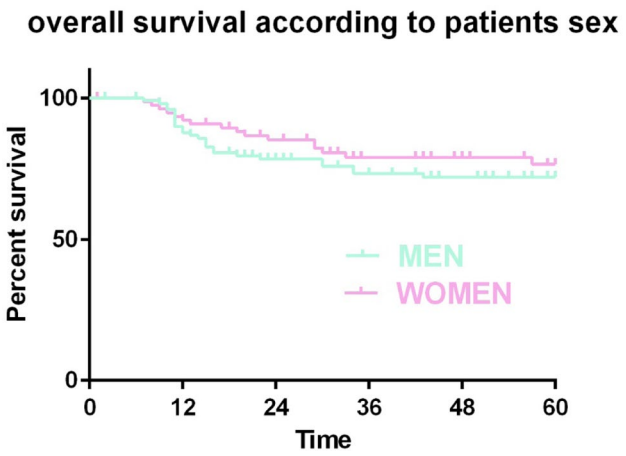

Fig. 4 Kaplan–Meier analysis of overall survival according to sex

Survival

Kaplan–Meier survival curves for overall survival are shown on Figs. 2, 3 and 4. The 2 and 5-year overall survival rates (around 80% and 74%, respectively) were similar in both groups. Reported cause of death was local evolution for 12 patients (28%), cervical node evolution for six patients (14%) metastatic evolution for 22 patients (51%), and other intercurrent cause for 3 patients (7%). Overall survival was not significantly different between NS and S ($p = 0.847$), nor between genders ($p = 0.263$). Patients with a history of leukoplakia had a significantly improved overall survival ($p = 0.018$) compared to patients with no previous history of leukoplakia, although there was no significant difference in the T stage or the N stage (Fisher exact test, $p = 0.280$ and $p = 0.750$) according to a history of leukoplakia.

Discussion

To the best of our knowledge, this is the first study analysing characteristics and clinical outcomes of young adults with OTSCC according to their smoking status. Opposite to what is usually observed in patients with HNSCC [19], about two-thirds of patients in this young adult population were NS, while France is a country where the prevalence of smoking remains high [20]. Also, NS patients were significantly younger than S, as already observed by Harris et al. studying young patients with HNSCC [21]. Regrettably, most published studies on OTSCC in young adults do not take into account their smoking status. The higher proportion of female patients observed in this study compared to the overall HNSCC population [2] is consistent with observations in the literature reporting a higher proportion of females among OTSCC patients < 40, with 46.6% and

42.6% of females reported by Oliver et al. [22] and Pitman et al., respectively [23]. More precisely, in the present study, a higher proportion of females was observed in the NS group than in the S group, although not significant. The overrepresentation of females among patients without exogenous risk factors is in line with observations made by Wiseman et al. [24] and Kruse et al. [25] who reported, respectively, 78% and 67.2% of females among patients without risk factors for OTSCC and HNSCC overall.

Compared to S, NS had a statistically significantly lower prevalence of cannabis use and alcohol consumption, suggesting that neither plays a major role in OTSCC development in NS young adults. Nevertheless, regarding alcohol consumption, it has been suggested that the usual threshold for defining non-drinkers may be too high for some patients, in particular in a subgroup of patients metabolising alcohol into acetaldehyde, a major carcinogen in the oral cavity [26]. Therefore, for these patients, low level of intra-oral alcohol, including mouthwash, may have topical carcinogenic effects after a certain amount of time [27]. However, if relevant, the probability of underestimation of alcohol may be non-differential between NS and S, suggesting that alcohol consumption might not be a predominant risk factor in NS. Regarding cannabis, although consumption might be underreported, it does not seem to be associated with oral cavity cancer nor to be involved in the specific population of NS OTSCC according to data from nine case–control studies from the US and Latin America in the INHANCE consortium [28].

Only a small subset of OTSCC patients in the present study presented with a past medical history of cancer or previous chemo- or radiotherapy [29]. Absence of between-group difference does not support the hypothesis of a particular sensitivity to cancers in general for NS young adult OTSCC patients.

Interestingly, this study found a higher rate of medical history of oral leukoplakia in the NS group than the S group, which may seem paradoxical since tobacco is a major risk factor for oral leukoplakia [30]. Due to the retrospective character of our study, the total number of patients with leukoplakia may have been underreported, especially in S for whom clinicians may not systematically investigated leukoplakia history carefully. Besides, as the study covered a long period of time, some patients were lost to follow-up and their records were reviewed by a different clinician. However, NS, especially non-smoking women, have been consistently reported to be at greater risk of malignant transformation of leukoplakia compared to smoking women [17, 31]. In addition to tobacco or smokeless tobacco use, other reported risk factors for malignant transformation of oral leukoplakia included large size, non-homogeneous clinical aspect female sex, old age, location on the tongue or floor of mouth, and high-grade dysplasia [17, 32]. We also found that patients with leukoplakia had a significantly improved survival compared to patients with no history of leukoplakia. Some studies suggested that leukoplakia diagnosis leads to closer follow-up allowing for earlier oral squamous cell carcinoma detection and thus reduced mortality [33]. However, in the present study, there was no significant difference in stage of OTSCC at diagnosis between patients with and without leukoplakia.

Despite young adults having been reported to have more aggressive OTSCC [34], the large majority of patients in the present study presented with well-differentiated T1–T2 stage tumours at time of diagnosis, i.e. with earlier stages than in the overall HNSCC population [25]. Gamez et al. reported around 2/3 of early stages in this specific population [35]. While Farquhar et al. [36] also found significantly earlier stages of OTSCC in young patients than in patients over 45 years old, analysis of the National Cancer Database by Oliver et al. did not identify any differences in tumour stage nor differentiation at diagnosis between the two groups, but found a significantly higher rate of nodal metastases and lymphovascular invasion in young adults with OTSCC [22]. In our study, there was no difference in OTSCC T, N, or M stages, or tumour grade between NS and S.

Similarly to previous studies focusing on SCC of the oral cavity, surgery was used as primary curative treatment for the large majority of patients in this study. Clear margins rate around 70% in our study is high, but similar to a previous study of the group about young patients squamous cell carcinomas [37]. It is possible that surgeons tend to take a wider surgical margin in younger patients, as they are often suspected of having more aggressive tumours.

Despite similar tumour stage and quality of resection margins, NS patients in the present study had significantly higher local recurrence rate than S patients. While the rate of local recurrence in S patients was similar to the recurrence rate of 9% to 15% reported in previous studies, the local recurrence rate in NS in the present study was two times higher [38], yet the median delay of recurrence was similar in both groups. OTSCCs in young adults have been described as significantly more likely to recur than in older patients by Friedlander et al. [39]. However, the authors did not take into account the smoking status in their matching, and it is possible that the observed difference was actually due to a high rate of NS among the young patients group. Yamamoto et al. suggested that differences in local histopathological pattern of invasion might be responsible for the increased rate of local recurrence in some OTSCC and a role of tumour satellites at distance of the tumour has been suggested by the authors [38]. Unfortunately, we have not been able to analyse these parameters in this retrospective study.

While tobacco smoking at diagnosis is an independent prognostic factor for survival in HNSCC patients [19], survival in this study was comparable between NS and S.

Similarly, Bachar et al. observed no differences between NS and S [40] patients with OTSCC. However, when an analysis of people aged < 40 years at diagnosis was made, they found a worse overall ($p = 0.015$) and disease-free survival ($p = 0.038$) in NS compared to S [40]. Regretfully, except in few studies, little attention was paid to risk factors although traditional behavioural risk factors are known to be present in younger people as well [41]. Overall, the available literature is inconsistent regarding the prognosis of OTSCC in young adults. Survival has been described as better [42, 43] in some studies, similar in others [15, 23, 44–46], and sometimes poorer in additional studies [47, 48]. Popovttzer et al. has suggested that the clinical course of OTSCC in younger patients might follow two distinct patterns: either an extremely aggressive oncological behaviour with a 40% mortality rate within 2 years, or an indolent course with high long-term survival [46]. These divergent observations may be due to the rarity of the disease and the small sample size of most studies, especially in the young age group. Besides, the observation of different patterns of survival of OTSCC in the younger patients may be in favour of distinct clinical and biological entities. The different patterns of survival observed in patients with or without past medical history of leukoplakia in the present study might be in line with this hypothesis.

Studies did report the occurrence of second localisations of primary HNSCC in NS [24], which is intriguing. Indeed, those synchronous or metachronous HNSCC are supposed to be related with the concept of field carcinogenesis [49]. This concept assumes that the carcinogenic exposure of a large field of cells leading to groups of related histologically normal, premalignant groups of cells can carry distinct genetic alterations that spread to cover a large epithelial surface. We also found second HNSCC primaries in the NS population (although those were significantly more frequent in the S population) suggesting exposure to a mutagenic agent, to date still unknown. A dedicated national prospective study on OTSCC in young patients with questionnaires about environmental and professional exposure would be needed to better understand this pathology identify an aetiology.

Finally, the caveats of our study include the lack of matched controls and the retrospective study design, implying the use of TNM 7th edition, and the lack of more detailed information on previous leukoplakia as it is likely that informations about leukoplakia obtained from the patient's records were incomplete. Moreover, the retrospective design of this study did not allow to collect information on other factors of interest that have been suggested as a possible aetiology for HNSCC such as second-hand smoke [50], socio-economic status [51], environmental and occupational exposures [52], dietary habits [53], or chronic dental trauma [54]. Despite those limitations, our study is one of the largest multicentric studies in young adults with OTSCC below 40 years of age, with an important follow-up time, and few missing data.

Conclusion

The present study analysed the clinical characteristics and outcomes of a French population of 185 patients below 40 years of age, with diagnosis of OTSCC, according to their smoking status. It suggested the existence of a specific clinical entity of OTSCC in non-smoking young adults, as most young patients with OTSCC had no known risk factors, were younger, and had a more frequent history of leukoplakia than smokers. The overall survival, as well as the stage of the disease, was similar regardless of the smoking status. However, NS were more prone to experience local relapse than S, even if the surgical margins of the operative specimen were clear. Additional research is needed to better understand the aetiology of OTSCC in young NS, as well as the reasons why they were more prone to local relapses.

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