In this issue of the Journal, Lefebvre et al. (1) report the results of a randomized controlled trial addressing preservation of the larynx in patients with cancers of the hypopharynx and the larynx. This is the second controlled trial from the European Organization for Research and Treatment of Cancer (EORTC) to focus on the strategy of induction chemotherapy (ie, administering several cycles of cisplatin plus 5-fluorouracil), followed by radiotherapy in the patients who respond to treatment (responders). The first trial, which was published in 1996 (2), was limited to patients with cancer of the hypopharynx and compared up to three cycles of cisplatin plus 5-fluorouracil, followed by radiotherapy with laryngopharyngectomy alone. In that study, they found that the larynx could be preserved in 42% of patients at 3 years but that survival did not differ statistically significantly between the two treatment groups. These results and those of another trial that was limited to patients with larynx cancer (3) solidified organ preservation as a treatment option for patients with cancers of either the larynx or the hypopharynx.

The current trial attempts to take another step forward by comparing four cycles of induction chemotherapy with cisplatin plus 5-fluorouracil, followed by radiotherapy in the responders (control group) with a regimen of alternating cisplatin plus 5-fluorouracil chemotherapy and radiotherapy. The results show some trends for improved outcomes with the alternating approach but overall no statistically significant difference for larynx preservation, pattern of treatment failure, or survival outcomes. The alternating regimen was chosen as the experimental treatment because it was previously shown (4) to confer a survival advantage compared with radiotherapy alone and because of the notion that the associated toxicity would be less than a concomitant regimen. Investigators in the United States (5), by contrast, compared concomitant cisplatin and radiotherapy with induction cisplatin plus 5-fluorouracil in patients with locally advanced larynx cancer and reported statistically significantly better larynx preservation and local control with concomitant cisplatin but no difference in survival outcomes. How should we view the results of the EORTC trial on the current management of larynx and hypopharynx cancers?

First, the primary site terminology warrants clarification. The Europeans use the term epilarynx for the anatomical site that is the medial wall of the pyriform sinus, which is a subsite of the hypopharynx in the American Joint Commission on Cancer staging system (6). With that in mind, only 95 (21%) of the 450 patients enrolled had cancers arising in the larynx, and so the study was not powered for efficacy analysis for this small cohort. The primary site is important because cancers arising in the hypopharynx (including pyriform sinus) are biologically distinct from those arising in the larynx, with a worse overall prognosis and a high rate of distant dissemination (7). Additionally, the radiotherapy ports differ, so that patients with hypopharynx cancer are at greater risk for pharyngeal strictures and gastrostomy tube dependence because of a larger target volume and higher radiotherapy dose to the pharyngeal constrictors.

We can conclude that findings from the EORTC trial 24954 are similar to those reported in 1996 (2) that support induction therapy with cisplatin plus 5-fluorouracil as an alternative to laryngopharyngectomy for stage T2–T4, N0–N2 cancers arising in the hypopharynx. These results lead to several questions, including what is the definition of response to induction therapy with cisplatin plus 5-fluorouracil, how many cycles of induction therapy with cisplatin plus 5-fluorouracil should be given, what is the role of combination therapy with taxane and cisplatin plus 5-fluorouracil, and what is the definition of the larynx preservation endpoint.

The most commonly used definition of response for induction organ preservation trials that allows patients to proceed with radiotherapy is a partial response (≥50% regression) of the primary tumor. However, this definition varies from complete response, which was used in the first EORTC hypopharynx trial (2), to the requirement for “substantial” reduction in tumor and partial recovery of larynx mobility as specified in the trial conducted by Lefebvre et al. (1). The reduction of tumor in response to cisplatin-based therapy is a crude surrogate biomarker for sensitivity to subsequent radiotherapy that is based on the similarity of mechanism of DNA strand breakage caused by alkylating agents and radiotherapy. However, there has not been a systematic study of the degree of response and success of subsequent radiotherapy to control the disease, and some believe that it is the rapidity of tumor shrinkage that predicts outcome (8). Additionally, it has been repeatedly shown that induction cisplatin plus 5-fluorouracil does not affect local–regional control but can suppress distant metastases. By contrast, concomitant administration of cisplatin and radiotherapy can theoretically kill cells that are resistant to one or the other modality, and statistically significant improvement in local–regional control and survival is well documented (9). With the emergence of combination regimens with taxane and cisplatin plus 5-fluorouracil, which have been found to be superior to cisplatin plus 5-fluorouracil (10–12), agreed-upon definitions of response, the number of cycles of cisplatin plus 5-fluorouracil, and goal of induction (as a surrogate biomarker to

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select patients and/or to provide additional systemic therapy for distant disease control) are important to establish for future trials. Given the difficulty of obtaining a reproducible measurement of the primary and similar larynx preservation rates in these successive EORTC trials (as stated in text but with no data provided), regain of mobility of the larynx may be a more relevant predictor of subsequent outcome.

The optimal number of cycles of induction chemotherapy to maximize response has been discussed for decades. Studies have shown that the overall response rate to cisplatin plus 5-fluorouracil does not increase beyond two cycles and the proportion of complete responders is maximal after three cycles (13,14). The EORTC 24954 trial was designed with four cycles of induction chemotherapy with cisplatin plus 5-fluorouracil to match the number of cycles of cisplatin plus 5-fluorouracil in the alternating regimen; otherwise, there is no compelling rationale for exceeding three cycles because the incidence of peripheral neuropathy and ototoxicity is increased when more than three cycles are administered. The results of the three published trials that compared taxane and cisplatin plus 5-fluorouracil induction chemotherapy with induction chemotherapy with cisplatin plus 5-fluorouracil (10–12) are not uniform; however, together, their results clearly support use of the three-drug regimen when induction therapy is indicated. Hypopharynx cancer is such an indication, and future prospective controlled trials should use induction chemotherapy with taxane and cisplatin plus 5-fluorouracil as the control group.

Another area that makes larynx preservation trials difficult to interpret is the use of different definitions of “larynx preservation.” The Radiation Therapy Oncology Group (RTOG) created laryngectomy-free survival as a surrogate endpoint to power the RTOG 91-11 trial, in which survival was not expected to be different between the arms (7). However, limitations of this composite endpoint are now recognized.

First, many patients will die, with an intact larynx, from causes that are not related to the index cancer. In the RTOG larynx trial, approximately 15% of patients died of non-cancer-related causes at 3 years’ follow-up. This percentage increased to 24% at 5 years, when intercurrent deaths accounted for 45% of all causes of death (14). The numerical value of the laryngectomy-free survival endpoint will inevitably continue to decline as deaths continue to occur, eclipsing the laryngectomy rate at 2–3 years, and generating a composite metric that says much more about survival than organ preservation. This dynamic component is even more pronounced in the EORTC 24954 trial, in which approximately 50% of patients died of causes unrelated to the index cancer at a median follow-up of 6.5 years. Exactly how many of these patients died with an intact larynx was not reported.

Second, laryngectomy-free survival weighs death and loss of larynx as equally bad outcomes. Does life without a larynx hold the same value as no life at all? This valuation is not supported by patient priorities (15). Patient surveys suggest that loss of larynx carries a utility-weighted value of 0.6 compared with survival in good health (16). We believe reporting the rate of larynx preservation is the cleanest and most easily interpreted organ preservation endpoint and the best reflection of treatment intent. Adverse events and functional outcomes should be reported and compared separately (eg, tracheostomy or feeding tube rates).

EORTC has chosen “survival with a functional larynx,” which is defined as “without laryngectomy and feeding tube or gastrostomy for longer than 3 months,” and gives these events health state values equal to death. This definition is an extension of the laryngectomy-free survival concept and thus carries the same limitations, with the addition of feeding tube dependence as another source of failure. Loss of these organ functions accounts for 10%–15% of failures in the EORTC trial. This factor likely lowers the differences in reported “organ preservation” rates between the treatment groups. Although survival with larynx function is a reasonable endpoint to consider, the casual reader may assume that survival with function is a valid substitute for larynx preservation, even though this putative surrogate has not been validated and is clearly not the same.

There is a strong need to standardize endpoint definitions. Toward this end, the National Cancer Institute Head and Neck Steering Committee has appointed a Working Group on Endpoints, including definitions and use of composite organ preservation endpoints and local–regional progression. Formal recommendations are expected in 2009 (A. Trotti, MD and A. A. Forastiere, MD, personal communication, November 20, 2008).

In summary, the EORTC 24954 trial showed no advantage for alternating chemotherapy and radiotherapy over traditional cisplatin plus 5-fluorouracil induction chemotherapy in hypopharynx cancer. More effective and less toxic approaches are needed. This trial also illustrates the need for common definitions and metrics to facilitate interpretation and to compare results across trials.

References


