Observational Study

Diagnosis and management of head and neck cancers in a high-incidence area in France
A population-based study

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Abstract
Head and neck cancers have a very poor prognosis and are common in France. They are subject to various recommendations for early detection and management, but there is no detailed data in the French general population to fuel the public health debate on it.

A high-resolution population-based study about cancer management was conducted, using cancers registries in the north-west of France, on 1729 tumors diagnosed between 2008 and 2010.

The tumors were diagnosed late (70.3% stage III–IV), mainly after the onset of symptoms (93.2%). After adjustment, advanced stages were more frequent in patients with hypopharyngeal [adjusted odds ratio (ORa): 4.68; 95% confidence interval [CI] 3.11–7.05] and oropharyngeal tumors (ORa: 2.84; 95% CI 2.02–3.99) compared with oral cavity ones. They were also more frequent in patients with moderate (ORa 1.68; 95% CI 1.12–2.52) or severe comorbidities (ORa 1.86; 95% CI: 1.23–2.80). A multidisciplinary meeting (MM) had taken place in 96.9% of cases. The assessment included a panendoscopy in 89.3% of cases, a cervix CT scan in 87.3%. The vast majority of patients (90.7%) had received treatment, with surgery in 48.7% of cases and/or radiotherapy in 76.9%.

Despite the recommendations for early detection, diagnoses are often made late, even for tumors that can be detected by a direct visual and tactile examination of the oral cavity. However, the major risk of advanced stage concerns deep tumors and the most weakened subjects. Otherwise, diagnostic assessment is broadly consistent with the recommendations, and multidisciplinary treatment decisions are widespread.

Abbreviations: CI = confidence interval, CT scan = computed tomography, HNC = head and neck cancers, ICD-O 3 = International Classification of Diseases for Oncology, 3rd edition, IRIS = lits Regroupés pour l’information Statistique, MM = multidisciplinary meeting, MRI = magnetic resonance imaging, NOS = not otherwise specified, ORa = adjusted odds ratio, PET = positron emission tomography, py = person-years, SC-CUP = cervical nodal metastasis of squamous cell carcinoma of unknown primary site.

Keywords: cancers registry, head and neck cancer, management, population-based study, stage

1. Introduction
In Europe, head and neck cancers (HNC) are the fourth most common group of cancers among men.[1] France has one of the highest incidence rates, although it is steadily decreasing[2]; in 2012, the world-standardized incidence for men was 21.5 cases per 100,000 person-years (py). With over 35 cases per 100,000 py for men, the north-west of France is the region with the highest incidence of these cancers.[3,4] The occurrence of such cancers is strongly associated with the consumption of tobacco, alcohol,[5] and social factors.[6] Nonetheless, the influence of social position after taking lifestyle factors into account remains unclear.

In France the 5-year net survival of this heterogeneous group of cancers varies from 28% for hypopharynx to 57% for larynx, being extremely poor and showing no real improvement in the last 20 years.[7] This survival is among the lowest of European countries.[8]

As for all cancer localization, stage at diagnosis is the main prognostic factor. Whatever the sub-localization, stages III and IV are associated with a low survival.[9]

These cancers often occur in fragile patients and their management is complex, requiring a multidisciplinary approach. The HNC clinical practice guidelines of the European Society for Medical Oncology (ESMO)[9] and the Société Française d’ORL
(SFORL), have issued recommendations for optimal care, by specifying diagnosis conditions and appropriate patterns of care. Since 2003, the French cancer plans recommend early detection of cancers (oral cavity included), multidisciplinary decisions concerning treatment, the implementation of coordinated paths for care and improved availability of imaging, positron emission tomography (PET), and radiotherapy treatment. Unfortunately, to date, despite the frequency and lethality of these cancers, no detailed general population-based study has described the management of such cancers.

In accordance with the pressing concern in public health, the objective of this study was to determine the conditions of diagnosis and therapeutic management of patients with HNC in a high incidence area and identify factors associated with late stage at diagnosis.

2. Methods

2.1. Population

This high-resolution population-based study concerns all patients aged over 20 years with a diagnosis of invasive HNC in the period 2008 to 2010. These patients were recorded in the cancer registries of the French Départements Calvados, Manche and Somme, and the area of Lille (for the Somme, the period covered 2009 and 2010). These registries meet high-quality criteria: the completeness and data quality are regularly assessed by the Comité National des Registres (French Institute of Health and Medical Research [INSERM], National Cancer Institute [Inca], Institut de veille sanitaire [InVS]). Only carcinomas were included. Cancer sites were as follows (International Classification of Diseases for Oncology—third edition—ICD-O 3): oral cavity (C01–C06), oropharynx (C09–C10), hypopharynx (C12–C14), larynx (C32), cervical nodal metastasis of squamous cell carcinoma of unknown primary site (SC-CUP) (C76.0).

Patients with prior history of invasive or in situ cancer (except basal or squamous cell carcinoma of the skin) were excluded from the study. In total, 19.8% of incident cases were excluded. The analysis included 1667 patients (1383 men and 284 women). In this group, 3.6% had synchronous lesions, so 1729 patients were analyzed (Table 1).

The study was authorised by the CNIL (the French national data protection agency)—no. 907,276. For this type of study, formal consent is not required.

2.2. Data

Data were collected by reviewing medical records 6 months after diagnosis. They concerned identity, place of residence, comorbidities, date of diagnosis, topography, and morphology of cancer (ICD-O 3), circumstances of discovery, the staging performed, clinical stage at diagnosis (TNM stage from the International Union Against Cancer (ICD-O 3): oral cavity (C01–C06), oropharynx (C09–C10), hypopharynx (C12–C14), larynx (C32), cervical nodal metastasis of squamous cell carcinoma of unknown primary site (SC-CUP) (C76.0).

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2.3. Data analysis

We tested for associations between qualitative variables using the chi-square test or Fisher exact test. For association between qualitative and quantitative variables, a one-way analysis of variance or the Kruskal–Wallis test were used. P values < 0.05 were considered significant.

To ascertain the determinants of advanced stage at diagnosis, logistic regression was used to calculate the adjusted odds ratio (ORa) with a 95% confidence interval (IC95%) of early stage (stages I–II) versus advanced stage (stages III–IV) of disease. Clinically, relevant variables and deprivation index were entered into the regression model. A stepwise procedure (Backward) was used to select variables significant at the 10% level. The model included only cases with no missing values for the variables studied. SC-CUP sites were not included in the regression model (stage III and IV only).

Analyses were conducted using StataIC 13 software (StataCorp. Stata: Statistical Software Release 13, College Station, TX. StataCorp LP).

3. Results

3.1. Characteristics of patients and tumors (Table 1)

The sex ratio was 4.9. The mean age at diagnosis was 60.2 years (range 22–102 years). More than a third of patients were very under-privileged. Only 8.1% had no comorbidity.

The lesions were mainly diagnosed on symptoms, and nearly a third of patients had severe symptoms (cervical swelling or general impairment). The majority were late stage at diagnosis (73.6%). A third of the lesions (35.3%) were located in the oral cavity.

Distribution by site was different depending on sex (P < 0.001). The most common sites for men were the larynx and pyriform sinus, and for women the oral tongue, tonsil, and larynx.

The mean age differed according to site, ranging from 56.3 years for floor of mouth tumors to 67.1 years for gum tumors (P < 0.001). The mean age by sex differed only for pyriform sinus (men: 60.8 years, women: 55.4 years, P = 0.02) and larynx (men: 61.1 years, women: 66.1 years, P = 0.02) (results not shown).

More than half of the laryngeal tumors were diagnosed on dysphonia (58.7%). The mean age at diagnosis differed according to the mode of discovery (P < 0.001). Patients diagnosed after oral bleeding were older (65.4 years) and those diagnosed owing to cervical swelling were younger (58.3 years). Tumors diagnosed after non-symptom-driven examination were mainly localized in the oral cavity and larynx, and involved patients whose mean age was 59.8 years (results not shown).

3.2. Diagnostic assessment (Table 2)

The diagnostic report included panendoscopy in 80.3% of cases and a cervical CT-scan in 89.3% (94.7% for the hypopharynx or larynx). Cervical magnetic resonance imaging (MRI) was
performed in 19.6% of cases (31.1% for the oral cavity or oropharynx). A PET scan was performed in 58.9% of SC-CUP. Patients with cancer of the oropharynx or hypopharynx had an oesophageal exploration in 82.0% of cases.

Patients had undergone minimal thoracic exploration in 92.3% of cases. A thoracic CT-scan had been performed in 87.3% of cases and bronchoscopy in 38.8%. For cases with a high risk of metastasis (N ≥ 2b), a PET scan had been performed in 19.2%.

### 3.3. Stage (Table 3)

The majority of lesions were diagnosed at the highest clinical stage (stage IV = 56.6%). For 4.1% the stage could not be determined due to the lack of relevant elements. Locally advanced tumors (cT3 – 4) accounted for 45.1% of cases and up to 67.4% of pyriform sinus tumors. More than half of the cases had at least one clinically apparent lymph node at diagnosis (57.9%), this being so for more than 80% for tumors whose location was base of tongue, pyriform sinus, or pharynx not specified otherwise (NOS). However there were few distant metastases (M1 = 7.1%).

By anatomic region, lesions diagnosed the latest were those of the hypopharynx (stage IV = 73.7%) and SC-CUP (*P < .001*).

Subsite analysis showed that the lesions diagnosed the latest were those at the base of tongue (stage IV = 81.2%). Tumors diagnosed the earliest were those of oral tongue (stage I = 29.8%), floor of mouth (stage I = 27.6%), and larynx (stage I = 26.4%).

### Table 1

| Characteristics of head-and-neck-cancer patients by stage at diagnosis. | Stage I–II (N = 444) | Stage III–IV (N = 1236) | Stage unknown (N = 49) | Total (N = 1729) |
|---|---|---|---|---|
| Patient/Tumor characteristics | N | % | N | % | Univariate P value | N | % | N | % |
| Sex | | | | | | | | | |
| Men | 366 | 82.4 | 1037 | 83.9 | .48 | 36 | 73.5 | 1439 | 83.2 |
| Women | 78 | 17.6 | 199 | 16.1 | 13 | 26.5 | 290 | 16.8 |
| Age at diagnosis | | | | | | | | | |
| <55 y | 149 | 33.6 | 389 | 31.4 | .39 | 12 | 24.5 | 550 | 31.8 |
| [55–65 years] | 165 | 37.1 | 505 | 40.9 | 12 | 24.5 | 682 | 39.5 |
| ≥65 years | 130 | 29.3 | 342 | 27.7 | 25 | 51.0 | 497 | 28.7 |
| Department | | | | | | | | | |
| Calvados | 120 | 27.0 | 346 | 28.0 | .82 | 23 | 46.9 | 489 | 28.3 |
| Manche | 90 | 20.3 | 270 | 21.8 | 11 | 22.4 | 371 | 21.5 |
| Lille area | 161 | 36.3 | 425 | 34.4 | 9 | 18.4 | 595 | 34.4 |
| Somme | 73 | 16.4 | 195 | 15.8 | 6 | 12.2 | 274 | 15.8 |
| Charlson score | | | | | | | | | |
| None = 0 | 52 | 11.7 | 83 | 6.7 | .004 | 5 | 10.4 | 140 | 8.1 |
| Moderate = 1–2 | 211 | 47.5 | 606 | 49.0 | 18 | 37.5 | 835 | 48.3 |
| Severe ≥ 3 | 181 | 40.8 | 547 | 44.3 | 25 | 52.1 | 753 | 43.6 |
| Unknown | 0 | — | 0 | — | | 1 | — | 1 | — |
| Mode of discovery | | | | | | | | | |
| Pain | 191 | 48.0 | 447 | 37.8 | <.001 | 19 | 46.3 | 657 | 40.5 |
| Dyspnea | 5 | 1.3 | 38 | 3.2 | .05 | 1 | 2.4 | 44 | 2.7 |
| Dysphonia | 113 | 28.4 | 160 | 13.5 | <.001 | 10 | 24.4 | 283 | 17.4 |
| Oral bleeding | 8 | 2.0 | 17 | 1.4 | .43 | 1 | 2.4 | 26 | 1.6 |
| Cervical swelling | 22 | 5.5 | 322 | 27.2 | <.001 | 4 | 9.8 | 348 | 21.5 |
| Impaired general status | 9 | 2.3 | 145 | 12.3 | <.001 | 0 | 0.0 | 154 | 9.5 |
| Clinical examination without symptoms | 24 | 6.0 | 22 | 1.9 | <.001 | 3 | 7.3 | 49 | 2.7 |
| Fortuitous | 26 | 6.5 | 32 | 2.7 | <.001 | 3 | 7.3 | 61 | 3.8 |
| Unknown | 46 | — | 53 | — | .22 | 8 | — | 107 | — |
| Year of diagnosis | | | | | | | | | |
| 2008 | 116 | 26.1 | 353 | 28.6 | | 21 | 42.8 | 490 | 28.3 |
| 2009 | 146 | 32.9 | 434 | 35.1 | | 14 | 28.6 | 594 | 34.4 |
| 2010 | 182 | 41.0 | 449 | 36.3 | | 14 | 28.6 | 645 | 37.3 |
| Topography | | <.001 | | | | | | | |
| Oral cavity | 201 | 45.3 | 384 | 31.1 | | 26 | 53.1 | 611 | 35.3 |
| Oropharynx | 54 | 12.2 | 296 | 23.9 | | 2 | 4.1 | 352 | 20.4 |
| Hypopharynx | 31 | 7.0 | 291 | 23.5 | | 5 | 10.2 | 327 | 18.9 |
| Larynx | 158 | 35.6 | 190 | 15.4 | | 16 | 32.6 | 364 | 21.1 |
| SC-CUP | — | — | 75 | 6.1 | | — | — | 75 | 4.3 |
| Deprivation quintile | | .55 | | | | | | | |
| Privileged 1 | 54 | 12.2 | 123 | 10.2 | | 6 | 12.2 | 185 | 10.8 |
| Quite privileged 2 | 58 | 13.1 | 151 | 12.2 | | 6 | 12.2 | 213 | 12.4 |
| Quite underprivileged 3 | 64 | 14.5 | 192 | 15.7 | | 14 | 28.6 | 270 | 15.7 |
| Underprivileged 4 | 114 | 25.7 | 297 | 24.2 | | 7 | 14.3 | 418 | 24.3 |
| Very underprivileged 5 | 153 | 34.5 | 462 | 37.7 | | 16 | 32.7 | 631 | 36.8 |
| Unknown | 1 | — | 11 | — | | 0 | — | 12 | — |

SC-CUP = cervical nodal metastasis of squamous cell carcinoma of unknown primary site.

*22 cases with metastasis statute not determined with T3 or N1, were reclassified as stage II–IV.

*Period covered 2009 – 2010.*
The univariate analysis (Table 1) showed that patients with moderate or severe comorbidities were more frequent in the Stage III-IV group ($P = 0.004$). Advanced-stage lesions were more often discovered on cervical swelling ($P < 0.001$), impaired general status ($P < 0.001$), and dyspnoea ($P = 0.05$). Pain, dysphonia, fortuitous discovery, or clinical examination without symptoms, were more common among early stage lesions ($P < 0.001$). There were 38.8% stage I lesions among tumors detected, during clinical examinations in the absence of specific symptoms. (Result not shown).

After adjusting for sex, age group, *département*, deprivation quintile, and year of diagnosis, advanced stages were more frequent in patients with hypopharyngeal (ORa: 4.68; 95% CI: 3.11–7.05) and oropharyngeal tumors (ORa: 2.84; 95% CI: 2.02–3.99), and less frequent for larynx tumors (ORa:0.60; 95% CI: 0.45–0.79) compared with oral cavity ones. They were also...
frequently an advanced lesion (stage IV = older (mean = 64.8 years, \( P = .03 \)) and were less likely to have received treatment (55.6\% vs. 91.8\%, \( P < .001 \)). There was no significant difference in anatomical region, stage, deprivation index, or Charlson score.

Treated patients (N = 1568) had received surgery for their primary tumor (T) in the course of treatment in 48.7\% of cases, most often performed in a university hospital (45.0\%). They had received radiotherapy (alone or combined) in 76.9\% of cases and chemotherapy (alone or combined) in 45.3\% of cases. In 18 cases, including 9 oral tongue cancers, patients had received brachytherapy (alone or combined). Radiotherapy and chemotherapy was usually performed in a regional care center (44.3\% and 34.3\%, respectively), or a private clinic (39.3\% and 31.5\%, respectively).

The first treatment was surgery on T in 43.4\% of cases (Fig. 1). Among treated patients, 51.7\% had received two treatments or more and 6.3\% had received three treatments or more. The most frequent sequence was surgery on T associated with radiotherapy alone (14.8\% of treated patients).

Among patients with treatment administered, this was discontinued in 15.6\% of cases.

In 161 cases (9.3\% of the lesions), no form of treatment was used (among them 25 refused to be treated). These patients were older (mean = 64.5 years, \( P < .001 \)), had a higher Charlson score (\( P < .001 \)), a higher deprivation index (\( P = .02 \)), and more frequently an advanced lesion (stage IV = 82.6\%, \( P < .001 \)); 26.8\% of them died within a month of diagnosis. The proportion of these patients ranged from 7.1\% for laryngeal tumors to 11.1\% for the oropharynx, but no difference was observed in relation to the site.

4. Discussion

This is the first high-resolution population-based study of the management of HNC in France. Data were issued from cancer registries located in a French high-incidence area, where the distribution of lesions per site and the mean age of the patients were similar to those encountered generally in France.[3]

Our results show that tumors were discovered as a result of symptoms, which were severe in nearly a third of cases. They were diagnosed late (45.1\% cT3–4, 70.3\% stage III–IV). There were also a high percentage of comorbidities possibly related to risk factors for these tumors. Diagnosis assessment included panendoscopy, cervical, and thoracic CT-scan in over 80\% of cases. The vast majority of patients received treatment. This included surgery in fewer than half the cases and radiotherapy in three-quarters of them.

Concerning stage, few population-based data are available.[14]

Gatta et al[8] have presented the distribution of stage at diagnosis of HNC for 9 European cancer registries: localized stage was 36\%, regional stage 50\%, and metastatic stage 4\%. Comparatively, the analysis of our data showed a higher proportion of extended stage: 25.5\%, 56.5\%, and 7.5\% respectively for localized, regional, and metastatic stages. The high proportion of hypopharynx cancers—which are diagnosed at an advanced stage—in France may explain in part these differences. Moreover, the analysis of stage by topography showed less localized stages in our study for oral cavity, tongue, and lingual tonsil compared with the 9 European cancer registries.[14]

We found an association between advanced stage at diagnosis and topography of the cancer, and comorbidities. According to most studies, oropharyngeal and hypopharyngeal cancers were associated with a higher stage at diagnosis.[6,15] These cancers cannot be readily investigated by mere visual inspection, and they are not revealed by specific symptoms such as the dysphonia in laryngeal cancer.

The presence of comorbidities was also associated with an advanced stage at diagnosis, perhaps owing to a delay in diagnosis in those patients who are already weakened by exposure to tobacco and alcohol. It is possible also that the physician focused solely on comorbidities and missed the opportunity for an early diagnosis of HNC.[16]

No association was found in other studies between comorbidities and an advanced stage at diagnosis.[17,18]

Unlike in other studies, age and sex were not found to be related to the stage.[18,19] Likewise, the deprivation which is a risk factor for HNC[6] was not related to stage.

Early diagnosis of these cancers is a pressing concern in public health, and was recommended in the “French Cancer Plan 2009–2013”[11] particularly for oral cavity lesions, which are easily accessible to direct visual and tactile examination.

In fact, in our study very few patients (N = 49) were diagnosed during clinical examinations in the absence of specific symptoms. The distribution of stage showed that only 33\% of tumors of the oral cavity were diagnosed with a size of less than 4 cm and without local or distant metastasis. By subcategory, oral tongue, floor of mouth, and palate the percentage varied from 35\% to 48\% of cases. So, early detection may increase this percentage, especially for these localizations. In view of this, recently the French National Cancer Institute (INCa) set up multimedia training for dentist and general practitioners to teach them how to detect suspicious lesions through an in-depth examination of the oral cavity in high-risk patients.[20]

The diagnosis assessment was conducted in most cases in accordance with the latest recommendations of learned socie-
ties.\cite{14,15} However, one-fifth of patients had not received panendoscopy, which is recommended for all HNC. Cervical CT scan was performed more systematically, particularly for hypopharyngeal and laryngeal cancers. Cervical MRI, the most powerful tool for assessing tumors of the oral cavity and oropharynx, was carried out in less than a third of cases in these locations. In accordance with recommendations, chest CT scan was the most frequently performed test. However, few high-risk patients (N2, N3b) received an additional exploration by PET, probably owing to its lack of availability. The therapeutic decision was multidisciplinary, in accordance with the recommendations applicable in France,\cite{3,11} and Europe.\cite{9}

Despite a high percentage of late diagnoses, the vast majority of patients were treated. Recommended treatments are multiple because they depend both on the location and the stage. However, it can be seen that treatment referred to as curative (surgery of tumor or combined radiotherapy), was set up in almost two-thirds of cases.

The main strength of this study resides in its design based on the method of “high-resolution population-based study”: data were collected in a precise and rigorous manner from the medical files in order to know all the characteristics of the cancer cases included. Thus, despite some absent data from medical records, missing values were scarce. The inclusion of patients from the cancer registries allowed us to overcome the recruitment bias of hospital studies and give information on the totality of cancer cases in a given geographic area.

The main limit of our study is the limited study area and, consequently, the relatively small number of patients. However, this study has required an extended, standardized, dedicated registration, since French cancer registries do not routinely collect stage and management. Furthermore, it does not exist in France structures for recording such data on the entire territory. So the study provides, for the first time in France and in general population, information on the stage, the diagnosis assessment, and the treatment in a high-incidence area.

Another limitation is the design of this study which did not assess the patient delay (time between first symptoms and the first consultation). It is generally long (3.5–5.4 months) and is often associated with the stage although its influence is variable according to different studies.\cite{21}

Despite the recommendations for early detection, HNC are still diagnosed late in France, including those tumors which are easily accessible on clinical examination, perhaps owing to the profiles of the patients. However, the major risk of advanced stage concerns deep tumors and the most weakened subjects. Nevertheless, patients usually receive therapeutic care.

The diagnostic assessment is broadly consistent with the recommendations, even though cervical MRI or PET should be more commonly used in patients concerned. The multidisciplinary therapeutic decision is effective 5 years after the first French recommendations.

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