

# Review Article

## Salvage Surgery for Recurrent Oral and Oropharyngeal Carcinoma

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### Abstract

Local and regional recurrences are the main sites of treatment failure in patients with oral and oropharyngeal squamous cell carcinoma. Treatment failure depends fundamentally on tumor biologic behavior, previous treatment and the initial clinical stage. The rates of loco-regional recurrences range from 25 to 48%, and distant metastasis rarely occur in an isolated manner. When recurrent cancer is significant and there are no distant metastasis salvage surgery is the most widely used treatment approach. Most of these patients were previously treated with radiotherapy. Therefore, when recurrence occurs, salvage surgery is the only possible treatment option with curative intent. The aim of this study was to review the data in the literature regarding results of salvage surgical treatment for patients with recurrent oral and oropharyngeal carcinomas.

**Key Words:** Salvage surgery. Mouth neoplasms. Oropharynx neoplasms.

### Introduction

Carcinomas of the oral cavity and oropharynx are the neoplasias of the upper airways and digestive tract with the highest rates of incidence in Brazil.<sup>1-2</sup> These tumors are usually present in advanced clinical stages<sup>3-4</sup> and are associated with high rates of loco-regional recurrences.<sup>5</sup>

The most used treatment for advanced cancer of the oral cavity, when it is resectable, is radical surgery associated with radiotherapy, which may be associated with chemotherapy for patients with a high risk for recurrences.<sup>6-7</sup> For carcinomas of the oropharynx, the present trend in the literature is the use of radiotherapy and chemotherapy, usually concomitant.<sup>8</sup> Treatment failure depends fundamentally on tumor biologic behavior, therapy previously used and the initial clinical stage. The rates of loco-regional recurrences range from 25 to 48%, and distant metastasis rarely occur in an isolated manner.<sup>5</sup>

Most of the patients with recurrent disease were treated with radiotherapy in the first approach, either as an exclusive treatment for the tumors in early clinical stages (CS I or II) or as part of the treatment of those with clinical stages III or IV. Therefore, when recurrence occurs, salvage surgery is generally the only possible treatment option with curative intent,<sup>9-10</sup> since in the majority of cases it is not possible to use a new course of radiotherapy. When technically feasible, re-irradiation is an option, but it is associated with modest survival results and loco-regional control,<sup>11-12</sup> and high rates of complications.<sup>13</sup> Systemic chemotherapy is generally

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considered a palliative treatment for these patients.<sup>14</sup>

The aim of this article was to review the data in the literature with regard to the long term results of salvage surgery for patients with recurrent carcinomas of the oral cavity and oropharynx.

## **The rationale for the indication of salvage treatment for recurrent oral and oropharyngeal squamous cell carcinoma**

The majority of recurrences of oral cavity and oropharynx squamous cell carcinoma (SCC) occur at the site of the primary tumor or in the neck nodes; distant metastases are not frequent. Carvalho et al.<sup>5</sup> evaluated the results of treatment of 2,067 patients with carcinomas of the oral cavity or oropharynx. The overall recurrence rate observed by the authors was 52.2%, and in 27.1% of the cases recurrence was local, in 8.1% in the neck and in 12.2% it was loco-regional. Recurrence presented as distant metastasis was seen in only 4.8% of patients.

This low rate of distant metastasis was confirmed by Kowalski et al.<sup>15</sup> in a study in which 513 patients with diagnosis of SCC of the oral cavity were analyzed. These patients were submitted to surgical treatment, in some cases associated with adjuvant radiotherapy, and in only 2.9% of the cases the location of recurrence was isolated distant metastasis. Other authors presented similar results with regard to the pattern of recurrence after radical treatment of these neoplasias.<sup>16-17</sup>

The biologic behavior of these neoplasias, which are rarely associated with distant metastases, justifies the indication of surgery with curative intent for recurrent carcinomas of the oral cavity and oropharynx, provided the patient presents clinical conditions to be submitted to the procedure and the tumor is resectable. The morbidity of these surgical procedures is acceptable.<sup>18</sup>

## **Survival results reported in the literature justify the indication of salvage surgery**

Survival rates of patients submitted to salvage surgery for carcinomas of the mouth and oropharynx, published in the literature, range from 9% to 59.7% in 5 years,<sup>19-23</sup> including all clinical stages. Yuen et al.<sup>22</sup> reported an experience with 32 patients with oral squamous cell carcinomas of the tongue, with local recurrences

after surgical treatment. In 11 patients (34.0%) it was possible to indicate salvage surgery. The overall survival after 5 years was 9.0% and only 1 patient was alive and disease free at the end of the follow up. Cherian et al.<sup>24</sup> evaluated 78 patients with recurrent buccal mucosa SCC after radiotherapy submitted to salvage surgery. In this study the overall actuarial survival in 5 years was 59.7%. The high survival rate could be associated with the possibility of performing a second salvage surgery in 36% of the patients. In another study that evaluated 50 patients with tonsil carcinoma at clinical stages III and IV with recurrence after radiotherapy, submitted to salvage surgery, the authors reported an overall survival of 24.0% in 5 years.<sup>21</sup>

In a literature review, Goodwin Jr.<sup>25</sup> assessed survival rates in patients submitted to salvage surgery for recurrent SCC of the upper aerodigestive tracts (all sites). In this study, 1,633 patients were included, compiled from 32 studies published in English language literature, and in 99% of the cases the previous treatment was radiotherapy alone or associated with chemotherapy. The overall survival rate in 3 years was 43% for cancer of the oral cavity and 26% for carcinoma of the oropharynx.

The experience of the Departamento de Cirurgia de Cabeça e Pescoço e Otorrinolaringologia (Department of Head and Neck and Otorhinolaryngology) of Hospital A.C. Camargo was recently analyzed. The charts of 246 patients with carcinomas of the oral cavity and oropharynx, with proven histologic diagnosis of recurrent squamous cell carcinoma (SCC), submitted to salvage surgery with curative intent from 1985 and 1999, were reviewed, and patients with local, regional and loco-regional recurrences were included. One hundred and fifty-four patients presented local recurrences (62.6%), while 59 presented regional recurrences (24%) and 33 patients (13.4%) presented loco-regional recurrences. Overall survival was 32% in 5 years. Patients with carcinomas of the oral cavity had an actuarial survival in 5 years of 34%. For patients with carcinomas of the oropharynx, the survival rate was 26%, while those with lip carcinomas presented the best survival in 5 years (42%). However, these differences were not statistically significant. In this study, the type of recurrence did not influence the prognosis. When the recurrence was local, the overall survival in 5 years was 30.5%, in cases of nodal recurrence it was 24.1%, and in the cases of loco-regional recurrence it was 35.9%. In spite of the worse survival in cases with nodal recurrence, this difference was not statistically significant.<sup>10</sup>

## Prognostic factors associated with recurrent oral squamous cell carcinomas

In a series of 246 cases treated at the Hospital A.C. Camargo, the significant clinical variables for defining prognosis in multivariate analyses were the clinical stage of the recurrence (rTNM) and disease-free interval. Patients that presented recurrences in the initial clinical stages (rCS I and II) had a 5 years survival of 43.6%, while those with more advanced clinical stages (rCS III and IV) presented a rate of 29.1%<sup>10</sup>.

TNM staging remains the main predictor of prognosis in squamous cell carcinomas of the oral cavity and oropharynx. The staging of the recurrent tumor follows the same criteria used for the primary lesion with the prefix "r" preceding the clinical stage (for example rCS I). However, the staging of recurrent tumors has not been used in a routine manner and only few authors use this classification when presenting their results with salvage surgery. In the literature review conducted by Goodwin Jr.<sup>25</sup> it was not possible to assess the impact of restaging on prognosis, because this datum were not part of the majority of the authors' reports. Nevertheless, the same author in a series of 109 patients, evaluated prospectively, including tumors of the oral cavity, pharynx and larynx, verified that the clinical stage of the recurrence was the main predictive factor of survival.

Schwartz et al.<sup>26</sup> presented an experience with 38 patients with recurrent SCC in the oral cavity from which twenty-six patients (71.1%) were submitted to salvage surgery. The overall survival of the patients was not influenced by the clinical stage of recurrence. The authors attribute this result to the small number of cases studied, an also to the fact that survival analysis did not discriminate between the groups of salvage surgery and other forms of salvage treatment. On the other hand, Davidson et al.<sup>27</sup>, in a study evaluating recurrent carcinomas of the larynx and hypopharynx submitted to salvage surgery observed that the clinical stage of recurrence had a significant impact on prognosis.

The disease-free interval was another clinical variable predictive of prognosis in our own series. Patients with early recurrences (< 1 year) presented a worse prognosis, with overall survival in 5 years of 26.7%, while those with late recurrences (> 1 year) presented survival of 42.1%.<sup>10</sup> The short disease-free interval (early recurrence) was associated with the worst prognosis. Early recurrence can occur as a result of an unfavorable biology of the tumor, or due to inadequate previous treatment. Disease-free survival is recognized as a prognostic factor for some

recurrent neoplasias, such as colorectal carcinoma, and frequently, this variable is decisive in the therapeutic decision for these tumors.<sup>28</sup>

Only a few authors studied disease-free interval as a prognostic factor in SCC of the upper airways and digestive tracts. Llewelyn et al.<sup>29</sup> studied 58 patients submitted to salvage surgery for squamous cell carcinoma of the oral cavity and found a direct relationship between disease-free interval and survival; as the disease-free interval increased, there was an improvement in prognosis. Stell<sup>30</sup> also studied the association of disease-free interval with prognosis in a series of 515 patients presenting recurrent SCC of the upper aerodigestive tracts, after treatment with radiotherapy alone. In 168 cases the tumor was located in the mouth or oropharynx. The author divided his casuistic by the median of the disease-free interval, which was 36 weeks. The patients that presented recurrence after an interval longer than 36 weeks had a better prognosis, with an overall survival in five years of 20%, higher than those with a median of follow-up of less than 36 weeks. This observation was not confirmed by Goodwin Jr.,<sup>25</sup> who did not identify disease-free interval as a predictive factor of survival.

## Biologic markers and the therapeutic decision among patients with recurrent oral carcinomas

In a study by the Departamento de Cirurgia de Cabeça e Pescoço e Otorrinolaringologia of Hospital A.C. Camargo, the charts of 111 patients with local recurrent squamous cell carcinomas of the oral cavity and oropharynx submitted to salvage surgery were reviewed with the objective of evaluating the expression of proteins associated with the development of these tumors and their relationship with prognosis.<sup>31</sup> The proteins evaluated were EGFR (epidermal growth factor receptor), Metalloproteinases 2 and 9 (MMP2 and MMP9) and VEGF (vascular endothelial growth factor).

EGFR over-expression was associated with the worst result of the treatment. The patients with EGFR positive status had a cancer-specific survival in 3 years of 27%, while patients with negative status attained 64% survival in 3 years. MMP-2, MMP-9 and VEGF overexpression also presented association with prognosis; patients in whom these proteins were overexpressed had the worst survival results. Nevertheless, these differences did not attain statistical significance. In multivariate

analysis, EGFR overexpression was maintained as a significant variable for prognosis, being associated with an increase of up to 4.2 times in the risk of recurrence and death.<sup>31</sup>

Ang et al.,<sup>32</sup> assessed the influence of the immunohistochemical expression of EGFR in patients with carcinomas of the head and neck, treated with radiotherapy, as part of a Phase III study conducted by the RTOG (Radiation Therapy Oncology Group). One hundred and fifty-five patients with tumors of the oral cavity, oropharynx, hypopharynx and larynx were assessed. The high expression of EGFR was associated with the worst overall survival and disease-free survival results, in addition to the worst result in loco-regional control. In multivariate analysis the high expression of this receptor was a significant independent prognostic factor.

Chen et al.<sup>33</sup> studied the expression of EGFR and its relationship with the prognosis in a sample of 59 patients with SCC of the oral cavity, treated by surgery associated with radiotherapy for cases considered at higher risk for recurrence. EGFR overexpression was associated with the worst overall survival rates in univariate and multivariate analyses. In this study a direct relationship between overexpression of EGFR and clinical parameters such as T and N stages and presence of extracapsular spread was also verified. Demiral et al.<sup>34</sup> also demonstrated an association between the expression of EGFR and worse prognosis for patients with SCC of the larynx.

The worst prognosis of patients with SCC of the head and neck with a high expression of EGFR may be related to resistance to the treatment with radiotherapy. Based on this hypothesis, a Phase III study was conducted comparing exclusive radiotherapy (RT) and RT associated with an anti-EGFR antibody, cetuximab, for patients with SCC of the oropharynx, larynx or hypopharynx at clinical stages III or IV.<sup>35</sup> Immunohistochemistry showed the profile of EGFR expression to be similar in the two groups. There was better loco-regional control, better disease progression-free survival and better overall survival for patients of the study arm under investigation (association of radiotherapy with cetuximab).<sup>35</sup>

## Conclusion

Patients presenting loco-regional recurrences of squamous cell carcinomas of the oral cavity and oropharynx are candidates for salvage treatment provided they present favorable clinical conditions. For patients in whom surgery is possible, that is, who present resectable

tumors, salvage surgery is the best therapeutic option. The main clinical prognostic factors are disease-free interval and clinical re-staging. The expression of EGFR has recently been shown to be an important prognostic factor. Overexpression of this protein seems to be a prognostic factor as important as the clinical variables, and could become a valuable tool for therapeutic decision. Furthermore, there is the possibility of anti-EGFR drugs being used in clinical trials with the intention of improving survival results of patients submitted to salvage surgery.

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