Editorial

Chemoradiotherapy vs. total laryngectomy for primary treatment of advanced laryngeal squamous cell carcinoma

Introduction

For decades, total laryngectomy followed by post-operative radiotherapy represented a gold standard for the treatment of locally advanced laryngeal squamous cell carcinoma. Though cured of malignancy, the physical incapacity and social stigmatization of many laryngectomized patients resulted in significant impairment in quality of life (QoL). As a logical consequence, efforts to preserve the larynx with non-surgical treatment regimens that would result in comparable (or improved) cure rates and QoL scores are one of the enduring areas of clinical research in head and neck oncology. The aim of our discussion is to briefly review the current status of larynx-preservation treatment options vs. total laryngectomy in patients with advanced laryngeal squamous cell carcinoma and to present research data that might have the potential to alter the existing treatment paradigms.

Lessons from the past

The major breakthrough in the field was made possible by the results of the Department of Veterans Affairs (VA) Laryngeal Cancer Group study published in 1991. For patients with advanced laryngeal cancer that could only be treated surgically with the removal of the entire larynx, the comparison of total laryngectomy and a cisplatin/5-fluorouracil (PF) induction chemotherapy followed by radiotherapy in responding patients resulted in no survival advantage for either of the tested regimens (68% at 2 years in both groups), but preserved the larynx in 64% of the surviving patients assigned to induction chemotherapy followed by radiotherapy. More local failures occurred in the chemoradiation arm, whereas in surgically-treated patients, systemic metastases were more common.

The next important step was taken by the Radiation Therapy Oncology Group (RTOG) 91-11 trial, the results of which were first reported in 2003. Comparing three radiotherapy-based treatments as alternatives to total laryngectomy, i.e., combination of PF-induction chemotherapy followed by radiotherapy (in responders, as in the VA study), concomitant platinum-based chemoradiotherapy, and radiotherapy alone, at 2 years no difference in the overall survival was observed across the three arms (76%, 74% and 75%, respectively), whereas a superior locoregional control (61%, 78% and 56%) and the highest rate of larynx preservation (75%, 88% and 70%) were observed in patients treated with concomitant chemoradiotherapy. The authors concluded that concurrent administration of cisplatin-based chemotherapy and radiotherapy was a new standard in the treatment for patients with stage III or IV laryngeal squamous cell carcinoma without significant invasion of the tongue base or gross destruction of cartilage (T4 tumors), and that laryngectomy should be reserved only for salvage.

Several other reports confirmed that in properly-selected cases, the larynx can be preserved in approximately two-thirds of patients with radiation-sensitive tumors, and that no larynx-sparing strategy offers a survival advantage over total laryngectomy with adjuvant radiotherapy.

To compare apples to apples

First of all, the aim of larynx-preservation approaches is to preserve the functional organ without compromising survival. Avoiding surgery at the expense of losing the ability to swallow and/or speak with other mode(s) of therapy cannot be considered a success. To summarize the assessments of survival and functional outcomes, the Larynx Preservation Consensus Panel in 2009 proposed laryngo-esophageal dysfunction-free survival as the clinically most relevant primary endpoint for larynx-preservation trials, considering death, local relapse, total laryngectomy, tracheotomy and feeding tube/gastrostomy insertion (at 2 years or later) as a composite event. Unfortunately, in published randomized trials on larynx preservation, discrepancies in the definition of laryngeal preservation limit an unbiased comparison of their results. For example, although the VA study reported the estimated rate of larynx preservation, the main endpoints of the RTOG 91-11 study were laryngectomy-free survival with laryngectomy or death from any cause.

Secondly, proper selection of patients who are candidates for laryngeal preservation is crucial. Driven by the VA study results demonstrating significantly higher rate of salvage laryngectomies among patients with T4 tumors compared to those with smaller tumors, it could be argued that non-surgical treatment should be limited to patients with T2 and T3 primaries of supraglottic or glottic origin as an alternative to partial laryngectomy. In patients with extensive T4 tumors, non-surgical treatments often resulted in laryngeal dysfunction requiring permanent gastrostomy and/or tracheostomy. Furthermore, patients with baseline laryngeal dysfunction, i.e., with tracheotomy, gastric tube or a recent history of pneumonia implying aspiration, as well as those aged 70 years and older, should also be excluded from larynx-preservation protocols to ensure safe administration of systemic drugs and radiotherapy and a satisfactory post-treatment restoration of laryngeal function. Any deviation from these recommendations could...
compromise local control and functional outcome which must be at least thoroughly discussed with the patient. For example, tracheostomy was found independently associated with a feeding-tube dependence which had the most negative impact on QoL in patients with head and neck cancer.8,9

Last but not least, QoL is an issue, even more in situations where none of the available treatments ensure a survival advantage. In the VA study, patients randomized to the induction chemotherapy arm had better QoL scores compared to the surgery plus radiotherapy arm. This was attributed mainly to reduced pain, better emotional well-being and a lower level of depression in the former group, whereas speech domain scores were comparable between the two groups.10 Even in patients with T4 tumors, QoL scores may exceed pre-treatment levels after induction chemotherapy followed by chemoradiation.11 However, the interpretation of QoL outcomes remains challenging with several factors and aspects necessary to consider, including coping differences and timing of measurements.12–14

**Is it time to modify the existing practices?**

Recognizing concurrent chemoradiotherapy as the most effective non-surgical treatment option among the larynx-preserving strategies, although with no proven survival benefit,1 the main issue in non-surgical scenarios seems to be the identification of patients with tumors sensitive to chemotherapeutics and irradiation. To answer this question, one may look into the results of trials on sequential chemoradiation, which confirmed that tumor response to induction chemotherapy, convincingly predicts the effect of subsequent (chemo)radiotherapy.15–17 As the best in vivo assay of tumor chemo/radioresitivity currently available, induction chemotherapy can be considered an important strategy for patient selection for subsequent surgical vs. non-surgical therapy which requires additional investigation. This conclusion is not challenged even by the recently presented results of two phase III randomized studies which show no survival advantage associated with adding induction docetaxel-cisplatin-5-fluorouracil (TPF) chemotherapy to concomitant chemoradiotherapy vs. concomitant chemoradiotherapy alone (i.e., the DeCIDE and PARADIGM trials).18,19

By this conclusion, the question is posed on the optimal number of chemotherapy cycles required to obtain the most reliable estimate of a tumor’s chemo/radioresitivity. While the Larynx Preservation Consensus Panel20 in 2009 recommended that a treatment decision should be based on the response assessment after the second cycle of induction chemotherapy, there are several arguments speaking in favor of reducing this number. In 1996, the University of Michigan group20 showed that the dynamics of tumor shrinkage during the induction part of larynx-preservation treatment was of prognostic importance, and that the assessment of the response after only one cycle of induction chemotherapy predicted the response (down-staging to T1 or complete response) after additional chemotherapy correctly 90% of the time. Bearing in mind the negative effect of accelerated repopulation of the surviving clonogens in the tumor provoked by repeated chemotherapy administrations, and the prolongation of the overall treatment time, as well as negative results of the DeCIDE and PARADIGM trials, it seems that one cycle of systemic agents would be informative enough to allow for reliable decision-making about subsequent treatment. According to the well-established superiority of TPF chemotherapy over PF in the induction setting,21,22 a more rapid and pronounced reduction of gross tumor volume can be expected after one cycle of TPF. This should increase the probability that all viable tumor cells will be subsequently encompassed by a high-dose radiotherapy volume, and may prevent urgent tracheostomy and improve the nutritional status of the patient prior to chemoradiation by effectively diminishing pain and dysphagia.17

The results of a phase II study reported by the University of Michigan23 support this approach. After one cycle of PF induction chemotherapy followed by concomitant platinum-based chemoradiotherapy, 73 out of 97 patients (75%) enrolled in the trial achieved at least a partial response at primary site, results that appear comparable to the larynx-preservation trials employing more than one PF (59–85%)2,3,24 or TPF chemotherapy applications (80%).24 Furthermore, the rates of 2-year larynx preservation in the VA study, the RTOG 91-11 study (best treatment arm) and the French Head and Neck Oncology Radiotherapy Group study (best treatment arm, at 3 years) were 66%, 88% and 70%, respectively, whereas in the Michigan study the larynx-preservation-free survival at 2 and 3 years (with laryngectomy, cancer recurrence and cancer-related death scored as events) was 63% and 61%, respectively. With regard to overall survival rates, 85% at 3 years in the Michigan study compares favorably with 60–75% in other three studies mentioned above; the figures for disease-free survival were 80% vs. >60–76% (at 2 years).2,3,16,23,24 However, in view of a substantially higher proportion of T4 tumors in the University of Michigan series (33%) compared to the VA study (26%) and the other two trials (from 9% to 15.5%), these favorable results strongly support the concept of single-cycle induction chemotherapy as a selection tool for larynx preservation, and a randomized comparison of the this approach vs. standard concurrent chemoradiotherapy is warranted. The contribution of additional chemotherapy, following concurrent chemoradiotherapy, to the outcome in responders appears questionable, as adherence to further intensification of treatment is usually low. Almost half of the patients from the University of Michigan series received no adjuvant chemotherapy at all, as was observed in some other studies.23,25

After using the identical chemoselection strategy in specifically in patients with T4 tumors, the reported laryngectomy-free survival, disease-specific survival and overall-survival at 3 years of 58%, 80%, and 78%, respectively, favorably compares to those of the T3 group. These results advocate that chemoselection could be a feasible alternative to a total laryngectomy even in T4 cases, without compromising QoL of these patients.26

So, tumor response to induction chemotherapy convincingly predicts the effect of subsequent (chemo)radiotherapy with favorable outcome in good responders. The question may arise if, conversely, patients who are poor responders to induction chemotherapy fare better with surgery vs. chemo-radiotherapy. Again, there is quite some prospective trial evidence that a non-responder to induction chemotherapy has a very poor outcome compared to responders. This observation was questioned for the first time in the VA Larynx trial where non-responders to induction chemotherapy who were then treated immediately with adequate (total laryngectomy) surgery had survival outcomes identical to patients who were responders.2 This was the first demonstration that non-responders could have an excellent prognosis when treated with surgery. This prospective trial evidence was the first demonstration that outcomes might be improved by proper treatment selection. The earlier cited prospective phase II validation of this approach confirmed exceptionally high (>80%) survival rates for non-responders undergoing surgery and radiation.22,27 Moreover, compared to patients achieving a complete response to induction chemotherapy who receive radiation and to non-responders subjected to total laryngectomy, partial responders treated with subsequent radiation therapy appear to have significantly inferior survival.16 Therefore, although there are no randomized data comparing this treatment approach to continued treatment of non-responders with further chemoradiation, the historical data suggest that outcome in such patients is poor.

However, there are still several burning issues that need to be addressed in the future. The first of these refers to the drug(s) con-
currently administered with radiotherapy. As in other primaries, the most frequently used chemotherapy regimens in larynx-preservation protocols are platinum-based, although other drug candidates also appear to be of relevance. The second is the value of intensity-modulated radiotherapy and its ability to modulate a toxicity profile, given its parotid-saving and swallowing-sparing capacities. Finally, chemotherapy alone, a tantalizing concept, will need new drug protocols and prospective randomized trials to be able to be envisioned for organ preservation for advanced laryngeal cancer.

So, chemoradiotherapy or total laryngectomy?

The selection of any treatment must be based on the premise: “What is the best solution for the patient given both patient and tumor factors?” The decision-making process must take into account the standard to the patient for preservation of voice and/or swallowing function as well as the likelihood of success in meeting standard cure rates. There is no doubt that good performance status patients with T2 and T3 tumors not considered for partial surgical procedures can be treated in larynx-preserving non-surgical programs with high likelihood of achieving both functional organ preservation and tumor control. Whether this group could be extended to include T4 cases is by all means debatable at the moment: the eventual decision to avoid total laryngectomy in such patients should be influenced at least by the expertise of the treatment and supporting teams. In addition, from a functional point of view and with respect to tumor volume and degree of larynx destruction, the T4 tumors are heterogeneous. Apart from the oncologic outcome, within the group of patients with T4 tumors, the functional status of the larynx may vary widely and impacts the functional outcome of non-surgical treatment regimens. An initially “non-functional larynx” with tracheostomy will most likely remain non-functional even if the cancer has been treated effectively and thus probably warrants consideration of upfront total laryngectomy. In patients with more limited T4 tumors and minimal functional impairment, analogous to lower stage tumors, non-surgical treatment may be considered despite the known higher rate of salvage laryngectomy in this setting.

The second group of surgical candidates are those who have chemo-radio-resistant tumors, possibly identified by induction chemotherapy (or in the future, predictive biomarkers), or those with either early or late local failure after the concurrent chemoradiotherapy phase of treatment. Of note, the concept of patient selection, though of great potential clinical utility, requires additional research and validation in multicenter trials prior to widespread adoption as a standard. According to the available data, one third (16–46%) of those undergoing organ-preservation treatments require salvage laryngectomy. Chondroradionecrosis, severe aspiration and/or dysphagia after (chemo)radiotherapy are rare indications for laryngectomy, occurring in 1.4% of patients from the RTOG 91-11 study and in 1% of patients from the University of Michigan series (i.e., 5.4% and 3.4%, respectively, of all laryngectomy cases).

In summary, non-surgical larynx-preservation treatment programs represent a viable alternative to total laryngectomy in a significant proportion of patients with advanced laryngeal cancer. However, total laryngectomy remains an integral part of all larynx-preservation strategies, being the only option for a great majority of patients with T4 tumors.

Conflict of interest statement

None declared.

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