



**Forastiere et al. Long-Term Results of RTOG 91-11: A Comparison of Three Nonsurgical Treatment Strategies To Preserve the Larynx in Patients With Locally Advanced Larynx Cancer.
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Summary: Forastiere et al (3) report the long-term results of the Intergroup Radiation Therapy Oncology Group (RTOG) 91-11 study evaluating the contribution of chemotherapy added to radiation therapy (RT) for larynx preservation. Patients with stage III or IV glottic or supraglottic squamous cell carcinoma were randomly assigned to receive induction cisplatin with fluorouracil (PF) followed by RT (control arm), concomitant cisplatin with RT, or RT alone. The composite endpoint of laryngectomy-free survival (LFS) was the primary endpoint. A total of 520 patients were analyzed at a median follow-up of 10.8 years. Both of the chemotherapy regimens significantly improved LFS compared with RT alone (induction chemotherapy vs RT alone: hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.59-0.95; PZ.02; concomitant chemotherapy vs RT alone: HR, 0.78; 95% CI, 0.78- 0.98; PZ.03). Overall survival (OS) did not differ significantly, although there was the possibility of worse outcome with concomitant relative to induction chemotherapy (HR, 1.25; 95% CI, 0.98-1.61; PZ.08). Concomitant cisplatin with RT significantly improved the larynx preservation rate over that of induction PF followed by RT (HR, 0.58; 95% CI, 0.37-0.89; PZ.0050), as well as over RT alone (P<.001); however, induction PF followed by RT was not better than treatment with RT alone (HR, 1.26; 95% CI, 0.88-1.82; PZ.35). No differences in late effects were detected, but deaths not attributed to laryngeal cancer or treatment were higher with concomitant chemotherapy (30.8% vs 20.8% with induction chemotherapy and 16.9% with RT alone). In conclusion, induction PF followed by RT and concomitant cisplatin with RT show similar efficacy for the composite endpoint of LFS, while larynx preservation was significantly improved for concomitant cisplatin with RT compared to the induction arm or RT alone.

Oncology Scan—Rethinking Treatment Strategies for Cancers of the Larynx and Pharynx

By Giuseppe Sanguineti, MD, *Associate Editor*

Sanguineti's (2)Comment:

When it was initially published in 2003 with a median follow-up of 3.8 years (4), the RTOG 91-11 study led to a change in the treatment paradigm for larynx preservation of stage III and IV operable laryngeal cancer, from induction PF followed by RT in good responders (5) to concomitant cisplatin with RT. Now, with a median follow-up of 10.8 years, the interpretation of the results seems less straightforward. Contrary to the first publication, laryngectomy-free survival (LFS or survival with an "intact larynx") rates are not dissimilar between the induction and concomitant chemotherapy arms (both superior to RT alone), despite the fact that concomitant chemotherapy offers higher locoregional control and larynx preservation rates than induction chemotherapy. Because LFS is a composite endpoint of local control and survival, this would imply that the advantage of larynx preservation is offset by extra mortality (indeed, long-term overall survival tends to be worse with concomitant chemotherapy compared to that of induction). A simple c2 analysis of Table 3 (3) shows that the distribution of deaths "unrelated to cancer or treatment" is significantly different among arms, with the concomitant arm having a significantly higher rate than RT alone (PZ.01) and a nearly significant difference compared to induction (PZ.07). LFS, although originally defined as the primary endpoint of the study, was later considered by the authors as "less informative" (than larynx preservation) because it is prone to competing causes of mortality. While this is true from a pragmatic viewpoint (to interpret study findings), there is little doubt that the preserved larynx can only be used by a living subject. Therefore, in my view, both concomitant and induction (PF) chemotherapy are reasonable options for the patient whose surgical alternative is total laryngectomy. In my practice, concomitant chemotherapy is offered to the fit patient who wants to maximize the chance to skip a (major) surgical operation, while induction is reserved for the patient with borderline fitness (acute toxicity during RT is lower with induction), that is until more data clarify the cause of intercurrent deaths and help to select patients accordingly. Two additional remarks: on average (see Table A1 [3]) roughly 1 of 3 patients developed a grade 3 to 5 late event during follow-up. This contrasts to some extent with the "excellent" functional patient-reported outcomes. While current radiation therapy treatment

techniques may provide some sparing of toxicity, there is still much to be done to appropriately select patients for organpreserving strategies and limit their toxicity both during and after treatment. Finally, the present data show that RT alone (70 Gy in 7 weeks) still has a role as preservation strategy, with survival rates comparable to those of chemotherapy options (meaning that local failures are successfully salvaged [see Fig. 3D]) (3) with larynx preservation rates up to 70%. Unfortunately, often in tumor boards, a preservation strategy without the word “chemo” is not even considered. RT alone (70 Gy/7 weeks or, even better, altered fractionation per RTOG protocol 9003 [6]) is a reasonable option for the patient who is not fit for or refuses chemotherapy.

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C O R R E S P O N D E N C E

Nonsurgical Conservative Approach for Laryngeal Cancer: What Information Should Patients Be Given?(3)

Elvio Russi et Al.

TO THE EDITOR: The investigators of the Radiation Therapy Oncology Group (RTOG) 91-11 study are to be commended for providing information about the long-term results of the three treatments compared in their larynx-preservation trial. These results are extremely helpful in evaluating the overall consequences of the treatment choices offered to patients with laryngeal cancer, but with respect to short-term results,² create some more concerns, mainly regarding the excess number of deaths after 4.3 years and the higher percentage of patients classified as “can only swallow soft foods” in the concomitant group. Thus, even though nearly twice as many patients will undergo laryngectomy if treated with sequential or radiotherapy alone approach instead of concomitant one, the effects on long-term survival make the recommendation of front-line concomitant treatment less obvious.

Recently, Lefebvre et al³ have warned about “the excess of cancerunrelated/ unknown deaths observed in the experimental arm (sequential arm)” in 10-year results of the European Organisation for Research and Treatment of Cancer 24891 laryngeal conservative approach. Despite the fact that the sequential approach of chemoradiotherapy does not seem detrimental to short-term survival compared with laryngectomy,⁴ with few exceptions,⁵ the concomitant chemoradiotherapy approach has never been compared with laryngectomy in the laryngeal preservation approach. Furthermore, recently

Cooper et al⁶ have shown higher long-term cancer unrelated/unknown deaths in the concomitant arm albeit in an adjuvant context. Thus, speculative concerns have been raised by some authors^{7,8} concerning the survival rate of the conservative nonsurgical approach. However, as Forastiere et al¹ point out, it is possible that the decreased long-term survival in the concomitant arm could be a random occurrence or associated with the risk factors at present not well-known or with latent iatrogenic functional decline not identified with the current system of monitoring.

New biopathologic knowledge regarding the inflammatory reaction induced by chemoradiotherapy⁹ could lead to a better understanding of the efficacy and the detrimental effects of cell-killing aggressiveness in long-term results as well. Indeed, the importance of the inflammatory state in acute adverse events (eg, mucositis,¹⁰ cachexia, ¹¹ biochemical inflammatory proteins¹²) has recently begun to emerge and it might also be relevant in the long-term mortality as in other inflammatory pathologies.¹³

In the light of these considerations, as we can not be sure about the effects of chemoradiotherapy aggressiveness on long-term survival and as concomitant chemoradiotherapy has never been compared with a conventional standard (laryngectomy plus radiotherapy), from a thorough interpretation of the results of the RTOG 91-11 study, we suggest that the most correct information that can be given to patients is that the surgical approach can give the highest chance of survival, while the conservative approach might give the same, but certainly not better, survival. This means that 38.8% (sequential treatment), 27.5% (concomitant treatment), and 31.5% (radiotherapy alone) of patients will survive at 10 years. As 67.5% (sequential treatment), 81.7% (concomitant treatment), and 63.8% (radiotherapy alone) will preserve the larynx, roughly speaking, it follows that 28.9%, 23.5%, and 17.2% respectively will preserve both larynx and life at 10 years. Moreover, 13% to 14% in the sequential group, 17% to 24% in the concomitant group and 10% to 17% in the radiotherapy alone group will have severe swallowing dysfunction (ability to swallow soft food only). Probably, a single end point like the laryngoesophageal dysfunction-free survival,¹⁴ which includes the events of death, local relapse, total or partial laryngectomy, tracheotomy at longer than 2 years, or feeding tube at longer than 2 years, would make the assessment of the efficacy of the choice more readily understandable, notwithstanding Forastiere et al's concerns¹⁵ that this composite end point might obscure the significant difference in larynx preservation rates. Indeed, the increasing noncancer deaths over time of patients with functional larynx could eclipse the best laryngectomy rate, usually obtained at 2 to 3 years. The difference in survival among the different arms in the long-term, as shown by RTOG and European Organisation for Research and Treatment of Cancer studies, makes their concerns less important, considering that death only survivors benefit from larynx preservation. Besides, a laryngoesophageal dysfunction-free survival-like end point could permit studies which compare arms utilizing new emerging conservative approaches (such as partial laryngectomy). In the meantime, we are not fully convinced that all patients should be counseled to

undergo concomitant chemoradiation. The possible disadvantage in terms of survival should be part of a fully informed and personal choice.

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