ORIGINAL ARTICLE

Functional and Oncological Results of Non-surgical vs Surgical Treatment in Squamous Cell Carcinomas of the Oropharynx

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Abstract
Introduction and objectives: Squamous cell carcinomas of the oropharynx are aggressive tumours usually diagnosed at advanced stage. Their optimal treatment has not been established. The aim of this study was to compare the oncological and functional outcomes in patients with carcinomas of the oropharynx treated by radiotherapy (with chemotherapy in advanced stages) vs surgery (with radiotherapy in advanced stages).
Methods: A retrospective study on 50 patients with squamous cell cancer of the oropharynx treated by radiotherapy (with or without chemotherapy) at our institution between 1998 and 2008 was carried out. The oncological and functional results were compared with patients with same cancer location and stage treated by surgery (with or without radiotherapy). In both groups, the patients were classified as follows: 10% Stage I, 12% Stage II, 16% Stage III, 48% Stage IVa and 14% Stage IVb.
Results: The 5-year disease-specific survival was 33% in the radiotherapy group and 52% in the surgical group (P=.17). Five-year disease-specific survival for Stage I and II patients was 82% in the radiotherapy group and 70% in the surgical group. In Stages III and IV disease, 5-year disease-specific survival was higher in the surgical group (47% vs 17%). The functional results were similar; anatomical and functional preservation of the larynx was higher in the radiotherapy group but the successful return to oral food intake was higher in the surgical group.
Conclusions: The prognosis of squamous cell carcinoma of the oropharynx is poor. Oncological results in Stages I and II were similar for radiotherapy and surgical treatments. In advanced stages, the prognosis was better in patients treated by surgery with or without radiotherapy. Functional results were similar in both treatment modalities.

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Introduction

Oropharyngeal tumours account for between 10% and 15% of malignant tumours in the head and neck region. In most cases they are squamous cell carcinomas with varying degrees of differentiation, although keratinising types are predominant. Their most common location is the lateral wall (50%-60%) followed by the tongue base (20%-35%) and, to a lesser extent, the posterior wall (5%-10%).

Aetiological agents involved include tobacco, alcohol and, recently, the role of human papillomavirus (HPV), especially serotype 16, is gaining recognition. They are locally aggressive neoplasms with a high rate of lymphatic metastasis, which leads them to be diagnosed in advanced stages.

At present, there is insufficient consensus and protocolisation regarding their optimal treatment. Oncological and functional results in early stages (I and II) are similar among patients treated with surgery and those treated with radiotherapy (Rt). HPV-positive tumours present a more favourable evolution when treated with radiochemotherapy (RCT).

Oncological and functional results in advanced stages are poor, a fact that explains the use of combined therapeutic strategies. The therapeutic modalities employed include surgery (with or without additional Rt), Rt and RCT. Patients treated with surgery in locally advanced stages often suffer significant functional sequelae, including the need for total laryngectomy in some selected cases, leading to a decreased quality of life. Therefore, some authors do not recommend surgery in T3 and T4 tumours. In order to assess which treatment modality offers the best results, we designed a retrospective study to evaluate the oncological and functional results of patients with oropharyngeal tumours who were treated with Rt or RCT, comparing them with a similar group treated with surgery alone or surgery and postoperative Rt.

Material and Method

We conducted a retrospective review of patients diagnosed with oropharyngeal squamous cell carcinoma treated with Rt or RCT at our hospital between 1998 and 2008. All patients had an initial diagnosis of this tumour, excluding those with previous surgery, relapsed tumours or metastases at diagnosis. The minimum follow-up period was 24 months. We thus obtained a group of 50 patients (radiotherapy group, RtG) who met the inclusion criteria. We performed staging according to the TNM classification of UICC (6th edition) for oropharyngeal carcinoma. Similarly, we selected another group of 50 patients with tumours in the same location and the same TNM classification, treated at our centre through surgery alone or surgery associated with postoperative Rt during the same period (surgery group, SG). Table 1 shows the clinical and pathological data of both groups.

All patients were thoroughly evaluated, both clinically and radiologically, before being proposed a therapeutic strategy. The decision to conduct Rt, RCT or surgery was agreed at the Cancer Committee. This decision was influenced by the clinical characteristics and preferences of...
patients, as well as tumour extension. As a general rule, for patients in advanced stages without contraindication for Ct we conducted concomitant RCT (77% in stages III and IV) with different schemes and drugs according to their medical history and tolerance to treatment.

All RtG patients received a radical dose of Rt. In all cases, the total dosage on the primary tumour and affected lymph node chains was over 70 Gy. The Rt scheme used was standard fractionation, with doses between 1.8 and 2 Gy per session, 5 days a week for 6–7 weeks. We conducted a therapeutic plan with intention to treat radically, so those patients who did not complete the treatment and died of the disease were computed as therapeutic failures.

In total, 30 (60%) of the 50 patients received concomitant Rt with the following drugs: cisplatin in 20 cases, cetuximab in 9 and carboplatin in 1. The scheme used for cisplatin included 3 doses of 75 mg/m², 1 every 21 days (on days 1, 22 and 43). The scheme for cetuximab included 1 initial dose of 400 mg/m² followed by a weekly dose of 250 mg/m² until the end of Rt. The scheme used for carboplatin was 400 mg/m² every 4 weeks until the end of Rt.

In the SG, the type of surgical approach (transoral, transmandibular or transpharyngeal) depended on primary tumour extension. Lymph node dissections were performed in 96% of patients (44% unilateral and 52% bilateral) undergoing primary tumour surgery. The dissections were functional in patients without clinical metastases and radical in patients with clinical metastases. In 27 (54%) cases we also administered complementary postoperative Rt (68% in stages III or IV). The indication for this Rt was the presence of more than 2 positive lymphadenopathies, extracapsular extension, locally advanced tumours (T4) and affected surgical margins.

In order to evaluate the oncological results, we described locoregional control, overall survival at 5 years and disease-specific survival at 5 years.

The functional results described were: anatomical preservation of the larynx, absence of tracheotomy and preservation of oral feeding.

Statistical analysis was carried out using the software package SPSS version 15.0, through the chi-square test, with Yates’s correlation when appropriate, and Fischer’s exact test. Survival was calculated according to the Kaplan–Meier method. The differences between the survival times were analysed using the log-rank method. Statistical significance was set at P<.05.

Results

The mean follow-up period was 62 months for the RtG (range: 24–163 months) and 82 months for the SG (range: 24–140 months).

Of the 50 patients in the RtG, 32 (64%) presented disease progression: 11 (22%) at a local level, 3 (6%) at a regional level, 9 (18%) distant metastases, 4 (8%) at a locoregional level and 5 (10%) both locoregional and distant. In 6 of the 20 patients in whom local disease control failed, progression occurred within 6 months after treatment, so they were considered as tumour persistence. The mean time until onset of recurrence was 9 months (range: 7–29 months).

We were able to perform rescue surgery in 4 patients (13%) of the RtG who presented recurrence or persistence. Two of them underwent radical lymph node dissection due to cervical persistence, with evolution being favourable in both cases. The other 2 cases developed local recurrences. One case was treated by glosso-epiglottectomy and subsequently presented a new, unresectable recurrence 1 year after surgery. The other case was treated by an intraoral approach and 2 years later developed a new, local recurrence which was resected, but the patient died due to distant metastases 1 year after the second surgery.

In the SG, 26 patients (52%) presented disease progression: 11 (22%) at a local level, 2 (4%) distant metastases, 11 (22%) at a locoregional level and 2 (4%) both locoregional and distant. The forms of progression are summarised in Table 2.

The association between local disease control and T category in the TNM classification is shown in Table 3. In both studied groups, local recurrences were more frequent with increased T category, with the increase of local recurrences in the RtG as cT increased being statistically significant (P=.040).

Overall survival at 5 years in the RtG was 24%, whereas in the SG it was 38% (P=.431). Disease-specific survival at 5 years was 33% and 52%, respectively for both groups, without reaching significant differences (P=.17; Fig. 1a). In early
stages (I–II), disease-specific survival at 5 years was similar between both treatment groups, 82% for the RtG and 70% for the SG (P = .749; Fig. 1b), while in stages III and IV the SG had a disease-specific survival above that of the RtG: 47% and 17%, respectively (P = .111; Fig. 1c). Patients in stages III and IV treated exclusively with Rt had a much lower specific survival (0%) than those treated with RCt in the same stages (24%) (P = .198). In the SG, patients in stages III–IV who received no complementary Rt presented a lower disease-specific survival (41%) than those who received it (50%) (P = .356).

In relation to the sequelae of treatment, 46 patients (92%) in the RtG developed mucositis after completing Rt: 5 (10%) in stage I, 6 (12%) in stage II, 29 (58%) in stage III and 6 (12%) in stage IV. In addition, 42 patients (84%) developed radiodermatitis: 14 (28%) in stage I, 13 (26%) in stage II, 14 (28%) in stage III and 1 (2%) in stage IV. We found no significant differences when comparing the severity of mucositis and radiodermatitis with the use or not of Ct (P = .748 and P = .343).

In the RtG, at the end of treatment, 41 patients (82%) were capable of oral feeding, 2 required a nasogastric tube and 7 required a gastrostomy. The 9 patients who could not be fed orally developed local recurrences or persistence of primary tumours, whereas the 14 patients who were alive at the end of treatment were capable of oral feeding. Tracheotomy was performed in 5 patients (10%) in the RtG, all due to early local relapses, who died from the tumour before being decannulated.

In the SG, 48 patients (96%) were capable of oral feeding and 2 (4%) required gastrostomy. Laryngeal function was preserved in 46 (92%) patients, with total laryngectomy being necessary in 4 (8%) cases: 3 due to tumour invasion and 1 due to intractable aspiration. Tracheotomy was performed in 39 patients; on a provisional basis in 29 cases, although 10 (26%) of these could not be decannulated, all due to early relapses.

The functional results in terms of anatomical preservation of the larynx (P = .017) and absence of tracheotomy

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**Figure 1** Disease-specific survival in patients with oropharyngeal squamous cell carcinomas comparing the treatments administered according to the Kaplan–Meier method: in the entire series (A), early stages (B) and advanced stages (C).
(P=.577) were better in the RtG, whereas the SG presented a better percentage of oral feeding (P=.051). However, no significant differences were observed between both groups when comparing patients who were alive without tumour at 24 months follow-up.

Discussion

Oropharyngeal squamous cell carcinomas are aggressive neoplasms which are diagnosed in advanced stages in over 75% of cases.\textsuperscript{13} This fact is evident in our series, since 78% of patients were in stages III and IV.

Consumption of alcohol and tobacco was present in most patients in our study, since the vast majority were smokers and consumed alcohol (Table 1). HPV was not studied in this work, although the clinical characteristics of the series (toxic habits, age over 60 years, male/female ratio 9/1) lead us to believe that its aetiological involvement in oropharyngeal tumours in our environment is less than the 18% reported worldwide.\textsuperscript{13-14} This could partly explain the poor oncological results of our series, similar to those obtained in other countries in our environment, since HPV-positive tumours have a better prognosis, which has been attributed to increased sensitivity to RT.\textsuperscript{15,16} Therefore, as has been proposed, it would be interesting to study HPV before selecting a treatment modality, indicating RT in HPV-positive tumours, whereas surgery and complementary Rt would be the best option for HPV-negative tumours in advanced stages.\textsuperscript{17}

Regardless of the aetiological factor, the oncological results of oropharyngeal tumours depend on their stage, with good results in early stages (I–II), regardless of the treatment modality used. Survival at 5 years in stages I and II treated with surgery is over 80%,\textsuperscript{1,7,18} reaching 91% in T1-2 treated with Rt.\textsuperscript{19} We found a 5-year survival rate of 82% in stages I and II treated with Rt, which was better than that observed with surgery (70%), although without reaching significant difference.

By contrast, the prognosis of oropharyngeal carcinomas in advanced stages (III–IV) is poor,\textsuperscript{19,20} making it necessary to combine therapeutic modalities such as surgery with complementary Rt or concomitant RCT. The lack of prospective, randomised studies comparing the different strategies determines that treatment of these tumours remains controversial.

In our series, disease-specific survival in the RtG was 33%, which was lower than for the SG (52%), although the differences were not statistically significant, probably due to the small sample sizes. This difference in survival could be explained by the advanced stages (III–IV), since there were no differences in early stages (I–II) between both treatment modalities, as mentioned previously. We should bear in mind that tumours in early stages were only treated with 1 therapeutic modality, whereas for those in advanced stages we employed combined treatments in most cases. Furthermore, patients in advanced stages who received combination therapy showed a significantly better disease-specific survival: 24% for those treated with RCT vs 0% for those treated only with Rt (P=.198), and 50% for those treated with surgery plus complementary Rt vs 41% for those treated with surgery alone (P=.356).

Being a retrospective study, we must take into account a possible bias in patient selection, generally favouring the surgical group as this was the preferred treatment modality employed at our service, so most RtG patients were poor surgical candidates.

RtG overall survival (24%) was lower than that described by other authors.\textsuperscript{21-23} This group included all patients originally selected for radical treatment with Rt, thus enabling an analysis by intention to treat. Few studies in the medical literature employed the same methodology, making it difficult to obtain objective data on the effectiveness of Rt in these tumours. The study by Zhen et al.,\textsuperscript{24} which used U.S.A. cancer data, described a higher specific survival in advanced tongue base tumours which were treated with surgery plus complementary Rt, 51.2% vs 24.3% with RT alone and vs 25.6% with RCT. Another study of oropharyngeal tumours presented a 20% increase in specific survival when the treatment modality was surgery associated with complementary Rt compared with RCT.\textsuperscript{25}

In our series, the main cause of treatment failure in the RtG was lack of local control over the primary tumour, since 28% of patients developed local recurrences and 12% presented tumour persistence. This fact could be explained by the high rate of locally advanced tumours, which reached 70% in our series. In the literature, tumour volume was linked with a worse therapeutic response to Rt in tumours of the oropharynx and larynx, especially when tumour volumes exceeded 35 cm.\textsuperscript{3,16}

Distant metastases were detected more frequently in the RtG (28%) compared to the SG (8%), with this difference being statistically significant (P=.043). This fact, observed in patients treated with RCT, could be explained by the selection of a subclone of radiochemoresistant tumour cells capable of developing distant metastasis.\textsuperscript{27}

As noted by other authors,\textsuperscript{28} isolated cervical recurrence after RCT is uncommon and we only detected it in 3 patients in our series (1 N0, 1 N2b and 1 N3). In order to obtain an early diagnosis, a careful clinical and radiological evaluation is required once the treatment has been completed, with a computed tomography (CT) scan being recommended at 8 weeks.\textsuperscript{29} The radiological signs of tumoural progression or persistence include: lymphadenopathy >1.5 cm, extracapsular extension and calcifications.\textsuperscript{30} Another alternative when there are doubts concerning complete tumoural eradication is the performance of a PET-CT scan 12 weeks after the treatment,\textsuperscript{31} especially since cervical rescue surgery can increase survival rates, as observed in 2 patients in our series.

The second aspect analysed in our study was related to functional alterations caused by the therapeutic modalities, surgery and Rt in the studied groups. Some authors have observed that side effects are frequent with Rt/RCT and may cause delays in completing the total Rt dose or dropouts in treatment.\textsuperscript{32} In our series, the RtG showed grade III–IV mucositis in 70% of cases, while 30% suffered radiodermatitis of similar grade. These toxic effects of Rt delayed treatment and led to nasogastric tube feeding in some patients, but they did not cause any dropouts.

There is clinical controversy regarding which treatment modality offers better functional results and quality of life. Mowry et al.\textsuperscript{33} did not observe any significant differences in quality of life when comparing patients with
oropharyngeal tumours treated by RCT vs surgery plus complementary RT. Other authors have reported differences in favour of RT in domains related to swallowing and ability to speak and work.34 Our functional results were also in this line, since we achieved laryngeal preservation in all cases and function was maintained in 90%, superior figures to those obtained in the SG.

The ability to feed orally in the RTG was preserved in 100% of patients without recurrence and in 82% of the group total. These figures were somewhat lower than those obtained in the SG (96%). The fundamental cause of this failure, as previously noted, was failure in local tumour control.

In conclusion, we can say that the treatment of oropharyngeal squamous cell carcinomas in early stages through RT with curative intent obtains good functional and oncological results, comparable to those achieved through surgery. Oncological results in advanced stages are poor and inferior to those obtained through surgery (plus complementary RT), especially if RT is not accompanied by concomitant Ct, with decreased locoregional tumour control. The functional results were similar for both treatment modalities, although somewhat better in the radiotherapy group when tumour control was achieved.

Conflict of Interests
The authors have no conflict of interests to declare.

References


