Salvage treatment for oropharyngeal squamous cell carcinoma

Original Article

Authors

Joselina Antunes
Serviço de Otorrinolaringologia, Hospital Prof. Dr. Fernando Fonseca

Pedro Alexandre
Serviço de Otorrinolaringologia, Centro Hospitalar Universitário de São João, Portugal

Luís Rodrigues
Serviço de Otorrinolaringologia, Hospital Beatriz Ângelo, Portugal

Sara Ramalho
Serviço de Otorrinolaringologia, Instituto Português de Oncologia de Lisboa, Portugal

Pedro Montalvão
Serviço de Otorrinolaringologia, Instituto Português de Oncologia de Lisboa, Portugal

Miguel Magalhães
Serviço de Otorrinolaringologia, Instituto Português de Oncologia de Lisboa, Portugal

Correspondence:
Joselina Antunes
joselinarant@gmail.com

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Abstract

Objectives: Evaluate salvage surgery efficiency for treatment of residual/recurrent oropharyngeal squamous cell carcinoma after radiotherapy or chemorradiotherapy.
Methods: Retrospective study that included patients followed at Instituto Português de Oncologia de Lisboa Francisco Gentil, between 2010 and 2021. The study included 160 patients with diagnosis of squamous cell carcinoma of oropharynx, from which 44 patients with diagnosis of residual/recurrent tumor were selected.
Results: Diagnosis of residual/recurrent disease was made in 27,5% of the population initially selected. Between the ones that had local residual/recurrent disease, 8 patients (53,3%) were submitted to surgery, with a three-year overall survival of 50,0%, and the remaining 7 patients did not have favorable surgical conditions.
Conclusions: Salvage surgery for treatment of residual/recurrent oropharyngeal squamous cell carcinoma is one of the available treatments with best survival rates. Despite the aforementioned, survival rates are limited and depend on surgical margins, so this kind of treatment should be carefully considered.

Keywords: Squamous cell carcinoma; Oropharyngeal neoplasms; Salvage therapy; Recurrence

Introduction

Squamous cell carcinoma (SCC) of the upper aerodigestive tract is strongly associated with smoking and drinking habits. In the last few decades, changes in the relative prevalence of various types of SCC have been observed, with an increase in SCC of the oropharynx and decrease in SCC of the hypopharynx and larynx[1]. These changes have been correlated with a decline in the consumption of alcohol and tobacco—risk factors for laryngopharyngeal SCC—and the identification of exposure to human papillomavirus (HPV) of high oncogenic risk as a risk factor for SCC of the oropharynx[1,2].

The treatment of early-stage head and neck SCC of CPC is usually unimodal through surgery or radiotherapy (RT). However, when the tumor is diagnosed at a more advanced stage, it is often treated in a multimodal manner through surgery and adjuvant RT or chemoradiotherapy (CRT)[1]. Surgical treatment of oropharyngeal SCC, especially when extensive resection is necessary, may be associated with dysphagia and/or speech impairments that have a significant impact on the quality of life. In the last few decades, the treatment of SCC of the oropharynx using CRT has reduced the need for oropharyngeal resection and subsequent morbidity associated with this procedure[3,4]. Thus, the treatment of oropharyngeal SCC with RT or CRT has replaced surgery as the preferred primary treatment method, particularly when it is not possible to achieve free margins with low morbidity, although surgery remains a salvage treatment option[3,5,6].

Although the conservative treatment of oropharyngeal SCC has good survival rates and good functional results, it is associated with local or regional relapse in 9–20% of cases and distant metastasis in 7–10% of cases[7,8]. Despite the therapeutic limitations in the case of distant relapse, salvage surgery is a viable option when relapse occurs at the local or regional level[8]. Cervical lymph node excision in regional relapse after RT or CRT is frequently an effective treatment option and has good survival rates[3]. However, the use of salvage surgery for local relapse is an option in only 20–30% of patients[4].

The main salvage treatment options for this entity are surgery, re-irradiation, or palliative treatment[4]. The use of re-irradiation in selected patients may provide prolonged local control of the disease or even cure. However, this treatment should be carefully considered because it is associated with significant morbimortality—xerostomia, mucosa or skin ulcerations, trismus, dysphagia, myelopathy, osteoradionecrosis, and carotid blowout syndrome[9]. Salvage surgery for oropharyngeal SCC is usually complicated by sequelae from previous treatments. After RT, the ability of tissues to heal is usually diminished, and multifocal relapses can still be observed in the irradiated tissue, which hinders total resection. After chemotherapy (CT), the overall condition of the patients is usually worse, which leads to salvage surgery being more frequently associated with complications, a longer postoperative hospital stay, and a higher likelihood of dysfunction due to total or partial removal of the organ (dysphagia and dyspnea)[4]. Nevertheless, salvage surgery is the only curative option, and survival is reasonable compared to alternative treatments[4,10].

The primary treatment of HPV-associated oropharyngeal SCC is associated with a better prognosis[1,11]. However, up to 25% of patients treated with RT (combined with CT [RT±CT] or not) end up relapsing within the first five years after treatment[11]. Unlike with primary treatment, the association with HPV does not appear to affect the efficacy of salvage treatment of oropharyngeal SCC[3,11].

This study aimed to assess, in a population with a diagnosis of oropharyngeal SCC, the prevalence of disease persistence or relapse after primary treatment and compare the demographic, clinical, and overall survival data among the salvage treatments.

Materials and Methods

This was a retrospective observational study that included patients followed in the outpatient clinic of the Instituto Português de Oncologia de Lisboa Francisco Gentil (IPO-LFG) between 2006 and 2021.

To select patients for this study, a search was performed in the database of the otorhinolaryngology (ORL) department of IPO-LGF, which includes ORL outpatients. Patient selection criteria were used sequentially: histological diagnosis of oropharyngeal SCC, non-surgical primary treatment, and disease persistence or relapse. All patients met the following inclusion criteria: diagnosis of oropharyngeal SCC was made by biopsy, whose histology was assessed or reviewed at the IPO-LFG between 2006 and 2018;

regular follow-up with documentation of the ORL objective examination in the outpatient ORL consultation at IPO-LFG; persistence or relapse of the disease as confirmed by biopsy with histopathological analysis performed at IPO-LFG; follow-up of at least 60 months. Initially, 160 patients diagnosed with oropharyngeal SCC were selected, treated primarily with RT or CRT and with no evidence of synchronous tumor. Of these, 44 had persistent or relapsing disease, as confirmed by biopsy with histopathological evaluation. Patients with synchronous tumors, those with biopsy slides reviewed at IPO-LFG and given a diagnosis different from SCC, those who refused treatment, or those who were lost to follow-up were excluded.

Tumor persistence (residual tumor) was considered when disease was present up to six months after the end of the primary treatment. Tumor relapse was considered when the disease appeared more than six months after the end of the primary treatment.

The decision regarding which modality of salvage treatment was suitable to use in each individual patient was made in a multidisciplinary meeting of histopathology, imaging, medical oncology, ORL, and radiotherapy specialties. Patients were referred for surgical treatment when the tumor was deemed resectable; otherwise, they were offered treatment with CT, with or without re-irradiation. Tumor unresectability is usually associated with the T4b stage (involvement of the pterygoid muscles or skull base, extension to the lateral walls of the nasopharynx, or looping of the internal carotid artery) and, in cervical tumors, with direct invasion of the skin, mediastinal structures, prevertebral fascia, or cervical disks and the presence of subdermal metastases. None of these situations is an absolute contraindication to surgical resection in selected patients in whom negative margins can be obtained[12].

Statistical analysis was performed using SPSS software version 26.0 (International Business Machines Corporation, US). The results were expressed as medians (25^{th}–75^{th} percentiles). The Mann-Whitney and Fisher tests were used to compare the groups. The level of statistical significance was set at $p<0.05$.

Results

Initially, 160 patients diagnosed with oropharyngeal SCC who underwent primary non-surgical treatment (CRT in 53.4%, RT in 28.6%, and induction CT followed by CRT in 18.0%) were selected. The median dose of radiation used in RT was 69.96 Gy (69.9–70.0). The demographic data, location and cT, cN, and cM staging of the primary tumor, and primary treatment used in the sample of 160 patients are shown in Table 1[12].

Disease persistence or relapse occurred in 44 patients or 27.5% of the initially selected sample. Disease persistence occurred in 17 patients, and the median time to its diagnosis was 4.3 months (3.6 to 5.5). Relapse occurred in the remaining 27 patients, and the median time to its diagnosis was 8.8 months (6.9 to 12.9). The clinical outcomes of the 160 patients are shown in Image 1.

Persistence or relapse of oropharyngeal SCC was diagnosed locally in 15/160 patients (9.4%), regionally in 32/160 patients (20.0%), and in distant organs in 5/160 patients (3.1%). Persistence or relapse were diagnosed concomitantly at the local and regional levels in four patients, at the local and distant levels in one patient, at the regional and distant levels in one patient, and at all three levels in one patient.

The 44 patients diagnosed with persistent or relapsing oropharyngeal SCC (27.5%) included 42 men (95.5%) and 2 women, and the median age was 59.0 years (52.3 to 65.8). The selected primary treatment was CRT in 47.7% of patients, RT in 25.0%, and CT followed by CRT in 27.3%. The stage of locally persistent or relapsing disease (n=15) was cT1 in 26.7% of patients, cT2 in 13.2%, cT3 in 26.7%, and cT4 in 33.4%. The stage of regionally persistent or relapsing disease (n=32) was cN1 in 59.3%, cN2 in 28.2%, and cN3 in 12.5% patients. The p16 status for the proportion of patients with disease persistence or relapse was unknown

Table 1
Demographic data, location, and cT, cN, and cM staging of the primary tumor, and primary treatment used in the sample of 160 patients diagnosed with oropharyngeal SCC

Variable	Percentage of the total (%)	Median (percentiles 25–75)
Age (years)	-	58,0 (53,0-65,0)
Sex		
Female (%)	13,8	-
Male (%)	86,2	-
Habits		
Tobacco use (%)	86,7	-
Alcohol use (%)	75,6	-
Smoking load (pack-years)	-	40,0 (30,0-61,5)
Location of primary tumor		
Palatine tonsil (%)	47,2	-
Soft palate (%)	15,5	-
Palatine tonsil+ Soft palate (%)	27,3	-
Palatine tonsil +Base of tongue (%)	4,3	-
Lateral wall of the oropharynx (%)	3,1	-
Posterior wall of the oropharynx (%)	2,5	-
T classification		
cT1 (%)	5,7	-
cT2 (%)	22,2	-
cT3 (%)	32,9	-
cT4 (%)	39,2	-
N classification		
cN0 (%)	24,1	-
cN1 (%)	13,3	-
cN2 (%)	46,2	-
cN3 (%)	16,5	-
M classification		
cM0 (%)	100,0	-
Primary treatment		
RT (%)	28,6	-
CRT (%)	53,4	-
CT+CRT (%)	18,0	-

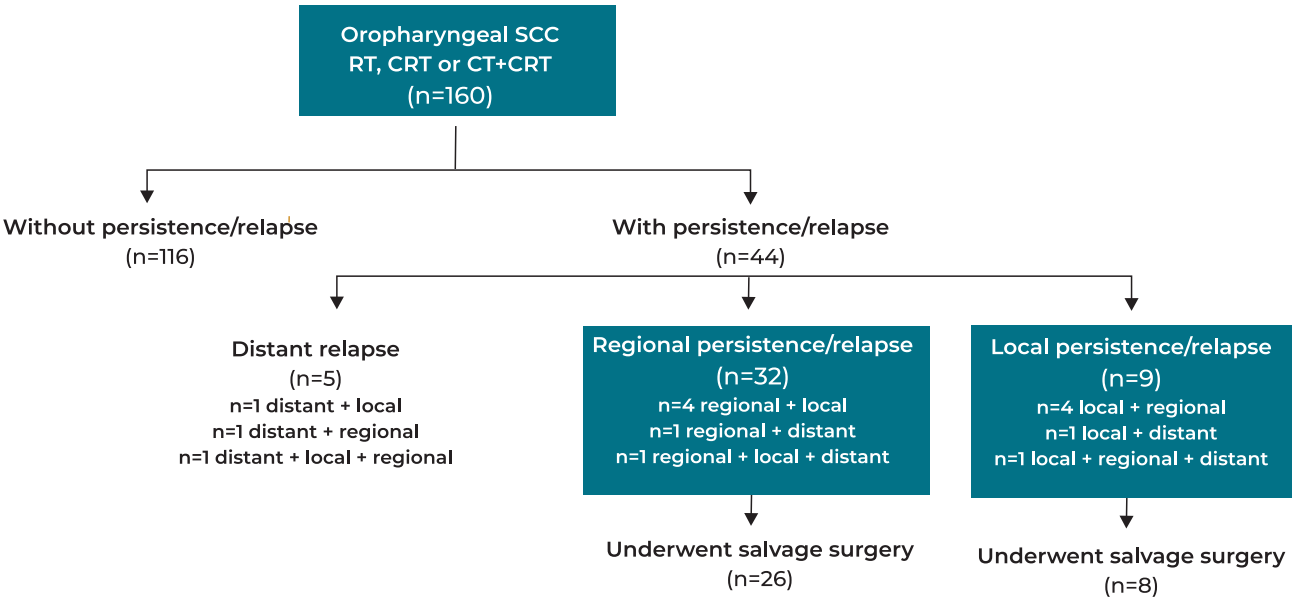
Abbreviations: RT, radiotherapy; CRT, chemoradiotherapy; CT, chemotherapy; SCC, squamous cell carcinoma

in 61.4%, negative in 25.0%, and positive in 13.6%. The demographic data, location of the primary tumor, and primary treatment used in patients with and without disease persistence or relapse are shown in Table 2.

There were no statistically significant differences in the analyzed data between patients with and without disease persistence or relapse.

Among the 15 patients who had local disease persistence or relapse, eight (53.3%) underwent surgery with curative intent. Tumor location and the surgical procedure are described in Table 3. The 3- and 5-year overall survival rates of this population were 50.0% and 25.0% respectively. The other seven patients were not considered candidates for curative treatment through surgery because four of them had locally advanced disease, which was deemed unresectable, two of them had concomitant distant disease relapse, and another had unresectable lymph node disease. As such, this group of patients was referred for palliative treatment with CT with or without re-irradiation. Survival at 3 and 5 years in this group was 0.0%. Figures 2 and

Image 1
Clinical outcomes of patients diagnosed with oropharyngeal SCC who underwent conservative primary treatment



Abbreviations: RT, radiotherapy; CRT, chemoradiotherapy; CT, chemotherapy; SCC, squamous cell carcinoma.

Table 2
Demographic data, location of the primary tumor, and primary treatment used in patients with and without disease persistence or relapse

Variable	Without persistence/ relapse (n=116)	With persistence/ relapse (n=44)	p-value
Age (years)	58,0 (53,0-65,0)	59,0 (52,3-65,8)	0,734
Sex			
Female (%)	16,2	4,5	0,099
Male (%)	83,9	95,5	
Location of the primary tumor			
Palatine tonsil (%)	45,1	53,8	
Soft palate (%)	13,9	20,5	
Palatine tonsil+Soft palate (%)	27,9	25,6	0,088
Palatine tonsil+Base of tongue (%)	5,7	0	
Lateral wall of the oropharynx (%)	4,1	0	
Posterior wall of the oropharynx (%)	3,3	0	
Primary treatment			
RT (%)	31,1	25,0	0,071
CRT (%)	54,9	47,7	
CT+CRT (%)	13,9	27,3	

Abbreviations: RT, radiotherapy; CRT, chemoradiotherapy; CT, chemotherapy.

3 show the survival curves at 3 and 5 years, respectively, of patients with locally persistent or relapsing disease, according to whether the patients underwent surgery or CT with or without re-irradiation.

In the group of patients with regional persistent or relapsing disease (n=32), 26 patients were referred for cervical lymph node excision (81.3%). The 3- and 5-year overall survival rates in this group were 73.1% and 61.5%, respectively. Among the six remaining patients, four were diagnosed with unresectable regional disease, and the other two had concomitant distant disease and were not considered candidates for curative treatment with surgery. Thus, this group of patients was referred for treatment

Table 3
Location of the locally persistent or relapsing tumor and the surgical procedure performed in the subgroup of patients with locally persistent or relapsing disease who were referred for surgical treatment (n=8)

Number of patients (Total=8)	Tumor location	Surgical procedure
3	Lateral wall of the pharynx	Partial pharyngectomy
2	Tonsil	Transmandibular buccopharyngectomy
1	Base of the tongue with extension to the hypopharynx	Total glossectomy + total laryngectomy
1	Posterior wall of the oropharynx	Partial pharyngectomy
1	Masticator space with invasion of the mandible	Segmental hemimandibulectomy via external route

Images 2 and 3
Overall survival at 3 and 5 years, respectively, of patients with locally persistent or relapsing disease, according to whether they underwent surgical treatment or treatment with chemotherapy (CT) with or without radiotherapy (RT)

Image 2

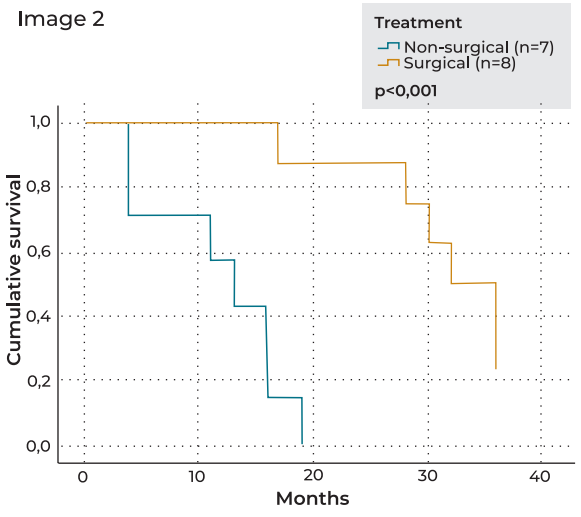
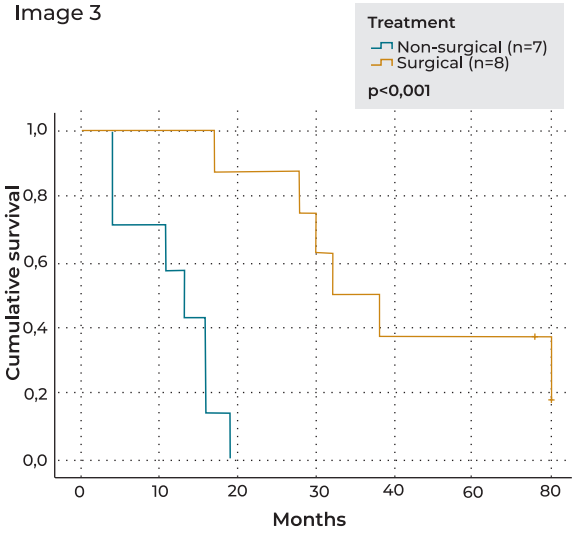


Image 3



Images 4 and 5
Overall survival at 3 and 5 years, respectively, of patients with regionally persistent or relapsing disease, according to whether they underwent surgical treatment or treatment with chemotherapy (CT) with or without radiotherapy (RT)

Image 4

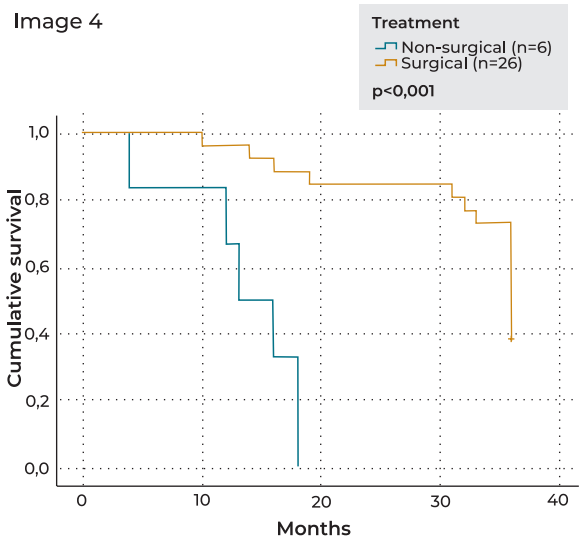
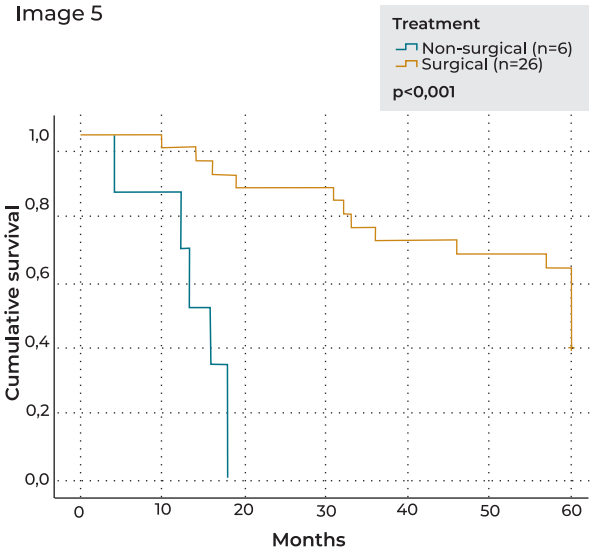


Image 5



with CT alone or combined with re-irradiation, and the 3- and 5-year survival rate was 0.0%. Figures 4 and 5 show the survival curves at 3 and 5 years of patients with regionally persistent or relapsing disease, according to whether the patients underwent surgery or CT with or without re-irradiation.

Discussion

Local relapse or persistence of oropharyngeal SCC after primary treatment is associated with mortality and pain, obstruction of the airways, and dysphagia, which can lead to a significant loss of quality of life for the patient[3]. Salvage surgery for the treatment of oropharyngeal SCC that persists or relapses after primary treatment with RT or CRT has been gaining importance, given the increasing use of conservative treatment for this type of cancer[3]. Omura et al. described the persistence or relapse of SCC of the oropharynx after RT or CRT in 39 of 98 patients (39.8%), at the local, regional, and distant levels in 23.5%, 7.1%, and 9.2% of patients, respectively[3]. The results of this study are similar to those obtained by these authors and others because disease persistence or relapse was found in 27.5% of the patients, at the local, regional, and distant levels in 9.4%, 20.0%, and 3.1% of patients, respectively[3,4].

Surgical treatment of regionally persistent or relapsing disease is more feasible than that of locally persistent or relapsing disease, and its survival rates are also acceptable[3]. Surgical treatment of locally persistent or relapsing disease is more difficult—the achievement of negative margins due to the adjacent critical structures such as the internal carotid artery or the base of the skull[3]. This is in line with the findings of this study, in which the tumor was resectable in 53.3% of locally persistent or relapsing cases and 81.3% of the regionally persistent or relapsing cases. Additionally, the overall survival rates at 3 and 5 years after surgical treatment were 50.0% and 25.0% in patients with local persistence or relapse and 73.1% and 61.5% in patients with regional persistence or relapse, respectively.

Several authors have reported 3- and 5-year overall survival rates of 42% and 21%, respectively, after salvage surgery in patients with persistent or relapsing oropharyngeal SCC[3,8,13]. In this study, the overall survival rates at 3 and 5 years after salvage surgery for SCC of the oropharynx were 50.0% and 25.0% respectively, which is concurrent with the results of previous studies[3,8,13].

Salvage surgery is associated with a higher risk of postoperative complications because previous RT affects surgical wound healing, with an increase in the risk of wound dehiscence or infection. As these patients potentially exhibit sequelae from the primary treatment, even if total resection of the oropharyngeal tumor is achieved, the function of the partially or totally excised organ may be compromised[3,14,15]. Therefore, the usefulness of salvage surgery should be carefully considered, especially in cases of local persistence or relapse by weighing the benefits versus risks. Although we tried to evaluate the postoperative complications of salvage surgery in this study, the unavailability of relevant data for most of the patients limited our analysis.

The 3- and 5-year overall survival rates were higher in the group that underwent salvage surgery for locally or regionally persistent or relapsing disease than in the alternative treatments groups. Palliative treatments such as re-irradiation or systemic CT have been shown to be of limited use, with low survival rates and high rates of acute and late toxicity[3]. CT regimens can be used for palliative treatment because they are not usually associated with complete cure or long-term control of the disease[3]. Several authors state that salvage surgery is the best therapeutic strategy for persistent or relapsing oropharyngeal SCC if the tumor is resectable, and it is the only treatment with curative intent[3,4,10].

Although we tried to include the analysis of p16 in this study, several factors limited its use—the fact that the data were not available for all patients included in the study. Moreover, most patients had significant tobacco and/or alcohol

use habits, which hindered the formation of two groups with distinct risk factors. Furthermore, most patients with disease relapse and known p16 status were negative for the protein. Locoregional relapse occurs less frequently in patients with p16-positive oropharyngeal SCC, which limits the number of patients that can be included in studies to assess the treatment of persistent or relapsed p16-positive SCC. HPV plays an important role in the prognosis of SCC of the oropharynx when considering the primary treatment but does not appear to have the same prognostic impact on the salvage treatment of persistent or relapsing disease[3,11,16]. Another important limitation of this study was the small sample size—the number of patients with local disease relapse/persistence who underwent surgery (n=8). This group of patients exhibited different tumor locations and stages, which may also have influenced survival.

Conclusion

The prognosis of patients with local persistence or relapse of oropharyngeal SCC after non-surgical primary treatment is poor. The indication for salvage surgery in these patients should be carefully considered because of the low associated survival, likelihood of postoperative complications, and potential subsequent comorbidities with an impact on the quality of life. However, this treatment modality leads to better survival results and should be chosen if the tumor is resectable.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Data Confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

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Availability of scientific data

There are no datasets available, publicly related to this work.

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