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Impact of Therapeutic Advances in Locoregionally Recurrent Head and Neck Squamous Cell Carcinoma

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ABSTRACT

Objectives: Our main goal was to assess the impact on overall survival (OS) of the advances in the cornerstone therapies in locoregional recurrence (LRR) of locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Methods: We retrospectively evaluated 56 patients with LRR-SCCHN (2018- 2020) in our hospital. Patients were categorized into 4 groups according to the first treatment (surgery, radiotherapy (RDT), chemotherapy (CT) + cetuximab, immunotherapy (IT)). We included an expansion cohort of patients treated with IT (n=13). A descriptive analysis of patients and disease characteristics and treatments as well as a median OS (mOS) analysis were performed.

Results: The mOS was 24.9 months (mo) [CI 95%: 11.6-38.2]. mOS by subgroup was: 40.4 mo for surgery (n=32), 8.6 mo for RDT (n=8), 10.7 mo for CT+ cetuximab (n=10), and 30 mo for IT (n=3) (p=0.067). The mOS

of the expansion cohort was 15 mo. We identified a statistical difference in mOS depending on the residual tumor (p=0.042) in operated patients and performance status (PS) (p=0.009). There was also a statistical difference in mOS depending on whether they received IT (n=14) or not (n=14) in any line (p=0.012).

Conclusion: mOS of SCCHN patients with LRR remains poor despite new therapeutic strategies. Our results suggest that surgery is the best treatment when the tumor can be resected with free margins, especially in patients with prolonged DFS. If local therapy is not possible, an early use of IT should be assessed. Therapeutic decisions should be made by a multidisciplinary team.

INTRODUCTION

Squamous cell carcinoma of the head and neck (SCCHN) is the seventh most common cancer worldwide [1]. This is a group of malignant neoplasms that are potentially curable if diagnosed at an early stage. Unfortunately, two-thirds of cases continue to be detected in advanced locoregional stages [2], which involve the modest prognosis of these patients, with an overall survival (OS) of less than 40% at 5 years, due to 50-60% of local recurrences and 20-30% of distant metastasis at 2 years [3-7].

For locally advanced disease patients, the most common cause of death is locoregional recurrence (LRR), which occurs in 40-60% of these patients and frequently within the first 2 years after the primary diagnosis [8-10]. The median OS (mOS) of LRR-SCCHN is about 12 months (mo) despite treatments [8].

The best treatment for LRR-SCCHN remains unclear.11 Historically, the optimal therapeutic approach has been surgery, being chemoradiotherapy (CRT) the alternative for non-operable and/or unresectable patients. However, the criteria for unresectability are not fully established, although there are poor prognostic factors described in different series [11]. If neither of these treatments is an option, systemic therapy could be considered, achieving a mOS of 10 mo with chemotherapy (CT) plus cetuximab in the pre-immunotherapy era [8,12].

Recent improvements in surgical and radiotherapy (RT) techniques and systemic treatments require a reassessment of the approach of LRR-SCCHN patients. Transoral robotic surgery (TORS) has proven to be a safe and effective technique, with improved functional outcomes (better preservation of swallowing mechanisms and speech) in oropharyngeal cancer [13,14]. New technological concepts in maxillofacial surgery, like 3D computer-assisted design and microvascular tissue transfer after ablative tumor surgery, have improved the percentage of involved margins with better functional and aesthetic outcomes [15]. Technologic advances have also improved oncologic results and expanded the indications for RT in clinical practice [16]. These advances include intensity-modulated RT (IMRT), enabling more precision in RT dose administration which increases the number of patients with LRR suitable for reirradiation; and adaptative RT, consisting of replanning RT according to patients and/or tumor modifications [16]. In the systemic setting, the introduction of a monoclonal antibody targeting Epidermal Growth Factor receptor (EGFR) (cetuximab) and Programmed cell death protein 1 (PD1) (pembrolizumab and nivolumab), have achieved an increased mOS in patients not suitable for local treatment, with a very favorable toxicity profile [10,17-20].

Our main goal was to assess the impact of the above-mentioned improvements, affecting the cornerstone therapies of LRR-SCCHN, in the overall survival of the patients treated in the multidisciplinary head and neck cancer unit of our censer, as well as assess their characteristics and prognostic factors.

MATERIAL AND METHODS

This was a retrospective analysis of prospectively collected data on 56 patients with LRR-SCCHN diagnosed from January 2018 to December 2020 in the multidisciplinary head and neck oncological functional unit of our hospital, with a follow-up until March 2022. We considered LRR-SCCHN as the relapse of malignancy in the head and neck area after having achieved a complete response to a previous SCCHN. A second neoplasm in the area after a radical treatment of the previous one was not considered a LRR-SCCHN. Patients were categorized into 4 treatment groups according to the primary treatment received: surgery (± adjuvant therapy with RT or CRT), RT (alone ± CT or cetuximab), CT with cetuximab or immunotherapy (IT). As anti-PD1 therapy in platinum-sensitive setting was not reimbursed in Spain until November 2021, in order to include more patients treated with first-line (1L) IT, we have extended the cohort with all patients treated until December 2023 in the same multifunctional unit (n=13) (we will now call it expansion cohort), taking into account the limitations of a short follow-up. We collected clinical information from electronic medical records, including medical history and patient and tumor characteristics. If surgery was performed, we collected the pathological stage (pTNM), presence of extranodal extension, residual tumor, and the type of reconstruction carried out. Residual tumor was considered R0 if there was a minimum free margin of 1 mm. Otherwise, it would be R1 resection or, in case of macroscopic disease left on the surgery, R2. All this information was also collected from the relapses that took place after the index LRR. We also collected the date of the last visit, state, and the cause of death. The database chart used in the study was approved by the hospital ethics committee (REF: PI-17-267).

A descriptive analysis of patients and disease characteristics as well as treatments was performed. Categorical variables were summarized through frequencies and percentages, and quantitative variables using the median and confidence interval (CI) of 95%. The analysis of mOS was performed using the Kaplan-Meier model, comparing different mOS with Chi-Square (Long Rank Mantel-Cox). We used Cox regression to detect associations among the patients and disease characteristics or treatments and mOS. All analyses were performed with the Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Macintosh, Version 23.0. Armonk, NY: IBM Corp.). A p-value < 0.05 was considered significant.

RESULTS

The study included 56 patients with LRR-SCCHN. The mean follow-up was 21.6 mo. Most of the included patients were males (82%), with mild comorbidities (43%), current or former smokers (87%), and PS 1 (68%). Median age was 65 years [CI 95%: 37-92]. In the entire cohort, 25% of the patients had moderate or severe comorbidities, only 13% were never smokers, and 18% had a PS2. Most tumors were located in the oral cavity (32%), 57% of all tumors were resectable and 11% of all patients were metastatic (added to the LRR). 71% of all patients underwent surgery previously to the index LRR 57% of all the patients had a DFS
< 12 mo in the index LRR. The characteristics of all patients and by treatment group are shown in Table 1. The first treatment of LRR was decided in the multidisciplinary unit, according to the decision treatment algorithm shown in Figure 1, and is shown in Table 2. The treatment of LRR was surgery-based in 57%, primary RT-based in 14%, CT plus cetuximab in 18%, IT in 5% and BSC in 5%. In our cohort, we did not find any patient that was

suitable for reirradiation of the LRR. mOS was 24.9 mo [CI 95%: 11.6-38.2], as seen in the Kaplan-Meier plot in Figure 2.

Table 1: Patient characteristics in the study cohort.

	Surgery n=32 N (%)	RDT based n=8 N (%)	CT based n=10 N (%)	IT n=3 N (%)	BSC n=3 N (%)	All patients n=56 N (%)
Sex						
Male	26 (81)	6 (75)	9 (90)	2 (67)	3 (100)	46 (82)
Female	6 (19)	2 (25)	1 (10)	1 (33)	0 (0)	10 (18)
Age (mean)	64	74	65	56	62	65
Performance Status (PS)						
0	7 (22)	0 (0)	0 (0)	1 (33)	0 (0)	8 (14)
1	23 (72)	4 (50)	9 (90)	2 (67)	0 (0)	38 (68)
2	2 (6)	4 (50)	1 (10)	0 (0)	3 (100)	10 (18)
Comorbidities (ACE-27 score)						
None	13 (40.6)	2 (25)	1 (10)	1 (33)	1 (33)	18 (32)
Mild	14 (43.8)	3 (37.5)	6 (60)	1 (33)	0 (0)	24 (43)
Moderate	4 (12.5)	3 (37.5)	3 (30)	1 (33)	0 (0)	11 (20)
Severe	1 (3.1)	0 (0)	0 (0)	0 (0)	2 (67)	3 (5)
Smoking habit						
Current	10 (31.3)	3 (37.5)	3 (30)	1 (33)	0 (0)	17 (30)
Former	16 (50)	4 (50)	7 (70)	2 (67)	3 (100)	32 (57)
Never	6 (18.7)	1 (12.5)	0 (0)	0 (0)	0 (0)	7 (13)
Tumor location						
Oral cavity	12 (37.5)	2 (25)	2 (20)	2 (67)	0 (0)	18 (32)
Oropharynx	8 (25)	2 (25)	1 (10)	0 (0)	2 (67)	13 (23)
Hypopharynx	4 (12.5)	1 (12.5)	3 (30)	0 (0)	0 (0)	8 (14)
Larynx	8 (25)	2 (25)	3 (30)	1 (33)	1 (33)	15 (27)
CUP	0 (0)	1 (12.5)	1 (10)	0 (0)	0 (0)	2 (4)
Primary tumor stage						
0-III	20 (62.5)	4 (50)	3 (30)	2 (67)	1 (33)	30 (54)
IV	11 (34.4)	4 (50)	7 (70)	1 (33)	2 (67)	25 (44)
Unknown	1 (3.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Relapse tumour stage						
I-III	17 (53)	1 (12.5)	1 (10)	2 (67)	1 (33)	20 (36)
IVA	7 (22)	2 (25)	3 (30)	0 (0)	2 (67)	13 (23)
IVB	8 (25)	5 (62.5)	3 (30)	1 (33)	0 (0)	17 (30)
IVC	0 (0)	0 (0)	3 (30)	0 (0)	0 (0)	6 (11)
Resectability						
Resectable	32 (100)	0 (0)	0 (0)	0 (0)	0 (0)	32 (57)
Unresectable	0 (0)	8 (100)	7 (70)	2 (67)	1 (33)	18 (32)
Metastatic	0 (0)	0 (0)	3 (30)	1 (33)	2 (67)	6 (11)
Previous treatment						
Surgery	19 (59.4)	7 (87.5)	9 (90)	3 (100)	2 (67)	40 (71)
Radiotherapy	20 (62.5)	1 (12.5)	9 (90)	2 (67)	2 (67)	34 (61)
Disease-free survival (DFS) (mo)						
<12	17 (53.1)	6 (75)	6 (60)	2 (67)	1 (33)	32 (57)
≥12	15 (46.9)	2 (25)	4 (40)	1 (33)	2 (67)	24 (43)

Table 2: First treatment of LRR.

Group of treatment	N (%)	mOS (mo) (CI 95%)
Locoregional treatment		
Surgery +/- (RT or CRT)	32 (57)	40.4 (21.4-NR)
Margin		
· R0	29 (91)	NR
· R1	3 (9)	16.8 (0-34)
		p 0.042
DFS		
· < 12 mo	17(53)	21,39 (13.6-29.17) NR
· ≥ 12 mo	15 (47)	p 0.091
RDT alone or with CT or cetuximab	8 (14)	8.6 (0-18.5)
Only systemic treatment		
CT + cetuximab	10 (18)	10.7 (6.4-15.13)
Immunotherapy	3 (5)	30 (7.3- NR)
TOTAL:		21,39.9 mo (11.6-38.2) p 0.067

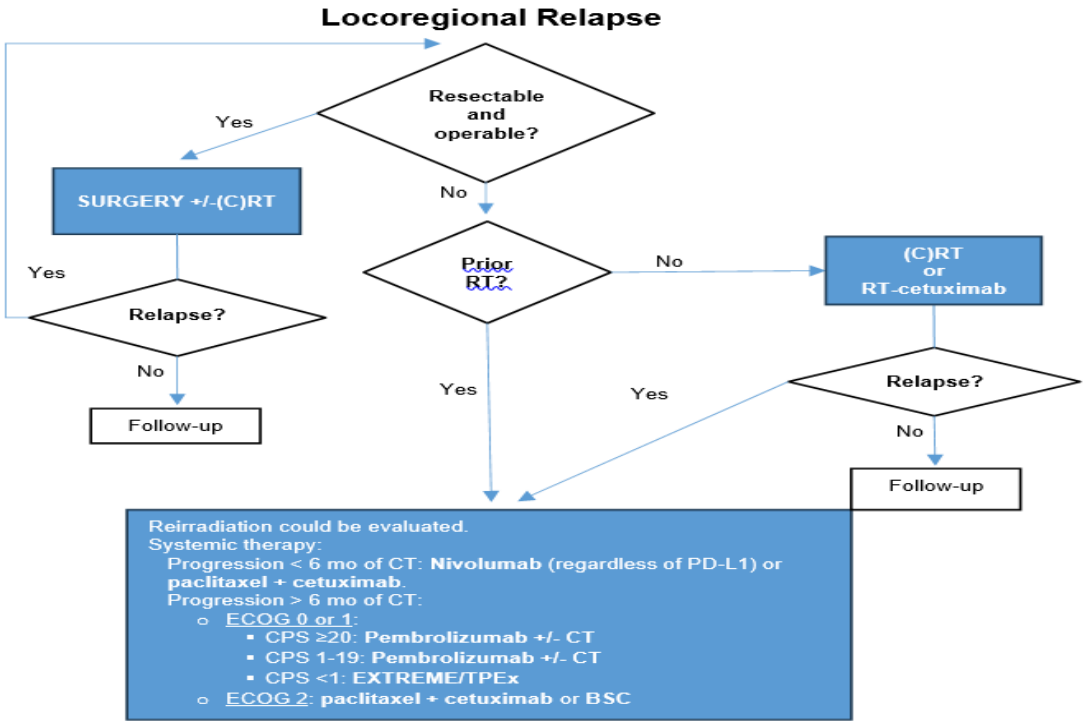
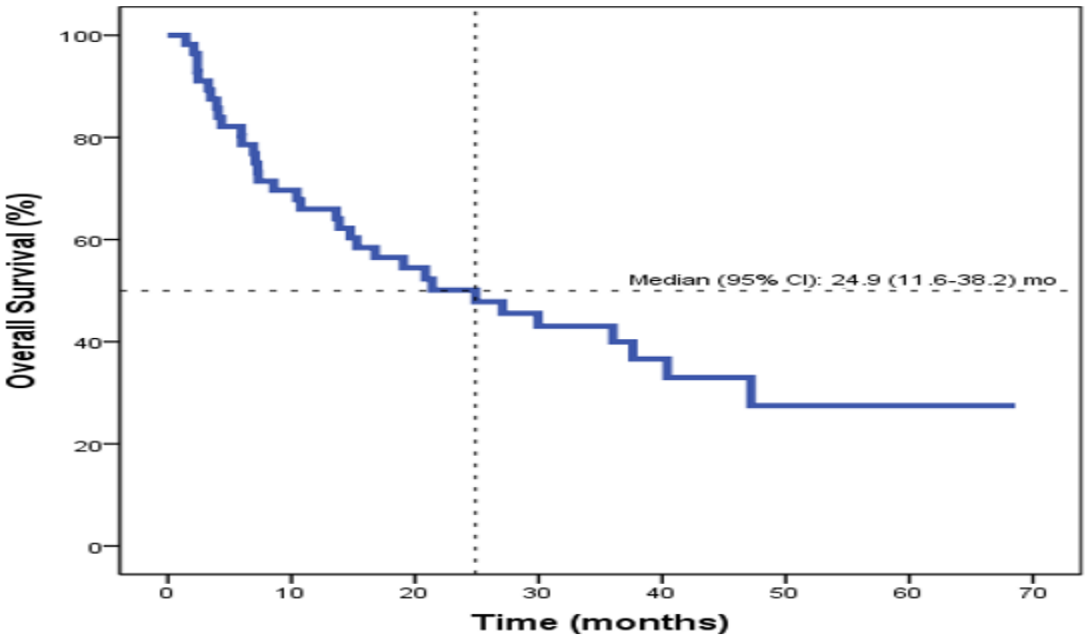


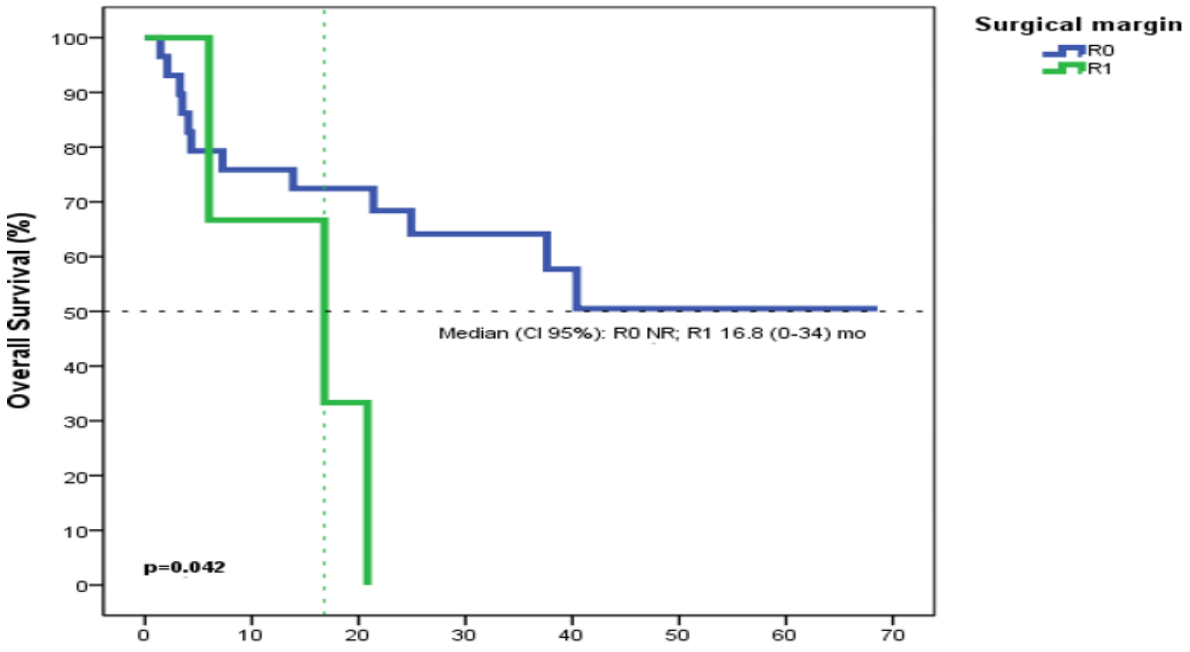
Figure 1: Treatment-decision algorithm in patients with locoregional relapse. mo: months; CRT: chemoradiotherapy; CT: chemotherapy; EXTREME: combination of platinum (cisplatin or carboplatin), fluorouracil and cetuximab; TPEx: combination of cisplatin, docetaxel and cetuximab; BSC: Best Supportive Care.



Month	0	10	20	30	40	50	60	70
Number at risk	56	39	27	17	10	4	1	0

Figure 2: Overall survival of all patients analyzed (n=56)

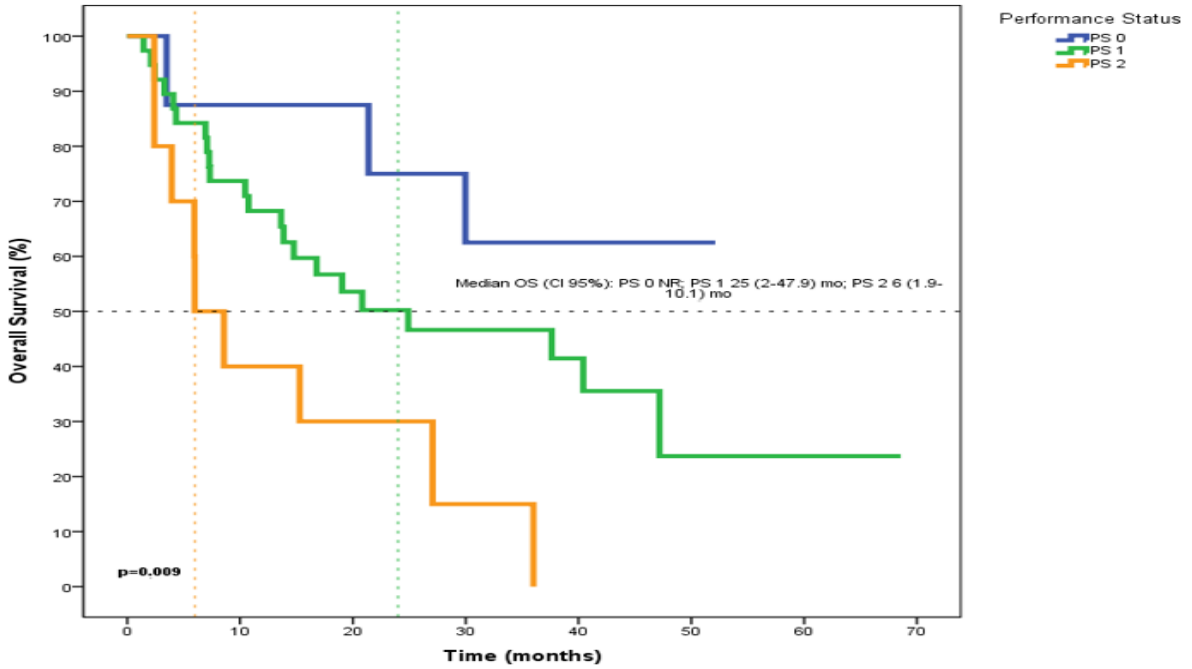
In the subgroup of patients who underwent surgery (n=32), mOS was 40.4 mo [CI 95%: 21.4-not reached (NR)]. A negative impact in this mOS was observed in those patients with involved margins, being 16.8 mo for R1 surgery and not reached in R0 surgery (p=0.042), as seen in Figure 3. Depending on DFS, mOS was 21.39 mo for DFS < 12 mo and was not reached for DFS ≥ 12 mo (p 0.091). Patients treated with RDT (alone or in combination with CT or cetuximab) (n=8) had a mOS of 8.6 mo [95% CI: 0-18] and those treated with systemic therapy (either with CT or IT) (n=13) had a mOS of 10.7 mo [CI 95%: 6.3-15.13] for CT + cetuximab (n=10) and 30 mo (7.3-NR) for IT (n=3) (p=0.660).



Month	0	10	20	30	40	50	60	70
Number at risk	32	24	20	14	8	4	1	0
R0	29	22	19	14	8	4	1	0
R1	3	2	1	0	0	0	0	0

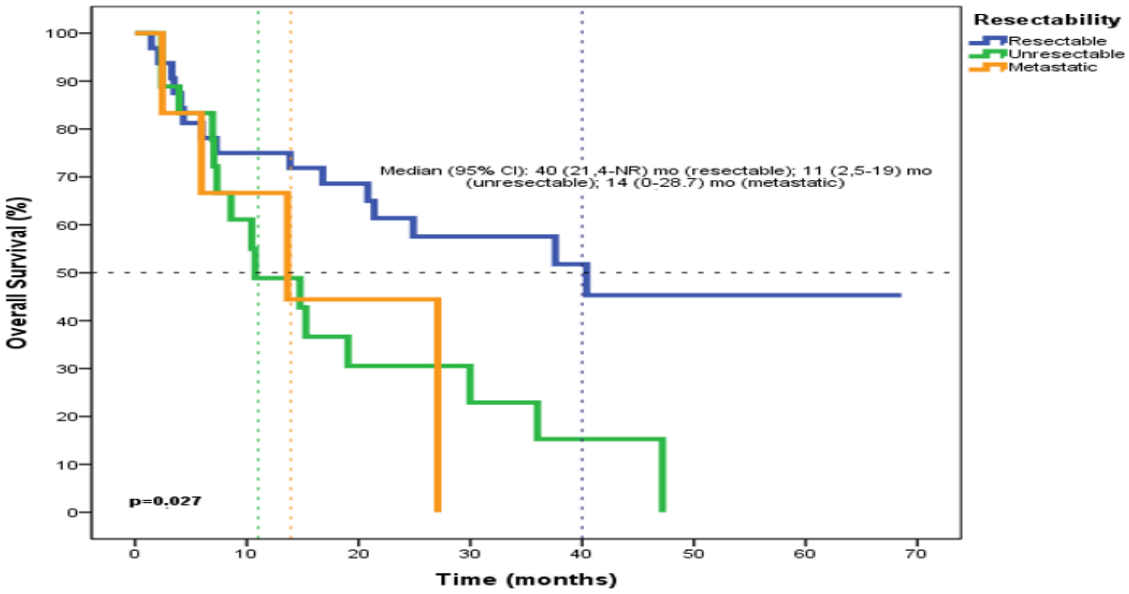
Figure 3: Overall survival depending on residual disease (R0 vs R1) in patients undergoing surgery.

Seventy-one percent of deaths (24 patients out of a total of 34 deaths) were related to progression disease (PD). There was a statistically significant difference in mOS depending on the patient's PS (p=0.009): not reached (NR) for PS0, 25 mo for PS1, and 6 mo for PS2 (see Figure 4). Patients with DFS < 12 mo had a mOS of 16.8 mo [95% CI: 8-25.6] compared to 36 mo [95% CI: 19-53] for patients with DFS ≥ 12 mo in all 56 patients studied (p=0.224). The mOS was statistically different (p=0.027) according to the characteristics of the relapse: 40 mo for resectable locally advanced, 11 mo for unresectable locally advanced, and 14 mo for metastatic (see Figure 5).



Month	0	10	20	30	40	50	60	70
Number at risk	56	39	27	17	10	4	1	0
PS 0	8	7	7	5	3	2	0	0
PS 1	38	28	17	11	7	2	1	0
PS 2	10	4	3	1	0	0	0	0

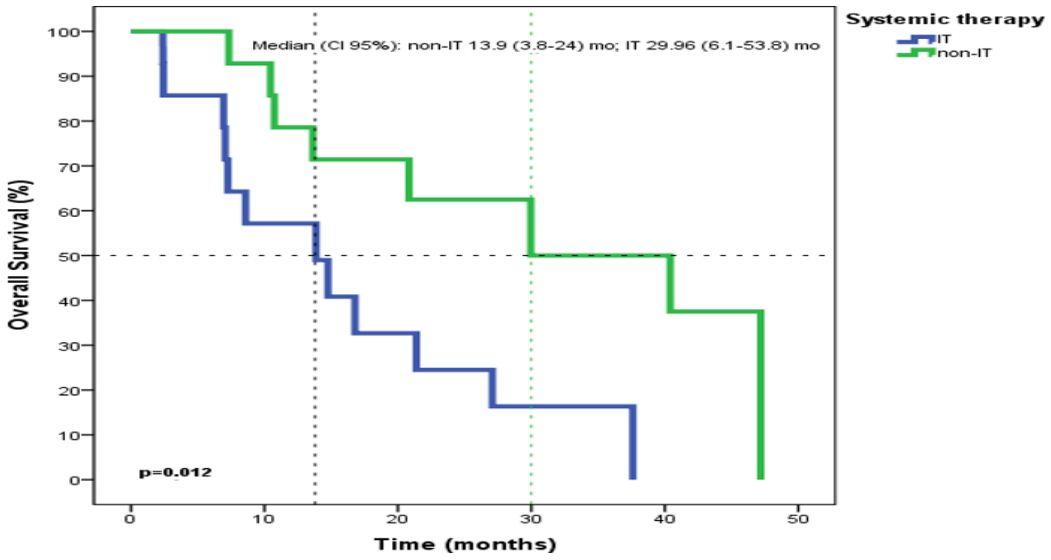
Figure 4: Overall survival curve depending on Performance Status.



Month	0	10	20	30	40	50	60	70
Number at risk	56	39	27	17	10	4	1	0
Resectable	32	24	20	14	8	4	1	0
Unresectable	18	11	5	3	2	0	0	0
Metastatic	6	4	2	0	0	0	0	0

Figure 5: Overall survival curve depending on resectability.

We analyzed the outcomes of those patients who had an unresectable or metastatic relapse or progressed later and were treated with systemic therapy (n=28). Patients who received IT in any subsequent treatment line (n=14) reached a mOS of 29.96 mo (47.2 mo if PD-L1 positive (CPS > 1) (n=9) and 21 mo if PD-L1 negative (CPS < 1) (n=2) (p=0.389)), compared to a mOS of 13.9 mo for patients who had not received IT as a systemic therapy (n=14) (p=0.012) (Figure 6). 3 patients treated with IT had an unknown CPS.



Month	0	10	20	30	40	50
Number at risk	28	21	13	6	4	0
IT	14	8	4	2	0	0
non-IT	14	13	9	4	4	0

Figure 6: Overall survival depending on have received IT (n=14) vs not having received IT (n=14) as a systemic therapy.

We also analyzed a cohort of 13 patients (3 already included in the initial study cohort) that have been treated with IT (in combination with CT or as monotherapy) as 1L in the unresectable and/or inoperable LRR-HNSCC. The patients' characteristics of the expansion cohort can be seen in Supplemental Table 1. This cohort included platinum-sensitive and resistant patients and its mOS were 15 mo [95% CI: 4.1-25.8] (as seen in Supplemental Figures 1). The characteristics of the patients in the expansion cohort are similar to the 3 patients in the study cohort. The median follow-up of this expansion cohort was 11.2 mo [2.13-30.4].

DISCUSSION

Our cohort of patients with LRR-SCCHN confirms the bad prognosis of this population. The goal of this study was to assess the impact of the new therapeutic strategies as well as identify clinical factors that could have an impact on the mOS in this population. For this reason, we decided to select the patients treated for a locoregional relapse between January 2018 and December 2020, so that new therapeutic strategies such as IT and robotic surgery were already available in our center, but at the same time to ensure that the follow-up of the patients was adequate to evaluate its impact on their survival. The median follow-up was 21.6 mo.

The characteristics of our cohort are similar to what has been described previously in the literature in terms of median age, sex, and smoking habit [9,11,12,18,21]. However, 18% of the patients had a PS2 and the majority of oropharyngeal tumors were HPV-non-related, both characteristics conferring a worse prognosis in this scenario and being more prevalent in our cohort compared to other reported series [11,22]. Moreover, most of the patients had an early relapse (57% with DFS < 12 mo), a characteristic that predicts a more aggressive disease and shorter OS.11 Nevertheless, larynx cancer, a location that is associated with a better prognosis, represented 27% of the patients, similar to the prevalence found in trials on systemic therapies.

PS is an independent prognostic factor in our cohort regardless of the treatment that was performed in such a way that an increase in PS was linked to a worse OS. Moreover, even if it was not statistically significant, differences in mOS were also seen depending on the DFS (< 12 mo vs ≥ 12 mo), having a higher impact on patients who have undergone surgery. In the therapeutic field, statistical differences have also been seen among resectability status and surgical margins, being resectable disease and negative margins (R0) of better prognosis. However, other prognostic factors described previously in the literature, such as comorbidities and tobacco habit, have not been detected in our cohort.11,23 Neither tumor stage at the relapse, tumor location, and HPV relation were seen to impact OS. However, these results must be taken with caution due to the small population analyzed.

Patients treated with surgery had a mOS of 40 (21.4-NR) mo better than 28 mo reported by Chang et al. [11] This difference can be explained because 70% of the patients of that series had a relapse with DFS < 12 mo (being 53% in our cohort), a characteristic that is associated with a worse prognosis as it is linked to a more aggressive disease. Patients treated with radiotherapy (RDT alone, RDT + cetuximab or CRT) had a mOS of 8.6 mo, similar

to what has been seen in other cohorts of LRR-SCCHN [11,28]. The data suggest that surgery should be the first option in a locoregional relapse when free margins can be achieved. When surgery is not an option, the use of radiotherapy should be considered. Patients for RT have to be carefully selected based on their characteristics (e.g. age, PS, or comorbidities) and the experience of the institution. Patients that were treated with chemotherapy and cetuximab had a mOS 10.7 mo (6.3-15.13), similar to what has been seen in EXTREME12 (platin + fluorouracil + cetuximab as 1L systemic therapy in recurrent/metastatic (R/M) SCCHN) (mOS: 10.1 mo), even if our cohort was a non-selected population. However, compared to other combinations of CT + cetuximab, in our cohort mOS was lower than with TPEx24 (cisplatin + docetaxel + cetuximab in 1L R/M SCCHN) (mOS: 14 mo) and higher than with weekly paclitaxel plus cetuximab as 1L in R/M SCCHN25 (mOS: 8.1 mo). In the study cohort, those patients treated with systemic therapy with IT as 1L treatment (n=3) or at any line (n=14) had a mOS of 30 mo. In previous clinical trials of IT, patients treated with pembrolizumab in 1L had a mOS of 14.9 mo (for CPS>20), 12.3 mo (for CPS>1), and 11.6 mo when all CPS were included.18 In the expansion cohort of patients treated with IT as 1L in an unresectable and/or inoperable LRR-SCCHN (n=13) the mOS was of 15 mo [CI 95% 4.1-25.8], lower than the data of the study cohort but consistent with the results obtained in clinical trials.18,20 Nevertheless, in this expansion cohort, there were 69.2% of platinum- resistant patients and 61.5% of the patients with a DFS < 12 mo, both characteristics associated with a worse prognosis, and the follow-up is poor. However, regarding mOS results in patients who have been treated with IT in subsequent lines, our data are in line with those achieved in real-world data.26,27 These analyses have seen a major OS in patients who receive IT after a 1L CT, suggesting a potential boosting effect of previous CT.26,27 In our cohort, this benefit of OS was especially seen in patients with PD-L1 positive, however, patients with PD-L1 negative tumors also benefit from IT. This outstanding benefit of IT can be due to selection bias as patients treated with IT had better PS and better outcomes with previous therapies, suggesting a less aggressive disease. The mOS seen with IT are similar to what has been seen in patients treated with surgery but with affected margins (R1) in our cohort (mOS: 16.8 mo [CI 95%: 0-34]). Moreover, patients treated with surgery would also benefit from systemic therapy in the relapse, having these subsequent therapies also a benefit in the OS. All these data suggest that when a R0 surgery is not feasible, systemic therapy with IT should be considered as it could have a similar outcome and probably a surgery with positive margins does not offer a benefit in terms of OS but it involves important side effects for these patients.

The main limitations of the study are that the cohort has a small size, is unicentric, there is a short follow-up and data are collected retrospectively. In terms of seeing the impact of IT on this population, just 14 patients were treated with it at any time and the follow-up period was relatively short. However, we tried to overcome this limitation by evaluating an extended cohort of 13 patients treated with IT (in combination with CT or as monotherapy) as a 1L treatment of LRR- SCCHN. Nevertheless, as a strength, the therapeutic plan of all patients was assessed by the same multidisciplinary team, which confers homogeneity in the decision-making. Another strength of our study is that we have selected a population enriched with LRR-SCCHN, which has been rarely evaluated separately from other populations of SCCHN before. That has able us to compare locoregional therapies from systemic therapies in this population, including clinical and disease characteristics that can have an impact on the prognosis and the efficacy of the treatment. However, we still need more information on how to manage patients with LRR-SCCHN, a population that has already undergone a curative local therapy, with the side effects and implications that it has, and that has to be reassessed for, while possible, underwent another radical treatment.

Given the complexity of these patients, it is essential to discuss their management in a multidisciplinary committee to offer them the best therapy.

CONCLUSIONS

Our cohort reapproves the dismal prognosis of patients with LRR-HNSCC regardless of new therapeutic strategies. Despite of the introduction of immunotherapy in the treatment of SCCHN, surgery remains the standard treatment when the LRR-SCCHN can be resected with free margins (R0), especially in patients with prolonged DFS. Otherwise, RDT should be considered, bearing in mind patients' characteristics and the experience of the center. Patients that cannot be treated with local therapies, should be considered for an early use of IT, given its impact on OS. However, PS has also to be taken into consideration, as it is an independent prognostic factor, regardless of the type of treatment undergone. Given the complex management of LRR-SCCHN, decisions must be made by a multidisciplinary team.

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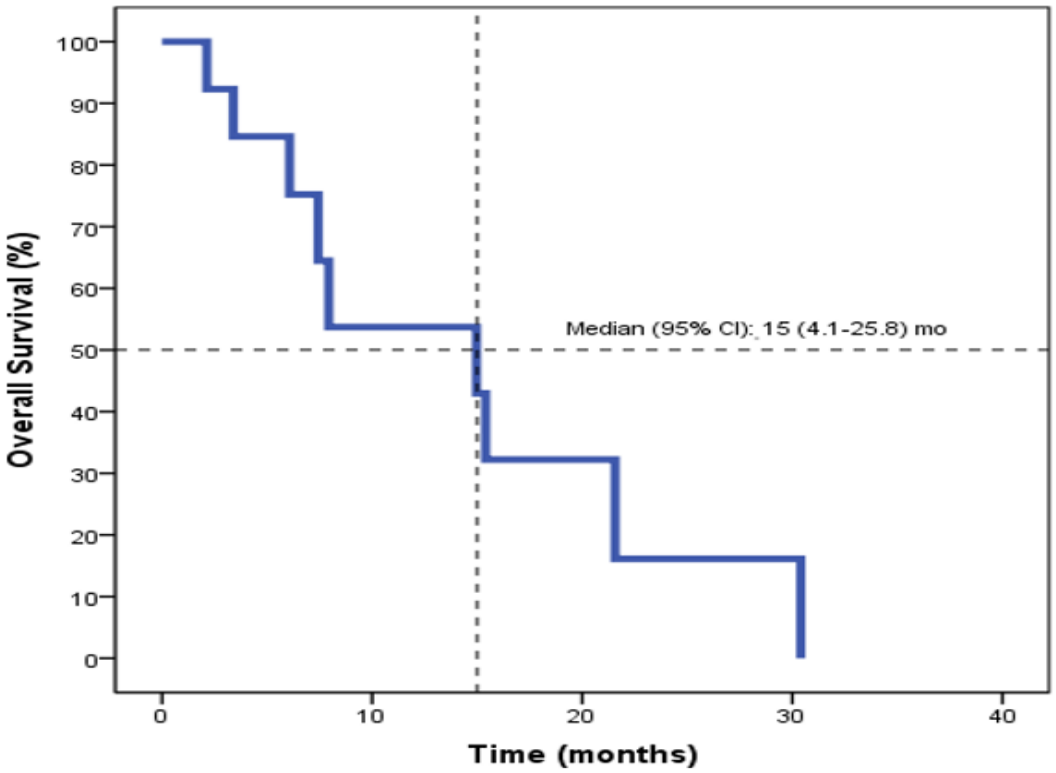
SUPPLEMENTARY DATA

Table 1: Patient's characteristics of the expansion cohort.

	Expansion cohort(n=13) N (%)	Patients of the expansion cohortalso included in the study cohort(n=3) N (%)
Sex Male	10 (76.9)	2 (66.7)
Female	3 (23.1)	1 (33.3)
Age (mean)	61 years [37-76]	56 years [37-71]
Performance Status (PS)		
0	2 (15.4)	1 (33.3)
1	10 (76.9)	2 (66.7)
2	1 (7.7)	0 (0)
Comorbidities (ACE-27 score)		
None	4 (30.8)	1 (33.3)
Mild	8 (61.5)	1 (33.3)
Moderate	1 (7.7)	1 (33.3)
Severe	0 (0)	0 (0)
Smoking habit		
Current	3 (23.1)	1 (33.3)
Former	10 (76.9)	2 (66.7)
Never	0 (0)	0 (0)
Tumor location		
Oral cavity	7 (53.8)	2 (66.7)
Oropharynx	2* (15.4)	0 (0)
Hypopharynx	0 (0)	0 (0)
Larynx	4 (30.8)	1 (33.3)
CUP	0 (0)	0 (0)
	* 1 HPV- related tumor	
Relapse tumour stage		
I-III	3 (23.1)	0 (0)
IVA	2 (15.4)	1 (33.3)
IVB	1 (7.7)	1 (33.3)
IVC	7 (53.8)	1 (33.3)
Disease-free survival (DFS) (mo) <12 ≥12	9 (69.2) 4 (30.8)	2 (66.7) 1 (33.3)
Platinum sensibility		
Platinum-sensitive or no previous CT	8 (61.5)	2 (66.7)
Platinum-resistant	5 (38.5)	1 (33.3)
Type of treatment		
Pembrolizumab	2 (1 in Clinical Trial) (15.3)	1 (in Clinical Trial) (33.3)
Pembrolizumab + CT	4 (30.8)	0 (0)
Nivolumab	4 (30.8)	1 (33.3)
Other	3 (23.1)	1 (33.3)



Month	0	10	20	30	40
Number at risk	13	5	3	1	0

Figure 1: Overall survival of the expansion cohort (n=13).