

CORRESPONDENCE



Nonsurgical Treatment of Laryngeal Cancer

TO THE EDITOR: Forastiere and colleagues (Nov. 27 issue)¹ are to be congratulated on their important study of concurrent chemotherapy and radiotherapy for organ preservation in patients with advanced laryngeal cancer. However, the final sentence of their report, which states that they “believe that in most patients with laryngeal cancer, the disease can be managed without a primary surgical approach,” lacks balance and may be misleading to readers. This study included a limited subgroup of patients with advanced laryngeal cancer, whose only surgical option was total laryngectomy. However, there is a large group of patients with advanced laryngeal cancer who are candidates for organ-preserving surgical techniques, including either open partial laryngectomy or endoscopic transoral resection, which are used to avoid total laryngectomy.² By not mentioning options involving less-than-total laryngectomy, the authors leave readers with the impression that total laryngectomy is the only surgical option for laryngeal cancer. When patients with early or advanced laryngeal cancer are candidates for surgical approaches that preserve the larynx, it is the standard of care to discuss the surgical and nonsurgical organ-preserving options with the patient and allow the patient to participate in the choice of appropriate treatment.³

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TO THE EDITOR: Forastiere et al. state that radiotherapy with concurrent cisplatin chemotherapy should be the standard of care for most patients with advanced laryngeal cancer. It does seem clear from the authors' report that chemotherapy added to radiotherapy of the sort used in their trial is superior to radiotherapy alone in terms of improved laryngeal preservation, though admittedly, there was no improvement in overall survival.

It may be argued that the radiotherapy schedule used in this study is less than ideal. It would not, I believe, be the prescribed schedule in most hospitals. Multicenter randomized studies, including one from the Radiation Therapy Oncology Group (RTOG), have shown that significantly improved tumor control and voice preservation can be achieved with altered fractionation schedules.¹⁻³ This improvement is, it seems, at least the equal of that obtained by adding concurrent chemotherapy.⁴

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I agree with the authors' conclusion that most cases of laryngeal cancer can be managed without a primary surgical approach. At present, the best method of achieving that goal is unclear.

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1. Fu K, Pajak T, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) Phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 2000;48:7-16.
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TO THE EDITOR: We believe that the report by Forastiere and colleagues on the RTOG 91-11 trial unjustifiably downplays the role of induction chemotherapy followed by radiotherapy for laryngeal preservation.¹⁻³ Seven patients in the group assigned to chemotherapy followed by radiotherapy underwent immediate laryngectomy after induction chemotherapy, skewing the results for the primary end point of laryngeal preservation. Had these patients received radiotherapy before undergoing laryngectomy, the larynx could have been preserved in a substantial proportion of them. Of the 11 patients with a partial response who received additional chemotherapy or radiotherapy, only 1 had to undergo salvage laryngectomy later.

The bias due to differences in the timing of protocol-specified assessments of disease among the treatment groups applies to the time-to-event occurrences but not to event rates. The rates of local control and laryngectomy-free survival were significantly better in the group that received concurrent chemotherapy and radiotherapy, but with significantly higher toxicity. The rates of distant metastases, disease-free survival, and overall survival were similar in the groups that received chemotherapy either as neoadjuvant treatment or as concurrent treatment with radiotherapy. Induction chemother-

apy followed by radiotherapy should still be considered "a worthy concept with continuing promise"⁴ as part of an organ-preservation protocol in a selected group of patients with moderately advanced cancer of the laryngopharynx.

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3. Vokes EE, Stenson K, Rosen FR, et al. Weekly carboplatin and paclitaxel followed by concomitant paclitaxel, fluorouracil, hydroxyurea chemoradiotherapy: curative and organ-preserving therapy for advanced head and neck cancer. *J Clin Oncol* 2003;21:320-6.
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TO THE EDITOR: Several questions are prompted by the report on the laryngeal-preservation trial. The authors state, "The primary end point was preservation of the larynx," with failure indicated by the performance of laryngectomy.¹ Yet in an earlier report, the authors stated that "the primary end point was laryngectomy-free survival,"² with failure indicated by either death or laryngectomy. Laryngectomy-free survival, used to calculate the sample size, appears in the current report as one of the six "other end points."¹ There was no statistical difference in laryngectomy-free survival between either experimental group and the control group. What was the primary end point in this protocol, and why the change in the label?

Dunnett's test³ was used to adjust for comparisons of laryngectomy-free survival between either of the two experimental groups and the control group.¹ How reliable is the conclusion that concurrent use of chemotherapy and radiotherapy is superior when that conclusion is based on the use of a different end point, comparisons between the experimental groups and between each of these groups and the control group, use of a method (Gray's) with no described adjustment for multiple

comparisons, and the exclusion of 5 percent of cases? These issues point to the difficulties of interpreting even extensively deliberated findings for patients, peers, students, and readers.

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TO THE EDITOR: The important role of surgery in the treatment of advanced laryngeal cancer is not delineated in the study by Forastiere et al. Half the study patients had lymph-node metastases and underwent neck dissection after radiotherapy. The role of neck dissection in the outcome was not analyzed. In this context, the figure in the accompanying Perspective article by Vokes and Stenson¹ is misleading. Staging of laryngeal cancer is influenced not only by the extension of the primary tumor site but, of course, also by regional and distant metastases.

The inclusion of patients with T2 disease, accounting for approximately 10 percent of the sample, is curious. For many cases of T2 disease and even some cases of T3 disease, treatment with transoral laser surgery or partial laryngectomy provides a much better outcome, with five-year survival rates exceeding 70 percent.^{2,3} Finally, it is difficult to interpret the functional results in this study. First, information on speech and swallowing was missing for about 20 percent of the patients. I wonder how this is possible in a prospective study. Second, it would be very important to know how many patients were dependent on a permanent tracheostomy after treatment.

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TO THE EDITOR: The findings in the RTOG 91-11 trial confirm the results of meta-analyses and other randomized studies.¹ It is well established that concomitant use of chemotherapy and radiotherapy offers an advantage over standard-fractionation (daily) radiotherapy in terms of locoregional control and overall survival in patients with advanced disease. The standard of care for laryngeal cancers consists of chemoradiotherapy or altered-fractionation radiotherapy; thus, two groups of patients in the RTOG 91-11 trial received suboptimal radiotherapy.² In addition, the patients in this study represent a very-low-risk group, since three quarters of them had N0 or N1 disease. The study does not address the problem of treating N2 or N3 disease, which is more advanced and more prevalent.

A striking finding is the higher rate of swallowing dysfunction at one year in the group assigned to concurrent chemotherapy and radiotherapy than in the group assigned to induction chemotherapy followed by radiotherapy (26 percent vs. 9 percent). With equivalent rates of overall survival and laryngectomy-free survival, we should offer patients the treatment approach associated with the least morbidity. One way to use chemotherapy and radiotherapy more rationally is to deliver the systemically aggressive regimens as induction therapy, followed by a chemoradiotherapy regimen prognostically selected to minimize toxicity and take advantage of radiosensitization. Such sequential approaches to therapy have had promising results and should be tested soon.³⁻⁵

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THE AUTHORS REPLY: The outcome of laryngeal preservation that we reported was not the protocol-designated end point. Instead, laryngectomy-free survival, as reported in an earlier abstract,¹ was the primary end point. We acknowledge that reporting laryngeal preservation as the primary end point was an error. The goal of the trial was to identify the optimal nonsurgical management for preserving the larynx, and because laryngeal preservation is an important manifestation of disease control, our report focused on that outcome. When the RTOG 91-11 trial was designed in 1990, there was insufficient information on laryngeal-preservation rates on which to base the sample size. Therefore, a composite end point of laryngectomy-free survival was used, even though competing causes of mortality make it a less informative end point. The subsequently published report on the Department of Veterans Affairs trial² and others have emphasized laryngeal preservation. None, to our knowledge, have reported laryngectomy-free survival. Over time, this led us to shift the emphasis to laryngeal preservation (or time to laryngectomy), and we have consistently presented this outcome, in addition to laryngectomy-free survival and overall survival, to the data monitoring committee, at major scientific meetings, and in abstracts. There was a significant difference in laryngectomy-free survival only for the comparison of the group that received concurrent chemotherapy and radiotherapy with the group that received radiotherapy alone. This finding does not alter the conclusions.

The statistical outcomes reported are valid. With the use of the RTOG 91-11 induction treatment as the base line, a reduction of the laryngectomy (failure) rate from 28.2 percent to 15.7 percent could be detected with 172 patients per group in the presence of the competing risk (i.e., death without laryngectomy), with the original statistical power of 80 percent and all the other original design specifications. With the use of a Bonferroni adjustment for an alpha

level of 0.025 for each of the two comparisons, the finding favoring the group assigned to concurrent chemotherapy and radiotherapy is still statistically significant ($P=0.005$ by Gray's test). If the excluded patients are added, the P value is unchanged.

There are no data from randomized, prospective trials to support organ-conserving laryngectomy over other organ-sparing strategies. Furthermore, there are insufficient outcome data to justify laser resection for intermediate or advanced vocal-cord lesions. Best practices dictate that management decisions be made by a multidisciplinary team that considers the stage of the disease and patient-related factors.

Randomized trials comparing accelerated radiation with standard fractionation have been completed since the 91-11 trial was designed.³⁻⁵ Only one had statistical power to determine the benefit for laryngeal cancer, specifically early-stage glottic cancer.⁵ Although institutional preferences for accelerated radiation do exist, its value for intermediate- and advanced-stage laryngeal cancer has not been proved yet.

With regard to induction chemotherapy, we showed that it did not result in a higher rate of laryngeal preservation than that associated with radiotherapy alone but had more toxic effects. The addition of induction chemotherapy to concurrent chemotherapy and radiotherapy is a different and important question that needs to be tested in prospective, randomized trials.

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Comparison of Regimens as Initial Therapy for HIV

TO THE EDITOR: Skolnik (Dec. 11 issue),¹ in his editorial accompanying the report by Robbins et al.² on initial therapy for human immunodeficiency virus (HIV) infection, suggests that nelfinavir, which was a component of the antiretroviral regimens used in the study by Robbins et al., may be less effective than other protease inhibitors for the initiation of HIV treatment. However, there was no meaningful difference between efavirenz and nelfinavir when combined with stavudine and didanosine. Moreover, after a median of 2.3 years, the percentage of successfully treated patients who started to take nelfinavir or efavirenz was virtually identical: nelfinavir, 170 of 310 patients (55 percent); efavirenz, 178 of 310 (57 percent). There was no difference among the study groups in improvements in CD4 cell counts.

These results confirm our finding, in a randomized, controlled trial,³ that there was no significant difference in the time to virologic failure between a regimen of nelfinavir plus zidovudine and lamivudine and a regimen of efavirenz plus stavudine and didanosine. HIV infection is lifelong, and antiretroviral agents should be used strategically. Data on resistance⁴ and clinical experience⁵⁻⁷ have proved that nelfinavir allows the future use of other regimens containing protease inhibitors or nonnucleoside reverse-transcriptase inhibitors and may therefore be a good and appropriate first option for a protease inhibitor.

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DR. SKOLNIK REPLIES: Several lines of evidence suggest that nelfinavir may be inferior to other protease inhibitors as an option for the initiation of HIV therapy in patients who have not received previous therapy. In 66 percent of subjects who had not previously received antiretroviral therapy, treatment with fosamprenavir led to suppression of HIV RNA (to a level below 400 copies per milliliter) after 48 weeks, as compared with 51 percent of subjects treated with nelfinavir.¹ The nucleoside reverse-transcriptase inhibitor “backbone” in this trial consisted of abacavir and lamivudine. Moreover, the subjects with an initial HIV RNA level of more than 100,000 copies per milliliter or CD4 cell counts of less than 50 per cubic millimeter fared better with fosamprenavir than with nelfinavir (48 percent vs. 24 percent had undetectable HIV RNA).

In a study comparing lopinavir–ritonavir with nelfinavir for the initial treatment of HIV infection, each given with stavudine and lamivudine, 67 percent of subjects who received lopinavir–ritonavir achieved an HIV RNA level of less than 50 copies per milliliter, as compared with 52 percent of those who received nelfinavir.² Moreover, the durability of the response was superior in the lopinavir–ritonavir group — 84 percent of subjects had undetectable HIV RNA through week 48, as compared with 66 percent of those in the nelfinavir group. The incidence of antiretroviral resistance during this study suggests the superiority of lopinavir–ritonavir to nel-