Results of treatment of stage III glottic laryngeal cancer with chemoradiotherapy. Intensity modulated radiotherapy

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Abstract

Introduction: Laryngeal cancer is one of the most common head and neck neoplasms. Most cases are diagnosed at advanced stages. In clinical Stage III larynx cancer organ preservation protocols, chemoradiotherapy is the treatment of choice, with high local control and laryngectomy free survival rates in well selected patients. In our country, exploration of this results has not been made. **Objectives:** To retrospectively describe organ preservation, local control and morbidity after a two years follow-up. **Materials and Methods:** Clinical and electronic records of patients diagnosed with glottic laryngeal cancer Stage III T3N0M0 treated with intensity-modulated radiation therapy (IMRT) concomitant with chemotherapy were reviewed in the period from January 2013 to December 2015. The study design was descriptive, observational, transversal and retrospective. **Results:** In the period between 2013 and 2015 at CMN SIGLO XXI Oncology Hospital, 266 patients with laryngeal cancer were treated; only 11 patients met the inclusion criteria for our study. After 2 years, locoregional control and organ preservation were 100%, no 3 or 4 grade morbidity was observed. **Conclusion:** In our study, the IMRT concomitant with chemotherapy in glottic laryngeal cancer Stage III T3N0M0 offers 100% organ preservation, and locoregional control, with acceptable morbidity at 2 years.

Key words: Glottic laryngeal cancer. Organ preservation. Locoregional control. Morbidity. IMRT technique.

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Date of reception: 22-10-2017

Date of acceptance: 14-04-2018

DOI: 10.24875/j.gamo.M19000169

Available online: 30-05-2019

Gac Mex Oncol. 2018;17:48-54

www.gamo-smeo.com

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Introduction

Malignant neoplasms of the larynx account for less than 2%; however, it is one of the most common head and neck neoplasms¹. In the world, there are 130,000 new cases of laryngeal cancer and 70,000 deaths every year. In Mexico, the incidence in 2012 was 2,479, with a mortality of 891 and 5-year prevalence of 6,990, being one of the most common neoplasms in both genders². In Mexico, at least 65% of cases are diagnosed at advanced stages³.

Malignant neoplasms of the larynx are caused by tobacco and alcohol consumption in more than 90% of cases. The most common tumor histopathology is squamous cell carcinoma, which accounts for > 95%. Its incidence and distribution according to subsite is: the glottis 69%, supraglottis 30% and subglottis 1%; when early diagnosed, 60% are located in the glottis.^{4,5,6}

Nodal incidence for glottic cancer according to tumor size is as follows: T1 0-2%, T2 2-7% and T3-T4 15-30%¹¹. Tumors of the glottic larynx usually occur with dysphonia and are more often diagnosed at early stages. Other symptoms include odynophagia, sore throat, otalgia (through the Arnold nerve/CN X), aspiration and cervical tumor^{7,8}.

The basis of diagnosis is physical examination, with the key exploration being laryngofibroscopy⁹. There is no screening method for these pathologies¹⁰⁻¹³. Computed tomography (CT) and magnetic resonance are imaging tests for locoregional staging. Positron emission tomography-CT plays two roles in this pathology: detection of distant metastases in locally advanced stages and aid the delimitation of target volumes^{14,15}.

The most important adverse prognostic factors are increases in T and N stages; others include gender, age, performance status and a variety of tumor pathological features, such as the grade and depth of invasion¹⁶⁻¹⁸.

Historically, treatment in advanced but resectable tumors has been laryngectomy or total pharyngolaryngectomy plus adjuvant treatment, with non-functional results, moderate morbidity results and good locoregional control. Currently, with concomitant chemotherapy/radiotherapy (CT/RT) techniques, functionality, low morbidity and good locoregional control are achieved, with higher organ preservation rates. The drug of choice for radical CT/RT is cisplatin (CDDP), and as an alternative to this drug, cetuximab or the combination of carboplatin/5-fluorouracil (5-FU) can be administered. For induction, the combination of choice is the docetaxel/CDDP/5-FU-based triplet^{19,20}.

In organ-preservation protocols for stage III laryngeal cancer, with CT/RT larynx-preservation intent, rates of LC of 66% and LFS of 60% have been achieved, with surgery being reserved for cases where tumor reduction to less than 50% is not obtained with induction CT cycles, with survival rates similar to those for surgery plus adjuvant RT, with the drawback of CT/RT toxicity^{21,22}.

In a study of the Department of Veterans Affairs, induction CT (CDDP-FU, 3 cycles) and RT (6,600-7,600 cGy) were observed to be effective for larynx preservation in up to 64% of cases, thus improving the quality of life of these patients. There were no differences in overall survival between both induction CT and concomitant CT/RT arms, with lower rates of distant metastasis ($p = 0.016$). Overall and disease-free survival of these patients was 64%, with a median follow-up of 33 months²³.

Larynx preservation does not mean total function preservation. Prior to proposing CT/RT, it is necessary to check for adequate function of at least one cricoarytenoid unit and an acceptable functional breathing reserve²⁴⁻²⁶.

In the study by Forastiere et al., results were obtained in the concomitant QT/RT group, with 88% organ preservation, with an emphasis on speech and swallowing, as well as LC of 78%, in comparison with 61% with induction CT, with no impact on overall survival in either arm. However, there was a lower incidence of distant metastasis and longer disease-free survival (DFS) with the regimens that included QT, with 84% organ preservation being confirmed after three years of follow-up in the concomitant CT group^{26,27}.

In a meta-analysis of 84 randomized clinical trials by Pignon et al., 602 patients with cancer of the larynx and hypopharynx treated with PF-based induction CT with organ preservation intent were analyzed, with 23% organ preservation at five years being demonstrated²⁸.

It is important mentioning that, in the cases of bulky tumors, several trials have demonstrated that induction CT followed by RT yields the same results in terms of overall survival, DFS and laryngeal preservation (up to 59%) in comparison with CT/RT²⁸⁻³⁰.

In tumors of the head and neck, intensity modulated radiation therapy (IMRT) has two potential advantages: covering the tumor with irradiation and decreasing toxicity to neighboring organs, due to the great complexity of the different structures that make up this area, as well as to their small size and extreme closeness between each other. IMRT does not increase toxicity and thus protects critical organs and improves patient quality of life³⁰.

Most common long-term complications include xerostomia, lymphedema, dysgeusia, cranial nerve X lesions, vascular events and fibrosis³¹.

Cozzi et al., in a head and neck cancer protocol based on IMRT treatment with multileaf collimator vs. 3D conformal radiation, evaluated dose plans in terms of physical quantities based on dose-volume histograms and isodose distributions. The authors found that irradiation of parotid glands or spinal cord improved; for parotids, it was reduced from 59 to 41 Gy ($p < 0.001$), while for the spinal cord, it was reduced from about 40 to about 30 Gy; thus, they concluded that the technique with IMRT reduces at-risk organs morbidity³².

We should mention that the most common long-term complication of RT and CT/RT for head and neck cancer is xerostomia, and the severity of this condition is dose-dependent, with parotid dysfunction being detectable at a dose of 10 to 15 Gy, and administration of a mean dose of 40 to 50 Gy negatively affecting the quality of life. Other complications include lymphedema (airway compromise and dysphagia), decreased taste and smell, nerve injuries, vascular events and fibrosis, all of them largely being decreased thanks to techniques such as IMRT^{33,34}.

Miah et al. assessed stage III and IV laryngeal cancer treated with concomitant CT/RT plus conventional fractionation vs. escalating-dose IMRT, with good results in locoregional control and progression-free survival in both groups (64.2 vs. 78.4%) and preservation rates of 88.7% vs. 96.4%, all in favor of escalating doses with IMRT. It should be noted that grade 3 toxicity was observed for dysphagia and benign stenosis of the pharynx at one year, which was higher in the escalating-dose group; other toxicities were comparable in both groups³⁵.

The results confirm the efficacy of IMRT in head and neck cancer. This technique offers excellent results in locoregional control, overall survival and at-risk organs decreased morbidity, thus improving the results in cancer of the larynx³⁶.

The purpose of the present study was to retrospectively describe organ preservation, locoregional control and two-year morbidity.

Material and methods

We reviewed the clinical and electronic records of patients diagnosed with stage III T3N0M0 glottic laryngeal cancer treated with induction CT and IMRT concomitant with CT at National Medical Center Siglo XXI in the period comprised between January 2013 and December 2015.

Table 1. Patient characteristics

Characteristics	Range/Average
Age (mean)	62 years (47-75)
Gender (M:F)	M:11 F:0 (M:100%)
Hemoglobin g/dL (mean)	14.24 (9.84-18.3)
Comorbidities	5 (45%)
DM	1 (9%)
HBP	3 (27.2%)
Other	1 (9%)
Smoking	11 (100%)
Alcohol consumption	11 (100%)

M: male; F: female; DM: diabetes mellitus; HBP: high blood pressure.

The design of the study was descriptive, observational, cross-sectional and retrospective. We included patients with stage III T3N0M0 glottic laryngeal cancer, treated with IMRT concomitant with CT in the period comprised between 2013 and 2015, older than 18 years, of both genders and histological type of squamous cell carcinoma. Patients previously treated with RT, treated with another RT technique, patients with previous surgery and patients with second neoplasms were excluded.

This study does not require sample size calculation, since it is merely a descriptive study. Our inclusion variable was IMRT and the observed variables were locoregional control, morbidity and organ preservation, while the descriptor variables were age, gender, comorbidities, smoking, alcohol consumption and hemoglobin concentration. The dosimetric descriptor variables were the conformity index (CI), homogeneity index (IH), prescription dose to the planning target volume (PTV), maximum dose to gross tumor volume (GTV) and maximum dose to at-risk organs.

Our protocol follows the ethical guidelines of the declaration of Helsinki of the World Medical Association, and was submitted to and accepted by the local research committee of the hospital where the study was carried out.

Statistical analysis

After clearance of the database, a descriptive analysis was carried out, which yielded frequencies and percentages for qualitative variables, and central tendency and dispersion measures for quantitative variables. The Microsoft Excel® and SPSS® v22 programs were used.

Table 2. Dosimetric descriptor variables

Patient no.	Prescription dose to PTV	Maximum dose to GTV	Mean dose to GTV	CI	HI
1	66 Gy/33 Fx	8074.9 cGy	7686.8 cGy	1.24	0.16
2	65 Gy/35 Fx	7299.3 cGy	6902.2 cGy	1.02	0.219
3	72.08 Gy/34 Fx	7697 cGy	7384.3 cGy	1.17	0.07
4	69.96 Gy/33 Fx	7471.6 cGy	7238.3 cGy	1.23	0.04
5	69.96 Gy/33 Fx	7961 cGy	7292.5 cGy	1.16	0.08
6	69.96 Gy/33 Fx	7597.4 cGy	7280.2 cGy	1.37	0.21
7	50 Gy/25 Fx	5538.1 cGy	5252.4 cGy	2.18	0.07
8	68.4 Gy/38 Fx	7586 cGy	7273.3 cGy	1.07	1.07
9	68.4 Gy/38 Fx	7850.4 cGy	7340.8 cGy	1.19	0.57
10	69.96 Gy/33 Fx	7860.7 cGy	7453.7 cGy	1.59	0.09
11	68.4 Gy/38 Fx	7777.5 cGy	7380.8 cGy	1.63	0.13
Average	67.10 Gy/33.9 Fx	7519.4 cGy	7135.02 cGy	1.35	0.261

CI: conformity index; HI: homogeneity index; PTV: planning target volume.

Table 3. Acute morbidity

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mucositis	3 (27.2%)	8 (72.7%)	0 (0%)	0 (0%)	0 (0%)
Radiodermatitis	6 (54.54%)	5 (45.4%)	0 (0%)	0 (0%)	0 (0%)
Dysphagia	3 (27.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Xerostomia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Results

At the CMN SIGLO XXI Oncology Hospital, 266 patients with laryngeal cancer received treatment in the period comprised between 2013 and 2015, but only 11 of them met the inclusion criteria of our study, since the rest of patients with stage III T3N0M0 were initially treated with radical surgery.

Patient average age was 62 years, with a range of 47 to 75 years; 100% were men, all with a positive history of more than 20 years of alcohol consumption and smoking. As for comorbidities, 27.2% were hypertensive and 9% had type 2 diabetes mellitus, 9% with COPD. Mean hemoglobin level was 14.24 g/dL, with a range of 9.84 to 18.3 g/dL; median value was 14 g/dL (Table 1).

IMRT was our inclusion constant, with 100% of our group being treated with this technique modality, 81.8% of them with VMAT type and 18.1% with Step and Shoot. Our dosimetric descriptor variables were the

prescription dose to PTV, maximum and average dose to GTV, CI, HI and maximum and mean dose received by at-risk organs, according to dose-volume histograms and isodose distributions (Table 2).

Mean dose was 67.10 Gy, ranging between 50 and 72.08 Gy, with CI being observed to be 1.35 on average, which indicates an ideal conformity according to the Radiation Therapy Oncology Group (RTOG), while HI was 0.261 on average, which was deemed to comply with the RTOG protocol.

The most widely used induction chemotherapeutic agent was the triplet based on TPF (docetaxel/CDDP/5-FU) in 63.6% of cases, FUP (CDDP-FU) in 36.3%, two cycles and continued with concomitant CT/RT with CDDP.

The most common acute morbidity was grade II mucositis in 72.7%, followed by grade I radiodermatitis in 54.54% and grade I mucositis and dysphagia in 27.2%. There were no morbidities higher than grade II (Table 3).

Table 4. Late morbidity

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mucositis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Radiodermatitis	6 (54.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dysphagia	2 (18.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Xerostomia	11 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 5. Descriptor variables

	CI	HI	Prescription dose to PTV	Maximum dose to GTV	Mucositis grade	Radiodermatitis grade	Dysphagia grade	Locoregional control at 2 years	Organ preservation at 2 years
1	1.24	0.16	66 Gy/33 Fx	8074.9 cGy	1	2	1	Yes	Yes
2	1.02	0.219	65 Gy/35 Fx	7299.3 cGy	2	1	2	Yes	Yes
3	1.17	0.07	72.08 Gy/34 Fx	7697 cGy	1	1	0	Yes	Yes
4	1.23	0.04	69.96 Gy/33 Fx	7471.6 cGy	1	2	0	Yes	Yes
5	1.16	0.08	69.96 Gy/33 Fx	7961 cGy	2	2	0	Yes	Yes
6	1.37	0.21	69.96 Gy/33 Fx	7597.4 cGy	2	1	0	Yes	Yes
7	2.18	0.07	50 Gy/25 Fx	5538.1 cGy	2	1	0	Yes	Yes
8	1.07	1.07	68.4 Gy/38 Fx	7586 cGy	2	1	0	Yes	Yes
9	1.19	0.57	68.4 Gy/38 Fx	7850.4 cGy	2	2	0	Yes	Yes
10	1.59	0.09	69.96 Gy/33 Fx	7860.7 cGy	1	1	0	Yes	Yes
11	1.63	0.13	68.4 Gy/38 Fx	7777.5 cGy	2	2	0	Yes	Yes

CI: conformity index; HI: homogeneity index; PTV: planning tumor volume; GTV: gross tumor volume.

The most common late morbidity was xerostomia in 100%, followed by grade I radiodermatitis in 54.5% and grade II dysphagia in 18.1% of our study patients (Table 4).

In the study, the descriptor variables (Table 5) did not influence on organ preservation or morbidity. At 2 years, 100% locoregional control and organ preservation were achieved (Table 6).

Discussion

Glottic laryngeal cancer is caused in more than 90% of cases by tobacco and alcohol consumption, which generate a synergy, as reported in the study by Hashibe et al. (2007), similar to our study group, where 100% of patients had a positive history of more than 20 years of smoking and alcohol consumption. The combination of IMRT with concomitant CT in stage III T3N0M0 glottic laryngeal cancer has obtained good results in terms of

locoregional control, preservation rates and morbidity. In our study, organ preservation and locoregional control rates of 100% were obtained, similar to those reported in the literature with two-year follow-up, as described in the studies by Miah et al. (2012) and Forastiere et al. (2003). It is important noting that one of our patients underwent a tracheostomy at one and a half years of follow-up owing to pneumonia; however, in the last follow-up panendoscopy, no evidence of tumor activity was observed, and thus it is still considered a case of organ preservation, hence the importance for organ preservation criteria to be reestablished in our hospital.

Average administered dose was 67.10 Gy/33.9 Fx (fractions), with treatment volume adequate coverage with IMRT being obtained, thus favoring adequate homogeneity and conformity, as established by RTOG.

Different factors were assessed (gender, age and comorbidities), but in our study none was found to have significant impact, probably owing to the small sample size.

Table 6. Organ preservation and locoregional control at two years

Patient no.	Prescription dose to PTV	Organ preservation	Locoregional control	p
1	66 Gy/33 Fx	Yes	Yes	0.9
2	65 Gy/35 Fx	Yes	Yes	0.9
3	72.08 Gy/34 Fx	Yes	Yes	0.9
4	69.96 Gy/33 Fx	Yes	Yes	0.8
5	69.96 Gy/33 Fx	Yes	Yes	0.8
6	69.96 Gy/33 Fx	Yes	Yes	0.8
7	50 Gy/25 Fx	Yes	Yes	0.9
8	68.4 Gy/38 Fx	Yes	Yes	0.8
9	68.4 Gy/38 Fx	Yes	Yes	0.8
10	69.96 Gy/33 Fx	Yes	Yes	0.8
11	68.4 Gy/38 Fx	Yes	Yes	0.8

PTV: planning tumor volume.

Table 7. Mean dose averages to healthy tissues in cGy

At-risk organs	Mean dose
Parotid glands	2911.05 cGy
Esophagus	2770.1 cGy
Posterior laryngeal wall	5502.75 cGy
Jawbone	2991.95 cGy
Spinal cord	2400 cGy

In our study, a hemoglobin concentration > 13g/dL prior to radiation was not a factor that influenced on the results, since it was not statistically significant. All patients had 100% locoregional control and organ preservation, unlike the results obtained in the study by Feinda et al. (1995).

Regarding morbidity, as assessed with the CTC version 3.0 and RTOG scales, grade II mucositis was found to be the most common, followed by grade I radiodermatitis, unlike figures reported in the literature, where higher morbidity rates are referred. As for late morbidity, xerostomia was present in 100% of our study group, similar to observations reported in the literature by Rancati et al. (2010).

As additional data, table 7 shows average doses to at-risk organs.

In the dose-volume histograms and isodose distributions, we obtained results of lower irradiation to the

parotid glands and to other at-risk organs, with better results being obtained with the VMAT-type modality than those reported by Miah et al. (2012), Bride et al. (2007) and Bonner et al. (2005), with a consequent impact on overall morbidity.

However, the present study has some limitations, such as being a retrospective, cross-sectional study that had no follow-up, with a single evaluation at two years and with a low number of patients.

The present study may give rise to future protocols with prospective assessment, strict follow-up, randomized distribution and in accordance to clinical practice guidelines, or even to carrying out comparative studies between different treatment modalities.

Conclusion

In our study, IMRT in concomitance with CT in stage III, T3N0M0 glottic laryngeal cancer offers 100% organ preservation and 100% locoregional control, with acceptable morbidity at two years.

Conflict of interests

The authors declare not having any conflict of interests.

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