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Original article

Epidemiology, prognosis and treatment of simultaneous squamous cell carcinomas of the oral cavity and hypopharynx

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ARTICLE INFO

Keywords:

Multiple primary cancers
Head and neck cancer
Endoscopy
Second primary tumour

ABSTRACT

Objective: The study was designed to assess the prevalence, management and survival of patients with simultaneous squamous cell carcinomas of the oral cavity and hypopharynx (OC/HP).

Material and methods: A multicenter, retrospective study (2 university hospitals) was conducted between 2003 and 2007 on a series of 96 patients with simultaneous squamous cell cancers of the OC/HP.

Results: A total of 88 men and 8 women were included in the study: 81 patients presented double sites, 14 presented triple sites and one presented quadruple sites. The tumour sites most frequently observed were: hypopharynx in 61% of cases (involving the pyriform sinus in 42% of cases) and the oropharynx in 59% of cases (involving the palatine tonsil in 30% of cases). Upper aerodigestive tract endoscopy under general anaesthesia revealed a simultaneous lesion not suspected on clinical examination in 45% of patients: the site discovered on endoscopy was hypopharyngeal in 2 out of 3 cases; the tumour was classified T1 or T2 in 95.5% of cases. Patients treated simultaneously for all sites had a better prognosis than patients in whom each tumour was treated separately. The 5-year specific survival was 34% and the 5-year overall survival was 28%.

Conclusion: The prevalence of simultaneous squamous cell carcinomas of the oral cavity and hypopharynx ranges between 1 to 7.4% in the literature and was 4.6% in the present series. A common treatment strategy for each of the patient's tumours appears to be superior to the current theoretical approach that consists of considering each tumour separately.

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1. Introduction

Since the first description by Billroth in the 19th century, a large number of studies have described the phenomenon of multiple cancers. However, few studies on simultaneous cancers of the oral cavity and hypopharynx have been published in the literature, but the management of these tumours raises specific problems. This article is designed to contribute to the study of these cancers based on clinical observation of a series of 96 patients managed in head and neck surgery departments at Amiens and Lille university hospitals between January 2003 and December 2007.

2. Material and methods

The medical charts of 2096 patients with primary cancer of the oral cavity and hypopharynx (OC/HP) were retrospectively

reviewed and 96 patients with simultaneous squamous cell carcinoma of the OC/HP were selected.

Inclusion criteria of these patients were:

- at least two simultaneous squamous cell carcinomas of the OC/HP;
- no previous history of cancer;
- no other simultaneous cancers other than in the OC/HP.

Paranasal sinus and nasopharyngeal tumours, due to their different epidemiology, and oesophageal and lung cancers were excluded. Data collection comprised epidemiological and histological parameters, anatomical distribution and tumour stage, and data concerning the treatment strategy and follow-up. Data collection was performed in two different centers, but by the same person. Survival was analysed according to the Kaplan–Meier method and statistical analysis was based on the log rank method and χ^2 test. Multivariate analyses were performed according to the Cox model. A *P* value less than 0.05 was considered significant.

Initial staging comprised the same examinations in both centers:

DOI of original article: <http://dx.doi.org/10.1016/j.annorl.2014.02.003>.

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- endoscopy under general anaesthesia, including oropharyngo-laryngoscopy;
- contrast-enhanced CT scan of the neck and mediastinum;
- upper GI fibroscopy and bronchoscopy.

The primary objective of the study was to determine the incidence of simultaneous OC/HP cancers. The secondary objectives were to evaluate the yield of endoscopic screening, identify patient groups at high risk of developing these simultaneous cancers, and finally analyse the management and survival of patients with multiple cancers.

The criteria used to define multiple cancers were established in 1932 by Warren and Gates [1] and were modified by Moertel [2].

These criteria are:

- each distinct tumour must be confirmed histologically;
- the possibility that one of the two tumours is a metastasis from the other tumour must be excluded;
- each tumour must be separated from the healthy mucosa by at least 1.5 cm (with no submucosal communication).

Finally, multiple cancers were classified into three groups according to their chronological order:

- simultaneous cancers are those diagnosed at the same time as the first tumour;
- synchronous cancers are those diagnosed during the six months following the diagnosis of the first tumour;
- metachronous cancers are those diagnosed more than six months after the diagnosis of the first tumour.

3. Results

The frequency of simultaneous cancers involving the OC/HP was therefore 4.6% (96/2096). This series comprised 88 men (92%) and 8 women (8%) with a mean age of 55 years (range: 40–75 years). The sex ratio was 1 female for 11 males. A history of smoking and drinking was reported by 89 patients (93%). The distribution by stage according to the UICC TNM classification was based on the stage of the most advanced tumour. This series comprised 12% of stage I, 15% of stage II, 21% of stage III, and 52% of stage IV tumours.

3.1. Anatomical distribution of simultaneous cancers

Eighty-one of these 96 patients had double tumour sites, 14 had triple tumour sites and one patient had quadruple tumour sites. The relative frequency of each anatomical site in this series of simultaneous cancers was determined on the basis of all tumours observed (Table 1).

This analysis demonstrated a very marked variability of the frequency of multiple cancers according to the tumour site (14% for the larynx and 32% and 35% for the oropharynx and hypopharynx, respectively). The larynx appeared to be underrepresented as a site of simultaneous cancers. In contrast, the oropharynx and especially the hypopharynx presented a higher risk of multifocal tumours. The pyriform sinus accounted for almost two-thirds of all hypopharyngeal tumours, while the tonsil accounted for almost one half of all oropharyngeal tumours.

3.2. Endoscopic findings

Endoscopy demonstrated a simultaneous tumour site not suspected on the initial clinical examination in 45% of patients ($n=43$). The tumour sites discovered on endoscopy predominantly concerned the hypopharynx (64%), especially the pyriform sinus (42%).

Table 1
Distribution of tumour sites in patients with multiple cancers.

	Number of tumours for each site (208)	
<i>Oral cavity</i>		$n=39$ (19%)
Floor of the mouth	23 (11%)	
Mobile tongue	9	
Oral commissure	7	
<i>Oropharynx</i>		$n=67$ (32%)
Palatine tonsil	30 (14%)	
Vallecula	11	
Soft palate	13	
Base of tongue	5	
Posterior wall	5	
Glosso-epiglottic fold	1	
Junctional zone	2	
<i>Larynx</i>		$n=29$ (14%)
Epiglottis	9	
Vocal cord	10	
Ventricular band	2	
Aryepiglottic fold	5	
Arytenoid	2	
Hemilarynx	1	
<i>Hypopharynx</i>		$n=73$ (35%)
Pyriform sinus	49 (24%)	
Pharyngeal wall	13	
Proximal oesophagus	2	
"Three-fold" region	7	
Retrocricoid	2	

The tumours discovered at endoscopy logically corresponded to less advanced tumours (95% of Tis, T1, and T2 tumours).

3.3. Treatment

Various treatment strategies were applied to each of these 208 tumours considered separately, as summarized in Fig. 1. Patients managed by symptomatic treatment ($n=6$) or palliative chemotherapy ($n=3$) were classified separately (9 patients, 19 sites).

Patients were classified into three groups according to the treatment strategy:

- common treatment group: all of the patient's tumours were treated according to the same treatment strategy;
- dissociated T treatment group: each of the patient's tumours were treated in a different way;
- dissociated T/N treatment group: different treatment modalities were proposed for the patient's tumours and lymph nodes.

3.4. Follow-up

Three patients were lost to follow-up. The mean follow-up was 32 months (range: 1–89 months). Progressive disease was observed in 27 patients (29%). No synchronous cancers were observed in this series. Nine patients developed a metachronous cancer (9.7%), 16 patients (17%) developed local recurrence, 21 patients (23%) developed metastases during follow-up and 5 patients (5.4%) developed lymph node recurrence.

3.5. Survival

Sixty-seven (72%) of the 93 patients of the series have died. Mean survival was 24 months. The five-year specific survival, i.e. the survival related to head and neck cancer was 34%, while the five-year overall survival was 28%. Survival curves were plotted according to the Kaplan–Meier method (Fig. 2). Univariate analysis of several parameters likely to influence survival was then performed using the log rank method. As expected TNM tumour stage and lymph node status had a statistically significant impact on

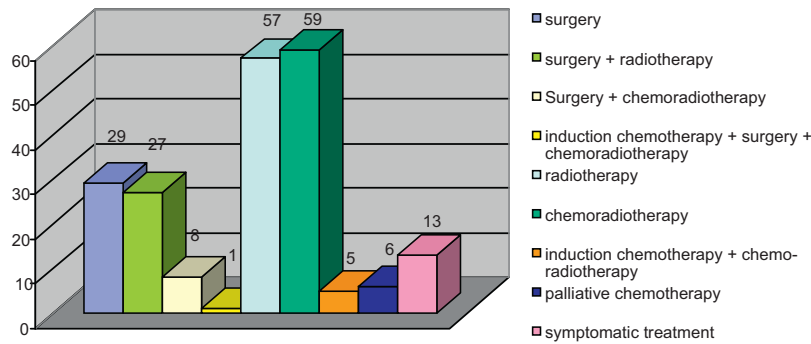


Fig. 1. Distribution of the various treatment modalities for each tumour site.

survival ($P=0.0001$ for both parameters): advanced tumour stage and lymph node status were pejorative parameters for overall survival. Poorly differentiated histology also had a negative impact versus well or moderately well differentiated histology ($P=0.01$). Body mass index (BMI) was also identified as a factor affecting survival ($P=0.04$), allowing patients to be classified into three groups: BMI less than 18, BMI between 18 and 25 and BMI greater than 25. Survival improved with increasing BMI. Gender was a discriminant factor for survival ($P=0.005$) with significantly better survival for men.

Finally, comparison of the various types of treatment revealed a significant difference ($P=0.04$): the group of patients receiving common treatment for all tumours obtained a better survival than the T/N and T dissociated treatment groups.

The number of tumours (2/3.4), the severity of smoking, and age were not identified as significant risk factors on univariate analysis. However, analysis according to three age groups (younger than 50 years, 50 to 60 years, older than 60 years) demonstrated a tendency to better survival for older patients.

Multivariate analysis was then performed on the following parameters likely to affect survival: histological differentiation, age, gender, TNM stage, BMI, type of treatment. TNM stage ($P=0.003$) and BMI ($P=0.001$) were the only parameters with a significant and similar impact on overall survival.

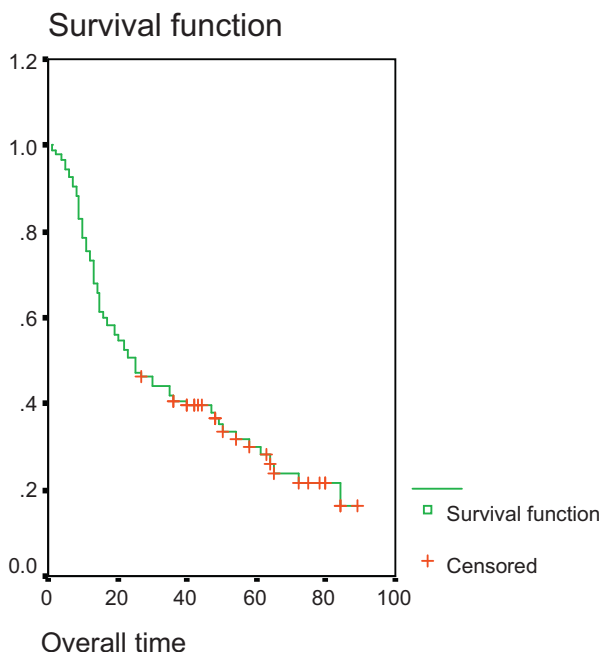


Fig. 2. Overall survival curve (Kaplan–Meier).

4. Discussion

4.1. Epidemiology

The incidence of multiple cancers and especially simultaneous cancers of the OC/HP reported in the literature varies considerably according to the population studied, the inclusion criteria (for example, whether or not carcinoma in situ is included), the inclusion or exclusion of lung and oesophageal tumours and the study methodology (prospective or retrospective study, with or without systematic endoscopy) [3].

The incidence of simultaneous tumours located in the OC/HP in a patient with squamous cell carcinoma ranges from 1 to 7.4% (Table 2). Prospective studies using systematic endoscopy published by Gluckman [4] and McGuirt [3] have reported higher rates of multiple tumours. It is difficult to compare the results of these various studies conducted according to very different methodologies, but the incidence of 4.5% reported in our study appears to be consistent with the mean incidence rates reported in the literature.

The incidence of three or more tumours was 0.71% in our study, while rates varying between 0.25 and 1.8% are reported in the literature, indicating that three or more simultaneous tumours remain exceptional [5].

Metastases were present at diagnosis in 3% of patients in our study, similar to the rate of 3.9% reported by Panosetti et al., and does not appear to be higher than the rate observed for single head and neck cancers [6].

4.2. Anatomical distribution of simultaneous cancers

Few studies in the literature have been specifically devoted to the analysis of simultaneous OC/HP cancers. The study by Pasche [7] demonstrated a predisposition for certain sites: 50% of patients with cancer of the soft palate presented multiple tumours. However, in addition to patients with simultaneous carcinoma of the

Table 2
Incidence of simultaneous cancers reported in the literature.

Author	Incidence of simultaneous tumours in all sites (including lung, oesophagus) (%)	Incidence of simultaneous tumours of the OC/HP (%)
Gluckman [4]	9.2	7.4
Shapsay et al. [5]	14	6
McGuirt [3]	16	6
Panosetti et al. [6]	4.1	2.4
Jones et al. [7]	1	–
Ricard et al. [8]	–	1
Haerle et al. [9]	4.8	2.8
Rennemo et al. [10]	1.3	–

OC/HP, this study also included patients with simultaneous lung and oesophageal cancers.

A different distribution was observed in our study: tumours of the soft palate represented only 6% of all patients of this series, while tumours of the hypopharynx were present in 61% of patients. Tumours of the oropharynx were observed in 59% of patients of this series. These differences can possibly be explained by the fact that lung and oesophageal tumours were included in the study by Pasche [7] and by the high rate of simultaneous soft palate, lung and oesophageal tumours.

4.3. Role of endoscopic screening

A general consensus has now been reached concerning the value of endoscopy, as it allows biopsies designed to confirm the histological diagnosis and also allows local tumour staging in order to assess resectability. An additional benefit of screening endoscopy is that it may reveal early lesions, as in many cases, only the largest lesion is responsible for symptoms. In 45% of patients in the present series, screening endoscopy revealed a second or even a third tumour site, illustrating the limitations of armchair ENT examination.

Patients with cancers of the OC/HP classically consult a specialist only at an advanced stage of disease: 73% of patients in this series presented stage III or IV disease. In contrast, the majority of tumours revealed by endoscopy were detected at an early stage (95.5% were stage T1, T2 tumours).

However, the value of systematic endoscopic work-up remains controversial in the literature.

Several authors [3,8] have shown that the double tumour rate was two-fold higher with the use of systematic endoscopy and have recommended that this examination be performed systematically.

However, other authors believe that endoscopic screening has a low yield and do not recommend systematic use of this examination [9,10]. For example, Cianfriglia et al. [9] reported a 1% rate of simultaneous tumours discovered during endoscopy.

In our experience, endoscopy, at least oropharyngolaryngoscopy, appears to be essential, as it demonstrated almost one half of all simultaneous tumours of this series.

However, only a few studies tend to suggest that early detection of simultaneous tumours actually improves survival [3,9], but early detection of simultaneous tumours may influence treatment of the first tumour and especially avoid mutilating treatment by leaving a second tumour in place. The absence of synchronous cancers in our series appears to validate the reliability of the initial endoscopic screening.

4.4. Treatment

Due to the diversity of the clinical situations encountered, a standard treatment strategy cannot be proposed and no definitive conclusions can be drawn. In the literature, although based on insufficient data, it is generally recommended to treat each lesion as if it were a solitary lesion. However, most patients (75%) in the present series were treated according to a common treatment modality for each tumour site. This common treatment predominantly (65%) consisted of chemoradiotherapy. In this series, as for single cancers, exclusive surgery was reserved for small T1 tumours, mainly involving the oral cavity. In this exceptional situation, exclusive surgery in these selected cases avoided the need for adjuvant radiotherapy. The group of patients treated exclusively by radiotherapy ± chemotherapy corresponded to very diverse situations, preventing any significant conclusions.

The dissociated T treatment strategy proved to be of limited value in this series ($n=17$) and was mainly used (in one half of cases) for patients with triple tumours. This strategy also appears

to be associated to a poorer prognosis than the common treatment strategy.

A common treatment strategy for each of the patient's tumours appears to be the most appropriate approach in our experience, which could possibly lead to a revision of the current approach based on treating each tumour as if it were an isolated tumour.

Finally, dissociated tumour/lymph node treatment was reserved to patients with advanced lymph node disease (N2, N3). It is therefore logical that this group presented poorer survival rates.

In the series published by McCollough et al. [11], 80% of lesions were treated by chemoradiotherapy, which currently appears to have a leading role in the management of these simultaneous cancers. It has the advantage of administering only a single sequence of treatment and therefore avoids delaying the management of a second or third tumour.

However, the use of radiotherapy for two separate tumours considerably increases the treatment volume, adverse effects and the risk of radiation-induced complications [11].

Several questions remain unresolved: what is the efficacy of radiotherapy compared to a combination of surgery and radiotherapy? What is the effect of irradiation on this high-risk mucosa?

4.5. Survival

Calculation of overall survival rates for patients with multiple cancers is of limited value in view of the diverse characteristics of these patient populations. However, overall survival rates can be used to compare this group of patients with simultaneous OC/HP cancers with the population of head and neck cancers as a whole. The 5-year overall survival rate is therefore about 35% for head and neck cancers in general [12]. The 5-year specific survival (34%) in our population was similar to the overall survival rate for head and neck cancers, but the 5-year overall survival was slightly different, with a value of 28%. Simultaneous cancers therefore appear to have a slightly poorer prognosis, but it nevertheless appears to be similar to that of squamous cell carcinomas of the head and neck, raising the question of whether multiple tumours are really associated with a poorer prognosis or whether the prognosis is simply related to the prognosis of the most advanced tumour.

McCollough et al. [11] reported a 5-year overall survival rate of 14% in a population identical to that of the present series, comprising 75% of stage III and IV patients compared to 73% in our study. According to McCollough et al., simultaneous lesions appear to be associated with a considerably poorer prognosis. Pasche [7] reported a 3-year overall survival rate of 22%.

Other published series have analysed simultaneous cancers involving all sites (including oesophagus and lung) and therefore reported poorer survival rates, but these results cannot be compared to those of our series due to the inclusion of simultaneous tumours with completely different prognoses.

Analysis of the various prognostic factors showed that nodal status, TNM stage and histological differentiation remain the major prognostic factors in this particular population, as in the population with single cancers.

BMI is a useful prognostic factor, as it can be easily determined at the time of diagnosis. Univariate and multivariate analysis showed that overweight patients (BMI greater than 25), despite the possible comorbidities related to this state, presented a better overall survival.

5. Conclusion

This study highlights the problem of simultaneous tumours of the OC/HP, which are observed in one out of every 22 patients.

The essential findings of this study are as follows:

- in total, 4.6% of patients with head and neck cancer have a simultaneous tumour of the OC/HP;
- cancers of the pyriform sinus and palatine tonsil are associated with a high incidence of multifocal tumours (42% and 30% of patients presenting at least one of these tumour sites, respectively);
- detection of a second tumour site in the OC/HP is based on systematic screening endoscopy, which demonstrated one or several simultaneous lesions in 45% of patients;
- treatment evaluation is essential in this group of patients, which raises specific problems. This evaluation is justified by the relatively comparable survival rates to those of single cancers (5-year specific survival: 34%, 5-year overall survival: 28%);
- in the absence of treatment guidelines, multidisciplinary consultation remains essential in these patients.

Disclosure of interest

The authors have not supplied their declaration of conflict of interest.

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