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## **Metachronous second primary neoplasia in oropharyngeal cancer patients: impact of tumor HPV status. A GETTEC multicentric study.**

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**Abbreviations**

HPV: Human Papillomavirus

OPSCC: oropharyngeal squamous cell carcinoma

RT: radiotherapy

CT: chemotherapy

ASA: American Society of Anesthesiologists

KFI: Kaplan-Feinstein Index

AJCC: American Joint Committee on Cancer

IHC: immunohistochemistry

OR: Odds Ratio

IC95%: confidence interval 95%

MSPN: Metachronous second primary neoplasia

**Key words:** oropharynx, cancer, human papilloma virus, second primary neoplasia

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impact of tumor HPV status. A GETTEC multicentric study.**

## **Abstract**

Introduction: Patients with oropharyngeal squamous cell carcinoma (OPSCC) display a significant risk to develop a metachronous second primary neoplasia (MSPN). HPV and non-HPV-related OPSCC are 2 distinct entities with biological, clinical and prognostic differences. The aims of our study were to analyze the impact of tumor HPV status and other relevant clinical factors, such as tobacco and/or alcohol (T/A) consumption, on the risk and distribution of MSPN in OPSCC patients and to assess the impact of MSPN on patient survival.

Material and methods: All OPSCC patients treated from 2009 to 2014 were included in this multicentric retrospective study. P16 immunohistochemical expression was used as a surrogate maker of tumor HPV status. The impact of tumor p16 status on the risk of MSPN was assessed in uni- and multivariate analyses. Overall survival (OS) was determined by Kaplan–Meier analysis.

Results: Among the 1291 patients included in this study, 138 (10.7%) displayed a MSPN which was preferentially located in the head and neck area (H&N) , lung and esophagus. Multivariate analyses showed that p16- tumor status ( $p = 0.003$ ), T/A consumption ( $p = 0.005$ ) and soft palate tumor site ( $p = 0.009$ ) were significantly associated with a higher risk of MSPN. We found no impact of p16 tumor status on the median time between index OPSCC diagnosis and MSPN development, but a higher proportion of MSPN arising outside the H&N, lung and esophagus was found in p16+ than in p16- patients. MSPN development had an unfavorable impact ( $p = 0.04$ ) on OS only in the p16+ patient group.

Conclusion: P16 tumor status and T/A consumption were the main predictive factors of MSPN in OPSCC patients. This study provides crucial results with a view to tailoring global management and follow-up of OPSCC patients.

## Introduction

Advances in surgery, radiotherapy and systemic therapies over the past 30 years have increased the life expectancy of head and neck cancer patients leading to a constantly increasing population of cancer “survivors”<sup>1,2</sup>. The risk of developing a metachronous second primary neoplasia (MSPN) is important in this population and represents a significant cause of death<sup>3</sup>. This risk varies in the different head and neck cancer subsites and with patient exposition to major head and neck cancer risk factors such as tobacco and/or alcohol (T/A) consumption.

Oropharyngeal squamous cell carcinoma (OPSCC), one of the most frequent head and neck cancers, includes two distinct entities: human papillomavirus (HPV)-induced and non-HPV-induced OPSCC with biological, clinical and prognostic differences. HPV- OPSCC patients display generally a higher T/A consumption than HPV+ OPSCC patients<sup>4</sup> and are therefore supposed to be at higher risk of developing a T/A-related MSPN (lung cancer, esophagus cancer, head and neck cancer, bladder cancer, liver cancer...)<sup>5-7</sup>. At the opposite, HPV is involved in carcinogenesis of several cancer in the anogenital area (cervix, anus, penile, vulva)<sup>8-11</sup>. Moreover, HPV+ OPSCC patients display a better prognosis than HPV- OPSCC patients<sup>12</sup>, resulting in a longer life expectancy which could also impact the risk of MSPN. The aims of our study were to analyze the impact of tumor HPV status and other relevant clinical factors, such as T/A consumption, on the risk and distribution of MSPN in OPSCC patients and to assess the impact of MSPN on patient survival.

## **Material and methods**

This retrospective multicenter study involving 7 French tertiary cancer care centers (Nice, Nimes, Villejuif, Marseille, Montpellier, Toulon and Toulouse) was conducted by the GETTEC (Groupe d'Etude des Tumeurs de la Tête et du Cou) collaborative study group.

### **Patients**

Patient inclusion criteria were as follows:

- previously untreated OPSCC diagnosed between 2009 and 2014
- p16 status of the OPSCC determined by immunohistochemistry

Exclusion criteria were as follows:

- metastatic OPSCC
- undetermined p16 tumor status
- medical history of head and neck cancer
- medical history of head and neck radiotherapy

### **Definition of MSPN**

MSPN definition was based on Warren and Gates criteria<sup>13</sup>. Each MSPN had to be histologically proven and must not be a recurrence of the OPSCC index. In addition, each case of MSPN had to be validated by a multidisciplinary tumor board.

### **Ethical considerations**

The study protocol was reviewed and approved by institutional ethics committees prior to the start of the study. The study was conducted in compliance with the Helsinki Declaration.

Informed consent was obtained prior to treatment to use their medical data for purpose of



research, and the database was declared. All the clinical data needed for the study were recorded in a computerized database after obtaining authorization from the French National Commission for Informatics and Liberties (database declaration number: 1996558 v 0).

### **Study measurements**

All data were collected within each center by the same investigator (last author). Patient comorbidity level was determined using the American Society of Anesthesiologists (ASA) and the Kaplan-Feinstein index (KFI). T/A consumption was noticed. Patients were staged according to the 2009 (7<sup>th</sup> edition) American Joint Committee on Cancer (AJCC) staging system. Anatomical subsite of the index OPSCC was noticed (base of tongue, lateral pharyngeal wall, glosso-tonsillar sulcus, posterior pharyngeal wall, soft palate).

Immunoexpression of protein p16 was used as a surrogate marker of HPV tumor status. Routine paraffin-embedded, formalin-fixed, pretreatment tumor tissues were tested for p16-expression by immunohistochemistry (IHC). As usually recommended<sup>14</sup>, tumors were classified as p16+ in the event of strong, diffuse nuclear and cytoplasmic staining in more than 70% of carcinoma cells, but tumors displaying unconventional keratinizing morphology together with a variable or patchy p16-expression staining pattern were classified as p16-. Date of diagnosis and location of MSPN were recorded. MSPN located to oral cavity, pharynx (naso-, oro or hypo-) or larynx were labelled as Head and Neck location.

### **Statistical analyses:**

Distribution of patients' clinical characteristics according to p16 tumor status was analyzed in univariate analysis. We investigated the impact of p16 tumor status and of other relevant clinical factors (gender, age, ASA score, KFI score, T/A consumption, T-stage, N-stage, tumor anatomical subsite) on the risk of MSPN in univariate analyses using Chi-2 tests,

confirmed by Fisher exact tests. For multivariate analyses, all variables associated with a  $p \leq 0.10$  in univariate analysis were included in logistic regression models.

Overall survival (OS) was defined from the date of diagnosis (index OPSCC) to death from any reason or censored if patients were alive at the last follow-up. OS was determined using Kaplan-Meier analysis. To analyze the impact of a MSPN on patient survival, we compared OS in patients with or without development of a MSPN in the subpopulation of patients without recurrence of the index OPSCC (to eliminate the impact on OS of the index OPSCC-related deaths) using Log-Rank test.

All statistical analyses were performed at 5% alpha risk or 95% confidence interval by the biostatistician using R.3.0.1 software on Windows.

## **Results**

### **Patients' clinical characteristics**

A total of 1291 patients, 966 men and 325 women, mean age 61.2 +/- 9.5 years, were included in the present study. Their main clinical characteristics, for the whole cohort and according to the p16 tumor status, are shown in Table 1.

### **Risk and predictive factors of MSPN**

Median follow-up was 40 months. One hundred thirty-eight (10.7%) patients developed a MSPN during follow-up.

The impact of p16 tumor status and of other relevant clinical factors on the risk of MSPN is shown in Table 2. Of note, in multivariate analysis, p16- tumor status ( $p = 0.003$ ; OR=1.87, IC95% [1.22-2.86]), T/A consumption ( $p = 0.005$ ; OR=3.43, IC95% [1.46-8.05]) and soft

palate tumor site ( $p = 0.009$ ;  $OR=1.69$ ,  $IC95\%$  [1.15-2.49]) were significantly associated with a higher risk of MSPN.

The incidence of MSPN according to p16 tumor status and T/A consumption is illustrated in Figure 1. In the p16- patient group, the incidence of MSPN was 16.1 and 3.3% in patients with or without T/A consumption, respectively ( $p = 0.0002$ ). In the p16+ patient group, the incidence of MSPN was not significantly different between patients with or without T/A consumption (6.8 vs. 5.9%, respectively,  $p = 0.68$ ).

### **Time of onset and anatomical locations of metachronous cancers**

MSPN were diagnosed after a median time of 29 months after the index OPSCC diagnosis (30 and 34 months for patients with p16- and p16+ OPSCC, respectively). The proportion of MSPN occurring in the first 3 years after OPSCC diagnosis was 69% and 57% in p16- and p16+ patients, respectively.

Locations of MSPN according to p16 status are shown in Table 3. Of note, in the whole cohort, most MSPN were located in the head and neck area (H&N) (35%), lung (31%) and esophagus (7%). The proportion of MSPN located in the H&N area was significantly higher in the p16- than in the p16+ group of patients (40% vs. 20%;  $p = 0.03$ ). The proportion of MSPN located outside the H&N, lung and esophagus was significantly higher in the p16+ than in the p16- group of patients (49% vs. 20%;  $p < 0.0001$ ). Of note, among p16+ OPSCC patients, we observed no cases of anogenital HPV-related MSPN.

### **Impact of MSPN on OS in patients without recurrence of the index OPSCC**

In the p16- patient group ( $n = 738$ ), 464 patients did not develop recurrence of the index OPSCC. Among these patients, 103 developed a MSPN during follow-up. MSPN development had no significant impact ( $p = 0.16$ ) on OS in this group of patients (Fig. 2).

In the p16+ patient group (n = 553), 429 patients did not develop recurrence of the index OPSCC. Among these patients, 35 developed a MSPN during follow-up. MSPN development had a significant negative impact (p = 0.04) on OS in this group of patients (Fig. 3).

## **Discussion**

In the present study, the rate of OPSCC patients developing a MSPN during follow-up was 10.7%. This result is consistent with literature data showing MSPN development rates between 7 and 26% in head and neck cancer patients<sup>15-17</sup>. Obviously, the cumulative rate of MSPN is dependent on the duration of patient follow-up after diagnosis of the index cancer. Indeed, Tiwana *et al.*, in a Canadian retrospective study on 1658 head and neck cancer patients diagnosed between 1986 and 1990, observed a rate of MSPN of 15.1% at 5 years and 61% at 25 years<sup>18</sup>. This rate was higher for index cancers of the oral cavity and hypopharynx. However, several important factors could not be analyzed in this study which was based on a regional register (alcohol and tobacco consumption, proportion of HPV-induced OPSCC)<sup>18</sup>. Other studies conducted in head and neck cancer patients reported an incidence of MSPN between 3 and 4% per year of follow-up which is also consistent with the rate found in the present study<sup>19,20</sup>.

In the present study, in accordance with literature data, p16- OPSCC patients had more comorbidities and more T/A consumption but also displayed a higher risk of MSPN (14.0 % vs. 6.3%) than p16+ OPSCC patients. In the same way, Boakye *et al*<sup>16</sup> carried out a retrospective study from the American national register (National Cancer Institute Surveillance, Epidemiology and Result Registry SERR) on 109,512 head and neck cancer patients in order to assess the MSPN occurrence rate. They found that patients with a HPV- tumor had a statistically increased risk of MSPN compared to patients with a HPV+ tumor.

During follow-up, 14% of p16- OPSCC patients developed a MSPN. The main site of MSPN for these patients was the H&N (40%). In order to explain this high rate of MSPN within a same anatomical region, Slaughter et al.<sup>21</sup> proposed the field cancerization theory for the first time in 1953. Several authors have since described this mechanism where precancerous cellular clusters disseminated in the upper aerodigestive tract epithelium carry multiple genetic alterations and an increased risk of malignant transformation despite a normal histological appearance<sup>22-24 25,26</sup>. In p16+ OPSCC patients, we found a 6.3% rate of MSPN, of which 20% affected the H&N. Thus, the proportion of MSPN located at the H&N was significantly higher in the p16- than in the p16+ group of patients suggesting that the field cancerization concept does not apply similarly in HPV-related and non-HPV-related OPSCC. Diaz et al.<sup>27</sup> also supported this hypothesis through an American national retrospective study based on the SEER database. They observed that the rate of MSPN within the H&N area fell concomitantly with the increase in the incidence of HPV-induced OPSCC during the study period (1973-2008).

In our series, the higher rate of MSPN was observed in p16- OPSCC patients with T/A consumption. In this group, MSPN were mainly located (82%) in the H&N area, lung and esophagus. The MSPN occurrence rate was low and reduced by more than 50% in the 3 other patient groups (i.e. p16- and no T/A consumption; p16+ and T/A consumption; p16+ and no T/A consumption). Interestingly, in a Canadian retrospective study of 406 OPSCC patients diagnosed between 2005 and 2009, Xu et al.<sup>28</sup> observed that p16- patients had significantly more tobacco-related MSPN than p16+ patients (incidence rate per 100 person-years of 8.5 vs. 0.7 for p16- and p16+ patients, respectively,  $p < 0.0001$ ). In a retrospective American monocentric study of 356 patients, Peck et al.<sup>29</sup> found that the risk of MSPN was reduced by 73% in non-smoking HPV-seropositive OPSCC patients and by 23% in smoking HPV-seropositive OPSCC patients compared with HPV-seronegative patients. In our series, for

p16+ patients, we did not observe difference among patients with or without T/A consumption, contrary to p16+ patients. This discrepancy is probably linked to the lower tobacco consumption for p16+ patient, even if higher to the most used cut off 10PY defined by Ang et al<sup>30</sup>.

Surprisingly, we found a comparable proportion of lung MSPN in the p16- and p16+ patient groups (33% versus 26%) despite a higher rate of smokers in the p16- group. A potential role of HPV in the development of lung cancer has already been reported in the literature<sup>31</sup>. In 1979, Syrjanen et al.<sup>32</sup> were the first authors to mention a possible involvement of HPV in lung cancer carcinogenesis. In 2015, Zhai et al.<sup>33</sup> carried out a meta-analysis on the link between HPV and lung cancer. They showed that presence of HPV (mainly HPV-16 and -18) in lung tissue was associated with an increased risk of lung cancer, and principally of squamous cell carcinomas (OR = 9.78; 95% CI: 6.28-15.22; p <0.001). In addition, Tsyganov et al.<sup>34</sup> showed a geographic disparity in the prevalence of HPV in lung cancer, but also a significantly higher prevalence of HPV infection in tumor lung tissue compared to normal lung tissue (OR = 5.38; 95% CI: 3.21-9.00; p <0.0001). However, this subject remains controversial with a HPV detection rate in lung cancer tissues varying from 0 to 75% depending on the studies<sup>34</sup>. A clear limitation of these studies, which is also a bias in the present study, is the difficulty to retrospectively differentiate a primary lung cancer from a unique lung metastasis, that can sometimes occur up to 10 years after initial diagnosis<sup>35,36</sup>. For HPV-induced OPSCC, HPV expression is constant in metastatic tissues and HPV-status can be determined in routine clinical practice on a biopsy of metastatic lesions (p16 expression, in situ hybridization)<sup>37,38</sup>.

A high difference in MSPN occurrence rate between patients with a HPV- OPSCC and a T/A consumption and patients with a HPV+ OPSCC and no T/A consumption have also been reported by Martel et al. (28.5% vs. 3.2%, respectively)<sup>39</sup>. Similarly to the present study,

Martel et al, observed no cases of anogenital HPV-induced MSPN during follow-up. This result may, at least in part, be explained by insufficient sample size and follow-up. Indeed, in a retrospective study from the American national registry (SEER) covering 113 272 survivors of HPV-associated cancers diagnosed between 1973 and 2014, Suk et al.<sup>40</sup> observed that those who had an index OPSCC had the highest risk of HPV-induced MSPN (standard incidence ratios: 19.8 [95% CI, 18.4-21.4] and 18.0 [95% CI, 16.9-19.1] among women and men, respectively; excess absolute risks: 80.6 and 61.5 per 10 000 person-years at risk among women and men, respectively). This increase in the risk of HPV-induced MSPN after an index HPV-induced OPSCC remains therefore to be confirmed by prospective studies. This observation could justify a multidisciplinary follow-up of HPV-induced OPSCC patients involving head and neck surgeons, medical and radiation oncologists but also gynecologists, proctologists and urologists<sup>41</sup>, in order to detect MSPN as early as possible<sup>11,42</sup>.

Soft palate tumor site was significantly associated with a higher risk of MSPN, in univariate and multivariate analysis. Soft palate carcinomas are most often HPV-negative and arise generally in patient with a high level of T/A consumption. This could explain the high rate of MSPN found in patients with soft palate tumor. However, it is surprising that this statistical correlation persists after multivariate analysis taking into account T/A consumption and tumor p16-status. Several other predictive factors of MSPN have been reported in head and neck cancer patients such as patient age, tumor stage and hypopharyngeal tumor site<sup>16,43</sup>.

Interpretation of such results has to consider the possible correlations between patient age, tumor stage and patient life expectancy as well as between tumor location and T/A consumption, that both can impact the risk of developing a MSPN.

In p16+ patients without recurrence of the index OPSCC, development of a MSPN had a significant unfavorable impact on OS. This result is concordant with several other studies in head and neck cancer patients<sup>17,44-46</sup>. Indeed, Jung et al.<sup>46</sup> found 5- and 10-years OS rates of

31.8% and 20.8% versus 57.8% and 45.7% in patients with or without MSPN, respectively.

At the opposite, in the present study, MSPN development had no impact on OS in p16-OPSCC patients. This surprising result could be explained by the multiple competing causes of mortality in these patients<sup>47</sup>. Indeed, p16-OPSCC patients exhibit generally a high level of comorbidity, in link with their important T/A consumption, such as cardiovascular diseases which represent the main causes of mortality<sup>48</sup>.

The median time between index OPSCC diagnosis and MSPN development was 29 months.

We observed no significant difference according to p16 status. The majority of MSPN occurred, in both groups, during the first 3 years of follow-up. This result has to be interpreted in regard of the median follow-up of our study (40 months). Indeed, MSPN can occur long-time after diagnosis of the index cancer and it is likely that prolonging patient follow-up results in delaying the median time between index OPSCC diagnosis and MSPN development.

The present study has several limitations. As mentioned above, median follow-up was 40 months in our study, and MSPN are likely to develop after this delay. Contrary to the recurrence risk of the index OPSCC which is known to decrease importantly after the first 3 years, the risk to develop MSPN is known to be more constant over time. One other significant weakness of the present study is that determination of the tumor HPV-status was based on p16 protein expression in immunohistochemistry, which is only an indirect and imperfect marker of the HPV-status of the tumor. However, the p16 tumor status is currently the only marker assessing the implication of HPV in OPSCC available in clinical practice, and therefore in retrospective studies. The main strengths of our study were the large number of patients included, in a multicentric manner and with a determined p16 tumor status, making this investigation the largest European series on this subject of crucial interest.

## **Conclusion**



In this large multicentric study on OPSCC patients, we observed a 10.7% MSPN occurrence rate with a median follow-up of 40 months. Patients with a p16- OPSCC and a T/A consumption had the highest MSPN development risk. A significantly higher proportion of H&N MSPN was found in p16- than in p16+ patients whereas a higher proportion of MSPN arising outside the H&N, lung and esophagus was found in p16+ than in p16- patients. These results need to be validated by prospective studies taking into account the different methods of clinical and radiological monitoring that can obviously impact the detection of MSPN. At the time of personalized medicine, where the objective is to adapt management of the patient to its own characteristics (clinical, biological, genetic, etc.), the long-term objective would be therefore to tailor patient follow-up to each patient.

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## **Figure legends**

**Figure 1:** Risk of metachronous second primary neoplasia (MSPN) according to p16 tumor status and tobacco and /or alcohol (T/A) consumption.

**Figure 2:** Kaplan-Meier overall survival (OS) curves of p16- OPSCC patients according to metachronous second primary neoplasia (MSPN) development.

**Figure 3:** Kaplan-Meier overall survival (OS) curves of p16+ OPSCC patients according to metachronous second primary neoplasia (MSPN) development.

Number of patients developing MSPN / All patients  
138 / 1291 (10.7%)

P16- group of patients  
103 / 738 (14.0%)

P16+ group of patients  
35 / 553 (6.3%)

T/A consumption +  
99 / 615 (16.1%)

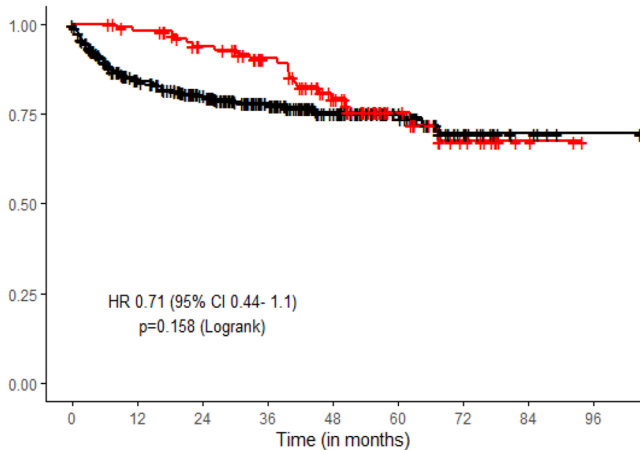
T/A consumption -  
4 / 123 (3.3%)

T/A consumption +  
17 / 250 (6.8%)

T/A consumption -  
18 / 303 (5.9%)

# p16- patients

Survival (%)

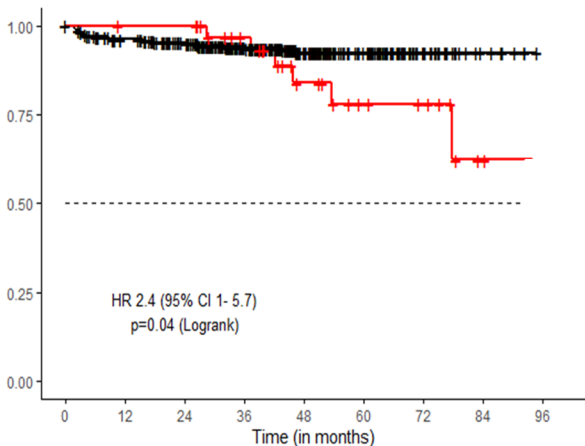


## Number at risk

	0	12	24	36	48	60	72	84	96
MSPN: No	361	254	207	145	93	51	18	5	1
MSPN: Yes	103	98	86	69	46	22	11	3	0

# p16+ patients

Survival (%)



## Number at risk

MSPN: No	394	356	319	233	139	85	30	8	0
MSPN: Yes	35	34	34	26	16	10	8	2	0
	0	12	24	36	48	60	72	84	96

Time (in months)

**Table 1: Patients' clinical characteristics according to their tumor p16 status**

<b>Clinical characteristics</b>	<b>All patients N = 1291 (%)</b>	<b>p16- patients N = 738 (%)</b>	<b>p16+ patients N = 553 (%)</b>	<b>UA</b>
<b>Gender:</b> male / female	966 (75) / 325 (25)	560 (76) / 178 (24)	406 (73) / 147 (27)	0.3
<b>Age (years):</b> average +/- SD	61.2 +/- 9.5	60.4 +/- 8.6	62.5 +/- 9.9	0.8
<b>ASA score:</b> < / = 3	987 (77) / 304 (24)	522 (71) / 216 (29)	465 (84) / 88 (16)	0.3
<b>KFI score:</b> < / ≥ 2	1004 (78) / 287 (12)	541 (73) / 197 (27)	463 (84) / 90 (16)	<0.0001
<b>Tobacco consumption:</b> < / ≥ 10 PY	478 (37) / 813 (63)	206 (28) / 532 (72)	272 (49) / 281 (51)	<0.0001
<b>Alcohol consumption:</b> yes / no	627 (49) / 664 (51)	480 (65) / 258 (35)	147 (27) / 406 (73)	<0.0001
<b>T/A consumption:</b> yes / no	931 (72) / 360 (18)	648 (88) / 90 (12)	283 (51) / 270 (49)	<0.0001
<b>T stage:</b> < / ≥ 3	625 (48) / 666 (52)	307 (42) / 431 (58)	313 (57) / 240 (43)	0.005
<b>N stage:</b> < / ≥ 2a	502 (32) / 789 (68)	286 (39) / 452 (61)	216 (39) / 337 (61)	1
<b>MSPN :</b> yes / no	138 (11) / 1153 (89)	103 (14) / 635 (86)	35 (6) / 518 (94)	0.0001
<b>Tumor site:</b> BOT / LPW / GTS / PPW / SP	509 (39) / 790 (61) / 421 (33) / 75 (6) / 304 (24)	305 (41) / 396 (54) / 251 (34) / 64 (9) / 215 (29)	204 (37) / 394 (71) / 170 (31) / 11 (2) / 91 (16)	0.9 / 0.003 / 0.9 / 0.001 / < 0.001

SD: standard deviation; ASA: American Society of Anesthesiologists; KFI: Kaplan Feinstein Index; PY: pack-years; T/A: tobacco (≥ 10 PY) and /or alcohol consumption; SPMN: second primary metachronous neoplasia; Tumor site: BOT: base of tongue; LPW: lateral pharyngeal wall; GTS: glosso-tonsillar sulcus; PPW: posterior pharyngeal wall; SP: soft palate; \*: only for patients treated with curative intent; UA: comparison between p16+ and p16- patients in univariate analysis.

**Table 2: Clinical factors associated with the risk of second primary metachronous neoplasia (SPMN)**

Clinical factors	Patients without MSPN	Patients with MSPN	UA	MA
	N = 1153 (%)	N = 138 (%)		
<b>Gender:</b> male / female	855 (74) / 298 (26)	111 (80) / 27 (20)	0.13	-
<b>Age (years):</b> average +/- SD	61.2 +/- 9.6	60.8 +/- 8.8	0.6	-
<b>ASA score:</b> < / = 3	895 (78) / 258 (22)	105 (76) / 33 (24)	0.9	-
<b>KFI score:</b> < / ≥ 2	897 (78) / 256 (22)	107 (77) / 31 (23)	1	-
<b>Tobacco consumption:</b> < / ≥ 10 PY	446 (39) / 707 (61)	32 (23) / 106 (77)	0.0001	NS
<b>Alcohol consumption:</b> yes / no	531 (46) / 622 (54)	96 (70) / 42 (30)	0.0001	NS
<b>T/A consumption:</b> yes / no	814 (71) / 339 (29)	117 (85) / 21 (15)	<0.0001	0.005
<b>T stage:</b> < / ≥ 3	554 (48) / 599 (52)	71 (51) / 67 (49)	0.5	-
<b>N stage:</b> < / ≥ 2a	430 (37) / 723 (63)	72 (52) / 66 (48)	0.002	NS
<b>Tumor p16 status:</b> + / -	518 (45) / 635 (55)	35 (25) / 103 (75)	<0.0001	0.003
<b>Tumor site:</b> BOT / LPW / GTS / PPW / SP	461 (40) / 708 (61) / 371 (32) / 66 (6) / 255 (22)	48 (35) / 82 (59) / 50 (36) / 9 (7) / 49 (36)	0.3 / 0.7 / 0.4 / 0.8 / 0.001	- / - / - / - / 0.01

SD: standard deviation; ASA: American Society of Anesthesiologists; KFI: Kaplan Feinstein Index; PY: pack-years; T/A: tobacco (≥10 PY) and /or alcohol consumption; Tumor site: BOT: base of tongue; LPW: lateral pharyngeal wall; GTS: glosso-tonsillar sulcus; PPW: posterior pharyngeal wall; SP: soft palate; UA and MA: comparison between patients with and without SPN in univariate analysis (UA) and multivariate analysis (MA); NS: non-significant p value.

**Table 3: Second primary metachronous neoplasia (SPMN) location according to tumor p16 status**

<b>SPMN location</b>	<b>All patients with MSPN</b>	<b>p16- patients with MSPN</b>	<b>p16+ patients with SPMN</b>	<b>UA</b>
	N = 138 (%)	N = 103 (%)	N = 35 (%)	
<b>Head and Neck</b>	48 (35)	41 (40)	7 (20)	0.03
- Nasopharynx	1 (1)	1 (1)	0 (0)	-
- Oral cavity	18 (13)	15 (15)	3 (8)	-
- Oropharynx	12 (9)	11 (10)	1 (3)	-
- Larynx	9 (6)	8 (8)	1 (3)	-
- Hypopharynx	8 (6)	6 (6)	2 (6)	-
<b>Esophagus</b>	9 (7)	9 (9)	0 (0)	0.07
<b>Lung</b>	43 (31)	34 (33)	9 (26)	0.42
<b>Others</b>	38 (28)	19 (20)	19 (49)	<0.0001
- Colorectal	10 (7)	6 (6)	4 (11)	-
- Prostate	7 (5)	5 (5)	2 (6)	-
- Bladder	5 (4)	2 (2)	3 (9)	-
- Breast	4 (3)	1 (1)	3 (9)	-
- Kydney	3 (2)	2 (2)	1 (3)	-
- Liver	2 (2)	2 (2)	0 (0)	-
- Ovary	1 (1)	0 (0)	1 (3)	-
- Lymphoma	2 (1)	0 (0)	2 (6)	-
- Skin	4 (2)	1 (1)	3 (9)	-

UA: comparison between the p16+ and p16- patient groups in univariate analysis