Correlation Between Subjective Evaluation of Symptoms and Objective Findings in Early Recurrent Head and Neck Squamous Cell Carcinoma

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Head and neck squamous cell carcinomas (HNSCCs) represent more than 90% of all head and neck cancers. In the oral cavity, oropharynx, larynx, and hypopharynx, 40% to 60% of tumors are diagnosed at an advanced stage (III or IV). In many cases, this requires combinations of surgery and radiotherapy (with or without chemotherapy). Such multimodal treatments have led to improved overall survival and locoregional control rates, but recurrent disease and long-term adverse effects are important problems in different ways after definitive therapy for HNSCC. Indeed, up to 50% of the patients treated for HNSCC die of cancer recurrence or of late complications related to cancer or its treatment within the 5-year posttherapy period. Recurrences occur in 20% to 40% of the treated patients, and up to 90% of these occur during the first 24 months following treatment.

Based on these premises, close follow-up regimens, including physical examination and diverse protocols of imaging and/or endoscopy, are advocated in most institutions treating patients with HNSCC. Theoretically, early detection of relapsing disease should offer better chances of success for any eventual salvage therapy.

One major challenge faced by head and neck cancer specialists is a precise evaluation of symptoms: on one hand, treatment-induced symptoms are common in treated patients and...
in some cases may lead to multiple complementary studies. On the other hand, some of the same symptoms may be due to recurrence. In patients without clear signs of recurrence on clinical examination, it is most often the physician's arbitrary decision whether to perform further investigations (radiologic and/or endoscopic). Therefore, it would be desirable to determine the value of subjective indicators correlating with tumor recurrence.

Methods

This study was approved by the Ethics Committee of the Réseau Santé Valais (Wallis Health Network), Sion, Switzerland.

Goal and Methodological Issues

The specific goal of this study was to assess the correlation between patients’ symptoms (subjective indicators) and oncologic status after complete head and neck examination (objective indicators).

A few concerns had to be considered initially: first, the retrospective design, which we considered appropriate given the relatively new way to approach this issue; and, second, the potentially biased symptom surveillance. For this study, we used standardized consultation forms specific to the follow-up of patients with HNSCC. These forms were completed by hand, and the data were subsequently transferred to a computer database. The Wallis Health Network has implemented the use of such databases for almost every medical specialty since 2006. Although the use of such forms reduces the bias due to surveillance, interobserver differences are still possible.

Finally, in this study, we deal with a relatively small population (because the Department of Otorhinolaryngology-Head and Neck Surgery at the Hôpital de Sion, Centre Hospitalier du Centre du Valais/Réseau Santé Valais was founded in July 2007).

Population and Selection Criteria

From January 1, 2008, through December 31, 2009, a total of 173 consecutive patients with a first diagnosis of HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx were treated at the Departments of Otorhinolaryngology-Head and Neck Surgery and Radiation Oncology at the Hôpital de Sion, Centre Hospitalier du Centre du Valais/Réseau Santé Valais.

Criteria for inclusion in the study were (1) absence of distant metastasis at initial diagnosis, (2) no history of concomitant or previous cancer (any type), (3) complete oncologic treatment received with curative intent, (4) minimum follow-up of 2 years, and (5) a disease-free period of more than 3 months after the end of treatment.

In addition to the patients who did not fulfill the inclusion criteria, we excluded (1) patients with distant metastases without concomitant locoregional disease during the follow-up period, (2) patients who died of causes other than recurrence, and (3) those who had incomplete follow-up data for at least 2 years posttreatment or were lost to follow-up.

Follow-up Modalities and Diagnosis of Recurrences

Patients were seen monthly during the first year and bimonthly during the second year. During these follow-up consultations, patients’ symptoms were recorded and a complete head and neck examination was performed. Such data were recorded on computer-based standardized consultation forms.

Routine follow-up imaging was performed at 4 months after the end of treatment (magnetic resonance imaging or $^{18}$F-fluorodeoxyglucose–positron emission tomography/computed tomography [FDG-PET/CT]) and then at 8 and 12 months following therapy with a CT scan. During the second year, patients underwent CT scans every 6 months. When recurrences were suspected, a CT scan and/or magnetic resonance imaging plus panendoscopy with biopsy under general anesthesia were performed to confirm and assess the local extension of the recurrences. Chest CT scan and/or FDG-PET/CT were used to exclude distant metastases. Subsequent management was decided by a multidisciplinary board.

Data Extraction

All authors participated in reviewing the patients’ medical records. Patients’ data and follow-up consultation reports were available on a computer database. The relevant data were transferred to the study database. Patients’ identities were not recorded in the latter. Instead, a study-specific code known only to the database managers (L.N. and R.G.) was used.

The following variables were extracted: sex, age, risk factors (tobacco and alcohol), primary tumor location, and staging according to the International Union Against Cancer classification—TNM 2009 (retrospective staging according to this classification was made for patients treated before publication of this version), type of treatment, moment and site of recurrence, and patients’ symptoms reported along with oncologic status (recurrence or remission).4

Regarding symptoms, we noted the following features: type, distribution during the study period (absent or present), and, when present, their trend (new onset and increasing or decreasing intensity). For a synthetic presentation of data, we documented reported symptoms and their trend, along with the oncologic status, by trimester. Whenever a recurrence was diagnosed, the patient was excluded from further analysis.

A nonmasked double check of every reviewer’s extracted data was performed, and discordant findings were resolved through discussion by 3 reviewers (L.N., R.L.M., and R.G.).

Statistical Analysis

For univariate analysis, we used the Fisher exact test. For multivariate analysis, we performed logistic regression analysis of the correlation between oncologic status and symptoms. We used symptoms as independent (or predictor) variables and the oncologic status (recurrence vs remission) as the independent variable. Before logistic regression analysis, we evaluated collinearity (ie, significant correlation between independent variables) using a correlation matrix. We did not obtain substantial correlation between 2 variables.
For correlation assessment at different moments of the follow-up period, at different sites, or for different trends, we used the \( r \) coefficient (also known as the mean square contingency coefficient). This coefficient, used to assess the correlation between binary variables, can be interpreted as the classic Pearson correlation coefficient (values between –1 and 1): –1 indicates perfect inverse correlation; 0, no correlation at all; and +1, perfect direct correlation. No quantitative measure of the correlation could be obtained with this analysis, but it provides a qualitative idea and allows comparisons. Comparison of 2 coefficients was done using the Fisher \( r \)-to-\( z \) transformation. Comparison of multiple regression coefficients was performed with the test for the equality of related correlation coefficients described by Wolfe.5 All P values were 2-sided, and those less than .05 indicated statistically significant differences.

### Results

In total, 101 patients were included in this study (Table 1). Most patients were male, with a mean (SD) age of 61.5 (13.7) years (range, 29-85 years), and had at least 1 risk factor (tobacco and alcohol; we started assessing human papillomavirus status in late 2008). Regarding the primary tumor site, the distribution of patients was quite similar for the oral cavity, oropharynx, and larynx, with fewer patients with hypopharyngeal malignant tumors (Table 1). One-third of the patients had early-stage tumors vs two-thirds with advanced-stage tumors. Also, two-thirds received unimodal treatment and one-third had multimodal treatment (Table 1).

Recurrences were seen in 30 patients: 20 with local, 4 with regional, and 6 with locoregional disease. In the primary tumor site, 11 recurrences were seen in oral cavity, 7 in oropharyngeal, 8 in laryngeal, and 4 in hypopharyngeal cancers.

Three months after the end of therapy, 82.2% of all patients had at least 1 symptom: dysphagia (44.6%), xerostomia (11.9%), odynophagia (9.9%), pain at the site of the primary tumor (4.0%), dysphonia (6.9%), and dyspnea (4.9%). At the end of the study period, 36.6% of the 71 patients without recurrences still had some symptoms. Symptoms tended to decrease in prevalence, except xerostomia and dyspnea, which remained at a constant rate (Figure 1). Another exception was pain, which tended to increase over the first 9 months following therapy and then to decrease progressively.

When comparing symptoms in patients with or without recurrence, pain and odynophagia were significantly more prevalent in patients with recurrences (Table 2). No significant differences were found for dysphagia, dysphonia, xerostomia, and dyspnea. Interestingly, there were no significant differences in the proportion of asymptomatic patients between the group with recurrence and the disease-free group.

Figure 2 illustrates patients’ distribution according to their oncologic status and the presence or absence of symptoms, as well as the increasing, decreasing, or unchanged symptom intensity, which refers to the severity of a given symptom and not to the number of symptoms. Three features are particularly relevant. First, 23.3% of patients with recurrences were asymptomatic at diagnosis. Second, two-thirds of the patients with symptomatic recurrences reported a variation of symptom intensity, with one-fifth describing a decrease in symptom intensity at diagnosis. Finally, most patients who did
not develop recurrences during the 2-year follow-up described having some of the heretofore mentioned symptoms (Figure 2).

In the multivariate analysis, we found an independent relationship between pain (odds ratio, 16.07; 95% CI, 5.94-43.51), odynophagia (11.20; 3.13-40.04), and dysphonia (5.90; 1.77-17.28) and oncologic status (Table 3). There was no independent relationship between xerostomia, dysphagia, or dyspnea and oncologic status (Table 3).

When considering symptom intensity trends, the best correlation was for new-onset symptoms or, to a lesser extent, symptoms with increasing intensity (Table 4). Symptoms with decreasing or unchanged intensity displayed correlation coefficients close to zero, indicating low or no correlation (Table 4). Comparison of correlation coefficients revealed significant differences \((P = .003)\).

Concerning the correlation between symptoms and oncologic status according to the lapse of time after treatment, we found a better correlation between 6 and 12 months and between 18 and 21 months. For the rest of the follow-up periods, the correlation coefficients were close to zero, indicating very low or no correlation between symptoms and oncologic status (Table 4). Comparison of the coefficients showed a statistically significant difference among these values \((P = .01)\).

In our series, two-thirds of the patients had advanced-stage disease (stage III or IV). When comparing the correlation between symptoms and oncologic status according to primary tumor stage (early vs advanced stage), we did not find a significant difference between these 2 groups (Table 4). In line with this, we did not find differences according to the primary T classification (T1-T2 vs T3-T4).

Interestingly, the correlation between symptoms and oncologic status was significantly better in patients who received unimodal treatment (surgery or radiotherapy) than in those who had multimodal treatment (ie, combinations of surgery and adjuvant radiotherapy) (Table 4).

Finally, because of the number of patients, analysis according to primary tumor site could be performed only for the oral cavity, oropharynx, and larynx. Although the oropharynx displayed the lowest correlation coefficient, comparison of correlation coefficients did not reveal significant differences (Table 4).

**Discussion**

The main findings of this study are as follows: (1) Most patients treated for HNSCC, with or without recurrence, describe having symptoms after the end of therapy. (2) The correlation between symptoms and recurrence is low during substantial periods of the follow-up. (3) New-onset symptoms and, to a lesser extent, symptoms with an increasing intensity better correlate with recurrence. (4) Pain and odynophagia have the best correlation with recurrence. (5) The correlation between symptoms and oncologic status is better in patients treated with unimodal therapy.
Specific symptom (larynx), and therefore this finding could be confirmed these findings, revealing in addition that dysphonia (hoarseness) was also independently associated with recurrence-free patients still had these symptoms at the end of the 2-year follow-up (Figure 1). The multivariate analysis considered of limited value. Nevertheless, patients with positive pathologic lymph nodes or with elective irradiation for advanced tumors received a 5000-cGy dose on the affected side or sides, and such forms of irradiation may have adverse effects involving the larynx, even when the primary tumor is not laryngeal.6 Finally, a limitation of our study is the fact that less than 10% of the patients had dysphonia (Table 2), which limits the statistical significance of this result.

Treatments for HNSCC induce symptoms but also modulate patients’ perceptions because of the surgical section or lesion of nerves and muscles, as well as the acute and late toxicities of chemoradiation. The most frequent local effects of oncologic treatments on the head and neck region are mucositis, increased secretions, dysphagia, xerostomia, dermatitis, and muscular dysfunction.7,8 This is in line with the fact that xerostomia and dysphagia did not display a significant correlation with recurrence because these symptoms are most likely treatment induced. It seems obvious that combining thorough resections and radiation is more likely to impair patients’ perceptions and induce more symptoms than one of these treatment options alone.

### Treatment-Induced Symptoms vs Symptoms Due to Tumor Recurrence

Patients’ symptoms are imperfect markers of the underlying oncologic status. Therefore, the major difficulty in the post-treatment follow-up of patients with HNSCC is distinguishing symptoms due to recurrence and symptoms induced by the treatment. The anatomic modifications due to surgical resection and the eventual reconstruction by flaps can render physical examination challenging. In such contexts, recurrences may not be obvious to the examiner.

In our series, only pain and odynophagia were significantly more prevalent in patients with recurrences, but 6.9% of recurrence-free patients still had these symptoms at the end of the 2-year follow-up (Figure 1). The multivariate analysis confirmed these findings, revealing in addition that dysphonia (hoarseness) was also independently associated with recurrence (Table 3). At first sight, dysphonia seems to be an organ-specific symptom (larynx), and therefore this finding could be

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*Calculated with the test for the equality of related correlation coefficients.

bCalculated using the Fisher $r$-to-$z$ transformation.
2. Patients with recurrences who report a decrease in symptom intensity: risk of reassurance for the patient and the physician. A rigorous approach is again essential.


Our study reflects the situations when patients’ reported symptoms and the physical examination findings are discordant, which is frequently observed in the everyday practice of head and neck cancer specialists. This probably explains the regular use of different protocols of imaging and/or endoscopy in most institutions treating patients with HNSCC.

Although radiologic imaging has a key role in the posttreatment follow-up, the most common imaging modalities have a low specificity in distinguishing tumor recurrence and treatment-induced tissue changes. This is especially true in the immediate posttreatment period, when the recurrence extension is more limited and therefore salvage therapy theoretically would be more feasible.13,14

In the diagnosis of early recurrence, FDG-PET/CT has shown an overall good precision, with a negative predictive value of 100% but a positive predictive value of only 77% in some series.15 Although FDG-PET/CT is a useful tool in diagnosing recurrence, the effect of this examination on the patient’s management and consequent survival has yet to be elucidated. Furthermore, the high cost of FDG-PET/CT makes this examination a tool of restricted access in most clinical settings.

The usefulness of endoscopic follow-up as a screening method after treatment for HNSCC is currently contested. While rigid endoscopy requires general anesthesia, fiberoptic endoscopy (bronchoscopy or esophagoscopy) is regarded as an unpleasant procedure by most patients, and some authors consider it an inadequate screening device.16,17 The costs as well as the potential complications related to these procedures must not be forgotten.

Besides the most pragmatic aspects, it must be kept in mind that close follow-up has other important goals, especially the identification and management of treatment-related complications and psychosocial support.9 Furthermore, close follow-up allows accurate evaluation of treatment outcomes and identification of patients not suitable for salvage therapy but for whom inclusion in new treatment protocols remains an option.12

Limitations and Future Research Areas

We approached this relatively new area with a retrospective design, and in doing so, our results must be treated accordingly. Nevertheless, our findings provide a promising ground for prospective studies in larger series. An issue that should be addressed is proper stratification according to the tumor site, since this could allow for clarification of the organ-specific nature of certain symptoms, such as dysphonia.

One can argue that our findings are generally acknowledged by physicians, but it is important to point out that few, if any, data support them in the literature.

We attempted to better understand and determine the relationship between the important information our patients provide us and our main point of interest during follow-up: recurrences. In this sense, prospective studies may help define more individually tailored follow-up strategies that consider symptoms and their patterns. Our ongoing prospective research on this issue will be published in due course.

Conclusions

The correlation between subjective symptoms and oncologic status is globally low for substantial periods within the first 2 years of follow-up, during which the recurrence rate is highest (90%). New-onset symptoms and especially pain, odynophagia, or dysphonia better correlate with tumor recurrence. This correlation is better in patients initially treated unimodally, who theoretically have a higher chance of successful salvage.

Further prospective studies should allow for more precise definition of the value of the symptoms in detecting recurrences in patients treated for HNSCC.


