Long-term survival after definitive radiotherapy combined with systemic therapy in locally-advanced head and neck squamous cell carcinoma in a single practice in Medellín, Colombia

Supervivencia a largo plazo posterior a la radioterapia definitiva combinada con terapia sistémica en carcinoma de células escamosas de cabeza y cuello localmente avanzado en una sola práctica médica en Medellín, Colombia.

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Abstract

Objetive: Describe survival outcomes in a cohort of patients with Locally-Advanced Head and Neck Squamous Cell Carcinoma (LA-HNSCC) treated in Colombia.

Materials and methods: We carried out an observational study. We retrospectively reviewed clinical characteristics and outcomes of all adult patients treated between 2001 and 2018 at a single medical practice in Colombia with LA-HNSCC. Overall survival (OS) and disease-free survival (DFS) were evaluated using Kaplan- Meier curves. Data processing was performed using SPSS v.22.

Results: 60 patients were included, 70% were males. The 30% of carcinomas were oropharyngeal. Stage IVA accounted for 29 (48.3%) patients. Surgery with curative intent was performed in 17 (28.3%). Concomitant cisplatin-based chemoradiotherapy or bioradiotherapy with cetuximab were delivered to 29 (48.3%) and 12 (20%), respectively. The remainder, 19 (31.7%) patients, were treated with radiation therapy and chemotherapy in various sequential or alternating approaches. There were no treatment-related deaths in this cohort. In 41 patients treated with radiotherapy concurrently with either cisplatin or cetuximab the 50-month survival was 75.5%, and no further progression or deaths were recorded on further follow-up. Median follow-up was 35.2 months (14.8-73.8). Median OS and DFS were both estimated at 118.9 months.

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Conclusions: The integration of systemic therapy to definitive radiation therapy is feasible in a Real-World scenario for locally- advanced HNSCC in Colombia.
Keywords: Oropharyngeal neoplasms; chemoradiotherapy; cetuximab; disease-free survival; survival analysis.

Resumen

Objetivo: Dar a conocer los resultados de supervivencia en una cohorte de pacientes con carcinoma de células escamosas de cabeza y cuello localmente avanzado tratados en Colombia.

Materiales y métodos: Estudio observacional, retrospectivo, con análisis de supervivencia.
Se obtuvieron las características clínicas y los resultados de los pacientes adultos con carcinoma de células escamosas de cabeza y cuello localmente avanzado, tratados entre 2001 y 2018 en una sola práctica médica en Colombia. Se realizó el análisis de supervivencia con curvas de Kaplan-Meier. Se utilizó el paquete estadístico SPSS v 22.

Resultados: Se incluyeron 60 pacientes, el 70% hombres. El 30% presentaron carcinomas orofaríngeos. Se encontraron 29(48,3%) pacientes en estadio IVA. La cirugía con intención curativa se realizó en 17(28,3%). Se administró quimiorradioterapia o bioradioterapia concomitante a base de cisplatino con cetuximab a 29(48,3%) y 12(20%) pacientes, respectivamente; mientras que 19 (31,7%) fueron tratados con radioterapia y quimioterapia en varios enfoques secuenciales o alternos. No hubo muertes relacionadas con el tratamiento en esta cohorte. En los 41 pacientes tratados con radioterapia concomitante con cisplatino o cetuximab, la supervivencia a los 50 meses fue del 75,5%, y no se registraron más progresiones ni muertes en el seguimiento posterior. La mediana de seguimiento fue de 35, 2 (14,8- 73,8 meses). Tanto la mediana para la supervivencia global como para la supervivencia libre de enfermedad fue de 118,9 meses (IC95%: 0-1). Al comparar la supervivencia global entre los pacientes que pertenecen al régimen de salud subsidiado versus contributivo, se encontraron diferencias estadísticamente significativas (HR 3,9; IC 95%: 1,5 -10,5; p <0,01).

Conclusiones: La integración de la terapia sistémica a la radioterapia definitiva en el tratamiento de este carcinoma en Colombia resultó en una supervivencia similar a la de los países desarrollados.

Palabras clave: Neoplasias orofaríngeas; quimioradioterapia; cetuximab; supervivencia sin enfermedad; análisis de supervivencia.

Introduction

Locally-Advanced Head and Neck Squamous Cell Carcinoma (LA-HNSCC) comprise a heterogeneous group of neoplasms that often can not be appropriately treated with surgery alone. It is defined as stage III/IVa/IVb (AJCC 8th Ed) squamous cell carcinoma (SCC) of the head and neck, comprising primary carcinomas of the lip, oral cavity, oropharynx, hypopharynx and larynx.

Radiation therapy was offered for many years as the preferred treatment modality, with disappointing results. Several clinical trials have demonstrated better disease control and survival with combined modality therapy including: post-operative chemoradiation therapy, concurrent chemoradiation and concurrent radiation with cetuximab[1-3]. These trials show a 5- year survival rate in the range of 45-55% with combined modality[2]. These data are further supported by several meta-analysis that have underscored a small, but significant, improvement in the disease-free survival (DFS) and overall survival (OS) with the addition of concomitant chemotherapy to radiotherapy in LA-HNSCC[1,3,5]. Therefore,

radiation combined with systemic chemotherapy or cetuximab have become standard-of-care for LA-HNSCC[5].

To our knowledge, survival outcomes for LA-HNSCC treated in Colombia have not been published. We undertook an observational, descriptive study of LA-HNSCC patients treated with combined modality radiation and systemic therapy in a solo-practice in Medellin, Colombia. Survival estimates are the main focus of this paper, and it is hoped that these are similar to those published in the literature.

Primary objective: To determine the OS and DFS of patients with locally advanced head and neck cancer, treated with chemotherapy and definitive concomitant or sequential radiotherapy, in the group of patients treated in the practice of Doctor Mauricio Lema, at the Clinica de Oncología Astorga and the Clínica SOMA, from May 1/2001, to the date of information collection.

Secondary objectives:

1. To describe the sociodemographic and clinical characteristics of patients diagnosed with locally advanced head and neck cancer.
2. To describe the treatment outcomes (response to treatment and progression) of patients diagnosed with locally advanced head and neck cancer.
3. To estimate the OS and DFS of patients with locally advanced head and neck cancer after treatment.

Materials and methods

Patients

Eligible patients were all consecutive patients aged 18 years or older, with histologically or cytologically confirmed squamous cell carcinoma of the lip, oral cavity, oropharynx, hypopharynx and larynx. All patients had AJCC 8th Edition stage III, IVA or IVB (mostly, T3/T4 or N1-3, M0). Patients with squamous cell carcinomas of unknown primary site with exclusive metastases to the neck were also included. All patients were treated by one of the authors (ML) at one of two private treatment settings in Medellín, Colombia: Clínica de Oncología Astorga or Clínica SOMA, between May 2001 and May 2018. Follow-up of at least 3 months was required to be included.

Exclusion criteria included: patients with insufficient data, stage I or II disease, and stage IVC (distant metastases) at presentation. Patients with primary cancers of the thyroid, nasopharynx, salivary gland, paranasal and nasal were also excluded. As were patients with initial presentation of relapsed/refractory HNSCC.

Study Design and Treatment

This a retrospective chart review of all eligible patients. Demographic data, TNM/stage, performance status, treatment delivered, treatment outcomes, disease-free and overall survival were recorded, if available. When survival data was unavailable, governmental databases provided date and cause of death, if applicable. The study protocol was approved by the Ethics Committee of the CIC (Centro de Investigaciones Clínicas) in Medellín, Colombia.

All patients underwent multimodal treatment with a curative-intent radiation along with systemic therapy. The delivery of both systemic and radiation therapies evolved over the years as new evidence was incorporated into clinical practice. As the years went on, Cisplatin-based chemo-radiotherapy or Cetuximab-based bio-radiotherapy became the preferred treatment strategies, respectively. In these, standard cisplatin 100 mg/m2 was to be delivered along with radiation therapy (70 Gy) on days 1, 29, and 43. For patients deemed cisplatin ineligible cetuximab was chosen at the standard dose or 400 mg/m2 day 1; one week later, cetuximab 250 mg/m2 was to be delivered every week along with radiation therapy (70 Gy).

Patients were deemed cisplatin ineligible if they met any of the following criteria: renal dysfunction (creatinine clearance ≤60 mL/min), older age (>70 years-old), coronary-artery disease, Eastern Cooperative Oncology Group performance status ≥2, sensorineural hearing loss, tinnitus or peripheral neuropathy. For cisplatin ineligible patients, cetuximab or carboplatin with paclitaxel were used as radio-sensitizing

agents.

Induction chemotherapy with cisplatin, fluorouracil and docetaxel was delivered before radiation therapy in some patients in whom organ-preservation was a main treatment objective.

Assessments

All patients were assessed at about 3 months after the end of therapy with either a computer tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography-CT (PET-CT). When possible, imaging was repeated every 6 to 12 months for at least 5 years. No evidence of disease (NED) status included complete response in those patients with measurable disease prior to definitive radiation. NED is also adjudicated to those patients rendered NED after surgery if NED was sustained after the end of radiation therapy.

Statistical Analysis

The population for both efficacy and safety analyses included all patients who received at least one dose of systemic anti-cancer therapy on a curative-intent radiation therapy.

Objective response rate (ORR), disease-free survival (DFS), and OS were evaluated. *Table 1* shows the definitions used for the evaluated variables.

Disease- free survival and OS were estimated using the Kaplan-Meier method, and 95% confidence interval (CI) were derived using the Greenwood method of asymptotic

variance. Disease-free survival was defined as the time interval from the start of any anti

Table1. Variable definitions

Survival concepts	
Overall survival (OS)	The length of time (months) from the start date of cancer treatment until the date of the last follow-up contact or the date of death of the patient. The patient's vital status is defined as alive or dead.
Response concepts	
Objective response rate (ORR)	According to Response Evaluation Criteria in Solid Tumors (RECIST), ORR is based on the changes in the size of the representative lesions (target) and reproducible during the follow-up using diagnostic images, using the same technique used in the initial study, following defined radiological measurement rules
Best overall response	It is the best response after starting treatment before the disease recurs or progresses.
Response categories (RECIST version 1.1) (12)	
Complete response (CR)	Disappearance of all known disease, confirmed at 4 weeks, lymph nodes must be < 10 mm short axis.
Partial response (PR)	≥ 30% decrease from baseline, confirmed at four weeks.
Stable disease (SD)	Neither PR nor PD criteria met.
Progressive disease (PD)	≥ 20% increase over smallest sum observed, no CR, PR, or SD, new lesion(s). The sum must also demonstrate an absolute increase of at least 5 mm.
Resection margin	
R0	Indicates complete removal of the entire tumor with microscopic examination of the margins showing no tumor cells.
R1	Indicates that the margins of the resected pieces demonstrate tumor cells when viewed under a microscope (microscopically compromised margins).
R2	Indicates that portions of a tumor visible to the naked eye were not removed (residual lesions macroscopically).

cancer treatment until evidence of progressive disease or death, whichever occurred first. A Cox regression model was used to explore the association between patient characteristics and OS. Hazzard-ratios (HR) and their 95% CIs were reported, where applicable. Data processing was performed using SPSS v.22.

Results

Patients and treatment

Between May 2001 and May 2018, 238 patients diagnosed with head and neck cancer were evaluated. Of these, 60 met the inclusion/exclusion criteria. All of them were included in the study (*Figure 1*).

Forty two (70%) were male. Median age at diagnosis was 58.9 years-old (interquartile range [IQR] 31-83). Most patients lived in Medellín and thereabouts and about half were privately insured (*Table 2*).

Thirty-four (56.7%) patients were current or former smokers. The most frequent tumor location was the oropharynx (30.0%), followed by head and neck not otherwise specified (20.0%).

Stage IVA and IVB accounted for 44 (73.3%) patients. ECOG performance status 0/1 was adjudicated to 51 (94.4%) patients (*Table 2*).

Concurrent cisplatin-based chemoradiotherapy was delivered to 29 (48.3%) patients. Cetuximab based bio-radiotherapy was administered to 12 (20.0%) patients.

In 19 patients (31.8%), neither Cisplatin, nor Cetuximab were administered. Ten of the latter (16.7%) received 3-week cycles of radiotherapy (2 weeks) alternating with cisplatin plus fluorouracil (1 week) based on Merlano, et al 6. Seventeen (28.3%) patients underwent major surgery for the primary tumor. Resection margin status could not be ascertained in 7 (41.2%) of these patients. Five (8.3%) patients underwent induction chemotherapy, 4 of them with cisplatin-based regimens. Median diagnosis to treatment initiation interval was 34.5 days (IQR 22.8 - 610 days) (*Table 3*).

Toxicity-induced treatment modification or discontinuation occurred in 4 (6.7%) and 13 (21.6%) patients, respectively. Myelosuppression, mucositis, both and renal toxicity were the main causes for treatment deviation in 4 (6.7%), 3 (5.0%), 2 (3.3%) and 5 (8.3%), respectively.

Although one patient died during therapy,

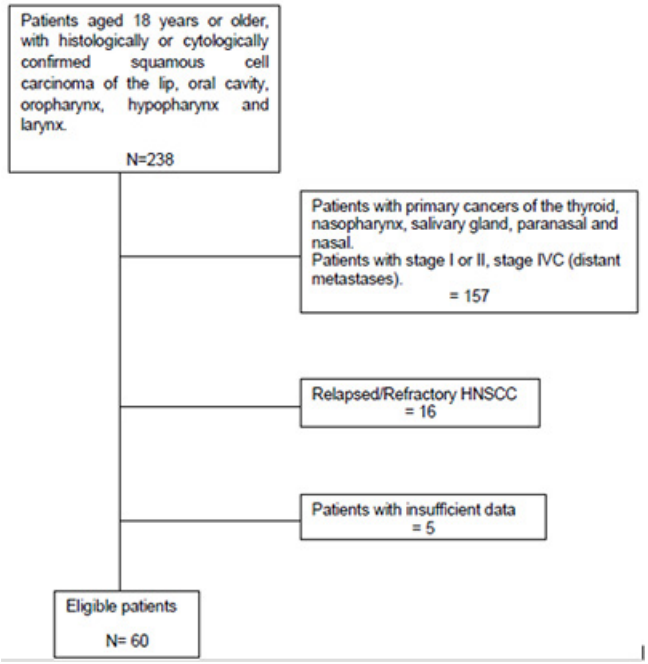

Figure 1. Flow chart of patient`s selection.

Table 2. Demographic and clinical characteristics of patients diagnosed with LA-HNSCC.

		N (N=60)	%
Demographic characteristics			
Sex	Men	42	70.0%
	Women	18	30.0%
Age (years)*	58.9 (± 11.5) years		
Place of residence	Medellín	42	70.0%
	Envigado	3	5.0%
	Other	15	25.0%
Health care system	Privately insured	51	85.0%
	State-only insured	8	13.3%
	None	1	1.7%
Clinical characteristics			
Smoking (n=58)	Yes	34	58.6%
	No	24	41.4%
Tumor location	Oropharynx	18	30.0%
	Head and neck	12	20.0%
	Larynx	8	13.3%
	Tongue	6	10.0%
	Hypopharynx	5	8.4%
	Other	11	18.3%
Stage	III	16	26.7%
	IVA	29	48.3%
	IVB	15	25.0%
ECOG (n=54)	0	7	11.7%
	1	44	73.3%
	2	3	5.0%

* Mean ± Standard deviation (SD).

Table 3. Treatment received by patients diagnosed with LA-HNSCC.

		N (N=60)	%
Major surgery			
No		43	71.7%
Yes:		17	28.3%
- Resection margin status	R0	5	29.4%
	R1	4	23.5%
	R2	1	5.9%
	Resection margin status could not be ascertained	7	41.2%
Medical treatment			
Type of treatment	Concurrent chemoradiation	31	51.7%
	Chemotherapy followed by radiotherapy (sequential)	3	5.0%
	Bioradiotherapy	12	20.0%
	Merlano (radiotherapy alternating with cisplatin plus fluorouracil)	9	15.0%
	Induction chemotherapy:	5	8.3%
	Docetaxel + cisplatino + fluoruracil	3	60.0%
	Carboplatino + paclitaxel	1	20.0%
	Cisplatin + paclitaxel	1	20.0%
Chemotherapy drugs received concomitantly or sequentially with radiotherapy	Cisplatin	29	48.3%
	Cetuximab	12	20.0%
	Cisplatin + fluorouracil	10	16.7%
	Other	9	15.0%

her death was not deemed treatment-related.

Efficacy

Response assessment at 3 months after the completion of therapy showed that the best response was complete response (CR) in 67.1% (30/44). No-evidence of disease status (NED) was 78.3% (47/60) after the inclusion of all R0 and R1 resections. Partial Response (PR) and Progressive disease (PD) as best responses were found in 8.3% and 11.7%, respectively. Sustained CR was maintained in 56.7%.

After a median follow-up of 35.2 months (IQR 14.8-73.8) 28 patients remain alive, 22 are dead and 10 are censored. Progression was observed in 24 patients, of whom 22 died. The median time elapsed between disease progression and death was 6.1 months (IQR 1.0- 14.6). Tumor progression was the cause of death in 15 out of 16 patients in whom the cause of death was known.

DFS at 12 and 42 months were 71.5%, and 59.8%, respectively. DFS at 118.9 months was 47.8% (*Figure 2*). OS at 6, 12, 60 and 118.9 months were 93.3%, 83.2%, 60.4% and 48.2%, respectively (*Figure 3*).

After a follow-up of 50 months 75.5% of the patients treated with radiation with concomitant cisplatin or cetuximab were alive. In this group of patients no further survival events were recorded during follow-up. Median OS was 13.6 months (95% CI 5.3-22.0) and 32.6 months (95% CI 9.7-55.5) in patients treated with, alternating chemo-radiation, and non-cisplatin treated patients respectively.

Median OS was 13.6 months (95% CI 18.2-19.0) for state-only insured patients, whereas median OS was not reached for privately insured patients. On univariate analysis this difference reached statistical significance (HR 3.9; 95% IC:1.5 -10.5; p <0.01).

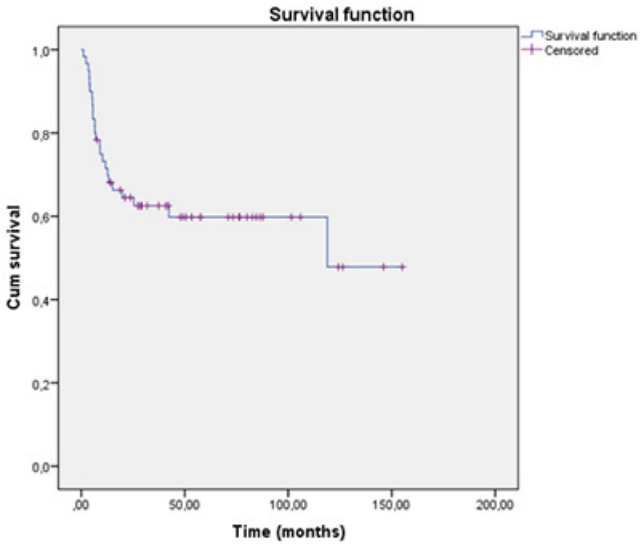

Figure 2. Kaplan-Meier disease free survival curve for LA-HNSCC patients.

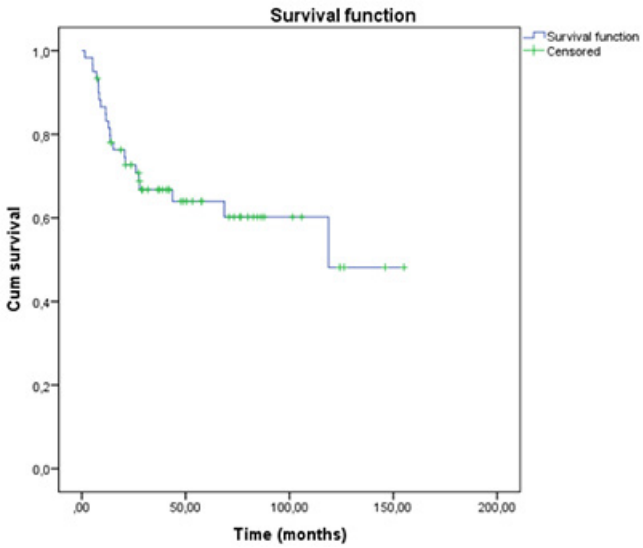

Figure 2. Kaplan-Meier disease free survival curve for LA-HNSCC patients.

Discussion

Definitive radiation combined with concurrent cisplatin or cetuximab is the current standard-of-care for LA-HNSCC based on several trials[7-10] and several meta-analyses[1,3,4,11]. The systemic component adds 5.5% to the absolute survival probability for this group of patients, bringing it to about 45-55% 5-year survival rate, depending on the clinical scenario (2). This Real World Evidence study reports long-term outcomes of 60 patients with LA-HNSCC treated, over many years, in a single-practice in Colombia - a middle-income country.

Some patients treated in the early 2000s were treated with alternating chemo-radiation; then, some patients, were treated with induction chemotherapy, followed by radiation or chemoradiation. Later, cetuximab became the preferred option for platinum ineligible patients. Not all patients in Colombia have access to cetuximab, or to even standard radiation therapy.

Only about half of the cohort had access to an acceptable global standard-of-care. With a 5-year DFS and OS of 59.8% and 64.0%, respectively, this report is in line with published data, if not better. The survival data is mature, and we can show that complete remission at month 42 probably means cure in this data-set.

We also show that combined modality therapy is highly toxic with rates of treatment modification and discontinuation in about 36% of the patients. Nevertheless, treatment-related mortality was low due to prompt access to hospitalization, intravenous fluids, and supportive care.

This is, to our knowledge, the first report on survival outcomes in patients with LA-HNSCC in Colombia. As such, this study shows that radiation therapy can be delivered with concurrent systemic therapy in a Real World scenario in Colombia.

This study has many limitations. First, it is retrospective in nature and many key variables were not adequately captured (of note, Human Papillomavirus status was not ascertained). The sample size is small, which tends to affect the calculation of the confidence intervals in some time-to-event variables. Some patients were lost to follow-up, but the overall survival data is reliable since it is also supported by other sources. We avoided selection bias by including all patients meeting the inclusion criteria. Another limitation of the study is the lack of homogeneity in the treatments delivered. This was unavoidable since some treatment options only became available or standard of care after some of the subjects were already treated.

On the other hand, we consider that one of the strongest aspects of this report is the long follow-up of many patients in the cohort. Another pitfall of this study is the lack of stringent criteria for treatment allocation among the available options, for these were not recorded in the medical charts. Another limitation is that it can not provide specific grade 3 or 4 toxicity assessments. But, we speculate that toxicity must have been grade 3 or 4 when therapy had to be modified or discontinued. A generalizable.

Conclusion

Combined modality radiation therapy with systemic therapy can be delivered to patients with LA-HNSCC in Colombia achieving long-term survival in excess of 50%. DFS at month 42 was tantamount to cure in this data-set.

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- **Conflicts of interest:** Doctor Lema has received honoraria for lectures by Merck, the manufacturers of Cetuximab. The other authors did not disclose any conflicts of interest for this paper.
- **Author contributions:**
- **Conception and design:** Mauricio Lema, Camila Lema, Beatriz E. Preciado
- **Administrative support:** Mauricio Lema.
- **Provision of study material or patients:** Mauricio Lema
- **Collection and assembly of data:** All.

- **Data analysis and interpretation:** Mauricio Lema, Camila Lema, Beatriz E.
- **Preciado Manuscript writing:** Mauricio Lema
- **Final approval of manuscript:** Mauricio Lema, Camila Lema, Beatriz E. Preciado
- **Accountable for all aspects of the work:** All.

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