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Original article

Head and neck squamous cell carcinoma and metachronous second primaries

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ABSTRACT

Objectives: To assess the rate of second (or more) primaries after treatment for head and neck squamous cell carcinoma (HNSCC), and survival compared to patients with a single head and neck cancer.
Material and method: A single-center retrospective study was performed in a University Hospital Center in 541 patients between 2002 and 2010.
Results: One hundred and forty-one patients (26.06%) presented 172 metachronous cancers. Overall 5-year survival was 20.3% with and 38.1% without metachronous cancer. Median and mean survival were respectively 21.9 and 51 months in patients with a single cancer, versus 13.9 and 26.5 months in case of metachronous cancer. Specific survival was comparable to overall survival. All-cause and specific survival were significantly poorer in metachronous cancer ($P = 0.001$; log-rank $\alpha = 0.05$).
Conclusion: At least a quarter of HNSCC patients go on to develop a metachronous second primary. These are of poor prognosis, whatever their location.

1. Introduction

Head and neck cancer includes malignant tumors (mainly squamous cell carcinoma) in the oral cavity, oropharynx, hypopharynx or larynx. According to the most recent data of the INCa national cancer institute in France, there were 15,264 new cases in 2017, 10,932 of which were in males (71.62%) [1]. Laryngeal cancer ranked 17th in frequency, taking all genders together, while all other head and neck locations taken together ranked 9th. Head and neck cancer accounts for 3.82% of all incident cancers in France [1]. Incidence and mortality have been decreasing for 30 years, especially in males, but prognosis remains poor overall and these cancers are a real public health issue, especially in the northern parts of France [1]. The main associated causes of death comprise: tumor progression, non-neoplastic complications of smoking and alcohol abuse, and onset of metachronous second primaries after treatment of the first cancer [2].

Various studies [3–14] sought to determine risk factors for metachronous second primaries, but few focused on survival [2,15–18]. Survival may be expected to be poorer in case of second primary, but is this really so? And does overall survival differ between second primaries and head and neck cancers in general?

The present study assessed the prevalence of metachronous second (or more) primaries in a series of 541 unselected patients. The principal objective was to compare all-cause and specific survival in patients treated for HNSCC with and without second primary.

2. Material and method

A single-center retrospective study included 541 patients, between January 1, 2004 and December 31, 2012, in a University Hospital Center.

2.1. Inclusions/exclusions

Inclusion criteria comprised: any age and gender; squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx or metastatic cervical adenopathy of a squamous cell carcinoma without known primary; decision-making in multidisciplinary team meeting. Exclusion criteria comprised: loss to follow-up immediately after treatment and/or follow-up elsewhere; head and neck cancer other than squamous cell carcinoma; location in nasopharynx, salivary glands, ear, paranasal sinuses, nasal cavities, thyroid gland or skin.

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Table 1
Population data.

	Group1400 patients	Group2141 patients	*P*
Gender			
Male	338 (84.5%)	127 (90.1%)	0.102
Female	62 (15.5%)	14 (9.9%)	0.102
Age (years)			
Mean/SD/median	**60.68**/11.06/59.95	**56.26**/9.23/55.42	**<0.0001**
Smoking			
Ceased	76 (19%)	23 (16.3%)	0.478
Active	277 (69.3%)	100 (70.9%)	0.710
Unknown	32 (8%)	12 (8.5%)	0.849
Never	15 (3.8%)	6 (4.3%)	0.789
Alcohol			
Ceased	38 (9.5%)	13 (9.2%)	0.922
Active	237 (59.3%)	89 (63.1%)	0.419
Unknown	34 (8.5%)	12 (8.5%)	0.997
Never	91 (22.8%)	27 (19.1%)	0.373
T			
1	51 (12.8%)	27 (19.1%)	0.063
2	**107 (26.8%)**	**53 (37.6%)**	**0.015**
3	**122 (30.5%)**	**30 (21.3%)**	**0.036**
4	103 (25.8%)	27 (19.1%)	0.115
x	17 (4.3%)	4 (2.8%)	0.455
N			
0	**139 (34.8%)**	**74 (52.5%)**	**<0.001**
1	67 (16.8%)	30 (21.3%)	0.228
2	**124 (31%)**	**29 (20.6%)**	**0.018**
3	**69 (17.3%)**	**6 (4.3%)**	**<0.001**
x	**1 (0.3%)**	**2 (1.4%)**	**0.108**
M			
0	**358 (89.5%)**	**136 (96.5%)**	**0.012**
1	**40 (10%)**	**3 (2.1%)**	**0.003**
x	2 (0.5%)	2 (1.4%)	0.274
UICC stage			
1	**28 (7%)**	**23 (16.3%)**	**0.001**
2	**53 (13.3%)**	**29 (20.6%)**	**0.037**
3	86 (21.5%)	31 (22%)	0.904
4A	146 (36.5%)	46 (32.6%)	0.408
4B	**49 (12.3%)**	**6 (4.3%)**	**0.007**
4 C	**38 (9.5%)**	**4 (2.8%)**	**0.011**
x	**0 (0%)**	**2 (1.4%)**	**0.017**
Location including			
Single	365 (90.3%)	131 (92.9%)	0.540
Oropharynx	123 (33.7%)	42 (32.1%)	0.733
Oral cavity	22 (6%)	12 (9.2%)	0.223
Hypopharynx	91 (24.9%)	25 (19.1%)	0.175
Larynx	114 (31.2%)	48 (36.6%)	0.258
Non-specific	15 (4.1%)	4 (3.1%)	0.589
Including			
Multiple synchronous	35 (8.8%)	10 (7.1%)	0.540
Lung	10 (28.6%)	1 (10%)	0.228
Esophagus	5 (14.3%)	1 (10%)	0.725
Upper aerodigestive tract	12 (34.3%)	6 (60%)	0.143
≥3 cancers	8 (22.9%)	2 (20%)	0.848
Treatment			
Induction then surgery	5 (1.3%)	1 (0.7%)	0.598
Induction then radiation therapy	15 (3.8%)	7 (5%)	0.530
Surgery	**50 (12.5%)**	**29 (20.6%)**	**0.020**
Radiation therapy	149 (37.3%)	42 (29.8%)	0.111
Surgery then radiation therapy	**116 (29%)**	**60 (42.6%)**	**0.003**
Dissociated	12 (3%)	2 (1.4%)	0.309
Isolated chemotherapy or palliative care	**27 (6.8%)**	**0**	**0.002**
Refusal	4 (1%)	0	0.233
Deterioration or death before treatment	**22 (5.5%)**	**0**	**0.004**
Follow-up (months)			
Mean/SD/Median			
After first cancer	27.53/27.54/17.10	69.32/58.79/51.08	**<0.0001**
After first metachronous cancer		16.03/19.38/6.95	**<0.0001**

In bold: % of cases.

2.2. Diagnosis

The initial cancer was defined as the first diagnosed head and neck squamous cell carcinoma (HNSCC) or, in synchronous cases, the cancer underlying diagnosis. Immunolabeling of $p16^{INK4A}$ protein in pathology analysis of diagnostic biopsy or operative specimen was not systematic in our center before 2013, and HPV status in oropharyngeal cancer could not be taken into account.

The second primaries were located in the upper aerodigestive tract, esophagus, bronchi and/or lung or bladder: i.e., cancers with relative risk of onset after initial HNSCC exceeding 1 according to the literature [3–5]. The Warren and Gates criteria for second

Table 2
Second primary data.

	1st cancer *n* = 141	2nd cancer*n* = 141	3rd	4th	5th	6th
Gender						
Male	127 (90.1%)					
Female	14 (9.9%)					
Age (years)						
Mean/SD/Median	56.26/9.23/55.42	60.79/8.8/59.7				
Time to onset (months)						
Mean/SD/Median	54.49/53.68/32.89					
Location including						
Single	131 (92.9%)	137 (97.2%)	26	1	1	
Oropharynx	42 (32.1%)	41 (29.9%)	7	1		1
Oral cavity	12 (9.2%)	17 (12.4%)	7			
Hypopharynx	25 (19.1%)	15 (10.9%)	2			
Larynx	48 (36.6%)	23 (16.8%)	3			
Non-specific	4 (3.1%)	9 (6.6%)	3			
Nasal cavity, nasopharynx		2 (1.5%)				
Including upper airway+						
Lung		22 (16.1%)	2			
Esophagus		6 (4.4%)	1			
Bladder		2 (1.5%)	1	1		
Multiple synchronous	10 (7.1%)	4 (2.8%)	0			
Lung	1 (10%)	2 (50%)				
Esophagus	1 (10%)	1 (25%)				
Upper aerodigestive tract	6 (60%)	1 (25%)				
≥3 cancers	2 (20%)	0				
Treatment of head and neck cancer						
Induction then surgery	1 (0.7%)	0	0			
Induction then RT	7 (5%)	3 (2.7%)	0			
Surgery	29 (20.6%)	28 (25.2%)	8	2		
Radiation therapy	42 (29.8%)	30 (27%)	4	1	1	
Surgery then radiation therapy Dissociated	60 (42.6%)	21 (18.9%)	1			
	2 (1.4%)	0	0			
Isolated chemo/palliative	0	25 (22.5%)	8			1
Refusal	0	1 (0.9%)	1			
Deterioration or death before treatment	0	3 (2.7%)	0			

primaries were applied [19]. A 6-month interval was used to classify second primaries as synchronous or metachronous.

2.3. Clinical data

Study data comprised: gender, age at diagnosis, date of diagnosis, risk factors (alcohol consumption; smoking: active, ceased for > 1 year at diagnosis, never, no data), follow-up (months), and date and cause of death (disease-specific or not). Data for first cancers comprised: initial location, TNM classification (or pTNM in case of surgery), Union for International Cancer Control (UICC) stage, and type of treatment. Data for second (or more) primaries comprised: gender, age at diagnosis, date of diagnosis, interval to onset, location (oral cavity, oropharynx, hypopharynx, larynx, other upper airway, bronchi/lung, esophagus, bladder), type of treatment, follow-up (months), and date and cause of death (disease-specific or not).

2.4. Treatment

Types of treatment comprised: induction chemotherapy followed by surgery or external radiation therapy, surgery alone, external radiation therapy alone, association of the two, dissociated treatment (lymph-node surgery followed by external radiation therapy), exclusive chemotherapy or palliative care, refusal of treatment, or non-implementation due to deteriorated health status or death. Radiation therapy could be associated to concomitant chemotherapy or to targeted therapy (cetuximab).

2.5. Post-therapeutic monitoring

As of 2006–2007, with the publication of the first guidelines of the French Society of ENT and Head and Neck Surgery (SFORL) on postoperative follow-up of adult HNSCC [20] (updated in 2015 [21]), follow-up conformed to these guidelines. Between 2002 and 2007, follow-up consisted in regular consultations with clinical examination, alternating between ENT and radiotherapy, every 3–4 months, with annual imaging (chest X-ray, possibly with chest and neck CT scan). As of 2004, annual chest CT or PET-scan instead of chest X-ray during follow-up was basically systematic, although with some variations, depending on the surgeon.

2.6. Survival

Survival was assessed as: after HNSCC for patients with a single cancer, or else after second primary. The event in overall survival was death from all causes, and cancer-related death in specific survival.

2.7. Statistics

The Chi^2 test was used to compare frequencies, and the Student *t* test for means. Overall and specific 3- and 5-year survival were estimated on Kaplan-Meier curves and compared on log-rank test. The significance threshold was set at $P < 0.05$.

3. Results

Eight hundred and fifty two patients were discussed in multidisciplinary ENT and head and neck oncology meetings between January 1, 2004 and December 31, 2012. Three hundred and eleven were excluded, being followed up elsewhere and rapidly lost to follow-up (follow-up < 6 months).

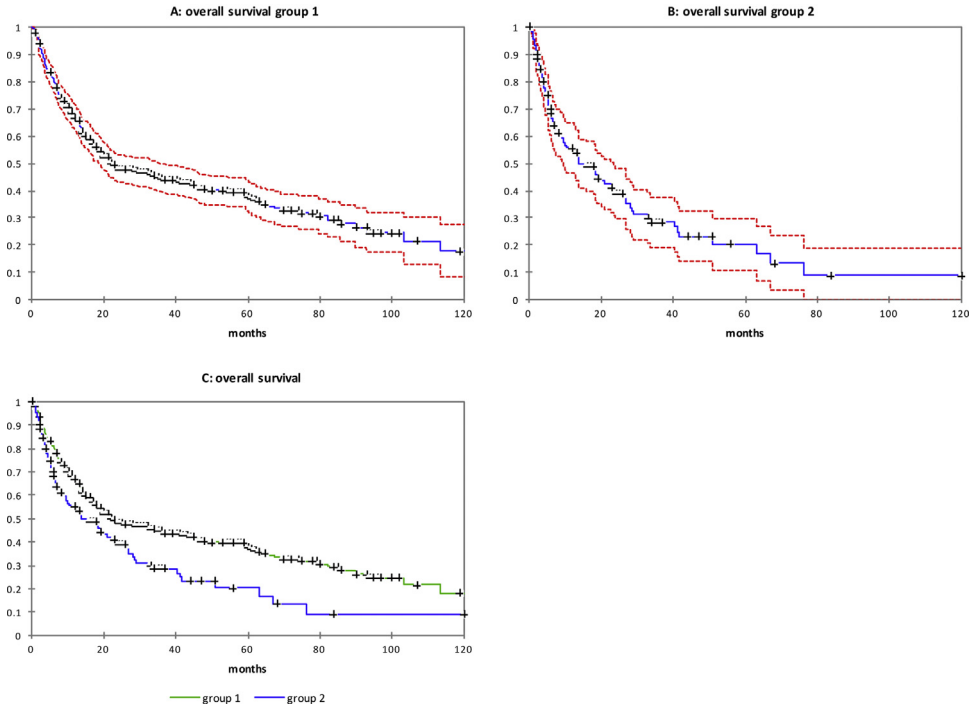

Fig. 1. Comparison of overall survival. A. Overall survival in group 1, with 95% confidence interval. B. Overall survival in group 2, with 95% confidence interval. C. Comparison of overall survival curves.

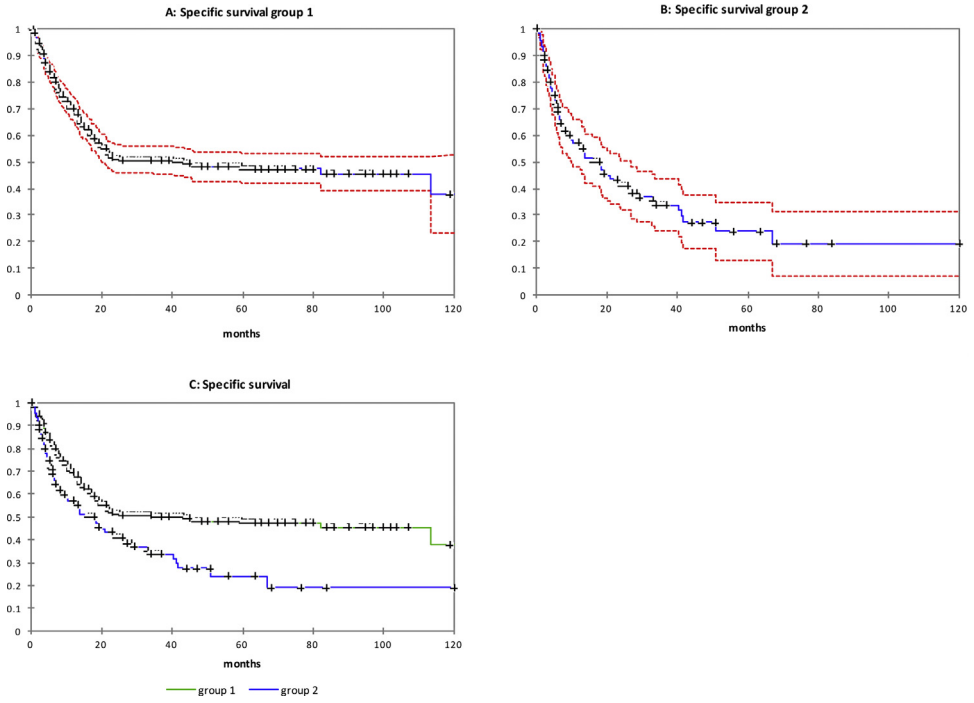

Fig. 2. Comparison of specific survival. A. Specific survival in group 1, with 95% confidence interval. B. Specific survival in group 2, with 95% confidence interval. C. Comparison of specific survival curves.

3.1. Patient groups

Five hundred and forty one patients were included, divided into 2 groups: 400 with a single HNSCC (group 1), and 141 (26.06%) with 172 metachronous second primaries (group 2). Table 1 presents population data. Table 2 presents second primary data. Figs. 1 and 2 show the survival curves.

3.2. Survival

Overall 3- and 5-year survival was respectively 44.7% and 38.1% in group 1 and 28.5% and 20.3% following the second primary in group 2. Median overall survival was 21.9 months (95% CI [18.6; 35]) in group 1 and 13.9 months (95% CI [9.4; 23.6]) following the second primary in group 2, with respective mean values of 51 ± 3.2 months and 26.5 ± 2.7 months. Overall survival was significantly poorer in group 2: $P = 0.001$; log-rank $\alpha = 0.05$.

Specific 3- and 5-year survival was respectively 50.4% and 47.3% in group 1, and 33.8% and 24% after the metachronous second primary in group 2. Median specific survival was respectively 40.5 months (95% CI [21; NK]) and 18.2 months (95% CI [9.9; 26.7]), with respective mean values of 67.7 ± 3.7 months and 29.2 ± 3 months. Specific survival was significantly poorer in group 2: $P < 0.001$; log-rank $\alpha = 0.05$.

3.3. Comparison of general data

The two groups were comparable for gender, age and risk factors (alcohol and smoking).

The first HNSCC showed lower tumor grades locally (T grade), regionally (N grade) and generally (M grade) than in group 2. Overall UICC stage likewise showed more stages 1 and 2 in group 2, and more $\geq$ 4B stages in group 1.

The two groups were comparable in terms of locations.

Thirty-five patients in group 1 had synchronous cancer: 10 lung, 5 esophageal, 12 upper airway. Eight of these patients had 3 synchronous cancers.

Ten patients in group 2 had synchronous cancer, including 6 with 2 head and neck locations. Mean follow-up after first HNSCC was 27.53 months in group 1, for a median 17.1 months and, in group 2, 69.32 months (median = 51.08 months) following first cancer and 16.03 months (median = 6.95 months) following second primary.

3.4. Characteristics of metachronous second primaries

Mean age at onset of second primary was 60.79 years (median = 59.7 years). In all, 78.1% of locations were upper aerodigestive tract, and 16.1% lung. Twenty-six patients had a third metachronous primary, mainly involving the upper aerodigestive tract. One patient developed 6 successive cancers during follow-up.

4. Discussion

The risk of developing a metachronous second primary following treatment of a first HNSCC is theoretically 3–7% per year [21], with incidence of 5–30% taking all first and second locations together [15]. No correlation has been demonstrated between initial HNSCC grade and rate of onset of metachronous second primary. However, initial laryngeal location is associated with higher risk of metachronous second primary in the lung [22] and initial oropharyngeal or oral cavity location with higher risk of esophageal metachronous second primary, with risk remaining constant over time [6]. Metachronous second primary rates vary according to initial location, secondary location and, above all, duration of follow-up (i.e., survival) after treatment of the first cancer. In the largest series [4,5], cumulative 20-year risk of metachronous second primary after a first HNSCC was 36% for Chuang (99,257 patients) [4] and 47% (after first laryngeal cancer) for Gao (20,074 patients) [5]; the upper aerodigestive tract was the most frequent secondary location, representing half of the cases [4,5].

4.1. Risk factors for onset of metachronous second primary

Risk factors for onset of metachronous second primary have been widely studied [2–18]. Yamamoto reported a higher risk of metachronous secondary in males [14]. For some authors, age was not a risk factor [7,8], whereas for others it was [16,17]. Rennemo reported higher rates in patients younger than the median [17]. Chuang found a relative risk of 14.6 in case of first HNSCC with onset earlier than 56 years of age, with risk decreasing with age at first onset ($P < 0.0001$) [4]. In the present study, mean age was lower at onset of first HNSCC in patients with a metachronous second primary.

Some studies [3,4,17] investigated whether risk of metachronous second primary was associated with location of the first HNSCC, with discordant findings. The highest-risk initial location was the larynx for Chuang [4], hypopharynx for Morris [3], and oral cavity and larynx for Rennemo [17]. In the present study, there was no initial location with particular risk.

Metachronous second primary location varies with initial location. Upper aerodigestive tract locations are more frequent after initial oral cavity or oropharynx cancer [3,9–11,17], and second primaries in the lung more frequent after initial laryngeal cancer [3,5,10,17]. Initial tumor stage also seems important: initial UICC low-stage head and neck cancer is associated with greater risk of metachronous second primary than is more advanced cancer [17]. A second metachronous primary is more likely to develop over time in patients with small initial tumor with low stage of local advancement thanks to good local control, and hence better post-treatment survival [2,12]. The present study confirmed these findings: the rates of T2, N0 and M0 tumor were lower and the rates of T3, N3 and M1 tumor higher in group 1 than group 2.

Alcohol and smoking are major risk factors for head and neck cancer, and excessive alcohol consumption [8,13,15] and active smoking [4,8–10,13] also increase the risk of metachronous second primaries, which increases with the level of smoking at diagnosis of the initial head and neck cancer and also is higher in patients who continue smoking after the initial treatment [11,12,23]. Conversely, in 1971 Moore demonstrated that smoking cessation reduced the risk of second cancer: 40% of patients who continued smoking after a first head and neck cancer developed a metachronous second cancer, versus 6% of those who ceased [24]. The risk of metachronous second primary is stable for at least 3 years after smoking cessation [12], the decreases [23]. In the present study, alcohol withdrawal and smoking cessation at onset of metachronous second primary could not be analyzed, for lack of data. There was, however, no significant difference in habits between the two groups at the time of initial data collection.

Another possible risk factor for metachronous second primary is history of external radiation therapy. Risk of onset of metachronous second primary decreases during the first 5 years ("protective effect") but then increases, even beyond the risk without radiation therapy [25]. Radiation therapy thus exerts a protective effect that is not lasting [5,25]. It is nevertheless a fairly minor risk factor, with relative risk of 1.1 [5]. In general, overall and specific survival are poorer after the metachronous second primary than after the initial head and neck cancer, as the most frequent locations of metachronous second primaries other than the upper airway are the esophagus and lung, both of which show very poor prognosis, entailing a significant reduction in survival [17]. Overall 5-year survival in patients with only one head and neck cancer is around

50% [7,15], compared to 20% after diagnosis of a metachronous second primary [4,8]. Chuang reported on the largest cohort, and found overall 5-year survival greater than 30% in head and neck metachronous second primaries, compared to 8% for other locations [4]. In the present series, this was not a significant feature, perhaps due to the small numbers of metachronous second primaries outside the head and neck region.

León reported 30% overall 5-year survival in head and neck second primaries, versus 50% for initial head and neck cancer [9]; survival decreased by about 10% for each new head and neck second primary location [9]. This poorer prognosis in second primaries than in initial cancer also applies to esophageal and lung locations of second primaries [9]. In the present study, some patients developed multiple successive primaries, but numbers were insufficient to allow comparison of survival.

Metachronous second primary reduces overall survival in well-controlled initial head and neck cancer [9], but is an important cause of death in patients with low-stage initial head and neck cancer [8]. Patients with poor initial prognosis do not live long enough to develop a metachronous second cancer [17].

4.2. Treatment

The main problem with onset of metachronous head and neck second primaries is that no curative treatment may be available for the second cancer, especially when surgery or repeat radiation therapy are unfeasible. In León's series of 4298 patients, rates of palliative management were 22% for second head and neck primaries, 41% for third and 75% for fourth [9]. In the present study, in contrast, curative treatment (isolated surgery or surgery followed by radiation therapy with or without chemotherapy, or isolated radiation therapy, or chemoradiation therapy) was more frequent in group 2, while chemotherapy and/or palliative support were more frequent in group 1. The poor health status of some patients in group 1 precluded initiation of curative treatment. Metachronous second primaries thus mainly developed in patients treated for or cured of their initial cancer or patients with the best survival.

5. Conclusion

Metachronous second primaries in patients treated for initial HNSCC are generally of poor prognosis, especially as therapy may be vitiated by previous treatments. Although risk factors for metachronous second primary can be identified, all patients are at high risk and should be monitored, especially if they have had curative treatment for the initial HNSCC. Alcohol withdrawal and smoking cessation should be recommended systematically and whenever possible undertaken. Monitoring, however, remains indispensable, and should be basically clinical for second head and neck cancers, in line with the SFORL guidelines.

Disclosure of interest

The authors declare that they have no competing interest.

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