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# Oncological Approach for Laryngeal Cancer

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## ABSTRACT

Laryngeal cancer represents a challenge for the clinician from the time of diagnosis until the time of decision-making regarding disease management. Staging is based clinically, with endoscopic and radiological assistance. Once a diagnosis is made, the following factors are taken into consideration: organ preservation when possible, quality of life, voice quality, surgical team experience, and treatment cost-benefit. These decisions are based on studies with a poor level of evidence; however, with good results. For early disease stages, we have different options like open surgery, transoral laser surgery, and radiotherapy. For advance disease and salvage, organ preservation can be considered using a combination of these tools without affecting survival and offering a good quality of life. At present, new technologies are being developed such as the use of robotics in the treatment of these tumors, but wider experience and adequate instrumentation are being awaited. (J CANCEROL. 2015;2:99-112)

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## INTRODUCTION

Larynx cancer represents 0.5% of all malignant neoplasms, and 3-4% of them are localized in the head and neck region. Worldwide, there are ~120,000 cases reported yearly[1,2]. In Europe, a total of 52,000 new cases are estimated, with an incidence for males of 3% and a 2% mortality rate. In females, the incidence and mortality rates did not surpass 1%. In the USA, a total of 9,500 to 11,000 cases are estimated and the incidence for males is 9,680 cases, with a mortality rate of 2,910 cases. For females, the incidence is 2,570 cases with a mortality rate of 760 patients per year. In regard to overall survival reported in Europe during two different time periods, a slight elevation was observed (60.6 to 63.1%). On the other hand, in the USA, a report from the National Cancer Database and Surveillance Epidemiology and End Results that includes a review of five-year survival demonstrates a decrease in different time periods for a total of 158,426 cases and, especially in those patients with T3N0M0 tumors, depending on the treatment provided. For surgically treated patients, the five-year survival was 63.3%, for surgery plus radiotherapy survival was 65.2%, for concomitant chemoradiotherapy it was 59.2%, and for exclusive radiotherapy it was 42.7%[3,4]. This contrasts with the report by Cosetti, et al.[5] where survival is affected mainly by regional disease at the time of diagnosis, and more importantly, when there is metastatic disease as well as host-related factors and criteria for proposing a treatment on the basis of preoperative studies. However, we believe that the difference in survival reported by European and US studies is related to the fact that there is a greater number of surgically treated patient groups compared with the USA where the tendency during the years of the study has focused more towards treatment with radiotherapy or chemoradiotherapy.

The main risk factors related to laryngeal carcinoma are alcohol (RR: 4 for 100 g/day) and tobacco, and when both are present there is a synergistic effect. There have been > 4,000 chemical substances found in tobacco smoke, of which > 60 are carcinogenic. This is added to the constant inflammation and irritation caused by the smoke, as well as interference with the natural protective barriers in the human body, leading to tumor initiation, growth of previously developed lesions, and performance as co-carcinogens. This also occurs with passive smokers because smoke inhaled from cigarettes has an even greater concentration of carcinogens. Other causal agents have been reported such as human papillomavirus (HPV), an infection that carries the consequence of laryngeal papillomatosis that is strongly related to subtypes 6 and 11, but the mechanism of transmission and its course is unpredictable. We know that there are alterations in the p53 pathway through the expression of the E6 oncogene with the consequent induction of proliferation of tumor cells. However, the synergy between the virus and other carcinogenic agents is hypothetical because existence of only the HPV seems to be insufficient for tumor development. However, there are studies suggesting that the risk of death from cancer related to HPV-associated tumors is less than in a population negative for the infection[6].

## DIAGNOSIS

An accurate staging of laryngeal cancer is required for optimal treatment planning, and for evaluation and comparison of the results of different treatment modalities. For laryngeal carcinoma of any subsite, the extension of dissemination and infiltration should be studied in each case on the basis of clinical, phoniatric, endoscopic, and imaging findings. Staging protocol should include indirect laryngoscopy, direct micro-laryngoscopy, contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) in selected cases. The combination of clinical/endoscopic evaluation and either CT or MRI resulted in a significantly improved staging accuracy (80 vs. 87%, respectively)[7]. The question is whether all stages should be subjected to the same study protocols or should the protocol be different for early versus advanced tumors?

### *Nasofibrolaryngoscopy*

Indirect laryngoscopy was first described by Garcia in 1854, inspecting his own larynx with a dental mirror illuminated with sunlight. This allowed for the beginning of a more adequate management of laryngeal tumors during this era[8]. It is important to note that the use of the mirror has continued until the present time. However, for an optimal and highly specialized evaluation, laryngoscopy through nasofibrolaryngoscopy or rigid laryngoscopies of 90° with or without the use of monitors has permitted a better initial evaluation, even with the possibility of obtaining a biopsy at the same time. This initial evaluation allows us to locate the lesion if it is found in the anterior third of the larynx and whether or not it involves the commissure, the mid-third of the vocal cord and involvement of the posterior third of the larynx with possible infiltration to the vocal process of the arytenoid. The extension and size allow us to establish clinical staging, especially during early stages. The problem of involvement of the anterior commissure will allow us to know with certainty the staging and will require extension studies to be able to determine tumor extension to classify it according to stages. It is important to note that T1 and T2 lesions will not advance to the following diagnostic level, and there are no studies that allow establishing the percentage of this group of patients.

### *Suspension microlaryngoscopy*

Direct rigid laryngoscopy is performed transorally so that the larynx is exposed facially in the majority of the cases. Various patient conditions have been identified as parameters for being unable to adequately expose the larynx such as short neck, macroglossia, muscular problems of the neck, obesity, mandibular tori, and limitation of neck extension due to various conditions such as previous surgery, rheumatic disease, or cervical spine lesions[9]. Suspension microlaryngoscopy (SML) has three main functions. The first is to allow establishing a histological diagnosis when it is not possible to do it by means of indirect laryngoscopy or it is not considered feasible in some outpatient groups. The second is to be able to delineate and stage the tumor extension through direct endoscopy as well because with 30°, 70° and 90° lenses we are able to adequately evaluate extension towards the ventricle, anterior commissure, or lesions that descend towards the subglottis, commonly referred to as obscure zones of the larynx[10,11]. Eryilmaz, et al.[12] demonstrated that direct laryngoscopy alone has a limited role in the obscure zones of the larynx, with a sensitivity of 50-70%. Clinical/endoscopic examination alone failed to identify tumor invasion of the laryngeal cartilages and of the extralaryngeal soft tissues, resulting in a low staging accuracy (57.5%)[7]. This limitation has been well recognized in glottic tumors in the anterior commissure that may be hidden by bulky tumors. Deep tumor extension such as infiltration of paraglottic and pre-epiglottic spaces, cartilaginous skeleton, and extralaryngeal structures cannot be evaluated[7]. The third function is the ability to treat the lesion through a transoral resection with a $CO_2$ laser and/or recent management via transoral robotic surgery (TORS). The latter is not currently considered as a standard option even in groups where this type of surgical management is part of their armamentarium. However, as has previously been mentioned, in cases where an adequate exposure is not achieved, one must opt for another type of management such as radiotherapy, open surgery, or surgery with SML using a $CO_2$ fiber optic laser (Fig. 1).

## LARYNX: IMAGING

### Computed tomography

Since 1976, CT has become a reliable technique for evaluating most head and neck tumors and has become the most important radiological adjunct in the pre-therapeutic staging of laryngopharyngeal cancer. Nevertheless, CT scanning of the larynx has some limitations, especially in determining cartilage


**Figure 1. A:** direct laryngoscopy. **B:** 30° telescope evaluation. **C:** 70° telescope evaluation.

invasion due to the irregular mixture of calcified, ossified, and non-calcified cartilage; therefore, CT in general underestimates cartilage infiltration.

When CT and 70° lens are combined, they are clearly superior, with a sensitivity of 70-100%. For the anterior commissure and ventricle they are both considered perfect, with a sensitivity of 100%; however, for the subglottis the rigid telescope is superior to CT, with a sensitivity of 70-90%[12].

### Magnetic resonance imaging

Recently, MRI has proven to be a reliable diagnostic method for the evaluation of laryngeal carcinoma. Based on the literature, MRI appears to be more suitable than CT in predicting neoplastic cartilage invasion. Becker, et al.[13] showed that the results of their study support the hypothesis that visualization of higher signal intensity on T2-weighted MR images and stronger enhancement in the cartilage compared with the adjacent tumor suggest peritumoral inflammation within the laryngeal cartilage, whereas a similar signal intensity on both T2-weighted and contrast-enhanced T1-weighted images correspond to intracartilaginous tumor. Thus, diagnostic MRI criteria are proposed to have the potential to improve the distinction between tumor tissue and peritumoral inflammation, allowing the reduction of overestimation with MRI.

Zbären, et al.[7], in a study comparing MRI and CT with histopathological correlation, as well as Daflo, et al.[14] in their study of MRI with histopathological correlation, reported that MRI appears to be the study of choice for detecting cartilage invasion as well as subglottis and anterior commissure. We agree with Zbären, et al.[7] because the potential pitfalls of both imaging techniques, namely, underestimation of cartilage invasion with CT and overestimation with MRI, are essential in decision making for the appropriate therapeutic choice. A careful interdisciplinary interpretation of CT and MRI findings with the head and neck surgeon, the radiologist, and the radiation oncologist, after taking into account the clinical and endoscopic findings, is mandatory in the avoidance of inappropriate treatment[7].

## MANAGEMENT OF T1A, T1B AND T2 TUMORS

At present, treatment of early-stage laryngeal cancer is based on studies with a low level of evidence. Available options are organ preservation surgery, whether transoral or open, and radiotherapy. Recently, “personalized medicine” has been in the spotlight; therefore, various aspects must be considered (patient preference, tumor localization, unsatisfactory larynx suspension, availability for radiotherapy application) when patient decisions are made regarding the best course of treatment.

## T1A/T1B, T2 AND T3 SELECTED TUMORS

It must be kept in mind that, in these stages, the larynx should be preserved and the patient should be treated with a curative intent independent of the treatment because the majority of these patients die as a result of a second primary tumor or other co-existing diseases. We must also remember that regional lymph node disease is an infrequent event during these stages due to the anatomic characteristics at the level of the glottis. Options for these stages are open surgery, transoral surgery and, finally, radiotherapy.

The first studies in the surgical management of laryngeal cancer published in Europe include procedures such as laryngofissure with cordectomy, frontolateral partial laryngectomy, procedures of the anterior commissure and hemilaryngectomy and supracricoid laryngectomy with cricohyoiod epiglotopexy and/or cricohyoidopexy. Lacourreye, et al.[15] compared two techniques in patients with T2 tumors and local control of up to 93.5% was reported, being an excellent option for treatment of these patients. In another series by the same authors, local control of up to 100% was reported in lesions of the mid-portion of the cord in comparison with those that occupy its totality. This resulted in guidelines for better staging of patients with the biological understanding of tumors localized to the larynx. At the same time in North America, there were studies such as those performed by Soo, et al.[16] at the Memorial Sloan-Kettering Hospital (New York), with 197 patients who underwent partial vertical laryngectomy, including patients in locally advanced stages. There was low morbidity and mortality and a reported five-year survival of 87%, which is in agreement with other reports[17-19].

Five-year control in conservative open surgery is reported to be from 90-98% and a tracheostomy was always previously considered to be necessary. At present, we are aware that it is not always necessary to perform a tracheostomy in all cases, resulting in lower morbidity[17,19]. For this reason, we conclude that the current indications for performing open surgery are those in which the patient has an invasive tumor which cannot be safely resected endoscopically.

Historically, after the studies by Steiner, et al. in Göttingen, Germany, the use of laser microsurgery for treatment of cancer of the larynx has been expanded to the rest of the world with numerous studies in this regard. Local control at five years in patients treated with laser surgery is reported to be from 85-98%, and the main advantages are reduced treatment time, lower cost, and the opportunity for other available options in case of a recurrence or a second primary tumor in the head and neck region[20].

A large number of articles exist in the literature relating to treatment of early glottic laryngeal cancer with transoral microsurgery with $CO_2$ laser, some of which include tumors localized to the supraglottis, which we excluded because they are not part of this analysis[21]. Use of the transoral microsurgical laser is not reserved only for patients with early tumors, but has also been used for the treatment of well-selected patients with T3 tumors with an adequate oncological control (local and locoregional control from 66 and 83%, respectively) and, as we will mention later, it is also useful in the management of patients with recurrence or bulky disease. It has been seen that in these patients, the percentage of laryngeal preservation can be decreased to 80.5%, such as what has been reported by Motta, et al.[22] or even less as reported by Peretti, et al.[23] (72.7% at five years). The percentage of organ preservation reported in the majority of the series for T1 and T2 tumors is > 95%.

In the analysis of local control, an important difference exists among series, ranging from 84.1% as reported by Pradhan, et al.[24], where the authors show a high percentage of patients with recurrent T2 tumors (23.1%). Local control was 72.9%, which was not observed for TIs, T1a and T1b where local

control was 84.5%. Therefore, we can conclude that local control is in direct relationship with tumor extension and location. Also, in those patients with a lesion located towards the anterior commissure, local control is affected because of the difficulties of exposure and margins which, in the majority of the cases, will be limited (≤ 1 mm), translating to a greater risk of recurrence[25].

Despite the fact that OS in some studies is reported at 36 months or even at 40 months, the behavior is similar in all reports and is > 90%. Disease-specific survival (DSS), although not reported in all series, is ~97%. An important aspect, as mentioned previously, is organ preservation, which impacts on the patient's quality of life. In the majority of the series with transoral laser microsurgery (TLM), it is reported to be ~90-100% and in the series where management is with radiotherapy, this high percentage is also obtained[26-29].

Before the advent of laser surgery, it was believed that the standard treatment for T1 tumors was radiotherapy, and local control at five years was reported from 82 to 89%. Cellai, et al.[30], with 831 patients treated with radiotherapy for T1 tumors, reported a local control of 84%, with DSS of 95%, and a high rate of laryngeal preservation (87%). In patients with T2 tumors treated with radiotherapy, the percentage of local control at five years decreased to 73%, as reported by Frata, et al.[31]. Similar figures are reported for treatment with laser surgery at the same clinical stage. It was also observed in this study that the factors that affect local control are tumor extension and altered cord mobility, which were statistically significant in the uni- and multivariate analysis.

Chera, et al.[32] recently updated the classic Mendenhall study in which the difference regarding local control and OS comparing patients with T1 and T2 tumors is made evident, as well as a slight difference in DSS, showing local control for T1a tumors of 94%; T1b, 93%; T2a, 80%; and T2b, 70%. The DSS and OS were T1a, 97 and 82%; T1b, 99 and 83%; T2a, 94 and 76%; and T2b, 90 and 78%, respectively, and laryngeal preservation at five years was T1a, 95%; T1b, 94%; T2a, 81%; and T2b, 74%.

Dinshaw, et al.[33] studied three treatment regimens based on the time and radiation dosage and reported a local control at 10 years of 82% for T1 and 57% for T2. In this study it is concluded that a greater dosage per fraction with short duration of treatment can be reflected in lower cost and similar toxicity.

An important aspect to evaluate in the management with radiotherapy is waiting time (from histopathological study to initiation of radiotherapy) and availability of equipment, for which Brouha, et al.[34] evaluated radiotherapy waiting time with patient's progress and noted a mean follow-up of 4.4 years and a mean wait time of 43 days. There was no significant relationship with progress in the Cox regression analysis (p = 0.88) because local control was 82.5%. Other authors have shown similar results; however, we know that radiotherapy has oncological results comparable to TLM, as demonstrated by other studies[35-39].

With all this history in the treatment of early laryngeal cancer, it was expected that there were would be controversy in relationship to the established management, whether it is radiotherapy or TLM, and although the majority of the studies are retrospective with a low level of evidence, various articles exist in this regard. As we have observed, the three options (open surgery, TLM, and radiotherapy) are oncologically safe. It is for this reason that differences now are based on voice quality, final treatment cost, and a consideration that has recently gained importance, organ preservation in the long-term evaluation. Of the studies analyzed for the present article, only seven actually retrospectively compare, point by point, both treatments.

When local control is evaluated comparing radiotherapy versus TLM, there is no statistically significant difference for both groups as in the meta-analysis

performed by Higgins[40], which included six series. However, it did not include the series by Schrijvers, et al.[41] who reported less local control for both groups.

There is an important bias in each of the series that influences the results. It is the fact of having more than one treatment modality, as in the series by Rosier, et al.[42] where 10/31 patients subjected to TLM received adjuvant radiotherapy due to positive margins, or that of Smith, et al.[43] where nine patients from the TLM group underwent other treatments such as vertical hemilaryngectomy, total laryngectomy or radiotherapy or, contrary to this, patients who were initially subjected to radiotherapy and who were later subjected to salvage endoscopic surgery.

When we specifically reviewed the percentage of patients who required laryngectomy in the study mentioned previously by Higgins[40], a slight difference exists when the initial treatment is TLM, as observed in the studies by Spector, et al.[44] (14% required laryngectomy for the radiotherapy group vs. 9.8% for the TLM group), Krengli, et al.[45] (8.8 vs. 4% for radiotherapy and TLM, respectively) and in the most recent study by Schrijvers[41] where the difference in preservation was higher for the TLM (95 vs. 77%; p = 0.043). We believe that the difference is important and should be taken into consideration together with the patient in order to carry out treatment[46,47].

Various factors must be taken into account to provide treatment for early laryngeal cancer. Although management is based on studies with a poor level of evidence, the majority of them conclude that there is no statistically significant difference in five-year control and in OS, but there is a greater laryngeal preservation in the long term in those patients who undergo TLM initially, with the advantage of leaving options available in cases of recurrence, and in the case of radiotherapy, the advantage resides discretely in a better voice quality. On the other hand, in the patient who is subjected to initial radiotherapy, we must consider that the opportunity for further radiotherapy is not available and, more frequently, the patient undergoes total laryngectomy.

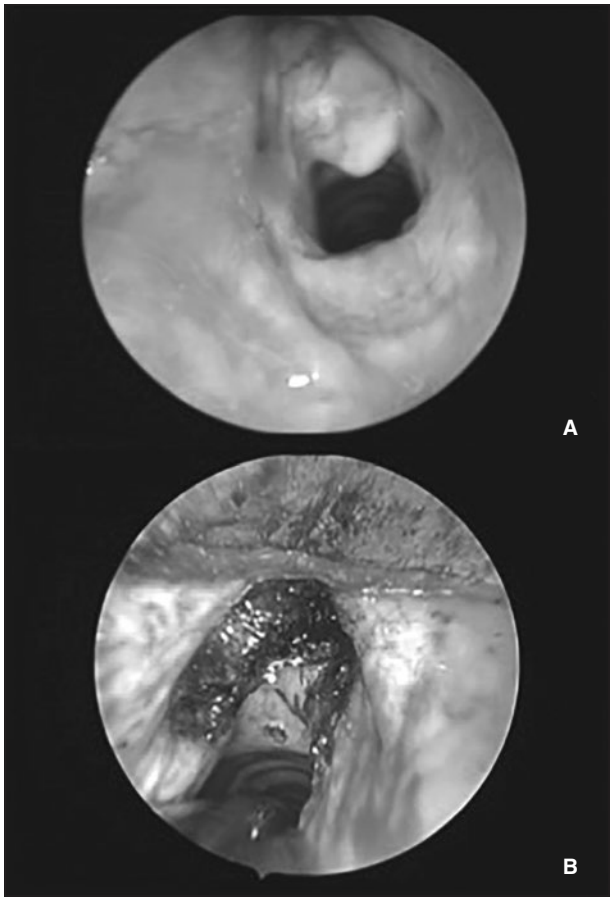


**Figure 2. A:** tumor located in the anterior commissure. **B:** image shows the larynx after laser resection.

In well-selected cases, patients can be rescued with laser surgery or organ-preserving open surgery.

No less important is the infrastructure of the facility where treatment is carried out. The experience of the surgical team is a strong point because it is a fact that the cost/benefit is better for treatment with TLM (Fig. 2).

## LOCALLY ADVANCED

Currently for patients with cancer of the larynx, the treatment model includes organ preservation with curative intent. In spite of this there are no prospective studies that compare conservative surgical treatment with nonsurgical treatment in patients

with locally advanced disease. Given the evidence that exists in the management of patients with T3 disease with an adequate evaluation and selection in relationship with local control with conservative surgery, this may be a viable option, but would depend on the experience of the surgical team and patient preference.

Regarding patients with tumors that require total laryngectomy, we know that there is no improvement in survival or local control with respect to nonsurgical treatment. However, various options for treatment have been studied, which initially were for palliative purposes and later for organ preservation, with the goal of improving quality of life with a functional larynx and with the potential effect of the chemotherapy to act as a systemic cytoreductor and local regional radiosensitizer. The early philosophy for these options were in accordance with the work of Tarpley, et al. in 1975[48] where the authors used methotrexate and leucovorin preoperatively in head and neck tumors.

Later, the first randomized study was the classic study by the Department of Veterans Affairs (VA) Laryngeal Cancer Study Group[49] where a total of 332 patients with stages III and IV laryngeal cancer were studied and were randomized into two treatment groups: total laryngectomy followed by radiotherapy versus chemotherapy followed by radiotherapy, and who responded to treatment and for surgery who did not respond to treatment. The five-year survival rate was the same for both groups (68%). An important characteristic is that the majority of patients were stage III and tumor was localized to the supraglottis. This represented a change in the point of view. Later on, studies such as that performed by GETEC (Groupe d'Etude des Tumeurs de la Teˆte et du Cou) were recognized where 68 patients were analyzed. However, in contrast to the VA study, all patients had arytenoid fixation and only 31% were supraglottic tumors. In this study, the two-year survival was greater than for the surgery group (84%); however, 42% of patients who had chemotherapy did not require laryngectomy[50].

The concomitant treatment bases its use on the concept of radiosensitization, which remains theoretic because it is believed that chemotherapy synchronizes the tumor cells during a phase of the cellular cycle (G2) where it has its greatest action to radiotherapy. Additionally, it could alter the DNA repair mechanisms and have antiangiogenic effects[51]. After the VA study, another key study was published in 2003 by the RTOG 91-11 (Radiation Therapy Oncology Group)[52], which randomized 547 patients with stages III and IV laryngeal cancer; however, they analyzed only 497 patients. The group where the greatest proportion of patients with an intact larynx was observed was that in which the patients received concomitant chemotherapy (cisplatin) and radiotherapy (88%), unlike the group with induction chemotherapy followed by radiotherapy (75%) or radiotherapy alone (70%). Also, the local regional group did better with the concomitant treatment (78 vs. 61% with induction CT, and 56% with radiotherapy alone). If the data in this study are analyzed, we will see that a high percentage of the patients had supraglottic tumors and also a lower proportion of patients had clinical stage IV. Also, patients with T2 tumors were included; however, laryngeal preservation was achieved in a high percentage of the cases.

Regarding the type of radiotherapy, a meta-analysis by Bourhis, et al.[53] analyzed whether the type of radiotherapy may have an impact on survival. Studies that compared conventional radiotherapy with accelerated or hyperfractionated therapy in patients with non-metastatic head and neck tumors were reviewed. There were a total of 15 studies with 5,615 patients. An absolute benefit in survival of 3-4% was observed in those patients who underwent an altered fractionation scheme, and the benefit was significantly greater in the hyperfractionated group (8% at five years) than with accelerated radiotherapy (2% with accelerated fractionation without reduction doses).

A recent study that explores the role of chemotherapy is the study by Pointreau, et al.[54] where the use of docetaxel (T) added to cisplatin and to

5-fluorouracil (PF) is examined in patients with advanced cancer of the larynx and hypopharynx. Laryngeal preservation was greater for the TPF vs. PF group (70.3 vs. 57.5%), which leads us to believe that organ preservation could be seen in a greater number of patients.

Finally, there is a meta-analysis where the role of chemoradiotherapy is evaluated in the treatment of laryngeal cancer. It was performed and updated by Pignon, et al.[55] where an improvement in survival is seen when compared with the use of sequential treatment or radiotherapy alone. Twenty-four new studies were analyzed with a total of 16,485 patients, where an absolute benefit of 6.5% at five years was seen for concomitance. A decrease of the effect of chemotherapy with age was also noted.

We therefore conclude that the patients should be evaluated by a multidisciplinary team. In the case of patients with locally advanced disease, we must be diligent with the feasibility of organ preservation according to degree of laryngeal involvement, its functionality at the time of evaluation, experience of the multidisciplinary team and, of course, patient choice.

## EXCLUSIVE CHEMOTHERAPY

The concept of exclusive chemotherapy or as sole treatment for management of cancer of the glottis has not been well studied worldwide. The concept has been widely studied in France[56,57] and recently by a group at the M.D. Anderson Cancer Center (Houston, TX)[58] as an alternative for organ preservation. The French group has established its results on the basis of platinum and platinum plus 5-fluorouracil with complete responders in up to 21/58 (36.2%) and 35/79 (33%) patients, respectively. The American group has based its chemotherapy results on the basis of TIP (paclitaxel plus ifosfamide plus cisplatin) with complete responders in 11/31 (37%) patients. This group of complete responders represents achievement of organ preservation in 100% of patients, including rescue patients. Organ preservation in general for the French group was 100% and two (5.7%) patients required radiotherapy[58]. The American group reported organ preservation in 83% and five (16%) patients required radiotherapy[59].

However, the observation of these groups is that a large percentage (85%) of patients were found in stages I (n = 9) and II (n = 21) in the French study[57], and in the American study[58] 71% of the patients were in stage II, without taking into account that the latter study had only 14 patients with cancer of the glottis. This may be different for advanced stages where the percentage of complete responders in advanced tumors is not as significant as demonstrated in the study by Laccourreye, et al.[59] where, in patients with induction chemotherapy followed by conservative surgery in stages T3-T4, complete response was shown in 6/60 (10%) patients. A recent review by Holsinger, et al.[60] of the database from the working group of the Hospital Georges Pompidou (Paris) of a cohort of 142 patients showed that in 71 patients (50%), the tumor was localized to the glottis, and in the majority of patients cisplatin plus 5-fluorouracil was the base drug. However, other treatment schemes were used. In this study, 65.5% of patients could have been candidates for conservative surgery from the onset, given the median of five cycles (range: 1-17 cycles) of chemotherapy. Average follow-up time was five years, and T2-T4 tumors were included. Higher OS was noted for tumors of the glottis. Recurrence was 83%; however, after rescue, a control of 97% was obtained for tumors of the glottis and 88.7% for non-glottic tumors (NS, p = 0.09). This suggests that the best candidates for exclusive chemotherapy are patients with carcinoma of the glottis, N0, and with low comorbidities. The limitation of this study is that it does not show the number of patients per T, which leads us to believe that because they are from the same group, the great majority are patients in T2. Validation of the use of chemotherapy is currently far from being the standard of care for organ preservation

of the larynx, and it is necessary to determine the subsite where it demonstrates its greatest utility, especially at present where tumor management in early stages with laser and conservative surgery has shown survival rates from 89 to 100% for T1, 83 to 100% for T2, and from 73 to 91% for stage III, with no toxicity when compared with chemotherapy alone. This approach should be based on institutional protocols with a multidisciplinary group, with strict follow-up for rescue of early recurrences.

## SALVAGE AFTER RECURRENCE IN THE GLOTTIS

Recurrence of carcinoma of the glottis has frequently been associated with radiotherapy alone, and recently to concomitant treatments with chemoradiotherapy. There are various reports in the literature on the management of these recurrences. However, in the era of organ preservation, these recurrences can also occur with transoral laser treatments or open conservative surgeries, or even laryngectomy, but few reports exist with large series where a definitive conclusion can be made.

## RECURRENCE AFTER RADIOTHERAPY

Management of recurrence after radiotherapy can presently encompass a wide range of options such as conservative management with TLS. In the near future we will certainly see reports with robotic approaches, a wide range of conservative surgeries such as frontolateral surgery, vertical laryngectomy, partial vertical laryngectomy, and partial supracricoid laryngectomy with cricohyoidoepiglotopexy or cricohyoidopexy. Ganly, et al.[61] demonstrated that patients who required total salvage laryngectomy had poorer OS and DSS compared with patients who required partial salvage laryngectomy (OS: 50 vs. 89%; p = 0.003; DSS: 51 vs. 93%; p = 0.002). This same observation was made by Holsinger, et al.[62] where overall mortality for patients with total laryngectomy was greater: 73.74% (54/73) vs. 59.4% (19/32) for patients who underwent conservative treatment (p = 0.011).

Piazza, et al.[63] demonstrated that salvage surgery consisted of endoscopic resection with $CO_2$ laser in 22 patients, partial open neck laryngectomy in 15 patients, and total laryngectomy in 34 patients. The pT category after salvage surgery was pT1 in 12 patients, pT2 in 20 patients, pT3 in 20 patients, and pT4a in 19 patients. Five-year DSS and disease-free survival (DFS) and laryngeal preservation for the entire series were 72, 61, and 40%, respectively. However, it is one of the few studies that included all Ts. In general, rescues with conservative surgery are geared towards T1 and T2 tumors and selected T3 cases. Roedel, et al.[64] included rT1 to rT4 with recurrence after radiotherapy in 53 patients who were managed with transoral laser micro-resection. In 24 (42%) patients, only one surgery was necessary and in 31 (58%) patients two surgeries were necessary. However, from this last group, 20 (38%) patients resulted in undergoing total laryngectomy or palliation. Three- and five-year locoregional control rates for all patients were 46.1 and 38.8%, respectively. Three- and five-year OS rates were 67.5 and 53.3%. The corresponding three- and five-year DSS rates were 68.6% each. There was no statistically significant difference in locoregional control or survival among patients presenting initially with early and advanced recurrence.

Partial laryngectomies (vertical laryngectomy, frontolateral laryngectomy, partial vertical laryngectomy, supracricoid with cricohyoidopexy or cricohyoidoepiglotopexy)[65-67] are an excellent option for management of recurrence. However, they can be performed in a third of the patients with laryngeal recurrences and are generally reserved for T1 and T2 tumors and in very carefully selected cases of T3. Organ preservation is achieved in 70-85% of the cases, and the three-year survival is 80-89%; however, at five years it may decrease to 50%, mainly due to local recurrence or metastatic disease[66].

Selection of the procedure is exclusively related to group experience or surgeon preference with some of the techniques. However, it seems that the group with the best survival prognosis is for the glottis, where it has been shown that tumors of the supraglottis have a clear decrease after performing conservative surgery when compared with the glottis[67].

For many years, total laryngectomy has been considered the treatment of choice for patients with recurrence after radiotherapy including, at present, groups who had not been considered candidates for conservative surgery or laser, and it continues to be the first choice. It is also clear that not all patients are candidates for conservative surgery, and currently ~70% of the rescue patients continue to be those with total laryngectomy[61,62].

## RECURRENCE AFTER LASER RESECTION

Resection after laser generally occurs in patients with early clinical stages because few groups are willing to perform laser treatment in advanced stages. Generally, in this group of patients, all treatment options remain open, as if they had not been previously treated. This is also true if the disease is detected in early stages. Mortuaire, et al.[29], in a series of 110 patients in stages Tis to T2, report management options in 22 patients with local recurrence (17 T1a, 1 T1b, and 4 T2): nine patients were managed with total laryngectomy, five patients with partial laryngectomy, four patients with further laser cordectomy, two patients with radiotherapy, and two patients had no curative treatment. Roedel, et al.[68] in the Göttingen group in Germany reported that 44 patients (78.6%) presented with early local recurrence in stages I/II, and 12 patients (21.4%) had advanced local or locoregional recurrence in stages III/IV. Three- and five-year locoregional control was significantly higher for patients treated for early recurrence (67.6 vs. 27.5% and 63.6 vs. 27.5%, respectively; p = 0.02). Salvage laryngectomy rates for patients with early and advanced recurrence were 9.1 and 25.0%, respectively. Three- and five-year OS rates for patients with early and advanced recurrence were 75.1 vs. 51.6% and 61.6 vs. 25.8%, respectively.

## RECURRENCE AFTER OPEN CONSERVATIVE SURGERY

The possibilities of organ preservation in a recurrence after conservative surgery are very low. Laccourreye, et al.[69] reported organ preservation of only 6.6% in patients with prior supracricoid laryngectomy, with a local control after treatment with total laryngectomy of radiotherapy of 80%. At the present time, another possibility could be concomitant chemoradiotherapy. However, this possibility is also seen as not suitable because the main symptom that these patients present is dyspnea. These patients are almost always candidates for radical surgery. Patients with low-grade recurrences may be candidates for laser treatment; however, at present this is almost anecdotal. Another series from China[70] reports salvage with partial laryngectomy in 26/77 (34%) patients. After salvage surgery, three- and five-year cumulative OS rates were 59.1 and 52.7%, respectively, and both the three- and five-year local recurrence rates were 30.7%. Most patients (48.4%) died due to failure at the primary sites. Luna-Ortiz, et al.[71], in a series of patients with vertical partial laryngectomy and reconstruction with imbrication of the false vocal cord, report the case of a patient who was able to be subjected to supracricoid laryngectomy with cricohyoidoepiglottopexy.

## NEW TECHNIQUES

The use of transoral robotic surgery (TORS) in head and neck surgery has yielded great advantages in tridimensional magnification, increasing the degrees of freedom of its arms and, therefore, a distal articulation that resembles the human hand regarding its movements. This technique has the goal of optimizing cancer management with a reduction in treatment-related morbidity. Its main indication at

the present time for management of laryngeal tumors has been limited to the supraglottis. The first report of TORS was made by McLeod and Melder in 2005[72] for a cystic lesion of the epiglottis. In the glottis, Park, et al.[73] reported three cases of cord lesion resection; however, a tracheostomy was performed, which is a disadvantage when compared with open conservative surgery or compared to SML and laser treatment. Robotic surgery allows *en bloc* resection as opposed to "piecemeal" cutting of the tumor with the laser. However, there is currently no advantage or disadvantage in making this statement in any study, and much less for the larynx where microscopic resection of early tumors allows for only the necessary resection without performing greater unnecessary tissue ablation[74]. For advanced tumors, it is possible to perform *en bloc* resection by means of SML and laser. In conclusion, at the present time, TORS has a limited application in the glottis, mainly due to poor exposure and for not having the appropriate instruments necessary to carry out this surgery in the glottis.

Endoscopic resection with microdissection electrodes[75] is an ultrafine tungsten design that consist of ultra sharp, tungsten needle electrodes (21-cm long) angled at 90° (right and left), 135° and 180°. The proximal portion of the shaft is bent and inserted into a conventional electric scalpel hand piece. The electrosurgical generator is set to an output power of 5-20 W for resection of soft tissue or cartilage. Bleeding is treated by clamping the vessels with mini-forceps and electrocoagulation. Exposure is under conventional suspension laryngoscopy, the same as laryngoscopes used for $CO_2$ laser. Microdissection electrodes have several advantages over $CO_2$ laser: shorter operating time, improved hemostasis, easier handling, and lower cost and maintenance of the equipment[75].

## CONCLUSIONS

Diagnosis at present should include management with 30°, 70°, and 90° telescopes as well as SML, with the goal of performing conservative management of the larynx. Imaging studies continue to be an important tool, especially when combined with endoscopic and clinical diagnosis. Treatments for early glottic tumors based on surgery, radiotherapy, or TLM have similar survival rates; however, there is a slight advantage in long-term organ preservation when initial treatment is done with TLM. Open surgery has the disadvantage of poor voice quality compared to that obtained with radiotherapy or TLM, as well as demonstrating higher morbidity. The T3N0M0 tumors could be considered for these modalities of treatment in strictly selected cases and with close follow-up to detect early recurrence. For advanced tumors in the era of organ preservation, as an option we can use chemoradiotherapy with proper patient selection. We must always consider pre- and post-treatment morbidity because, if treatment is not applicable to the patient, we are aware that there will be no difference in survival if treatment is done with radical surgery and adjuvant radiotherapy. When faced with recurrence, management will depend on the primary treatment. Patients treated with radiotherapy can be rescued with open surgery or, if it is early, for those patients who have undergone open surgery, radiotherapy or TLM should be an option. In selected cases, a new conservative surgery could be performed. For patients with initial TLM, all management options are reserved as rescue, as if it were a *de novo* treatment.

Exclusive chemotherapy is a treatment, which, until now, has not been fully explored. A high percentage of response has been noted; however, its maintenance is a high point of its use so a larger number of cases are required. The new technologies appear promising, but in the glottis their role is still unclear, as in the case of TORS.

## SEARCH STRATEGY AND SELECTION CRITERIA

References for this review were identified through searches of PubMed using the search terms "larynx",

"glottic cancer", "transoral laser microsurgery", and "radiotherapy" "chemoradiotherapy" from 1980 until August 2011. Articles were also identified through searches of the authors' own files. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

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