

## Original

# Management of advanced recurrent oral squamous cell carcinoma: is still salvage surgery indicated?

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### A B S T R A C T

**Introduction:** Locoregional recurrent disease (LRD) represents the most common cause of mortality in patients with oral squamous cell carcinoma (OSCC). Salvage surgery has been reported as the primary option for these patients. However, some groups have proposed it may be considered as therapeutic obstinacy, specially in advanced stages. This study wants to determine if salvage surgery is the most suitable treatment for LRD in advanced OSCC.

**Patients and methods:** A retrospective cohorts study was designed including patients diagnosed with recurrent OSCC between May 2012 and December 2015 (n = 32). Patients were divided in two groups depending on whether salvage surgery was performed or not. Patients were followed-up for five years.

**Results:** No differences were found between both groups according to sex, age, Charlson comorbidity index, initial TNM, stage, localization and treatment, recurrent TNM, stage and localization or time until recurrence. Statistically significant differences ( $p < 0.001$ ) were found in disease free survival and overall survival between both groups, even when stratified in early and advanced stages.

**Discussion and conclusion:** According to our results, salvage surgery provides both disease free survival and overall survival to patients with recurrent oral squamous cell carcinoma, even in advanced stages. However, it is true that salvage surgery is very likely to produce important comorbidities. We consider that these results should be explained to the patient in a comprehensive and compassionate talk and he or she should decide whether to go through this process or not.

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## Manejo del carcinoma de células escamosas recurrente en estadios avanzados en cavidad oral: ¿está la cirugía de rescate todavía indicada?

### R E S U M E N

#### Palabras clave:

Cáncer oral, carcinoma oral de células escamosas, recidiva, cirugía de rescate, obstinación terapéutica, cáncer de cabeza y cuello.

**Introducción:** La enfermedad recurrente locorregional representa la principal causa de mortalidad en pacientes con carcinoma oral de células escamosas. La cirugía de rescate ha sido la principal opción para estos pacientes. Sin embargo, algunos grupos han propuesto que pudiera ser considerada como obstinación terapéutica, especialmente en estadios avanzados. Este estudio quiere determinar si la cirugía de rescate es el tratamiento más indicado para el tratamiento de la enfermedad recurrente en estadios avanzados de carcinoma de células escamosas en cavidad oral.

**Pacientes y métodos:** Se diseñó un estudio retrospectivo de cohortes, incluyendo pacientes diagnosticados de carcinoma epidermoide recurrente de cavidad oral entre mayo de 2012 y diciembre de 2015 (n = 32). Se dividieron a los pacientes en dos grupos en función de si se había realizado cirugía de rescate o no, y fueron seguidos durante cinco años.

**Resultados:** No se encontraron diferencias estadísticamente significativas entre los grupos por sexo, edad, el índice de comorbilidad de Charlson, el TNM o estadio inicial, localización inicial, tratamiento realizado inicial, TNM o estadio de la recurrencia, localización de la recurrencia o tiempo hasta la recurrencia. Se encontraron diferencias estadísticamente significativas ( $p < 0,001$ ) en el tiempo libre de enfermedad y tiempo de supervivencia entre los grupos, también al estratificarlos por estadios iniciales o avanzados.

**Discusión:** Según nuestros resultados, la cirugía de rescate aporta tiempo libre de enfermedad y supervivencia a pacientes con recidiva de carcinoma de células escamosas en cavidad oral, incluso en estadios avanzados. Sin embargo, que la cirugía de rescate es probable que produzca importantes comorbilidades. Consideramos que estos resultados tienen que ser explicados al paciente de forma comprensible y compasiva, y él o ella debe tomar la decisión de pasar por este proceso o no.

## INTRODUCTION

A wide variety of therapies have been described for oral cavity squamous cell cancer (OCSCC) treatment. Although 5-year overall survival for early disease is 90 %, it remains low for advanced stages with poor prognosis and a high mortality rate<sup>1</sup>.

Locoregional recurrent disease (LRD), present in upto 20-50 % of the patients<sup>2</sup>, still represents the most common cause of mortality and occurs more frequently during the first two years from the primary treatment. Its treatment may be influenced by management of the primary tumor. Several factors may influence management options in LRD, such as: 1) performance of primary neck dissection, 2) presence of nodal disease; 3) locoregional tumor extension and resectability; 4) stage of the tumor; 5) administration of adjuvant radiation and chemotherapy; 6) interval between initial treatment and diagnosis of recurrence<sup>3</sup>.

Whenever resectable, salvage surgery has been reported as the primary option for the treatment of LRD in patients with good clinical performance status, with an overall survival of 44 months against the 11 months for unresectable diseases<sup>2</sup>. However, the quality of life of the patient often decreases afterwards, leading to dysphagia, dysarthria and

permanent tracheostomies and gastrostomies. Thus, medical comorbidities must be considered carefully in every patient undergoing salvage surgery so as to individualize best treatment choice<sup>4</sup>.

The objective of the present study was to determine if salvage surgery is the most suitable treatment for LRD in advanced OSCC.

## PATIENTS AND METHODS

A retrospective cohort study was designed including patients who were diagnosed of OSCC recurrence between May 2012 and December 2015. At least a follow-up period of 5 years was established for every single patient. All the patients included in the study underwent treatment for the primary tumor in our center. Exclusion criteria was the presence of one or more distant metastases at the diagnosis of the LRD. The analyzed database included all patients affected of OSCC in the region of Extremadura, Spain, which comprised a population of 1.065 million inhabitants at 2019.

These patients were divided in two cohorts depending on the treatment they received for LRD: 1) group A, with salvage surgery; 2) group B, without salvage surgery. Selection of patients for group A treatment protocol was based upon

the resectability of the tumor, once the patient was operable and agreed to surgery. Irresectability criteria were invasion of carotid artery, skull base or prevertebral fascia and cutaneous carcinomatosis. Some of our patients although had resectable tumors rejected salvage surgery after explaining its possible consequences.

The criteria followed to apply radiotherapy were the following. In the salvage surgery group the administration of radiotherapy depended on the analysis of the piece. Affected or very close borders, rT3/rT4 with great local invasion, undifferentiated or low differentiated lesions, perineural, lymphatic or vascular invasion, bone, skin or cartilage affection, extracapsular ganglionic extension, multiple adenopathies or one bigger than 1,5 cm. Radiotherapy with > 60-70 Gy was administered in oral cavity and > 50 Gy in cervical ganglionic chains, 1.8-2 Gy per session five times per week. If no surgery was performed, > 70 Gy radiotherapy was administered in the tumor and macroscopic adenopathies and > 50 Gy in other cervical levels, 1.8-2 Gy per session five times per week. If the area was radiated in the last year, a toxicity analysis was performed and reirradiation was individualized.

In some of the cases the radiotherapy that was prescribed was palliative if there is no possible healing intention treatment. In this cases it was indicated with antialgic and/or hemostatic intention.

Chemotherapy was proposed according to the following criteria. In the salvage surgery group chemotherapy was not initially indicated. Only when progression of the disease after treatment was seen, palliative chemotherapy was prescribed. Group B patients that were proposed to have radiotherapy were also proposed to have concomitant chemotherapy with cisplatin +/- carboplatin +/- cetuximab. In those patients who were neither candidates to radiotherapy, combinations of cisplatin +/- 5-FU +/- taxans were proposed. However, chemotherapy was individualized to each patient's characteristics and treatment objectives. Although we may consider salvage surgery after inductive chemotherapy and/or radiotherapy, none of our cases were candidate because whether patients had a complete response after this treatment, whether the tumors were still irresectable.

When the recurrence was located in oral cavity, salvage surgery's objective was to resect the tumor with at least one centimeter macroscopic margin. If the recurrence was cervical, tumor resection was performed and if previous neck dissection did not include I-V levels, they were completed. Functional neck dissection was always intended but if the structures were affected radical neck dissection was performed.

The following variables were included: age, sex, Charlson comorbidity index<sup>5</sup>, TNM and stage of the primary tumor, localization of the primary tumor, treatment of the primary tumor, time until recurrence, localization of the LRD and recurrent TNM and stage. Analytic statistics were performed using Chi-squared test for qualitative variables if the expected values of at least 80 % of the cells were bigger than five. If not, Fisher exact test was used. T-Student test was used for comparison of quantitative variables. Overall survival (OS) and disease free survival (DFS) were estimated using the Kaplan-Meier method and the Log-rank test was used to compare survival curves. Both groups were stratified in early and advanced stages (I-II versus III-IV) and OS and DFS were also determined for these

sub-groups. The Statistical Package for the Social Sciences (SPSS) v.25 was used for statistic calculations.

## RESULTS

Sixty four patients were recorded. Thirty patients were discarded because of lack of data or duplicity and two patients did not fulfill the exclusion criteria. Finally, thirty two patients were studied (n = 32).

Basal features of the patients are shown in Table I (qualitative variables) and Table II (quantitative variables). rOSCC is more frequent in men (81.3 %) with an average age of 64,3 ( $\sigma = 11$ ). The most frequent initial TN was T2 (46.9 %) and N0 (68.8 %) and IV initial stage (43.8 %). The most frequent localization of the initial tumor was the tongue on its anterior 2/3<sup>rd</sup>s (46.9 %). The average time until recurrence was 33.1 months ( $\sigma = 38.4$ ). When we analyze data of the recurrence, the most frequent recurrent TN was T4 (43.8 %) and N0 (65.6 %) and the most frequent recurrent stage was IV (62.5 %). The average Charlson comorbidity index was 4.5 ( $\sigma = 1.3$ ). Comparison of different characteristics between both groups did not found statistically significant differences.

DFS was analyzed among groups (Figure 1). Significant differences between both groups were observed ( $p < 0.001$ ) showing better results with those treatments that included salvage surgery (21.55 months,  $\sigma = 5.25$ ) than without (1 month,  $\sigma = 0.54$ ).

OS was also calculated for both groups (Figure 2). Significant differences in favor of salvage surgery were also observed ( $p < 0.001$ ) and the medias were 37.1 ( $\sigma = 4.9$ ) with surgery and 9.3 ( $\sigma = 2.7$ ) without.

The stratified analysis between early and advanced stages showed the following results. Analyzing DFS, favorable results for the groups including salvage surgery as treatment were found, even better in early stages ( $p < 0.001$ ). Medias were 38.8 months ( $\sigma = 8$ ) in early stages with salvage surgery, 0 months ( $\sigma = 0$ ) in early stages without salvage surgery, 9.62 ( $\sigma = 4.8$ ) in advanced stages with surgery and 1.1 ( $\sigma = 0.59$ ) in advanced stages without surgery (Figure 3).

Similar results were observed when analyzing OS, with statistically significant differences ( $p < 0.001$ ). Medias were 54.56 months ( $\sigma = 5.1$ ) in early stages with salvage surgery, 6 months ( $\sigma = 0$ ) in early stages without salvage surgery, 25 ( $\sigma = 5.36$ ) in advanced stages with surgery and 9.7 ( $\sigma = 2.73$ ) in advanced stages without surgery (Figure 4).

Only a single patient was included in the early stage group treated without surgery, thus no results were analyzed due to its insufficient sample size.

## DISCUSSION

According to our results, salvage surgery provides both disease free survival and overall survival to patients with recurrent oral squamous cell carcinoma. This difference is both statistically significant and clinically relevant.

The main limitations of our study are those inherent to the study design. A retrospective cohort study may be, fundamentally, skewed by the non-randomization of the groups.

**Table I. Comparison of qualitative variables studied. Chi squared test was used to compare them except for variable "Sex", where Fisher test was used.**

Variable	Overall	Treatment including salvage surgery	Treatment without salvage surgery	p
Sex				627
Male	26 (81.3 %)	18 (69.2 %)	8 (30.8 %)	
Female	6 (18.8 %)	4 (66.7 %)	2 (33.3 %)	
Initial T				0.233
T1	9 (28.1 %)	8 (88.9 %)	1 (11.1 %)	
T2	15 (46.9 %)	8 (53.3 %)	7 (46.7 %)	
T3	2 (6.3 %)	1 (50 %)	1 (50 %)	
T4	6 (18.8 %)	5 (83.3 %)	3 (16.7 %)	
Initial N				0.71
N0	22 (68.8 %)	17 (77.3 %)	5 (22.7 %)	
N1	2 (6.3 %)	2 (9.1 %)	0 (0 %)	
N2	8 (25 %)	3 (37.5 %)	5 (62.5 %)	
N3	0 (0 %)	0 (0 %)	0 (0 %)	
Initial stage				0.454
I	8 (25 %)	7 (87.5 %)	1 (12.5 %)	
II	9 (28.1 %)	5 (55.6 %)	4 (44.4 %)	
III	1 (3.1 %)	1 (4.5 %)	0 (0 %)	
IV	14 (43.8 %)	9 (64.3 %)	5 (35.7 %)	
Localization				0.785
Anterior tongue	15 (46.9 %)	11 (73.3 %)	4 (26.6 %)	
Gingiva	2 (6.3 %)	1 (50 %)	1 (50 %)	
Palate	2 (6.3 %)	2 (100 %)	0 (0 %)	
Mouth floor	6 (18.8 %)	3 (50 %)	3 (50 %)	
Base of tongue	4 (12.5 %)	3 (75 %)	1 (25 %)	
Retromolar trigone	3 (9.4 %)	2 (66.7 %)	1 (33.3 %)	

**Table II. Comparison of quantitative variables studied. T Student test was used to compare them.**

Variable	Overall	Treatment including salvage surgery	Treatment without salvage surgery	p
Age (years)	64.3	63.14	64.1	0.446
Charlson Comorbidity index	4.5	4.59	4.4	0.711
Time until recurrence (months)	33.1	33.27	32.7	0.448

The groups are formed attending to the indication of salvage surgery according to resectability and operability criteria. However, we have not seen statistically significant differences in the characteristics of the groups. Recurrent TNM and stage has been the variable chosen to study whether there could be differences between the size and extension of the tumor. Charlson comorbidity index<sup>5</sup> has been selected as variable to measure differences in operability criteria. Neither of them has evicted enough differences so as to consider the groups different. According to this, it could be said that the differences found between both groups may be considered as caused by the treatment given.

We have considered patients treated until 2015 because we wanted to analyze at least five years after treatment. Other techniques have been used and improved in these last years, specially in radiotherapy, and we cannot consider them here. This is why we need to balance both stable studies including long term results as ours with other studies that may consider more recent treatments but with short term outcomes. Newer treatments may decrease the gap between both groups and maybe, in a future, have better outcomes than salvage surgery.

Analyzing descriptive data we see that, in our groups, men in the seventh decade of life are more likely to present a rOSCC. This is consequent with the group that is more likely

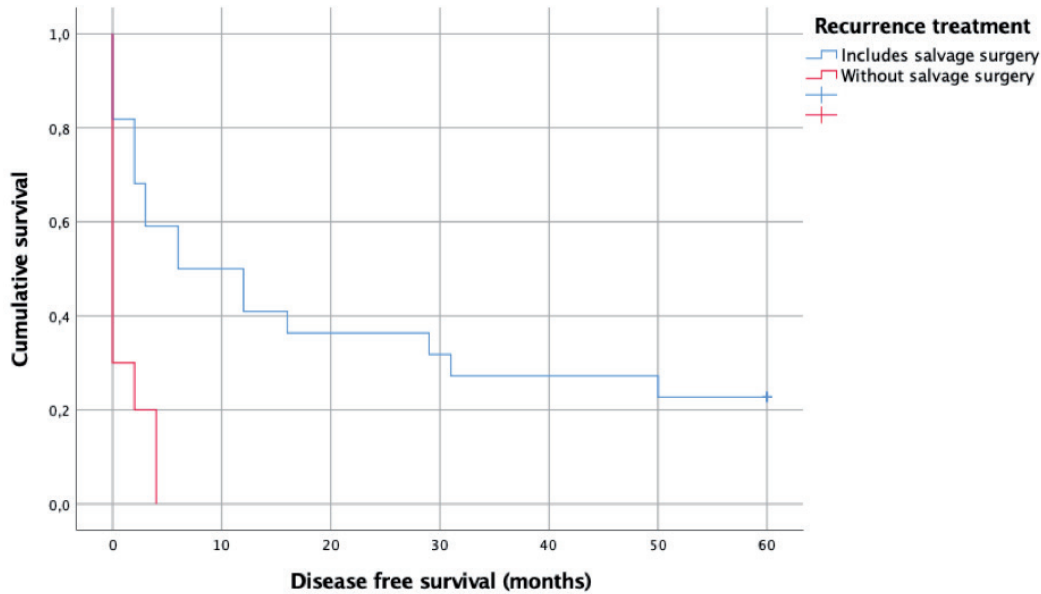


Figure 1. Disease free survival comparing patients treated with ( $\mu = 21.55$  months,  $\sigma = 5.25$ ) and without salvage surgery ( $\mu = 1$  months,  $\sigma = 0.54$ ).  $p < 0.001$ .

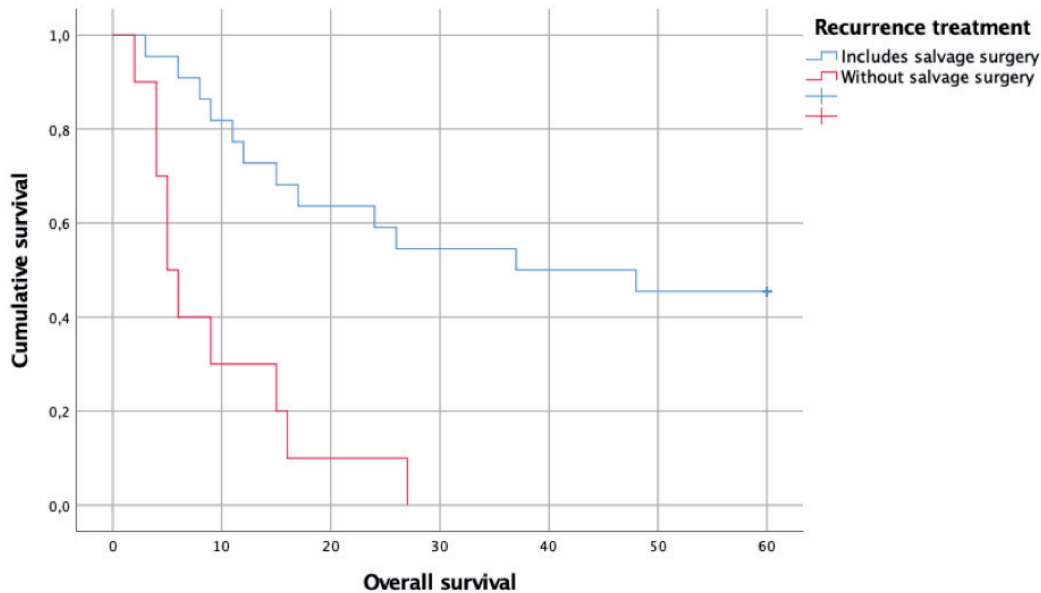


Figure 2. Overall survival comparing patients treated with ( $\mu = 37.1$  months,  $\sigma = 4.9$ ) and without salvage surgery ( $\mu = 9.3$  months,  $\sigma = 2.7$ ).  $p < 0.001$ .

to have OSCC in general. Time until recurrence was wide, with an average of 33.1 months but even showing patients with a recurrence after 140 months. This results support the proposal of considering structured, risk-adapted follow-up using locally-agreed protocols to detect disease recurrence or second primary cancer<sup>6</sup>. Nearly half of the rOSCC were localized previously on the anterior 2/3<sup>rd</sup>s of the tongue (46.9 %), so a special caution with this tumors may be necessary. According to our data, initial stage IV tumors are the most likely to recur, and

they tend to do it in also an advanced stage (III + IV stages = 68,8 % of the recurrences). This makes much more important to elucidate the management of advanced rOSCC.

Considering survival analysis, there are statistically significant differences between both groups in OS and DFS. Moreover, we consider that these differences are also clinically relevant. DFS in the group of patients without salvage surgery is short, with a maximum of 4 months. On the other hand, more than 20 % of the patients are free of disease after five years in the

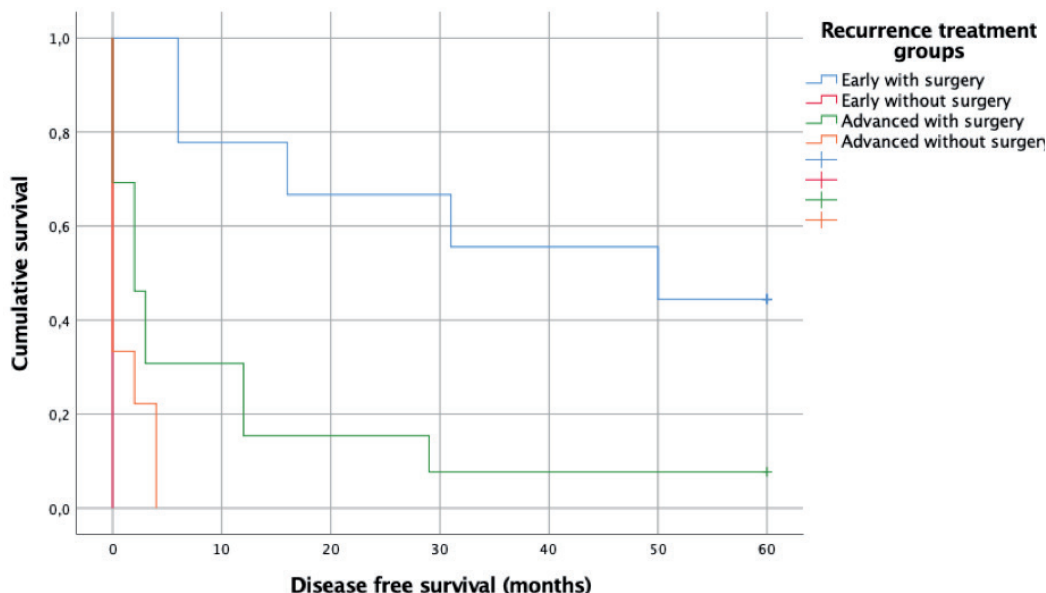


Figure 3. Disease free survival comparing patients in early recurrent stages treated with ( $\mu = 38.3$  months,  $\sigma = 8$ ) and without salvage surgery ( $\mu = 0$  months,  $\sigma = 0$ ) and patients in advanced recurrent stages treated with ( $\mu = 9.62$  months,  $\sigma = 4.8$ ) and without salvage surgery ( $\mu = 1.1$  months,  $\sigma = 0.59$ ).  $p < 0.001$ .

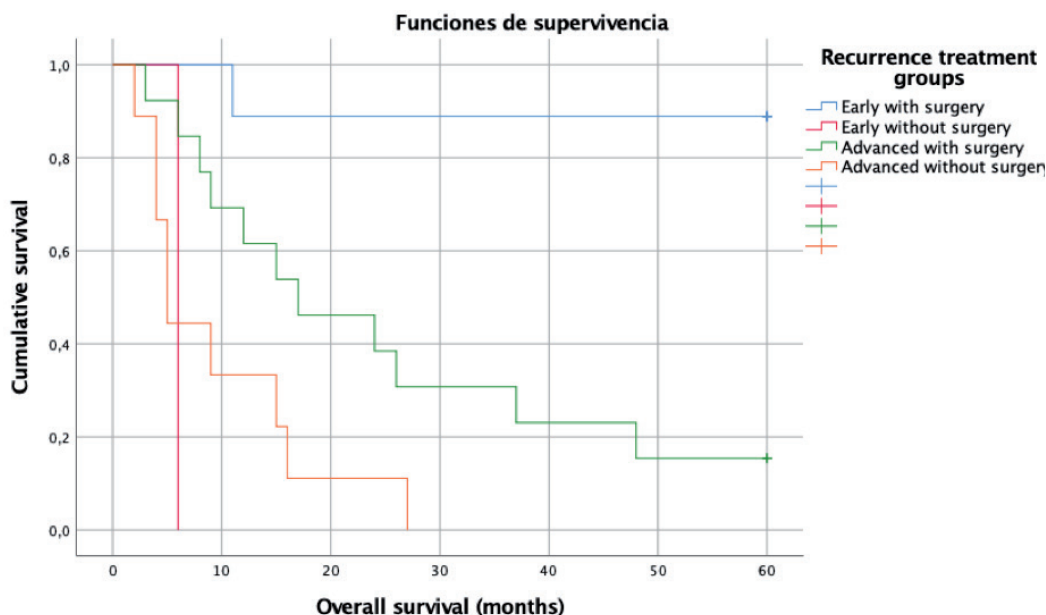


Figure 4. Overall survival comparing patients in early recurrent stages treated with ( $\mu = 54.56$  months,  $\sigma = 5.1$ ) and without salvage surgery ( $\mu = 6$  months,  $\sigma = 0$ ) and patients in advanced recurrent stages treated with ( $\mu = 25$  months,  $\sigma = 5.36$ ) and without salvage surgery ( $\mu = 9.7$  months,  $\sigma = 2.73$ ).  $p < 0.001$ .

salvage surgery group. This is very important for our patients because, although salvage surgery adds surgical comorbidity to our patients, it gives them a long lasting state of quality of life. When we analyze OS, we also see differences between both groups in favor of salvage surgery. None of the patients treated without salvage surgery lives more than 30 months and there are patients alive after 5 years in the salvage surgery

group. The relevance of this data is crucial because is the main objective of any oncological treatment.

Comparing our data with other articles published, our results are coherent with them. Goodwin Jr. published a meta-analysis of recurrent Head and Neck Scamous Cell Carcinoma (rHNSCC) where the 5-year-survival was 39 % in 1080 patients, compared to 43 % in our group. He also shows a prospective

study with DFS of 17.9 % at 5 years compared with 22 % in our group<sup>7</sup>. Elbers et al. published another meta-analysis in 2019 with 5-year-survival of 37 % in rHNSCC<sup>8</sup>. Studies that only include OSCC recurrence are weaker, but they also show similar results to ours<sup>9,10</sup>.

Many authors have discussed whether salvage surgery may be considered therapeutic obstinacy in advanced stages. Salvage surgery in these patients is much more aggressive and so are its consequences. Goodwin considers that only 25 % of salvage surgeries are justified in recurrent III and IV stages<sup>7</sup>. On the other hand, Patil et al. publish that salvage surgery leads to a substantial improvement in outcomes in head and neck cancers and should be the de facto standard of care in patients who are eligible for the same<sup>11</sup>. Borsetto recommends that the multidisciplinary team and the patient weigh these factors carefully when considering further treatment<sup>12</sup>.

In our sample we have concluded that both DFS and OS are favorable to salvage surgery, being these differences also clinically relevant. Although early stages have the best results, advanced stages also get benefit from this treatment, even compared with early stages treated without surgery.

## CONCLUSION

In conclusion and according to our results, salvage surgery may still be considered as the elective treatment for recurrent OSCC, even in advanced stages, in patients with eligible operability and resectability criteria. However, it is true that salvage surgery is very likely to produce important comorbidities such as dysphagia, permanent tracheostomy or gastrostomy, disarthria or other loss of function. We consider that these results should be explained to the patient in a comprehensive and compassionate talk and he or she should decide whether to go through this process or not.

## CONFLICT OF INTEREST

None declared.

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