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## Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer

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### ABSTRACT

#### BACKGROUND

Induction chemotherapy with cisplatin plus fluorouracil followed by radiotherapy is the standard alternative to total laryngectomy for patients with locally advanced laryngeal cancer. The value of adding chemotherapy to radiotherapy and the optimal timing of chemotherapy are unknown.

#### METHODS

We randomly assigned patients with locally advanced cancer of the larynx to one of three treatments: induction cisplatin plus fluorouracil followed by radiotherapy, radiotherapy with concurrent administration of cisplatin, or radiotherapy alone. The primary end point was preservation of the larynx.

#### RESULTS

A total of 547 patients were randomly assigned to one of the three study groups. The median follow-up period was 3.8 years. At two years, the proportion of patients who had an intact larynx after radiotherapy with concurrent cisplatin (88 percent) differed significantly from the proportions in the groups given induction chemotherapy followed by radiotherapy (75 percent,  $P=0.005$ ) or radiotherapy alone (70 percent,  $P<0.001$ ). The rate of locoregional control was also significantly better with radiotherapy and concurrent cisplatin (78 percent, vs. 61 percent with induction cisplatin plus fluorouracil followed by radiotherapy and 56 percent with radiotherapy alone). Both of the chemotherapy-based regimens suppressed distant metastases and resulted in better disease-free survival than radiotherapy alone. However, overall survival rates were similar in all three groups. The rate of high-grade toxic effects was greater with the chemotherapy-based regimens (81 percent with induction cisplatin plus fluorouracil followed by radiotherapy and 82 percent with radiotherapy with concurrent cisplatin, vs. 61 percent with radiotherapy alone). The mucosal toxicity of concurrent radiotherapy and cisplatin was nearly twice as frequent as the mucosal toxicity of the other two treatments during radiotherapy.

#### CONCLUSIONS

In patients with laryngeal cancer, radiotherapy with concurrent administration of cisplatin is superior to induction chemotherapy followed by radiotherapy or radiotherapy alone for laryngeal preservation and locoregional control.

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EACH YEAR, APPROXIMATELY 9500 PERSONS in the United States receive the diagnosis of cancer of the larynx.<sup>1</sup> Until the early 1990s, the standard treatment for locally advanced disease was total laryngectomy. This practice changed, however, after the landmark trial conducted by the Department of Veterans Affairs Laryngeal Cancer Study Group, in which induction chemotherapy (cisplatin plus fluorouracil) followed by radiotherapy was compared with surgery plus adjuvant radiotherapy.<sup>2</sup> The larynx was preserved in 64 percent of the patients who received the nonsurgical treatment, and the two-year survival rate was 68 percent in both groups. No significant difference in survival has been reported after more than 10 years of follow-up.<sup>3</sup> The ability to preserve the larynx without jeopardizing survival established the use of induction chemotherapy followed by radiotherapy as an alternative to laryngectomy for locally advanced laryngeal cancer.

To determine the contributions of chemotherapy and radiotherapy to larynx-preserving treatment, the Radiation Therapy Oncology Group and the Head and Neck Intergroup conducted a randomized trial (RTOG 91-11) to investigate three radiation-based treatments: induction cisplatin plus fluorouracil followed by radiotherapy if there was a response to the chemotherapy (a regimen identical to that given the “experimental” group in the Department of Veterans Affairs Laryngeal Cancer Study Group trial), radiotherapy with concurrent administration of cisplatin, and radiotherapy alone. The rationale for the second group was based on the enhancement of radiation effects on tumor cells by concurrent treatment with cisplatin. The primary objective of the trial was to compare the rates of laryngeal preservation associated with the three treatments. The study involved investigators from the Radiation Therapy Oncology Group (the coordinating group), the Southwest Oncology Group, and the Eastern Cooperative Oncology Group.

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## METHODS

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### PATIENTS

Patients were eligible if they had biopsy-proven, previously untreated stage III or IV (according to the staging system of the American Joint Commission on Cancer) squamous-cell carcinoma of the glottic or supraglottic larynx, the surgical treatment of which would require total laryngectomy. Patients

with a stage T1 primary tumor (defined as tumor limited to one subsite of the supraglottis or limited to the vocal cords, with normal vocal-cord mobility, according to the tumor–node–metastasis [TNM] staging system) or with large-volume stage T4 disease (defined as a tumor penetrating through the cartilage or extending more than 1 cm into the base of the tongue) were not eligible. The disease had to be considered curable with surgery and postoperative radiotherapy. A Karnofsky performance score of at least 60 (on a scale from 0 to 100, with higher scores indicating better performance and with a score of 60 indicating that the patient requires occasional assistance but is able to care for most of his or her own needs) was required. To be eligible, patients also had to have a white-cell count of at least 3500 per cubic millimeter, a platelet count of at least 100,000 per cubic millimeter, a normal serum calcium level, and a creatinine clearance of at least 50 ml per minute. All the patients gave written informed consent in accordance with institutional guidelines.

Pretreatment staging, involving laryngoscopy, measurement of the tumor, and high-resolution computed tomographic (CT) scanning of the primary tumor and the neck, was performed within four weeks before entry into the study. To rule out synchronous primary cancers, either CT imaging of the chest and barium esophagography or panendoscopy (i.e., esophagoscopy and bronchoscopy) was performed. Imaging was performed as clinically indicated to rule out metastatic disease.

### TREATMENT

#### *Chemotherapy*

Induction chemotherapy consisted of cisplatin given intravenously at a dose of 100 mg per square meter of body-surface area on day 1 and fluorouracil given at a dose of 1000 mg per square meter every 24 hours by continuous intravenous infusion for 120 hours, every three weeks for two courses. Patients then underwent evaluation by indirect laryngoscopy and CT imaging of the neck. If these examinations showed a complete or partial response of the primary tumor and no sign of progression in the neck, a third course of cisplatin plus fluorouracil was given, followed by radiotherapy. Patients with a less than partial response of the primary tumor or with progression in the neck underwent laryngectomy followed by adjuvant radiotherapy. Patients assigned to radiotherapy with concurrent cisplatin received intravenous cisplatin at a dose of 100 mg

per square meter on days 1, 22, and 43 of radiotherapy.

#### *Radiotherapy*

The dose of radiation and radiotherapy schedule were the same in all three study groups. The dose of radiation to the primary tumor and clinically positive nodes was 70 Gy, given in 35 fractions of 2 Gy each over a seven-week period. The entire neck, including the supraclavicular areas and the posterior neck, was irradiated with a minimum of 50 Gy. The dose to the clinically positive nodes was supplemented with the beams that covered the primary tumor, with electrons, or with tangential anteroposterior beams. The patients assigned to induction chemotherapy followed by radiotherapy who underwent salvage surgery because of a poor response to the chemotherapy received adjuvant radiotherapy (50 to 70 Gy), depending on the status of the margins on pathological review.

#### *Surgery*

Patients who had either a single lymph node 3 cm or greater in diameter or multiple lymph-node metastases on initial clinical staging of the neck were required to undergo neck dissection eight weeks after the completion of radiotherapy. Laryngectomy was performed in patients who had histologically proven persistent or recurrent carcinoma after the completion of treatment or who had an inadequate response after two courses of induction chemotherapy.

#### **FOLLOW-UP AFTER THE COMPLETION OF TREATMENT**

All the patients were evaluated eight weeks after the completion of therapy by examination of the head and neck and CT imaging. If persistent disease was suspected, examination while the patient was under anesthesia and direct laryngoscopy were performed. Complete examination of the head and neck, with evaluation for late toxicity, was performed at scheduled follow-up visits.

Two questionnaires, to be completed by the patients, were used to evaluate quality of life: the Functional Assessment of Cancer Therapy—Head and Neck Scale, version 2,<sup>4</sup> and the University of Washington Quality of Life instrument.<sup>5</sup> These questionnaires were to be filled out at base line and at each follow-up visit. Results with respect to swallowing ability and speech are reported in this article.

#### **STUDY DESIGN**

##### *Randomization*

Patients were stratified according to the site of the primary tumor (glottic or supraglottic), N stage (stage N0 or N1 or stage N2 or N3), and primary tumor stage (T2; T3 with fixed cord involvement; T3 with no cord fixation but with invasion of the postcricoid area, medial wall of the pyriform sinus, or preepiglottic tissues; or T4). The randomization scheme described by Zelen<sup>6</sup> was used to achieve balance in the treatment assignments among the institutions.

##### *Study End Points*

The primary end point was preservation of the larynx. Treatment was considered to have failed on the date laryngectomy was performed. Other end points analyzed were overall survival, disease-free survival, local control, locoregional control, the time to distant metastasis, and laryngectomy-free survival. All events were measured from the date of randomization to the date of their occurrence or the date of the last follow-up visit. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 1.0, during induction chemotherapy and according to the Radiation Therapy Oncology Group toxicity criteria during radiotherapy. All deaths occurring during treatment or within 30 days after the completion of treatment were considered to be possibly treatment-related.

#### **STATISTICAL ANALYSIS**

The trial was designed to test whether concurrent chemotherapy and radiotherapy or radiotherapy alone resulted in higher rates of laryngeal preservation than that achieved with standard induction chemotherapy followed by radiotherapy. Since the protocol involved the comparison of two groups receiving experimental treatments with a single control group, Dunnett's two-sided test<sup>7</sup> was used to adjust for multiple comparisons. The sample size was calculated with the use of Bristol's modification.<sup>8</sup> The study was designed to detect an absolute difference of 15 percent with type I and type II error rates of 0.05 and 0.20. The sample size was further increased by 10 percent to account for patients deemed ineligible or lost to follow-up before two years had elapsed. The targeted sample size was 546 patients, assuming a two-year laryngectomy-free survival rate of 65 percent.

Rates of overall survival, disease-free survival,

**Table 1. Characteristics of the Patients According to the Treatment Group.\***

| Characteristic   | Cisplatin plus Fluorouracil Followed by Radiation (N=173) | Radiotherapy with Concurrent Cisplatin (N=172) | Radiotherapy Alone (N=173) |
|--|---|--|----------------------------|
| <b>Age</b>   |   |  |                            |
| <60 yr — no. (%)   | 91 (53)   | 83 (48)  | 89 (51)                    |
| ≥60 yr — no. (%)   | 82 (47)   | 89 (52)  | 84 (49)                    |
| Median — yr  | 59  | 60   | 59                         |
| Range — yr   | 36–78   | 26–78  | 31–79                      |
| <b>Sex — no. (%)</b>                                       |   |  |                            |
| Male   | 131 (76)  | 137 (80)                                       | 133 (77)                   |
| Female   | 42 (24)   | 35 (20)  | 40 (23)                    |
| <b>Karnofsky performance score — no. (%)</b>               |   |  |                            |
| 100  | 35 (20)   | 32 (19)  | 26 (15)                    |
| 90   | 88 (51)   | 106 (62)                                       | 93 (54)                    |
| 80   | 38 (22)   | 27 (16)  | 41 (24)                    |
| 70   | 10 (6)  | 6 (3)  | 10 (6)                     |
| 60   | 2 (1)   | 1 (1)  | 3 (2)                      |
| <b>Site of tumor — no. (%)</b>                             |   |  |                            |
| Supraglottis   | 118 (68)  | 114 (66)                                       | 124 (72)                   |
| Glottis  | 55 (32)   | 58 (34)  | 49 (28)                    |
| <b>American Joint Commission on Cancer stage — no. (%)</b> |   |  |                            |
| III  | 111 (64)  | 115 (67)                                       | 111 (64)                   |
| IV   | 62 (36)   | 57 (33)  | 62 (36)                    |
| <b>Tumor–node–metastasis stage — no. (%)†</b>              |   |  |                            |
| <b>T stage</b>   |   |  |                            |
| T2   | 19 (11)   | 21 (12)  | 20 (12)                    |
| T3 with fixed cord involvement                             | 82 (47)   | 82 (48)  | 76 (44)                    |
| T3 without cord fixation                                   | 54 (31)   | 52 (30)  | 61 (35)                    |
| T4   | 18 (10)   | 17 (10)  | 16 (9)                     |
| <b>N stage</b>   |   |  |                            |
| N0   | 87 (50)   | 86 (50)  | 87 (50)                    |
| N1   | 38 (22)   | 39 (23)  | 32 (18)                    |
| N2A  | 2 (1)   | 7 (4)  | 3 (2)                      |
| N2B  | 17 (10)   | 13 (8)   | 13 (8)                     |
| N2C  | 26 (15)   | 23 (13)  | 36 (21)                    |
| N3   | 3 (2)   | 4 (2)  | 2 (1)                      |

\* Because of rounding, not all percentages total 100.

† T denotes tumor, and N node. The designation T4 was limited to low-volume disease that did not extend into the tongue base by more than 1 cm or penetrate through cartilage.

and laryngectomy-free survival were estimated by means of the Kaplan–Meier method with the log-rank test.<sup>9</sup> Rates of laryngeal preservation, local control, locoregional control, and distant metastasis were estimated by the method of cumulative

incidence<sup>10</sup> and were tested according to Gray’s method.<sup>11</sup>

Differences in the timing of protocol-specified assessments of disease among the treatment groups could bias the results. For example, patients in the induction-chemotherapy group could proceed to laryngectomy earlier than the other patients because of the evaluation performed at six weeks. To minimize such bias, all laryngectomies performed within the first six months after the start of treatment were considered to be early treatment failures and were analyzed as if they had occurred at the same time.

## RESULTS

### PATIENT POPULATION

From August 1992 to May 2000, 547 patients were enrolled and randomly assigned to one of the three treatment groups. Twenty-one of these patients proved to be ineligible, one withdrew consent after randomization, and seven were excluded because eligibility or outcome information was not submitted. Thus, data from 518 patients were included in the analysis. The characteristics of the patients are shown in Table 1. The site of the primary tumor and stage of disease were balanced among the three treatment groups.

### TOXIC EFFECTS

Severe acute toxic effects are listed in Table 2. During induction chemotherapy with cisplatin and fluorouracil, toxicity was manifested primarily as neutropenia, stomatitis, and nausea or vomiting.

The grade and frequency of toxic effects occurring during radiotherapy recorded in the group that received induction cisplatin plus fluorouracil followed by radiotherapy and the group that received radiotherapy alone were nearly identical and consisted mainly of grade 3 in-field effects on the skin and mucous membrane. In contrast, patients receiving radiotherapy with concurrent cisplatin had chemotherapy-related toxic effects (e.g., neutropenia and nausea or vomiting) and increased rates of severe radiation-related mucosal, pharyngeal, and esophageal effects.

The incidence of grade 3 or 4 late toxic effects was 24 percent in the group that received induction cisplatin plus fluorouracil followed by radiotherapy, 30 percent in the group that received radiotherapy with concurrent cisplatin, and 36 percent in the group that received radiotherapy alone. Most of

**Table 2. Grade 3 or 4 Acute Toxic Effects, According to the Treatment Group.\***

| Toxic Effect                      | Cisplatin plus Fluorouracil Followed by Radiotherapy |         |          |                             |         |         | Radiotherapy with Concurrent Cisplatin (N=171) |         |          | Radiotherapy Alone (N=171) |         |         |
|-----------------------------------|--|---------|----------|-----------------------------|---------|---------|--|---------|----------|----------------------------|---------|---------|
|                                   | Chemotherapy Period (N=168)                          |         |          | Radiotherapy Period (N=156) |         |         | grade 3  | grade 4 | total    | grade 3                    | grade 4 | total   |
|                                   | grade 3  | grade 4 | total    | grade 3                     | grade 4 | total   |  |         |          |                            |         |         |
|                                   | <i>number of patients (percent)</i>                  |         |          |                             |         |         |  |         |          |                            |         |         |
| Hematologic                       | 43   | 44      | 87 (52)  | 13                          | 10      | 23 (15) | 64   | 17      | 81 (47)  | 3                          | 2       | 5 (3)   |
| Infection                         | 4  | 5       | 9 (5)    | 2                           | 0       | 2 (1)   | 7  | 0       | 7 (4)    | 2                          | 0       | 2 (1)   |
| Mucosal (stomatitis)              | 27   | 7       | 34 (20)  | 36                          | 2       | 38 (24) | 64   | 9       | 73 (43)  | 40                         | 1       | 41 (24) |
| Pharyngeal or esophageal          | —  | —       | —        | 30                          | 0       | 30 (19) | 60   | 0       | 60 (35)  | 32                         | 0       | 32 (19) |
| Laryngeal                         | —  | —       | —        | 20                          | 1       | 21 (13) | 29   | 2       | 31 (18)  | 23                         | 5       | 28 (16) |
| Dermatologic (in radiation field) | —  | —       | —        | 16                          | 0       | 16 (10) | 10   | 2       | 12 (7)   | 15                         | 0       | 15 (9)  |
| Nausea or vomiting                | 20   | 3       | 23 (14)  | 0                           | 0       | 0       | 28   | 7       | 35 (20)  | 0                          | 0       | 0       |
| Renal or genitourinary            | 3  | 0       | 3 (2)    | 2                           | 0       | 2 (1)   | 6  | 1       | 7 (4)    | 0                          | 0       | 0       |
| Neurologic                        | 5  | 1       | 6 (4)    | 0                           | 0       | 0       | 8  | 1       | 9 (5)    | 0                          | 0       | 0       |
| Other                             | 20   | 7       | 27 (16)  | 16                          | 2       | 18 (12) | 58   | 11      | 69 (40)  | 9                          | 1       | 10 (6)  |
| Overall maximal severity          | 62   | 49      | 111 (66) | 66                          | 13      | 79 (51) | 99   | 32      | 131 (77) | 71                         | 9       | 80 (47) |

\* Dashes denote not applicable.

these effects were grade 3 and referable to the larynx, pharynx and esophagus, salivary glands, and subcutaneous tissues.

The total rates of severe toxic effects (acute and late) reported for all phases of the study were 81 percent in the group assigned to induction cisplatin plus fluorouracil followed by radiotherapy, 82 percent in the group assigned to radiotherapy with concurrent cisplatin, and 61 percent in the group assigned to radiotherapy alone. The total numbers of deaths that may have been related to treatment were five (3 percent), nine (5 percent), and five (3 percent), respectively; the relation of the death to treatment was confirmed for four, eight, and two of these deaths, respectively.

#### RESPONSE TO TREATMENT AND COMPLIANCE

A total of 168 of the 173 patients assigned to receive induction cisplatin plus fluorouracil followed by radiotherapy received induction chemotherapy. The response of the primary tumor after two courses of cisplatin and fluorouracil was complete in 36 of these patients (21 percent) and partial in 108 (64 percent). Eighty-four patients had nodal involvement, and the response was complete in 19 of them (23 percent), partial in 34 (40 percent), and stable in 15 (18 percent). Thus, 144 patients could proceed

to receive a third course of chemotherapy and a full course of radiotherapy. Of these, 134 received the third course; the remaining 10 discontinued chemotherapy.

Among the 24 patients in whom the response of the primary tumor to induction chemotherapy was less than partial, only 7 proceeded to immediate laryngectomy. Of the remaining 17 patients, 11 received additional chemotherapy or radiotherapy. All 11 had a complete response, and only 1 subsequently required a laryngectomy. Of the 172 patients randomly assigned to receive radiotherapy with concurrent cisplatin, 120 (70 percent) received all three planned doses of cisplatin and 40 (23 percent) received two doses.

Most of the patients (84 percent of those assigned to induction cisplatin plus fluorouracil followed by radiotherapy, 91 percent of those assigned to radiotherapy with concurrent cisplatin, and 94 percent of those assigned to radiotherapy alone) received more than 95 percent of the intended dose of radiotherapy (i.e., at least 67 Gy). At the completion of radiotherapy, 150 of the patients assigned to induction cisplatin plus fluorouracil followed by radiotherapy, 154 of those assigned to radiotherapy with concurrent cisplatin, and 148 of those assigned to radiotherapy alone had had a complete response.

**PRESERVATION OF THE LARYNX**

The rate of laryngeal preservation at a median follow-up of 3.8 years was significantly higher among patients receiving radiotherapy with concurrent cisplatin (145 of 172 patients [84 percent]) than among those receiving induction chemotherapy followed by radiotherapy (125 of 173 patients [72 percent],  $P=0.005$ ) or radiotherapy alone (116 of 173 patients [67 percent],  $P<0.001$ ). There was no significant difference between the group receiving induction chemotherapy followed by radiotherapy and the group receiving radiotherapy alone ( $P=0.27$ ) (Fig. 1).

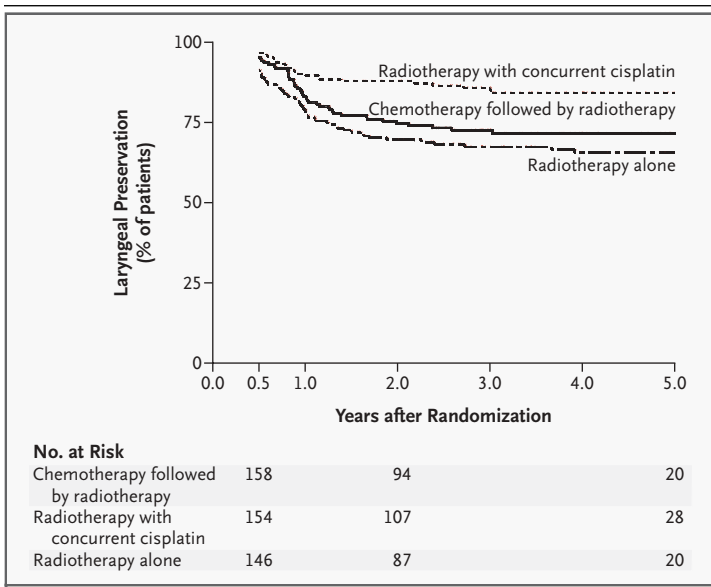
**SPEECH AND SWALLOWING**

Information on speech and swallowing collected from patients who were disease-free and had an intact larynx was available from 74 percent of those assigned to induction cisplatin plus fluorouracil followed by radiotherapy, 78 percent of those assigned

to radiotherapy with concurrent cisplatin, and 80 percent of those assigned to radiotherapy alone. There was no difference among the three treatment groups with regard to speech at either 12 or 24 months of follow-up. The reporting of moderate speech impairment (difficulty in pronouncing some words and being understood on the telephone) or worse speech impairment did not differ among the groups at one year (6 percent, 11 percent, and 13 percent, respectively) or two years (3 percent, 6 percent, and 8 percent, respectively).

At one year, 23 percent of the patients assigned to radiotherapy with concurrent cisplatin were able to swallow only soft foods or liquids, and 3 percent could not swallow at all. By contrast, of the patients assigned to induction cisplatin plus fluorouracil followed by radiotherapy, 9 percent were limited to soft foods or liquids, and none were unable to swallow ( $P=0.004$ ). The results for the patients who received only radiotherapy did not differ significantly from those for the patients in the other two groups; 15 percent were limited to soft foods or liquids, and 3 percent could not swallow. At two years, there was no significant difference among the groups in the percentage of patients reporting difficulty in swallowing (16 percent of those assigned to induction cisplatin plus fluorouracil followed by radiotherapy, 15 percent of those assigned to radiotherapy with concurrent cisplatin, and 14 percent of those assigned to radiotherapy alone).

For the composite end point of laryngectomy-free survival (on which the sample size of the trial was predicated), either laryngectomy or death from any cause constituted treatment failure. The two-year and five-year estimated rates of this end point were 59 percent and 43 percent, respectively, for patients assigned to induction cisplatin plus fluorouracil followed by radiotherapy, 66 percent and 45 percent for those assigned to radiotherapy with concurrent cisplatin, and 53 percent and 38 percent for those assigned to radiotherapy alone. The protocol-specified test of statistical significance did not yield a significant difference ( $P<0.05$ ) in pairwise comparisons between induction cisplatin plus fluorouracil followed by radiotherapy and radiotherapy with concurrent cisplatin ( $P=0.49$ ) or between induction cisplatin plus fluorouracil followed by radiotherapy and radiotherapy alone ( $P=0.08$ ). However, there was a significant difference in laryngectomy-free survival when concurrent radiotherapy and cisplatin was compared with radiotherapy alone ( $P=0.01$ ).



**Figure 1. Rates of Laryngeal Preservation According to the Treatment Group.**

At two years, the rates of laryngeal preservation were as follows: 75 percent (95 percent confidence interval, 68 to 81 percent) among the patients who received induction cisplatin plus fluorouracil followed by radiotherapy, 88 percent (95 percent confidence interval, 83 to 93 percent) among those who received radiotherapy with concurrent cisplatin, and 70 percent (95 percent confidence interval, 63 to 76 percent) among those who received radiotherapy alone ( $P=0.005$  for the comparison between induction cisplatin plus fluorouracil followed by radiotherapy and radiotherapy with concurrent cisplatin,  $P=0.27$  for the comparison between induction cisplatin plus fluorouracil followed by radiotherapy and radiotherapy alone, and  $P<0.001$  for the comparison between radiotherapy with concurrent cisplatin and radiotherapy alone, by Gray's test).

**SURVIVAL OUTCOMES**

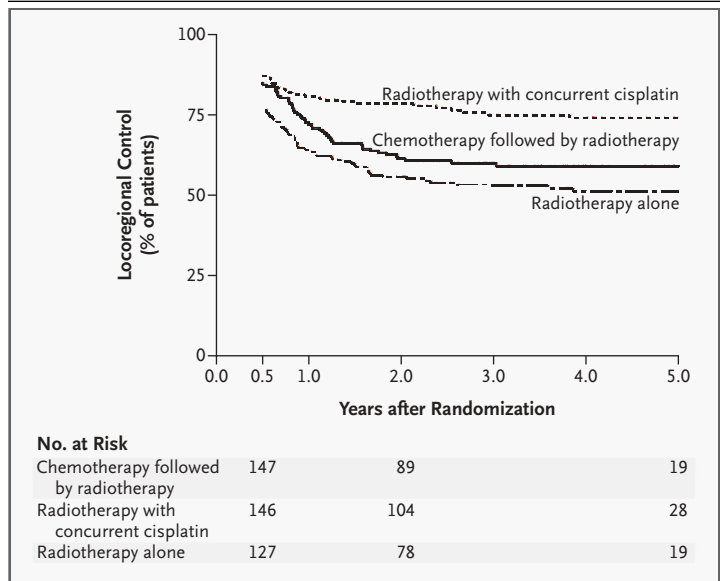
The median follow-up among surviving patients was 3.8 years. Two-year and five-year estimates of overall survival did not differ significantly according to the treatment: they were 76 percent and 55 percent, respectively, for induction cisplatin plus fluorouracil followed by radiotherapy, 74 percent and 54 percent for radiotherapy with concurrent cisplatin, and 75 percent and 56 percent for radiotherapy alone. Two-year and five-year estimates of disease-free survival were 52 percent and 38 percent, respectively, for induction cisplatin plus fluorouracil followed by radiotherapy, 61 percent and 36 percent for radiotherapy with concurrent cisplatin, and 44 percent and 27 percent for radiotherapy alone. Patients who received chemotherapy had significantly improved disease-free survival as compared with those who received radiotherapy alone ( $P=0.02$  for the comparison between induction cisplatin plus fluorouracil followed by radiotherapy and radiotherapy alone, and  $P=0.006$  for the comparison between radiotherapy with concurrent cisplatin and radiotherapy alone).

**PATTERN OF FAILURE**

At two years, the number of local treatment failures was 61 for induction cisplatin plus fluorouracil followed by radiotherapy, 35 for radiotherapy with concurrent cisplatin, and 72 for radiotherapy alone. The rates of local control were 64 percent, 80 percent, and 58 percent, respectively. Patients who received radiotherapy with concurrent cisplatin had significantly fewer failures than those who received induction cisplatin plus fluorouracil followed by radiotherapy ( $P=0.004$ ) and significantly fewer than those who received radiotherapy alone ( $P<0.001$ ). There was no significant difference with respect to treatment failures between patients who received induction cisplatin plus fluorouracil followed by radiotherapy and those who received radiotherapy alone ( $P=0.15$ ). Locoregional control was significantly better among the patients who received radiotherapy with concurrent cisplatin than among those who received either of the other treatments (Fig. 2).

**DISTANT METASTASIS**

Chemotherapy reduced the rate of distant metastasis. At two years, distant metastases had developed in 9 percent of the patients who had received induction cisplatin plus fluorouracil followed by radiotherapy, 8 percent of those who had received radiotherapy with concurrent cisplatin, and 16 percent of those who had received radiotherapy alone. At five years, the cumulative recurrence rates were 15 percent, 12 percent, and 22 percent, respectively. Overall, only the difference between the rates among those who received radiotherapy with concurrent cisplatin and those who received radiotherapy alone was significant ( $P=0.03$ ).



**Figure 2. Rates of Locoregional Control According to the Treatment Group.**

At two years, the rates of locoregional control were as follows: 61 percent (95 percent confidence interval, 54 to 69 percent) among the patients who received induction cisplatin plus fluorouracil followed by radiotherapy, 78 percent (95 percent confidence interval, 72 to 85 percent) among those who received radiotherapy with concurrent cisplatin, and 56 percent (95 percent confidence interval, 48 to 63 percent) among those who received radiotherapy alone ( $P=0.003$  for the comparison between induction cisplatin plus fluorouracil followed by radiotherapy and radiotherapy with concurrent cisplatin,  $P=0.16$  for the comparison between induction cisplatin plus fluorouracil followed by radiotherapy and radiotherapy alone, and  $P<0.001$  for the comparison between radiotherapy with concurrent cisplatin and radiotherapy alone).

**DISCUSSION**

In this trial, the overall survival among patients with stage III or IV laryngeal cancer was excellent (75 percent at two years) and did not differ significantly according to the treatment. Laryngeal preservation was best achieved with radiotherapy plus concurrent cisplatin; induction chemotherapy followed by radiotherapy was not significantly better than radiotherapy alone. With concurrent therapy, there was an absolute reduction in the rate of laryngectomy of 43 percent.

In addition, we found that chemotherapy suppressed distant metastasis. At two years, 91 percent of the patients who had received induction cisplatin plus fluorouracil followed by radiotherapy and 92 percent of those who had received radiotherapy with concurrent cisplatin were metastasis-free, as compared with 84 percent of those who had received radiotherapy alone. At five years, these rates were 85 percent, 88 percent, and 78 percent, respectively. Hence, the development of distant metastases was not merely delayed by chemotherapy.

Induction chemotherapy followed by radiotherapy was as toxic as concurrent therapy. Patients assigned to induction cisplatin plus fluorouracil followed by radiotherapy had chemotherapy-related toxic effects during the induction (preradiotherapy) phase. The rate of toxic effects on the mucous membranes and skin during radiotherapy in that group was nearly identical to the rate in the group assigned to radiotherapy alone, but the group assigned to radiotherapy with concurrent cisplatin had nearly twice the rate of mucosal effects. The increased rate of acute toxic effects on the mucous membranes with the use of radiotherapy with concurrent cisplatin probably contributed to the delayed recovery of swallowing in this group (according to patients' reported quality-of-life assessment).

Induction chemotherapy followed by radiotherapy, as compared with radiotherapy alone, did not significantly improve the rate of laryngeal preservation or survival. It did suppress the development of distant metastases and improve disease-free survival,

but rates of locoregional control did not differ significantly from those achieved with radiotherapy alone. In addition, total toxicity was substantially increased as compared with radiotherapy alone. Thus, for patients who desire laryngeal preservation when concurrent administration of chemotherapy and radiotherapy is not feasible, radiotherapy alone should be recommended.

Our finding—that concurrent administration of chemotherapy and radiotherapy is superior to sequential therapy or radiotherapy alone for achieving locoregional control—applies only to patients with stage III or IV disease (a T2, T3, or low-volume T4 primary tumor). It does not apply to patients with significant invasion of the tongue base or gross destruction of cartilage. Radiotherapy with concurrent cisplatin should be considered standard care for patients desiring laryngeal preservation whose cancer is within the categories of disease studied in this trial, and laryngectomy should be performed only as salvage therapy. We believe that in most patients with laryngeal cancer, the disease can be managed without a primary surgical approach.

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## CORRECTION

## Nonsurgical Treatment of Laryngeal Cancer

*To the Editor:* Forastiere and colleagues (Nov. 27 issue)<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup>

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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.<sup>1,2,3</sup> This improvement is, it seems, at least the equal of that obtained by adding concurrent chemotherapy.<sup>4</sup>

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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*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.<sup>1,2,3</sup> 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 chemotherapy followed by radiotherapy should still be considered "a worthy concept with continuing promise"<sup>4</sup> as part of an organ-preservation protocol in a selected group of patients with moderately advanced cancer of the laryngopharynx.

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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.<sup>1</sup> Yet in an earlier report, the authors stated that "the primary end point was laryngectomy-free survival,"<sup>2</sup> 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."<sup>1</sup> 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 test<sup>3</sup> was used to adjust for comparisons of laryngectomy-free survival between either of the two experimental groups and the control group.<sup>1</sup> 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 Stenson<sup>1</sup> 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.

*N Engl J Med* 2004;350:1049

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.<sup>2,3</sup> 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3,4,5</sup>

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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,<sup>1</sup> 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 trial<sup>2</sup> 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.<sup>3,4,5</sup> Only one had statistical power to determine the benefit for laryngeal cancer, specifically early-stage glottic cancer.<sup>5</sup> 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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