What Is the Optimal Larynx Preservation Approach and Who Are the Candidates?

Jean Louis Lefebvre

Since the beginning of the twentieth century two major options were available for the treatment of laryngeal and hypopharyngeal squamous cell carcinomas: definitive irradiation or laryngectomy with or without postoperative irradiation. The respective indications varied according to institutional policies.

In the past, there were no concerns about the function of the larynx in patients with early disease, as both partial laryngectomy and irradiation did not compromise laryngeal function. However, the contrary was true for patients with locoregionally advanced disease, who required total laryngectomy. Total laryngectomy was able to control most of these diseases but at the price of notable sequelae compromising the quality of life (loss of a normal voice and permanent tracheostomy). Radical irradiation was also able to control these diseases but sometimes with post irradiation sequelae (fibrosis for example) that could compromise the larynx function and the salvage surgery when required. The published series of surgery and of irradiation were difficult to compare. Actually these series did not consider similar populations (resectable diseases in operable patients in the surgical series vs less selected tumours and populations in the radiation ones). In addition all were retrospectives series.

Unfortunately there was no consensus for initiating what should have been the first larynx preservation randomized trial comparing radical surgery vs definitive irradiation in similar groups of advanced larynx cancer patients. This information is missing forever.

All along the century, surgical research aimed at extending the indications of partial laryngectomies as well as at improving the quality of voice rehabilitation (in particular with the use of trachea-oesophageal puncture and insertion of a voice prosthesis). In parallel the radiotherapy research aimed to improve the disease control in particular with different modalities of altered fractionation. These researches did not notably change the picture and the debate remained open.

J. L. Lefebvre
Centre Oscar Lambret, Lille, France

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For long there were no efficient chemotherapy regimens that could be integrated in the armamentarium of treatment with curative intent for head and neck cancers. Chemotherapy was mainly used for palliation. In the 1980s the Wayne Sate University published its experience of induction chemotherapy using cisplatin and 5-fluorouracil in previously untreated patients with head and neck cancers. In a series of 35 patients treated with three cycles of induction chemotherapy with cisplatin and 5-fluorouracil (the so-called PF protocol) they observed a reduction of at least 50% of the local disease in 94% of the patients and a complete clinical disappearance of the disease in 63% of the patients [1]. Despite it concerned a small series of patients these results showed that induction chemotherapy potentially could be used in protocols with curative intent. They also published their results in 60 patients treated by induction cisplatin-based chemotherapy showing that in the 42 patients who had demonstrated a tumour response over 50%, 97% of them were controlled by a subsequent irradiation. On the contrary only 6% of the 18 patients with a tumour reduction below 50% were controlled by a subsequent irradiation [2]. These results generated the concept of a possible selection role of induction chemotherapy that could be used in the frame of advanced larynx cancers treatment pending there was no deleterious impact on disease control and survival. In that respect, it is worth mentioning that the Chicago team published a prospective study in which they concluded that by far the priorities for head and neck patients are "being cured of the disease" and "living long" and patients are more willing than non-patients to undergo aggressive treatments and endure acute distress in the interest of these potential long-term gains [3]. On these bases the clinical research on larynx preservation started when the best definition of "larynx preservation" still had to be defined.

The Validation Trials

The concept of these prospective randomized larynx preservation trials was to compare in suitable previously untreated HNSCC patients total laryngectomy with postoperative irradiation as a control arm with a control arm an experimental arm i.e. induction PF followed in responders by irradiation and salvage surgery if required or by a total laryngectomy with postoperative irradiation in other patients. The goal of this research was to assess the safety of the concept and the primary endpoint was overall survival. Each cycle of chemotherapy consisted of cisplatin 100 mg/m^2 on day 1 followed by 5-fluorouracil 1000 mg/m^2/day during 5 days and was delivered every 3 weeks. Definitive irradiation was delivered at a dose of 70 Gy and postoperative irradiation at a dose of 60 Gy. "Responders" to chemotherapy were defined as patients with a tumour regression of at least 50%.

The Veterans Administration Larynx Cancer Study Group (VALCSG) Trial [4]

In the United States, the department of VALCSG conducted such a trial in 332 laryngeal cancer patients. Of those, 166 were randomly enrolled in the control arm and 166 in the experimental arm, which consisted of two cycles of PF followed in responders by a third cycle and irradiation or surgery and postoperative irradiation in non-responders. Overall survival was the primary endpoint. At a median follow-up of 33 months, the 2-year survival was 68% in both treatment arms (95% Confidence Interval [CI]: 60–75% in the surgery arm vs 60–76% in the chemotherapy arm, P = 0.9846) and the larynx was preserved in 64% of the patients in the experimental arm. In the chemotherapy arm, salvage laryngectomies were indicated significantly more often in patients with stage IV disease than in those with stage III (p = 0.048) and the same was true for those with T4 diseases versus those with T3 disease (P = 0.001). Of note distant metastases were observed less frequent in the chemotherapy arm.

The European Organization for Research an Treatment of Cancer (EORTC) 24891 Trial [5, 6]

In Europe, the EORTC Head and Neck Cooperative Group conducted a similar trial in patients with advanced hypopharyngeal and lateral epilarynx tumours requiring a total laryngectomy. In this EORTC 24891 trial, 194 previously untreated patients were enrolled. A partial response (PR) after two or three cycles of chemotherapy was required to receive radiation therapy. Chemotherapy consisted of 100 mg/m^2 cisplatin given intravenously over a 1-h period followed by fluorouracil 1000/m^2/day given as a 120-h infusion over 5 days (total dose 5000 mg/m^2). The primary endpoint was overall survival in terms of non-inferiority in the experimental arm with a hazard ratio (HR) $\leq$1.43. In the first evaluation the median duration of survival was 25 months in the immediate-surgery arm and 44 months in the induction-chemotherapy arm and, since the observed hazard ratio was 0.86 (log-rank test, P = 0.006), which was significantly less than 1.43, the two treatments were judged to be equivalent. The 3- and 5-year estimates of retaining a functional larynx in patients treated in the induction-chemotherapy arm were 42% (95% CI: 31–53%) and 35% (95% CI: 22–48%), respectively. In addition there were fewer distant metastases in the chemotherapy arm.

These results were confirmed by long-term evaluation. At a median follow-up of 10.5 years, the 5-year and 10-year overall survival rates were respectively 32.6% (95% CI: 23.0–42.1%) and 13.8% (95% CI: 6.1–21.6%) in the surgery arm vs

38.0% (95% CI: 28.4–47.6%) and 13.1% (95% CI: 5.6–20.6%) in the chemotherapy arm. In 37 patients still alive at 5 years in the chemotherapy arm, 22 (59.5%) had retained a normal larynx.

Conclusions of Theses Two Trials

These two trials showed that the concept was validated both for laryngeal and hypopharyngeal cancers, larynx preservation could be obtained in around two thirds of the patients without compromising survival or disease control. This clinical research therefore continued with larynx preservation (under various definitions) as the primary endpoint.

The Concept of Larynx Preservation

There are different ways to consider larynx preservation. The simplest one is to define it by the only one parameter: larynx in place (i.e. no laryngectomy), whatever the local control and the function. A more comprehensive one is to consider both the organ and its function: no laryngectomy, no long-term tracheotomy, and no long-term feeding tube, which implies also that local control is obtained. As survival is an important issue, it may also be integrated: either laryngectomy-free survival, or, more detailed, survival with a functional larynx in place. A group of experts has worked on the best definition of larynx preservation taking into account all parameters participating to the real benefit for the patients. They elaborated the "laryngoesophageal dysfunction-free survival" that combined as events: death, local failure, salvage laryngectomy, and tracheotomy or feeding tube at 2 years or later [7, 8]. Of course when evaluating a report on larynx preservation, it is of the upmost importance to consider which definition has been used before comparing the results with other reports. Rosenthal has applied these various definitions to the same database; the curves were impressively different [9].

Trial with Concomitant Administration of Chemotherapy and Radiation Therapy

The EORTC 24954 Trial for Alternating Chemo-Irradiation [10, 11]

The EORTC Head and Neck and Radiotherapy Oncology Cooperative Groups designed a randomized trial in order to assess whether more cycles of chemotherapy could improve both the survival and the larynx preservation rate. The EORTC 24954

trial compared two different schedules for delivering the chemotherapy cycles and the irradiation: a sequential schedule like in the previous trial versus an alternating one as described by Merlano et al. [12]. The sequential arm consisted of two cycles of PF with the same doses and administration as in the 24891 trial. After 2 cycles responders received two additional cycles of PF and were then treated with irradiation at a dose of 70 Gy. The non-responders were treated by total laryngectomy and postoperative irradiation. In the alternating arm, patients received on weeks 1, 4, 7, and 10 a cycle of chemotherapy consisting of cisplatin at a dose of 20 mg/m^2 per day on days 1–5 (for a total dose of 100 mg/m^2) and 5-fluorouracil by bolus infusion at a dose of 200 mg/m^2 per day on days 1–5 (for a total of 1000 mg/m^2). During the three two-week intervals patients were treated by irradiation at a dose of 20 Gy per course for a total of 60 Gy. As a result, the total doses of 5-fluorouracil and of irradiation were lower in the alternating arm. A total of 450 patients were enrolled in this trial (224 to the sequential arm and 226 to the alternating arm).

For the first evaluation the median follow-up was 6.5 years. Survival with a functional larynx was similar in the sequential and alternating arms (hazard ratio of death and/or event = 0.85, (95% CI: 0.68–1.06), as were median overall survival (4.4 and 5.1 years, respectively) and median progression-free interval (3.0 and 3.1 years, respectively). Grade 3 or 4 mucositis occurred in 64 (32%) of the 200 patients in the sequential arm who received radiotherapy and in 47 (21%) of the 220 patients in the alternating arm. Late severe oedema and/or fibrosis was observed in 32 (16%) patients in the sequential arm and in 25 (11%) in the alternating arm.

For the long-term evaluation, the median follow-up was 10.2 years. Ten-year survival with a functional larynx (primary end-point) and overall survival were similar in the sequential and alternating arms (18.7% and 33.6% versus 18.3% and 31.6% respectively). Late toxicity was also similar even if there was a trend for higher larynx preservation and better laryngeal function in the alternating arm. However due to the organizational difficulties when delivering such an alternating schedule in daily practice, it is rarely used.

The Radiation Therapy Oncology Group (RTOG) 91-11 Trial for Concurrent Chemo-Irradiation [13, 14]

A large meta-analysis [15] had demonstrated that concurrent radiotherapy plus cisplatin (100/m^2 on days 1, 22 and 43 of the radiotherapy) achieved a significantly higher survival benefit when compared with induction cisplatin fluorouracil.

The RTOG and the Head and Neck Intergroup in the US conducted a three-arm randomized trial comparing the standard alternative to total laryngectomy validated by previous trials (induction chemotherapy with cisplatin plus fluorouracil followed by radiotherapy) vs radiotherapy with concurrent cisplatin vs radiotherapy alone in 547 previously untreated patients with locally advanced larynx cancer. Laryngectomy-free survival was the primary endpoint while larynx preservation (larynx in place) and survival were secondary endpoints.

In the first report no difference was found in acute toxicity during the radiotherapy between the induction chemotherapy and the radiotherapy alone arm. There were fewer distant metastases in the two arms with chemotherapy when compared with radiotherapy alone, but only the difference between the concurrent and the radiotherapy alone arm was significant. Regarding the 2-year and the 5-year estimates for laryngectomy-free survival, these were respectively 59% and 43% in the induction arm, 66% and 45% in the concurrent arm, and 53% and 38% in the radiotherapy alone arm. The difference was not significant between the induction and the concurrent arms. The 2-year and 5-year overall survival did not differ significantly according to the treatment arm. The rate of larynx preservation at a median follow-up of 3.8 years was significantly higher in the concurrent arm (84%) when compared with the induction arm (72%, $P = 0.005$) or with the radiotherapy alone arm (67%, $P < 0.001$).

The long-term analysis with a median follow-up of 10.8 years in surviving patients confirmed that the two chemotherapy arms significantly improved laryngectomy-free survival compared with radiotherapy alone without significant difference between these two arms. Overall survival did not differ significantly between the treatment arms, although there was a trend for a higher survival in the induction arm. The difference favouring the concurrent arm with regards to the larynx preservation persisted at 10 years 67.5% (95% CI: 60.4–74.6%) in the induction arm, 81.7% (95% CI: 75.9–87.6%) in the concurrent arm, and 63.8% (95% CI: 56.5–71.1%) in the radiotherapy alone arm. There was no significant difference in late toxicity between the three arms. However the rate of deaths not related to the study cancer was significantly higher in the concurrent arm compared with the induction one (69.8% vs 52.8% respectively at 10 years, $P = 0.03$).

Trials Integrating Docetaxel or Cetuximab

Two large randomized trials [16, 17] had shown that adding docetaxel to cisplatin fluorouracil (the so-called TPF regimen) before irradiation (or chemoradiation) resulted in a significantly higher survival compared to that observed with the duplet regimen (PF).

Another randomized trial [18] had shown that adding cetuximab to irradiation resulted in a significantly higher survival and loco-regional control over irradiation alone.

The Groupe Oncologie Radiotherapie Tete Et Cou (GORTEC) 2000-01 Trial with Docetaxel [19, 20]

In France, the GORTEC conducted a two-arm randomized trial in 220 patients with a locoregionally advanced laryngeal or hypopharyngeal cancer eligible for a total laryngectomy. The aim of the trial was to assess if adding docetaxel to induction PF

could improve larynx preservation. The patients were randomized between 2 induction arms: an experimental one starting with TPF (docetaxel at 75 mg/m^2 on day 1, cisplatin at 75 mg/m^2 on day 1, and 5-fluorouracil at a dose of 750 mg/m^2 by 120-h continuous infusion over 5 days) compared with the classical PF one (cisplatin 100 mg/m^2 on day 1 and 5-fluorouracil given at a dose of 1000 mg/m^2 by 120-h continuous infusion over 5 days). Three cycles at a 3-week interval were planned in the two arms and responders were treated by irradiation while non-responders had total laryngectomy and postoperative irradiation. Larynx preservation was defined as a larynx in place without tumour, tracheostomy or feeding tube. Larynx preservation was the primary endpoint; overall survival and progression-free survival were secondary endpoints. 220 patients were enrolled, of whom 213 were eligible (110 in the TPF arm and 103 in the PF arm).

The first evaluation revealed different chemotherapy-induced toxicities with more alopecia, neutropenia in the TPF arm and more stomatitis, thrombocytopenia and creatinine elevation in the PF arm. In the TPF arm 69 patients (62.7%) could receive the complete treatment without delay or dose reduction versus 33 patients (32%) in the PF arm. The response rates were 80% with TPF arm and 59.2% with PF (P = 0.002). As a result, larynx preservation was offered to 78.8% of patients in the TPF arm versus 55.3% in the PF arm. With a median follow-up of 36 months, the 3-year actuarial larynx preservation rate was 70.3% in the TPF arm versus 57.5% in the PF arm (P = 0.002). However, there were no significant differences in terms of survival.

The long-term evaluation confirmed the initial results. The 5-year and 10-year larynx preservation rates were 74.0% (95% CI: 64–82%) versus 58.1% (95% CI: 47–68%) and 70.3% (95% CI: 58–80%) versus 46.5% (95% CI: 31–63%, P = 0.01) with TPF and PF, respectively. There was no significant difference in 5-year and 10-year overall survival, or disease-free survival. Importantly there were fewer grade 3–4 late toxicities in the TPF arm (9.3%) than in the PF arm (17.1%, P = 0.038).

Of note, in this trial it was left to institutional policies to deliver either radiotherapy alone or concurrent chemoradiotherapy in responders. In the TPF arm 17 patients and in the PF arm 9 patients received concurrent chemo-radiation (with either cisplatin or carboplatin plus fluorouracil). The impact of these chemoradiation protocols on the overall results is unknown.

The GORTEC "TREMPLIN Trial" with Docetaxel and Cetuximab [21]

Assuming that induction chemotherapy and concurrent chemotherapy could be complementary, there was a trend to combine induction chemotherapy and subsequent chemoradiotherapy in locally advanced head and neck cancers. A similar approach was tested in the larynx preservation setting. Anticipating an overall toxicity that could compromise the larynx function, and taking into account the results of the radiotherapy plus cetuximab trial [18], the GORTEC conducted a randomized phase II study to assess what could be the best post-induction protocol.

Patients with larynx or hypopharynx cancer justifying a total laryngectomy were eligible for that study. Patients received 3 cycles of TPF and responders were randomized between radiation plus cisplatin (100 mg/m^2 on day 1, 22 and 43 of irradiation) and radiation plus cetuximab (a loading dose of 400 mg/m^2 and 250 mg/m^2 per week during irradiation). The primary endpoint was larynx preservation (no residual disease justifying immediate salvage laryngectomy) 3 months after the end of treatment. The secondary endpoints were larynx function preservation and overall survival 18 months after the end of treatment.

Of the 153 enrolled patients, 116 were randomized (60 in the cisplatin arm, and 56 in the cetuximab arm). Substantial acute toxicity was observed in both arms, in particular in-field skin toxicity in the cetuximab arm and renal, haematological, and performance status alteration in the cisplatin arm. Limiting acute toxicity led to protocol modification in more patients in the cisplatin arm than in the cetuximab arm (71% and 43% vs 71%, respectively). Except for grade 1 renal toxicity (mainly in patients who had received in total 6 cycles of cisplatin in the chemo-radiation arm), late toxicity did not differ significantly between both arms. At last examination, there were fewer local recurrences in the cisplatin arm (8 patients) compared with 12 patients in the cetuximab arm, but successful salvage surgery could be performed only in the cetuximab arm.

There was no significant difference in larynx preservation at 3 months, being 95% (95% CI: 86–98%) in the cisplatin arm versus 93% (95% CI: 83–97%) in the cetuximab arm. There was no obvious difference in secondary endpoints at 18 months as well. The larynx function preservation was 87% (95% CI: 76–93%) in the cisplatin arm versus 82% (95% CI: 70–90%) in the cetuximab arm. The overall survival was 92% in the cisplatin arm (95% CI: 82–96%) and 89% (95% CI: 79–95%). At a median follow-up of 36 months overall survival was 75% (95% CI: 62–85%) and 73% (95% CI: 60–84%) in the cisplatin arm and cetuximab arm, respectively.

As the composite end-point of laryngoesophageal dysfunction-free survival had been described after the trial was initiated and had been published at the time of the trial evaluation, this end-point was tested in retrospect. Two years after the end of treatment there was no significant difference in that end-point: 79% (95% CI: 67–89%) with cisplatin versus 72% (95% CI: 65–89%) with cetuximab.

Of importance, the comparison of larynx preservation rates with previous trials must be taken with caution as in the TREMPLIN trial they related to the population selected after induction chemotherapy (i.e., 75% of the overall population).

The conclusion was that there was no signal that one arm was superior over the other one, and none appeared to be superior to induction TPF followed by irradiation alone when taking into consideration results of other trials (such as the GORTEC 2000-01 trial).

The German "Delos II Trial" with Docetaxel and Cetuximab [22]

The German Larynx Organ preservation Study group (DeLOS) conducted another randomized phase II study assessing the place of cetuximab in larynx preservation for patients with larynx or hypopharynx cancer. The initial trial design was to

compare induction TPF followed by irradiation with TPF plus cetuximab (E) followed by irradiation plus cetuximab. Due to 4 treatment-related deaths among the first 64 patients, the protocol was amended and fluorouracil was omitted from induction chemotherapy in both arms. There were no further treatment-related deaths thereafter. The evaluation was made after one cycle and responders continued the protocol while non-responders went to laryngectomy. The primary objective was a 2-year functional laryngectomy-free survival (fLFS) above 35%.

Of the 180 patients randomized in the trial, 173 fulfilled Intent To Treat (ITT) criteria. At final examination, the objective response rates in the arm without cetuximab were 79.1% in patients who had received PF, and 94.7% in patients who had received TP. In the arm with cetuximab they were 80% in patients who had received TPFE, and 94.9% in patients with TPE, 94.9% (i.e. similar to TPF). The primary objective was similarly met in both arms: 44.7% in the arm without cetuximab and 46.6% in the cetuximab arm (OR: 0.9268, 95% CI: 0.5094–1.6863). There was no difference in 2-year overall survival: 68.2% in the arm without cetuximab, and 69.3% in the cetuximab arm (OR: 0.9508, 95% CI: 0.4997–1.8091).

Conclusions

Considering these results, it must be underscored that, to date, only two protocols have been validated: induction TPF followed by irradiation alone (GORTEC 2000-01) and irradiation with concurrent cisplatin (RTOG 91-11). To translate these trials in daily practice it is important to strictly follow the study protocols with respect to initial work-up and eligibility criteria, chemotherapy protocols, prophylaxis/management of treatment-induced toxicity, response to treatment evaluation, as well as schedule and tools for post-treatment follow-up.

The majority of patients enrolled in these trials received conventional irradiation. The new radiotherapy technologies (such as IMRT) have reduced the radiotherapy side effects in particular at the level of pharyngeal constrictors muscles. This must be taken into consideration in future trials.

The decision of enrolling a patient in a larynx preservation protocol must be taken by a multidisciplinary tumour board. Patients eligible for a larynx preservation strategy today are patients with advanced larynx and hypopharynx cancers who are not eligible for partial surgery. Overall, T4 diseases and tumours extending to the post-cricoid area are not eligible for larynx preservation. Of note in hypopharynx cancer, only protocols based on induction chemotherapy have been evaluated, there are no data with concurrent chemoradiotherapy for this primary site.

The composite end-point of laryngoesophageal dysfunction free survival has been approved by a group of experts and should be used in further studies.

As the RTOG 91-11 trial was initiated before the TPF induction regimen has proved to be superior to the PF one, there is a need to compare the RTOG and the GORTEC trial. The on-going French phase III trial (GORTEC 2014-03-SALTORL) is comparing induction TPF followed by irradiation in responders vs concurrent cisplatin-based chemoradiotherapy.

Disclosure

JL Lefebvre has been member of the advisory boards of Sanofi-Aventis (docetaxel) and Merck Serono (cetuximab).

JL Lefebvre has been lecturer for Sanofi-Aventis and Merck Serono and is still lecturer for Merck.

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