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ORIGINAL ARTICLE

Hypopharyngeal cancer: analysis of the evolution and treatment results

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KEYWORDS
Hypopharyngeal cancer;
Treatment;
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Abstract
Objective: Hypopharyngeal carcinoma is an aggressive malignancy usually diagnosed at a late state, thereby resulting in overall poor prognosis and low survival rates for these patients. The purpose of this study is to present the progress and outcomes of patients treated for hypopharyngeal carcinoma at our department.
Material and method: We retrospectively reviewed 89 patients who had been diagnosed with hypopharyngeal carcinoma between 1980 and 2005. Most of the tumours were advanced (T3 and T4) and 73%showed palpable regional metastases at presentation.
Results: The 5-year survival rate was 40.7%. The overall incidence of distant metastases and subsequent primary neoplasms was 7.5%and 23.5%, respectively.
Conclusions: Hypopharyngeal cancer is still the one with the worst prognosis in the head and neck area. The poor survival rate seems to be related primarily to advanced stage disease at presentation and particularly to the status of cervical lymph-node metastases.

PALABRAS CLAVE
Cáncer de hipofaringe;
Tratamiento;
Supervivencia

Cáncer de hipofaringe: análisis de la evolución y los resultados del tratamiento en nuestro medio

Resumen
Objetivo: El cáncer de hipofaringe es un cáncer muy agresivo que generalmente se diagnostica en estadios muy avanzados, su pronóstico es desalentador y la tasa de supervivencia, muy baja. El objetivo de este estudio es presentar la evolución y los resultados de los pacientes tratados de cáncer de hipofaringe en nuestro servicio.

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Material y método: Realizamos un estudio retrospectivo en 89 pacientes diagnosticados de cáncer de hipofaringe entre los años 1980 y 2005. En su mayoría se trataba de tumores avanzados (T3 y T4) y el 73 %presentaba adenopatías palpables en el momento del diagnóstico.
Resultados: La supervivencia a los 5 años fue del 40,7%. Encontramos una incidencia de metástasis a distancia y segundos tumores primarios de un 7,5 y un 23,5%, respectivamente.
Conclusiones: El carcinoma de hipofaringe continúa siendo el cáncer de cabeza y cuello de pronóstico peor. La tasa de supervivencia parece estar relacionada primariamente con el estadio tumoral de presentación y, de forma particular, con el estado de los ganglios linfáticos cervicales.

Introduction

Hypopharyngeal cancer is a highly aggressive cancer generally diagnosed at very advanced stages; its prognosis is disheartening and its survival rate very low. In most cases, there is considerable delay in diagnosis, as the initial stages may be asymptomatic or the symptoms may be misinterpreted, so the tumour attains considerable size by the time of diagnosis.

In addition, hypopharyngeal cancer is able to extend submucosally, as well as cause lesions in distant areas, referred to as skip lesions. These are not observable by gross examination, leading to under-diagnosis of the tumour's real staging and the consideration of inappropriate surgical resections.[1]

There are no effective anatomical barriers to prevent dissemination of carcinoma of the hypopharynx into the soft tissues in the neck. There is a high rate of metastasis into lymph nodes and distant areas in the natural history of the condition, indicative of its aggressive nature.[2]

Treatment of these patients is felt to require ample surgical resection, generally including total laryngectomy with partial pharyngectomy or total laryngopharyngectomy associated with reconstruction techniques, followed in most cases by radiation therapy (RT).[3] It is also possible to apply larynx-sparing treatment in these patients using concomitant chemotherapy (CT) and RT protocols, or by laser surgery followed by RT, with or without CT, depending on each patient. Both treatment modalities have equivalent survival rates.[3-5]

Despite treatment, the 5 year survival rate is low, between 26% and 38%, depending on the series reviewed,[6-12] and the most frequent cause of failure is locoregional recurrence.

The goal of our study is to present the course and therapeutic results of patients diagnosed at our centre as having hypopharyngeal cancer and, furthermore, to relate, if possible, clinical and pathological parameters with the relapse and mortality rates.

Material and method

We are presenting a retrospective study analyzing the period between 1980 and 2005. During this interval, 89 hypopharyngeal carcinomas were diagnosed, 81 of which (91%) affected the pyriform sinus, and 8 (9%), the posterior pharyngeal wall.

The mean age of the patients studied is 56.94 years, with a range of 36-81 years; 87 patients were male and only 2 were female.

The association of this kind of cancer with smoking and alcohol intake is very striking; in this sense, we found that 95.3% (85) were smokers and 73% (65), regular drinkers. Both these toxic substances were present in 71.8% (64) of cases. Only 4.7% (4) of the cases were not or had ceased to be active smokers or drinkers.

Patients were classified using the TNM staging system. The tumours were mostly large, T_3 55.1% (49) and T_4 14.6% (13) (Figure 1), at an advanced stage; 87.4% (78) were at stages III and IV (Figure 2).

At the time of their diagnosis, 73% (65) presented palpable adenopathies and many of them were N_2, 38.9% (35) (Figure 3). Only 1 patient presented distant metastases and was given palliative treatment.

Initially, 73 patients were treated surgically and an organ-sparing protocol was begun in 15 of them. The decision on each mode of treatment was taken at the tumour committee, taking into account the characteristics of the tumour and nodes as well as those of the patient (conservative treatment was begun in all N_3 cases in whom nodal surgery was not possible, in women, in patients conserving mobility of the vocal cords, or when the patient rejected surgical treatment). In terms of the surgery performed, a partial pharyngectomy with total laryngectomy was performed in 96% (68) of them; a phonatory trachaeoesophageal prosthesis was inserted in 38.4% (26); only in 3 cases was a total circular pharyngolaryngectomy performed; there was 1 case of pharyngectomy and partial laryngectomy and 1 case of laser surgery (a T_1 patient subsequently given RT). In the cases of total circular surgery, reconstruction was by means of a free microvascular flap from the jejunum and the other 2 with a myocutaneous flap from the *pectoralis major*.

In 83.1% (74) of all patients, lymph node surgery was performed, 94.9% (69) of those not treated with the organ-sparing protocol. The techniques most frequently employed were radical homolateral dissection in 41% of cases (32), followed by radical homolateral and functional dissection of the contralateral node in 24.4% (19). Lymph node surgery was not performed in only 15 patients, either because they were treated under the organ-sparing protocol (11 cases), or else because of prior surgery (4 cases).

After the pathology study of the surgical specimens, we found that the most frequent pathology type reported

was squamous cell carcinoma in 71 patients (97.2%). From the standpoint of the degree of differentiation, 42.5% (31) were well differentiated; 35.6% (26), moderately differentiated; 17.8% (13), slightly differentiated; and 1.4%(3), undifferentiated.

As for pTN staging, they were mostly advanced pT_{3-4} stages, 43.1%(31) and 40.3%(29), respectively. There were 21%(15) who were pN_0 and 79%(56) were pN+, mostly pN_2, 55.2%(38). In general, they were well staged during the examination at the clinic, but there is a percentage of patients under-diagnosed both in terms of tumour size and in lymph node staging (Figures 1-3).

The pathology report indicated the existence of affected margins in 15.3%(11) of cases. We found extrapharyngeal involvement in 69.4%(50) of cases, and the larynx was the organ most often affected, with 54.2%(39), followed by the oropharynx and both. Multi-centric locations were seen in 5.5%(4).

Of the 106 dissections performed, 64.15% (68) were positive; in 54.71% (37), this was homolateral; and in 9.43%(6) they were contralateral (it has to be said that the homolateral one was also positive in these cases). In 23 patients, there was rupture of the capsule (32.9%) and 16 also presented invasion of the extralymphatic tissues. The mean nodes found by dissection was 20.52, with the mean number of nodes colonized in the positive dissections was 3.56.

Post-operative RT was administered in 60 patients initially treated with surgery (67.4%). It was not administered to the rest of the patients for the following reasons: 7 patients suffered recurrence prior to the start of RT, 2 had received prior RT for another primary tumour, 3 died in the immediate post-operative period, and in 2 pN_0 cases the tumour committee decided not to apply RT. In 9 patients it was decided to apply post-operative QT associated with RT.

We used the SPSS 13.0 statistical application to analyze the results. We worked with Pearson's χ^2 test, Fisher's exact test, and Kaplan-Meier curves for the study of survival.

Results

We studied the evolution of our patients over 3 and 5 years. The locoregional recurrence index at 5 years was 32.5%. The mean interval between surgery and relapse was 25.26 months (minimum of 1 month and a maximum of 78). In 5 cases, the relapse occurred before administration of RT. Distance metastases appeared in 7.5%(2 in the lungs, 2 in bones, 1 in the brain, and 1 in the liver). The incidence of a second primary tumour was 23.5%(6 in the lung, 3 in the tonsils, 2 in the tongue, 2 in the floor of the mouth, 2 in the posterior pharyngeal wall, 2 in the stomach, 1 in the pancreas, 1 in the thyroid, and 1 in the bladder). The mean interval between treatment and the onset of the second primary tumour was 3.5 years (range, 1.5-4.5).

Global survival after 3 years is 63.13% and 40.7% after 3 years.

The specific survival, discounting deaths due to causes other than the primary tumour, is 65.58%after 3 years, and 54.85%after 5 years.

We have studied separately the overall survival of patients treated according to the organ-sparing protocol and those

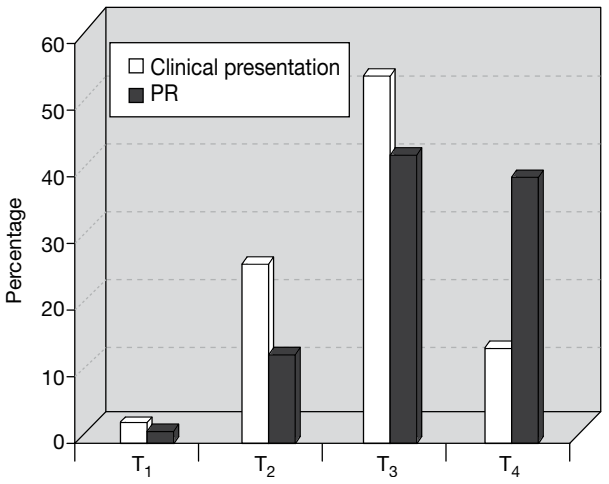

Figure 1 Distribution of patients by clinical tumour stage and pathology report. (The results are expressed as percentages to allow comparison of the pathology report staging, as these columns do not include the patients treated with organ-sparing protocol). PA indicates pathology report.

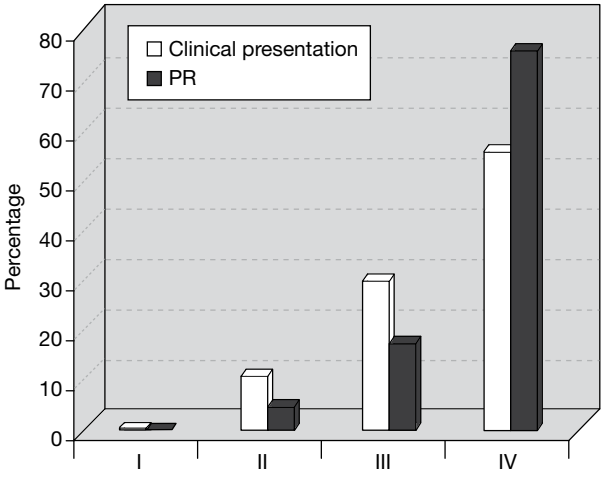

Figure 2 Distribution of patients by clinical tumour stage and pathology report. PR indicates pathology report.

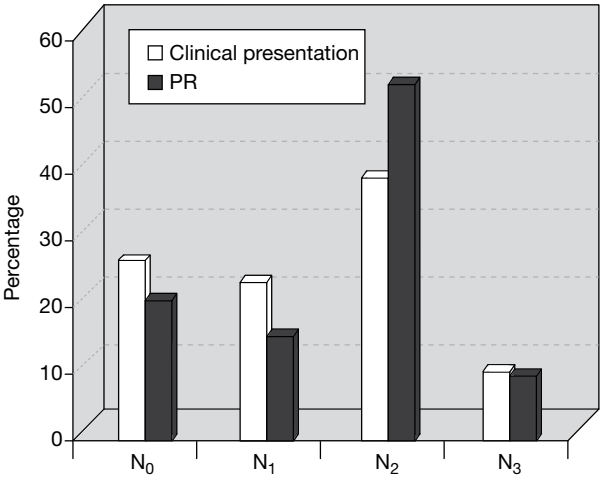

Figure 3 Distribution of patients by staging. PA indicates pathology report.

treated surgically, and it has been confirmed that both are comparable, without statistically significant differences between them; $P>.05$ ($P=.45$) (Figure 4).

We did not find statistically significant differences when relating margin involvement to recurrence ($P=.23$) nor between extrapharyngeal involvement and recurrence ($P=.19$).

A survival study was carried out for margin involvement, local recurrence, and regional recurrence.

With respect to the first, the relationship found was the opposite of that expected due to the few patients with affected margins, with a non-significant Breslow index (0.072).

To assess local recurrence, we related the presence of local recurrence with the tumour size according to the pathology report (following the TNM classification) in 4 categories (pT_1, pT_2, pT_3, and pT_4). The number of cases in each one is small, so the probability of finding statistically significant differences falls, as reflected by a Breslow index >0.05 ($P=.20$).

In regional recurrence, the relationship between results is logical: the larger the N value, the lower the survival

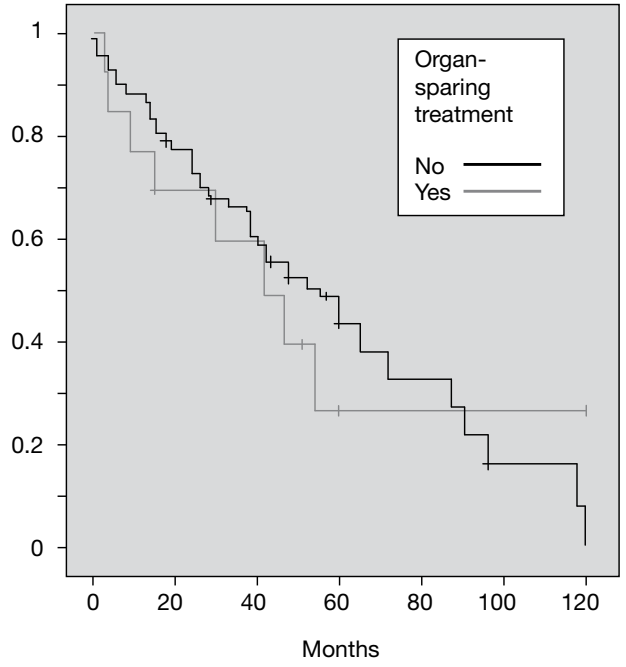

Figure 4 Survival of patients treated with surgery (top line) or organ-sparing protocol (bottom line).

Tabla Mean survival of patients in each of the stages of the regional recurrence

Factor	Number of cases	Mean survival
pN_0	15	74
pN_1	11	59
pN_2	32	44
pN_3	7	39

(Table). However, it does not reach optimal statistical significance (Breslow index=0.16) as there was a small sample size in each of the N categories.

Finally, we studied the mean number of lymph nodes colonized, showing a greater percentage of nodal recurrence, namely 4.3 nodes colonized (1.69 nodes more than patients who did not relapse). We cannot speak of significant differences due to the sample size ($P=.09$).

Discussion

In our series, the percentage of hypopharyngeal tumours is low in comparison with others. This may be due to the fact that, because of the large size these tumours usually reach before they are diagnosed, they have been classified as laryngeal tumours involving the hypopharynx instead of hypopharyngeal tumours extending into the larynx. This is more likely when there is involvement of the medial wall of the pyriform sinus and the aryepiglottic fold. In fact, 87.4% of these in our study were stages III or IV. If we observe the TpT distribution (Figure 1), we can see that 21.5% were under-diagnosed, probably due to the sub-mucosal extension of this kind of tumour, as well as skip lesions.

The tumour size and clinical staging are factors giving a poor prognosis with regard to survival[13]; the larger the tumour size at the time of diagnosis, the fewer the possibilities of survival after 5 years. In our study, we have been unable to find any significant differences between pT and recurrence of T or survival, probably because of the scant number of patients with pT_{1-2}, but it is logical to think that they would exist if a higher N count was present.

The other characteristic of these tumours is the high incidence of clinical adenopathies at the time of diagnosis. Coinciding with other series reviewed, 73% of the patients in our series presented palpable adenopathies at their first visit. As for the grade of nodal invasion, practically 80% of the patients were pN+, particularly pN_2 (53.5%).

According to the literature reviewed,[13,14] both rupture of the capsule and perineural invasion influence recurrence or survival, so they must be considered as prognostic factors for these tumours, although no statistically significant differences were found in our study.

There seems to be a correlation between the number of nodes involved in the lymph node dissections and the incidence of N recurrence. Leemans et al[15] observed that patients with 12 positive nodes had the same recurrence rate as those with greater lymph node involvement. In our study, we decided to explore the mean number of nodes colonized above which there is a higher percentage of N recurrence, namely 4.3, ie, 1.69 nodes more than in patients who did not relapse, although we did not reach statistical significance due to the sample size.

An aspect that is quite controversial is the possible role played in survival by the invasion of surgical margins. In the experience of some authors,[16] this was the most important predictive factor for survival in the 7 patients. Nonetheless, other series have not confirmed this influence.[10,17] In our series, this factor did not have any prognostic relevance, either due to the post-operative RT administered to these patients or because of poor interpretation of the margins of the surgical

specimen. Nor did we find a statistically significant relationship between extrapharyngeal involvement and recurrence.

One of the causes of treatment failure in hypopharyngeal cancer, despite the achievement of good locoregional control, is the onset of distant metastases or second primary tumours. In our study, distant metastases appeared in 7.5% of patients, which coincides with other series that found between 5% and 20%. A second primary tumour was diagnosed in 23.5% of patients, a percentage in the upper range of other series consulted (8.9%-31%).[6,7,18-21] The incidence of subsequent primary tumours in the hypopharynx is 3 times greater than that of laryngeal cancer.

The difficulty in performing excision of a tumour and lymph nodes to avoid recurrences and achieve high survival rates has led to numerous variations in therapy. The standard therapeutic modality for the treatment of hypopharyngeal cancer is partial/total pharyngectomy plus total laryngectomy plus dissection of the cervical lymph nodes (either functional or radical, unilateral or bilateral, depending on the characteristics of the patient in each case), followed by RT or even RT and CT at the same time, if there are poor prognostic factors in the pathology report. Nonetheless, with the advances in RT and CT, we can now offer patients the possibility of a treatment with the intention to preserve the larynx with good chances of success, according to the literature.[4,5] Despite this, it is important to bear in mind that salvage surgery in these patients entails a larger number of complications in the immediate post-operative period[5]. At our department, the vast majority of our patients were treated with the standard therapy. Through this treatment, we have achieved a 5year survival rate of 43.49%. In selected patients, following assessment by the tumour committee, we have opted for a larynx-sparing treatment using a protocol with CT followed by concomitant RT and CT. However, there was local recurrence forcing surgery to be undertaken in 5 of these 15 patients, therefore the larynx could not finally be spared. With this treatment, we have confirmed that there are no statistically significant differences with the conventional treatment in terms of survival. In any case, these results are subject to patient-selection biases, as the application of one treatment or the other was not at random. Our survival rates are comparable with those in the literature consulted, ranging between 25% and 40%.[4,5,9,10,21-24]

The use of RT as the sole therapeutic modality is limited to tumours at the initial stages, where the results found have been similar to those with surgery.[25]

Conclusions

Hypopharyngeal carcinoma is a tumour with a poor prognosis, although, with regard to survival, we have not found any relationship with classical prognostic factors such as involvement of margins and extrapharyngeal extension.

No differences have been observed between conventional and larynx-sparing treatment.

Bearing in mind tumour-related causes, the survival of our patients achieves 54.8%, despite the fact these are advanced tumours.

The number of positive nodes on dissection influences locoregional recurrence when it ≥4, albeit without achieving statistical significance, possibly because of the sample size.

The N and T categories do not seem to have an influence on survival in our series, possibly linked to the sample size and the fact that, for the most part, they were at advanced stages.

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