Clinical Investigation

Could the Addition of Cetuximab to Conventional Radiation Therapy Improve Organ Preservation in Those Patients With Locally Advanced Larynx Cancer Who Respond to Induction Chemotherapy? An Organ Preservation Spanish Head and Neck Cancer Cooperative Group Phase 2 Study

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Summary
In stage III and IVA larynx cancer, organ preservation protocols are optimal alternatives to total laryngectomy. Induction chemotherapy permits the selection of the best local treatment, being radiation therapy in patients with response. The addition of cetuximab could increase locoregional control and functional larynx preservation, in contrast to increasing chronic toxicity of a concomitant chemoradiotherapy alternative.

Purpose: To evaluate the efficacy and safety of induction chemotherapy (IC) followed by bioradiotherapy (BRT) to achieve functional larynx preservation in the setting of locally advanced head and neck tumors.

Methods and Materials: This was a phase 2, open-label, multicenter study of patients with stage III and IVA laryngeal carcinoma who were candidates for total laryngectomy. The primary endpoint was the rate of survival with functional larynx (SFL) at 3 years, with a critical value to consider the study positive of SFL >59%. Patients received 3 cycles of IC with TPF (docetaxel, cisplatin, and 5-fluorouracil), and those who responded received conventional BRT with cetuximab. In patients with residual nodal disease after BRT, neck dissection was planned 2 months after BRT. Patients who did not respond to IC underwent total laryngectomy plus neck dissection and radiation therapy.

Results: A total of 93 patients started TPF. Responses to IC on larynx target lesion were as follows: 37 patients (40%) showed a complete response; 38 patients (41%) showed a partial response; 8 patients (9%) showed stabilization; 2 patients (2%) showed progressive disease, and 8 patients (9%) were not evaluated (2 deaths, 5 adverse events, and 1 lost to follow-up). Seventy-three patients (78%) received BRT: 72 as per protocol, but 1 with only stable disease. Median follow-up was 53.7 months. Three-year actuarial rates were as follows: SFL: 70% (95% confidence interval [CI] 60%-79%); laryngectomy-free survival: 72% (95% CI 61%-81%); overall survival: 78% (95% CI: 63%-82%). The acute toxicity observed during both IC and BRT was as expected, with only 1 toxicity-related death (local bleeding) during BRT.

Conclusions: According to this protocol, the SFL rate was clearly higher than the critical value, with acceptable levels of toxicity. The use of cetuximab added to radiation therapy in patients with stage III and IVA laryngeal cancer who respond to TPF could improve functional larynx preservation. A phase 3 trial is warranted.

Introduction
The first study evaluating the possibility of avoiding total laryngectomy (TL) in patients with locally advanced laryngeal cancer was published 25 years ago (1). Induction chemotherapy (IC) followed by conventional radiation therapy (RT), in those patients who had responded, demonstrated organ preservation without significantly affecting overall survival.

A decade later, the usefulness of IC was questioned when a published article reported the first results of the Radiation Therapy Oncology Group (RTOG) 91-11 study (2), claiming that concomitant treatment with RT and cisplatin was superior in locoregional control and larynx preservation. These data were consistent with the results of the meta-analysis on the use of chemotherapy published a few years earlier (3), and as a result, most institutions changed their approach to larynx preservation from IC to concomitant chemotherapy.

Optimization of IC produced by introducing docetaxel (Taxotere, T) to the classic platinum plus fluorouracil (PF) scheme (4, 5) enabled its use in organ preservation protocols, and the GORTEC (Groupe d’Oncologie Radiothérapie Tête Et Cou) group demonstrated that the 3-drug schedule with TPF was clearly superior to PF for larynx preservation (6).

Cetuximab is a chimeric monoclonal antibody that binds with high affinity to the extracellular domain of the epidermal growth factor receptor and induces antibody-dependent cellular cytotoxicity (7). The combination of cetuximab plus RT has demonstrated superior efficacy and has only slightly increased toxicity as compared with RT alone (8).

Cetuximab combined with RT seems to be as effective as cisplatin in organ preservation, with a different pattern of acute toxicity after induction with TPF (9), which could result in higher rates of larynx preservation. The aim of our study was to evaluate survival with functional larynx (SFL) after RT plus cetuximab in patients who respond to IC with TPF.

Methods and Materials
Study patients
From October 2008 to February 2011, previously untreated patients between 18 and 70 years of age with stage III and IVA squamous cell carcinoma of the larynx, and candidates for TL according to each local multidisciplinary committee,
were included in this trial. Patients were followed up until May 2015. The protocol was approved by all institutional review boards at the participating institutions, and all the patients provided written, informed consent.

**Study design and treatment**

This was a prospective, multicenter, phase 2 study. Patients were initially treated with 3 cycles of TPF (docetaxel: 75 mg/m² on day 1; cisplatin: 75 mg/m² on day 1; and 5-fluorouracil 750 mg/m², continuous infusion, on days 1 to 5, with granulocyte–colony stimulating factor 300 μg/kg subcutaneous support from days 6 to 10). Patients with a local (laryngeal tumor) response (according to World Health Organization criteria) were measured clinically and by cervical computed tomography (CT) scan and received treatment with conventional RT (70 Gy/7 wk) with cetuximab at the standard dose (400 mg/m² as a starting dose 1 week before RT, followed by 250 mg/m² weekly during RT).

Radiation therapy treatment was performed with conformal 3-dimensional radiation. No patients were treated with intensity modulated radiation therapy. A thermoplastic mask was used for RT planning. Cervical CT was done before IC started (gross tumor volume plan) and repeated before the third cycle in case bulky nodal disease was present, to perform a second planning. The International Commission on Radiation Units and Measurements report 50 was used for volume design. Three dose levels were used: clinical target volume (CTV) high dose (70 Gy; 2 Gy per fraction); gross tumor volume plus 5 mm without bone and air; CTV intermediate dose (60 Gy; 2 Gy per fraction) in cases of positive lymph nodes; and CTV low dose (50 Gy; 2 Gy per fraction) in all patients at II to IV lymph node areas (10, 11). There were no differences between supraglottic and larynx doses, except for a 60-Gy boost in glottic tumors with a previous tracheostomy.

Salvage neck dissection was performed in patients with persistent nodal disease and primary tumor control. Nonresponders underwent TL plus postoperative RT (60-66 Gy).

**Study evaluations**

Basal tumor measurement was performed through a complete physical examination of the larynx and cervical lymph node areas, including physical measurements of tumor-affected areas, emphasizing the following characteristics: location (laryngeal affected subsites) and size (measured in 2 dimensions). Radiographic imaging methods (CT scan or magnetic resonance imaging) were also performed to enable a full study of locoregional tumor disease. Positron emission tomography—computed tomography was not part of the diagnostic study but was allowed in cases of suspected metastasis.

Laryngoscopy was repeated after each cycle of IC, and cervical imaging study was repeated after 3 cycles to evaluate the response to TPF. In the follow-up period, laryngoscopy was performed every 3 months for the first 3 years, then every 6 months until the fifth year. Cervical imaging assessments were performed every 6 months until the fifth year.

Baseline studies and radiologic evaluations were performed using identical techniques to ensure an adequate comparison. A basal chest X ray was taken, and then chest X rays were repeated annually.

**Study endpoints**

The primary endpoint of the study was to evaluate the specific SFL rate at 3 years in patients with local tumor response (T lesion) after TPF and sequential bioradiotherapy (BRT). Survival with functional larynx was defined as the time from the start of IC until death, local relapse, or loss of larynx function (absence of natural speech, the presence of a tracheostomy, and/or the presence of a feeding tube for >2 years after the end of treatment) (12).

Secondary endpoints included overall response rate after IC, specific response rate on local tumor (larynx), overall survival, disease-free survival, laryngectomy-free survival, locoregional control, and differences in these efficacy parameters according to IC response, safety of IC, and sequential BRT.

The acute toxicity of the treatment was evaluated through the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 3.0 (www.cancer.gov).

**Statistical methods**

We used the interactive program One Arm Survival to calculate sample size for null and alternative median survival rates assuming an exponential distribution (https://stattools.crab.org/). The study was designed to evaluate 3-year SFL in patients who responded to TPF. We considered 3-year survival rates of 50% as unacceptable and rates of 65% as acceptable. With a recruitment time of 24 months and a minimum follow-up of 36 months, a probability of declaring the experimental arm as active if the true rate is ≤50% of 0.05 (α, 1-tailed test), and a probability of rejecting the experimental arm if the true rate is compatible with 65% of 0.1 (β), we found that the required sample size was 74 patients. Assuming a response rate of 85% for the patients receiving TPF, we needed to include a total of 88 patients. An additional 7.5% was added to account for any loss of evaluable patients. The final required sample size was 94. According to this interactive program, the treatment efficacy after a minimum follow-up of 36 months was considered to be positive if the 3-year survival rate with
functional larynx was greater than 59% (critical value) and negative if it was lower than 59%.

An intent-to-treat analysis was performed. Descriptive statistics, including mean, standard deviation, median, minimum, and maximum for continuous data and number and percentage of subjects for categorical data, were used to describe patient demographics as well as pathologic and clinical characteristics. The distributions of SFL, overall survival, disease-free survival, laryngectomy-free survival, and locoregional control were estimated using the Kaplan-Meier method.

**Results**

**Patient characteristics**

A final total of 94 patients were enrolled in the study (see Fig. 1 for intent-to-treat population), and 1 patient was excluded because he did not fulfill 1 of the inclusion criteria (renal insufficiency) and therefore did not start IC. Demographic, clinical, and pathologic characteristics of the modified intent-to-treat population (n=93) are represented in Table 1. The following factors are also worth mentioning: the limited inclusion of women (8%), the high proportion of supraglottic localizations (66%), and the final inclusion of 2 patients with N3 disease (stage IV-B) considered resectable by the oncologic committee. Half of the patients were stage III, and half were stage IV. A tracheostomy was performed in 12 (13%) of the patients before IC started.

**Acute IC toxicity**

A total of 261 (94%) cycles of chemotherapy (TPF) were administered. A total of 86 patients (91%) showed adverse events (AEs) related to TPF. In 31 cases (33%) these AEs were grades 3 or 4, the most frequent being mucositis, asthenia, neutropenia, and febrile neutropenia. Other severe AEs cases included 2 patients with myocardial ischemia during fluorouracil infusion, 2 patients with enteritis, 1 patient with renal failure, 2 cases of electrolyte disorders, and 1 patient with sepsis. There were 2 nonrelated deaths (1 unknown and 1 due to esophageal varices bleeding in a patient with previously unknown cirrhosis). The main TPF toxicities are shown in Table 2.

**Chemotherapy compliance and response**

Induction chemotherapy with TPF was delivered to 83 patients (89%) according to the protocol, with a fully programmed dose intensity of 85% for docetaxel and cisplatin and 72% for fluorouracil. Ten patients (11%) did not complete the 3 cycles of TPF: 8 patients received only 1 cycle owing to AEs (1 myocardial ischemia, 1 grade 4 diarrhea, 2 grade 4 febrile neutropenia, and 2 renal insufficiency cases) and 2 deaths. Two patients only underwent 2 cycles: 1 nonresponder who underwent TL and 1 with an allergic reaction to chemotherapy. In addition, 3 patients had a delay, and 11 patients required a dose reduction due to AEs. The overall response rate to IC on targeted larynx lesions was 81% (37 [40%] complete responses [CRs] and 38 [41%] partial responses [PRs]). Stable and progressive disease was 8% and 2%, respectively. In 8 patients (9%) this response was not evaluated (2 deaths, 5 AEs, 1 lost to follow-up). Global response by CT scan (T + N) was 27% CR, 52% PR, 5% stable disease, 4% progression, and 12% unknown.

**RT plus cetuximab**

Radiation therapy plus cetuximab for larynx preservation was administered to 73 patients (78%) (72 as per protocol,
but 1 with only stable disease). Another 3 patients with partial response on the target larynx region did not continue with RT: 2 patients with no lymph node response (1 in disease progression) and the other because of the investigator’s decision. All but 2 patients (1 toxicity-related death and 1 non—toxicity-related death) completed the planning RT treatment. Patients received a median dose of 70 Gy, which was given in 35 fractions of 2 Gy each during 7 to 8 weeks (range, 14-74 Gy), except for 8 patients (11%) whose duration of RT was more than 8 weeks. The median number of cetuximab infusions was 8 (range, 4-11), and 71 patients (97%) received the planned dose without any reduction.

Of them, 65 (89%) showed at least 1 AE related to this treatment. In 34 patients (47%), the AEs were grades 3 to 4, and the most frequent events were mucositis, radiodermatitis, odynophagia, dysphagia, and skin toxicity outside the radiation field. There was only 1 toxicity-related death (local bleeding during concomitant treatment). The main toxicities to RT plus cetuximab are shown in Table 3.

**Surgery**

After IC, 9 patients (10%) underwent TL (3 with local progression, 1 with lymph node progression, 3 with stabilization after TPF, and 2 with severe AEs after the first cycle of IC). A total dose of 60 to 66 Gy was delivered, depending on surgical margin and lymph node status on pathologic review, as postoperative RT. Five patients (5%) underwent neck dissection due to residual neck disease. Two patients with stable disease were treated with concomitant chemoradiotherapy according to patient decision. Nine patients (12%) underwent TL because of a recurrence during the follow-up, and an additional 5 patients (7%) underwent neck dissection because of nodal recurrence.

**Efficacy parameters**

With a median follow-up of 54 months, the 3-year actuarial rates were as follows: SFL: 70% (95% confidence interval...
[CI] 60%-79%) (Fig. 2A); laryngectomy-free survival: 72% (95% CI 62%-81%) (Fig. 2B); disease-free survival: 69% (95% CI 60%-79%) (Fig. 2C); and overall survival: 78% (95% CI 69%-86%). Overall survival at 5 years was 73% (95% CI 63%-82%) (Fig. 2D). In total there were 24 deaths (26%) at the data cutoff (May 12, 2015), and the causes were as follows: 15 patients with disease progression, 5 patients with intercurrent disease, 1 toxicity-related death (tumoral hemorrhage during concomitant treatment), and 3 deaths of unknown cause.

According to the statistical design of our study, we considered this a positive study because the 3-year SFL was 69.7% (95% CI 60%-79%), a clearly better result than 59% (critical value established in the statistical design).

The quality of response to IC influenced the combined endpoint survival with a functional larynx, appreciating better results in patients who achieved complete remission (85% [95% CI 73%-97%] and 73% [95% CI 53%-92%] at 3 and 5 years, respectively) in relation to those with partial response (71% [95% CI 57%-86%] and 53% [95% CI 34%-72%] at 3 and 5 years) (Fig. 3A). However, there was no impact on overall survival (Fig. 3B).

Of the 12 patients with a previous tracheostomy, there was 1 CR, 8 PRs, 1 patient with stable disease, and 2 patients with disease progression reported, of whom the last 3 patients underwent TL after IC. Half of them remain alive and without progression, and 3 (25%) have regained a functional larynx.

**Discussion**

All trials investigating organ preservation that have used an IC arm have also used RT alone as the local treatment in patients who demonstrated an almost PR (1, 2, 6, 13). Our study was designed to evaluate the role of cetuximab added to RT in maintaining locoregional control and reducing chronic toxicity (pharyngo-larynx functionality). We found that BRT with cetuximab was superior to the use of RT alone in locoregional control (8), and possibly also in larynx preservation (14). Controversy continues regarding the standard treatment for organ preservation (2, 6).

The addition of cetuximab to RT in patients who responded to IC with TPF seems to increase survival with a functional larynx. When we calculated our critical value (59%) we relied on the preliminary results presented by the GORTEC 2000-01 trial (6), which reported approximately 70% of patients having a 3-year larynx preservation rate. We only somewhat reduced this value to calculate functionality (SFL) on the basis of our previous results with PF when comparing both items (15). Data reported at 5 to 10 years by the French group indicated that little is lost in larynx dysfunction—free survival from 3 years (16), unlike the loss that happened with concomitant chemoradiotherapy in RTOG 91-11 (17). We should also evaluate these parameters at 5 and 10 years to determine the BRT outcomes through further follow-up.

Previously published study results in which we used IC with PF followed by accelerated RT (15), to increase

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**Fig. 2.** Kaplan-Meier plots for survival with functional larynx (A); laryngectomy-free survival (B); disease-free survival (C); and overall survival (D). Abbreviation: mITT = modified intent to treat.
Locoregional control in patients with only stage III laryngeal cancer, achieved excellent results in larynx preservation, especially in patients with CR after IC. Nevertheless, the hyperfractionated RT used in that protocol was responsible for a 10% drop in laryngeal function. Some patients needed permanent tracheostomy or feeding tubes, whereas some with permanent larynx dysfunction underwent TL.

Induction chemotherapy allows the best selection of candidates to be treated by RT or BRT and avoid TL. The introduction of the new schemes with TPF showed an increment of locoregional control (5) and overall survival compared with PF (4, 5) in locally advanced disease and in organ preservation. Treatment with TPF also increases the laryngeal preservation rate and organ function (6). The addition of cisplatin to RT seems to lead to difficulties in compliance with the treatment and also provides more late toxicity (9). This also occurs with concomitant chemoradiotherapy without induction, whereby there is an increase in deaths unrelated to tumor or treatment (18) and possibly also a loss of laryngeal function in relation to the higher late toxicity related to chemoradiotherapy compared with BRT (19). The quality of response to IC influenced the combined endpoint survival with a functional larynx, achieving better results in patients with CR. However, there was no impact on overall survival because TL permits the rescue of patients with local recurrence.

We advocate the use of IC instead of concomitant chemoradiotherapy. Historical trials using induction with PF (1, 13) demonstrated similar results in overall survival as with the use of surgery. The next step was to compare IC with PF versus concomitant RT plus cisplatin; the former showed better results in locoregional control and larynx preservation (2). However, this trial (2) did not report its main endpoint until several years later, when an update was published (17): laryngectomy-free survival (LFS). The conclusion of the RTOG 91-11 study (2) was that induction PF followed by RT and concomitant cisplatin/RT showed similar efficacy for the composite endpoint of LFS. The patients included in our trial are similar to those included in RTOG 91-11. We have presented a 3-year LFS of 72% (95% CI 62%-81%), clearly better than the 60% achieved in the 2 arms of the RTOG trial and similar to the TPF arm of the GORTEC 2000-01 trial (70%) (6). Our sequence of treatment is more similar to the TREMPLIN trial (9), with a TPF arm followed by BRT. Comparing both, we can observe that the functional organ preservation rate and overall survival are very similar: a 3-year overall survival rate of 73% in the BRT arm and 75% in the concomitant cisplatin arm, and exactly the same 2-year laryngo-esophageal dysfunction-free survival rate (72% in both trials).

Concomitant treatment can increase locoregional control and therefore larynx preservation (2). However, the downside is the increase in competitive death (17, 20). Therefore, concomitant treatment is unable to improve the composite endpoint of laryngectomy-free survival—an essential factor in larynx preservation trials (12). Even the induction arm (PF) in this trial had better overall survival in the long term than the concomitant treatment arm, although this finding was not statistically significant (17). In fact, we know from studies (20) that the probability of death from the patient’s underlying condition is approximately 20% in patients included in clinical trials with concomitant chemoradiotherapy. Comorbidities play an important role in reducing overall survival in trials with concomitant treatments and possibly a smaller role in trials with induction followed by RT (6, 16) or BRT (9).

In conclusion, in patients with advanced laryngeal cancer who were candidates for TL, the addition of cetuximab to RT in those who respond to IC with TPF seems to increase SFL, with no increment of chronic toxicity that influences the loss of esophageal—laryngeal function in follow-up.

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