

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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ABSTRACT

Purpose

To report the long-term results of the Intergroup Radiation Therapy Oncology Group 91-11 study evaluating the contribution of chemotherapy added to radiation therapy (RT) for larynx preservation.

Patients and Methods

Patients with stage III or IV glottic or supraglottic squamous cell cancer were randomly assigned to induction cisplatin/fluorouracil (PF) followed by RT (control arm), concomitant cisplatin/RT, or RT alone. The composite end point of laryngectomy-free survival (LFS) was the primary end point.

Results

Five hundred twenty patients were analyzed. Median follow-up for surviving patients is 10.8 years. Both chemotherapy regimens significantly improved LFS compared with RT alone (induction chemotherapy v RT alone: hazard ratio [HR], 0.75; 95% CI, 0.59 to 0.95; $P = .02$; concomitant chemotherapy v RT alone: HR, 0.78; 95% CI, 0.78 to 0.98; $P = .03$). Overall survival did not differ significantly, although there was a possibility of worse outcome with concomitant relative to induction chemotherapy (HR, 1.25; 95% CI, 0.98 to 1.61; $P = .08$). Concomitant cisplatin/RT significantly improved the larynx preservation rate over induction PF followed by RT (HR, 0.58; 95% CI, 0.37 to 0.89; $P = .0050$) and over RT alone ($P < .001$), whereas induction PF followed by RT was not better than treatment with RT alone (HR, 1.26; 95% CI, 0.88 to 1.82; $P = .35$). No difference in late effects was detected, but deaths not attributed to larynx cancer or treatment were higher with concomitant chemotherapy (30.8% v 20.8% with induction chemotherapy and 16.9% with RT alone).

Conclusion

These 10-year results show that induction PF followed by RT and concomitant cisplatin/RT show similar efficacy for the composite end point of LFS. Locoregional control and larynx preservation were significantly improved with concomitant cisplatin/RT compared with the induction arm or RT alone. New strategies that improve organ preservation and function with less morbidity are needed.

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INTRODUCTION

Over the last decade, results of prospective, randomized controlled trials have changed the standard of care and clinical practice for management of locally advanced head and neck cancer. One of these trials, Radiation Therapy Oncology Group (RTOG) 91-11, for resectable stage III and IV cancer of the larynx, led to a change in the treatment paradigm for larynx preservation from induction cisplatin and

fluorouracil (PF) followed, in good responders, by radiotherapy (RT) to concomitant cisplatin/RT.^{1,2}

In 2003, we published the results of RTOG 91-11, a comparison of induction PF followed by RT, concomitant cisplatin/RT, and RT alone, after a median follow-up of 3.8 years.¹ The goals of this trial were to determine the contribution of chemotherapy added to RT and the optimal sequencing of chemotherapy and RT to achieve larynx preservation. Induction PF was the control group based on the

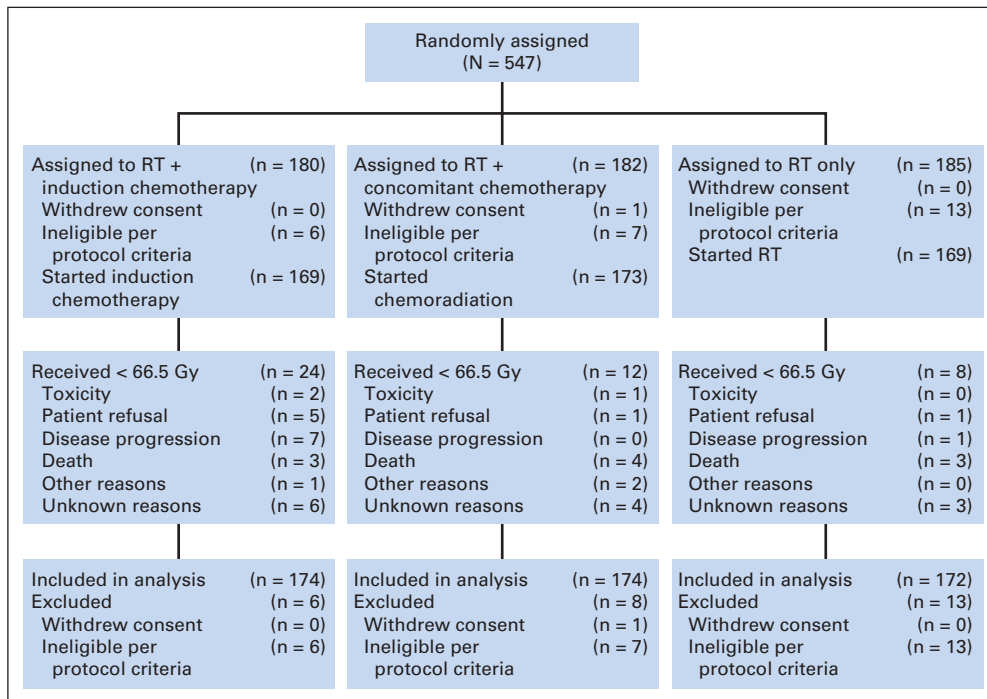


Fig 1. CONSORT diagram. RT, radiation therapy.

results of the Veterans Administration Laryngeal Study Group trial that compared induction PF followed by RT with laryngectomy followed by RT.² We now report the long-term update (5- and 10-year results) and analyses of pattern of failure, cause of death, and late effects.

PATIENTS AND METHODS

The details of eligibility, chemotherapy, and RT are provided in the previous report¹ and are summarized briefly here.

Table 1. The 5- and 10-Year Estimates of Efficacy End Points

End Point	RT + Induction Chemotherapy		RT + Concomitant Chemotherapy		RT Alone	
	Estimate (%)	95% CI (%)	Estimate (%)	95% CI (%)	Estimate (%)	95% CI (%)
Laryngectomy-free survival						
5 years	44.1	36.6 to 51.6	47.0	39.5 to 54.5	34.0	26.8 to 41.3
10 years	28.9	21.9 to 36.0	23.5	16.8 to 30.3	17.2	11.2 to 23.3
Larynx preservation						
5 years	70.8	63.9 to 77.6	83.6	78.1 to 89.2	65.8	58.7 to 73.0
10 years	67.5	60.4 to 74.6	81.7	75.9 to 87.6	63.8	56.5 to 71.1
Local control						
5 years	58.2	50.8 to 65.6	71.1	64.3 to 77.9	53.6	46.1 to 61.1
10 years	53.7	46.1 to 61.2	69.2	62.3 to 76.1	50.1	42.5 to 57.7
Locoregional control						
5 years	54.8	47.3 to 62.3	67.7	60.7 to 74.7	51.2	43.7 to 58.8
10 years	48.9	41.3 to 56.5	65.3	58.1 to 72.4	47.2	39.6 to 54.8
Distant control						
5 years	85.3	79.9 to 90.6	86.4	81.2 to 91.6	78.0	71.7 to 84.3
10 years	83.4	77.7 to 89.0	83.9	78.2 to 89.5	76.0	69.4 to 82.5
Disease-free survival						
5 years	37.7	30.4 to 45.0	38.0	30.8 to 45.3	28.0	21.1 to 34.8
10 years	20.4	14.0 to 26.7	21.6	15.2 to 28.0	14.8	9.2 to 20.3
Overall survival						
5 years	58.1	50.6 to 65.5	55.1	47.6 to 62.6	53.8	46.1 to 61.4
10 years	38.8	31.2 to 46.3	27.5	20.4 to 34.5	31.5	24.1 to 39.0

Abbreviation: RT, radiation therapy.

Patient Population

Eligible patients had stage III or IV squamous cell cancer of the supraglottic or glottic larynx curable with laryngectomy and RT. T1 primaries and high-volume T4 primaries (invasion > 1 cm into the base of tongue or penetration through cartilage) were excluded.

Random Assignment and Treatment

Patients were stratified for site (glottis or supraglottis), T stage (T2, T3 with fixed cord, T3 with no cord fixation, or T4), and N stage (N0-1 or N2-3) and then randomly assigned to one of three regimens. Group 1 (induction, control arm) received up to three cycles of PF (cisplatin 100 mg/m² on day 1 and fluorouracil 1,000 mg/m² per day for 5 days) every 3 weeks. Responders ($\geq 50\%$ reduction of the primary tumor and at least stable disease in the neck) received RT (2 Gy per fraction in 35 treatments to 70 Gy). Group 2 (concomitant) received cisplatin 100 mg/m² on days 1, 22, and 43 of RT (70 Gy). Group 3 (RT alone) received RT (70 Gy). Salvage surgery was performed for patients in group 1 who achieved less than a partial response at the primary site or who experienced progression in the neck after two cycles of PF or progression at any time during induction; salvage surgery was performed in all groups in patients with biopsy-proven persistent disease after completing RT or for subsequent recurrence. A planned neck dissection was recommended for patients with N2 or N3 disease at initial staging. Patients underwent a comprehensive head and neck examination approximately 8 weeks from completion of RT, every 3 months thereafter for 1 year, semi-annually during years 2 and 3, and then annually thereafter. Imaging of the neck was performed at the 8-week follow-up visit and then as clinically indicated.

Statistical Design and Analysis

The primary objective was maximizing survival with preservation of laryngeal function, with the control group being induction PF followed by RT. This primary end point was assessed through determination of survival with a preserved larynx (laryngectomy-free survival [LFS]), overall survival, disease-free survival, laryngectomy rate, pattern of relapse, acute and late effects, and quality-of-life measures. For LFS, disease-free survival, and overall survival, the Kaplan-Meier method was used to estimate the failure rates, and the log-rank test was used to compare patient groups.^{3,4} For other study end points with death as the only competing risk, the cumulative incidence method was used to estimate failure rates, and Gray's test was used to compare groups.⁵ All efficacy end points were measured from the date of random assignment to the date of the event or competing risk; otherwise, patients were censored at the date of their last follow-up visit. To account for differences in the timing of protocol-specified disease assessments between groups, patients with recurrence or censored before 6 months after random assignment were counted as having treatment failure or censored at 6 months, for efficacy end points other than overall survival. Cox proportional hazards models⁶ were used to compare patient groups. Eligible patients who received protocol treatment were included in the toxicity analysis, whereas all eligible patients were included in the efficacy analysis.

The cutoff for designating acute and late effects was 90 days after the end of radiotherapy. Speech and swallowing effects were updated yearly and were based on the percentage of patients who were disease free with intact larynx and with speech or swallowing information reported.

To explore the causes of death, an analysis of study cancer mortality and non-study cancer mortality, per the methods of Peto et al,^{6a} has been added. Deaths attributed to causes other than study cancer were categorized as deaths not caused by study cancer. All other deaths were categorized as study cancer deaths. To prevent late recurrences from biasing the analyses of cause-specific mortality, the log-rank analysis of non-study cancer mortality covered only the period before recurrence (ie, data are censored at the first recurrence).

RESULTS

A total of 547 patients were enrolled between August 1992 and May 2000 (Fig 1). This analysis was performed after a median follow-up for surviving patients of 10.8 years (range, 0.07 to 17 years); only 11.7% of

patients were alive with less than 10 years of follow-up. One patient withdrew consent and 26 patients were retrospectively declared ineligible, for a total of 520 analyzable patients (174 assigned to induction, 174 assigned to concomitant, and 172 assigned to RT alone). Sixty-four percent of patients had stage III disease; primary site was supraglottic in 69% of patients; and T and N stages were distributed as follows: T2, 11%; T3, 79%; T4, 10%; N0, 50%; N1, 21%; N2, 28%; and N3, 2% (American Joint Committee on Cancer TNM staging system).

Late Toxicity

Appendix Table A1 (online only) lists the worst late toxicity using the RTOG late toxicity scoring system. Subcutaneous, salivary gland, pharynx/esophagus, and larynx toxicities were the most frequent serious events. These complications led to fatal events in all groups (four deaths, three deaths, and one death in induction, concomitant, and RT alone arms, respectively). The 10-year cumulative rates of grade 3 to 5 late toxicity were 30.6%, 33.3%, and 38% in induction, concomitant, and RT alone arms, respectively. We did not detect any significant differences in cumulative incidence between treatment groups.

Preservation of the Larynx

The 5- and 10-year results are listed in Table 1; hazard ratios (HRs) are listed in Table 2. A total of 148 patients underwent laryngectomy, including 55 (67.5% larynx preservation), 32 (81.7%), and

Table 2. Hazard Ratios for Efficacy End Points

End Point	Hazard Ratio*	95% CI	P
Laryngectomy-free survival			
RT + concomitant v RT + induction	1.05	0.83 to 1.34	.68
RT alone v RT + induction	1.33	1.05 to 1.69	.02
RT + concomitant v RT alone	0.78	0.61 to 0.98	.03
Laryngeal preservation			
RT + concomitant v RT + induction	0.58	0.37 to 0.89	.005
RT alone v RT + induction	1.26	0.88 to 1.82	.35
RT + concomitant v RT alone	0.46	0.30 to 0.71	< .001
Local control			
RT + concomitant v RT + induction	0.66	0.47 to 0.93	.006
RT alone v RT + induction	1.18	0.87 to 1.60	.50
RT + concomitant v RT alone	0.57	0.40 to 0.80	< .001
Locoregional control			
RT + concomitant v RT + induction	0.66	0.48 to 0.92	.0037
RT alone v RT + induction	1.13	0.84 to 1.52	.72
RT + concomitant v RT alone	0.59	0.43 to 0.82	.0015
Distant control			
RT + concomitant v RT + induction	1.11	0.66 to 1.86	.88
RT alone v RT + induction	1.59	0.99 to 2.58	.06
RT + concomitant v RT alone	0.69	0.43 to 1.11	.08
Disease-free survival			
RT + concomitant v RT + induction	0.98	0.78 to 1.24	.88
RT alone v RT + induction	1.26	1.00 to 1.58	.06
RT + concomitant v RT alone	0.78	0.62 to 0.98	.04
Overall survival			
RT + concomitant v RT + induction	1.25	0.98 to 1.61	.08
RT alone v RT + induction	1.15	0.89 to 1.47	.29
RT + concomitant v RT alone	1.08	0.85 to 1.39	.53

Abbreviation: RT, radiation therapy.

*Hazard ratio = hazard for first treatment listed/hazard for second treatment listed.

61 patients (63.8%) in the induction, concomitant, and RT alone arms, respectively; 80% of laryngectomies were performed during the first 2 years (84 during year 1 and 35 during year 2). Laryngectomy was performed for persistent or recurrent disease except for three patients who were noncompliant with their assigned treatment and nine patients with laryngeal dysfunction (four patients in induction PF arm, two patients in concomitant cisplatin/RT arm, and three patients in RT alone arm). The significant advantage of concomitant cisplatin/RT for larynx preservation (compared with the induction and RT alone treatment groups) persists (Fig 2A). Concomitant cisplatin/RT resulted in a 54% relative reduction in risk of laryngectomy compared with RT alone (HR, 0.46; 95% CI, 0.30 to 0.71; $P < .001$) and a 42% reduction compared with the induction arm (HR, 0.58; 95% CI, 0.37 to 0.89; $P = .005$). There was no significant difference when comparing RT alone with induction (HR, 1.26; 95% CI, 0.88 to 1.82; $P = .35$).

Speech and Swallowing

We analyzed speech and swallowing based on symptom scales reported in patients alive and disease free with a retained larynx.

Impaired speech or voice quality described as “moderate difficulty saying some words, and cannot use the phone; only family and/or friends can understand me; or cannot be understood” was reported during years 2 to 5 in 3% to 9% of patients in the induction group, 4% to 8.5% of patients in the concomitant group, and 5% to 8.5% of patients in the RT alone group.

Swallowing dysfunction classified as “can only swallow soft foods” or worse reported over the same time interval fluctuated between 13% and 14% of patients in the induction group, 17% to 24% of patients in the concomitant group, and 10% to 17% of patients in the RT alone group. The ability to swallow only liquids was reported in less than 4% of patients in all groups, and inability to swallow was reported in less than 3% of patients in all groups at any time point. In view of diminishing numbers of patients and missing information, the interpretation of these data is limited but does not show any substantive differences in quality of function based on treatment.

For the composite end point of LFS, there is no difference between the concomitant arm (23.5% at 10 years) versus the induction arm (control arm; 28.9%), with an HR of 1.05 (95% CI, 0.83 to 1.34;

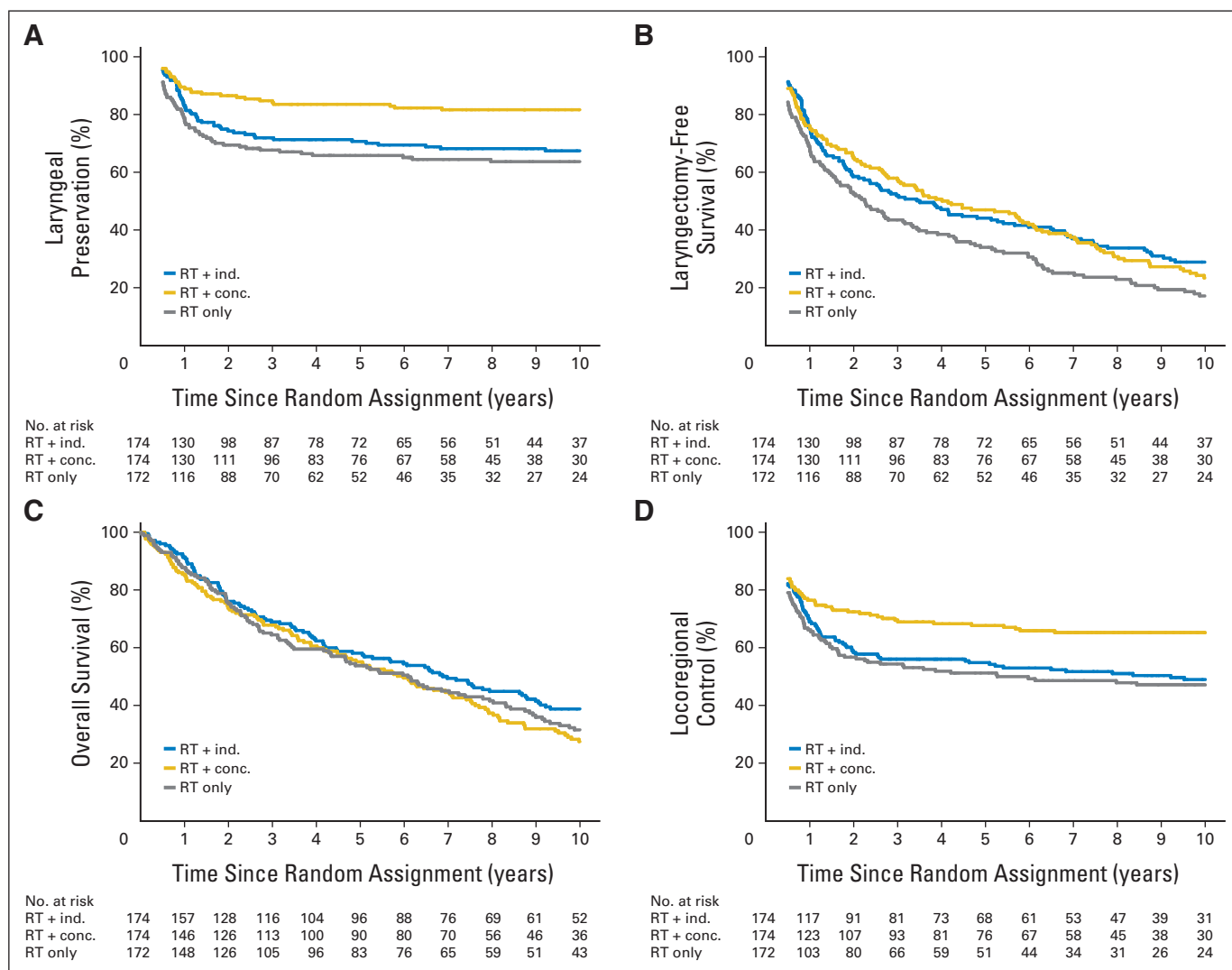


Fig 2. (A) Laryngeal preservation, (B) laryngectomy-free survival, (C) overall survival, and (D) locoregional control according to treatment group. conc., concomitant; ind., induction; RT, radiation therapy.

$P = .68$). However, LFS is significantly worse for the RT alone group (17.2%) versus both the induction group (HR, 1.33; 95% CI, 1.05 to 1.69; $P = .02$) and concomitant group (HR, 1.29; 95% CI, 1.03 to 1.63; $P = .03$; Fig 2B).

Survival Outcomes

Overall survival (Fig 2C) did not differ in any of the treatment comparisons, with 5- and 10-year estimates of 58% and 39% for induction, 55% and 28% for concomitant, and 54% and 32% for RT alone, respectively. After about 4.5 years, the curves begin to separate favoring induction, although the difference is not statistically significant. The HRs for the overall survival comparisons of all randomly assigned patients (intent to treat) were similar to those shown in Table 2 for the analysis of eligible patients (concomitant ν induction: HR, 1.25; 95% CI, 0.98 to 1.61; $P = .08$; RT alone ν induction: HR, 1.15; 95% CI, 0.89 to 1.47; $P = .29$; concomitant ν RT alone: HR, 1.08; 95% CI, 0.85 to 1.39; $P = .53$).

There was no significant difference in overall survival comparing patients who did and did not undergo salvage laryngectomy within 1 year of completing treatment ($P = .21$; Fig 3A). An exploratory anal-

ysis showed a significantly worse survival for patients who had a laryngectomy in both chemotherapy groups compared with those who did not (induction, $P = .03$; concomitant, $P = .01$) and no difference for RT alone ($P = .20$; Figs 3B to 3D). For disease-free survival, only the comparison of concomitant chemotherapy versus RT alone reaches statistical significance (HR, 0.78; 95% CI, 0.62 to 0.98; $P = .04$), although the comparison of RT versus induction is close (HR, 1.26; 95% CI, 1.00 to 1.58; $P = .06$).

Pattern of First Failure

The outcome for 444 patients (induction, $n = 144$; concomitant, $n = 152$; RT alone, $n = 148$) who were disease free after completing protocol radiation is shown in Appendix Table A2 (online only). Two hundred twenty-eight patients (51%) died without recurrence or are alive without recurrence. The proportions of patients in the induction, concomitant, and RT alone groups with recurrence and the site as a component of recurrence were as follows: local, 33.3%, 22.3%, and 35.8%; regional, 7.6%, 3.3%, and 11.5%; and distant, 10.4%, 11.2%, and 14.9%, respectively. The results for locoregional control (Fig 2D)

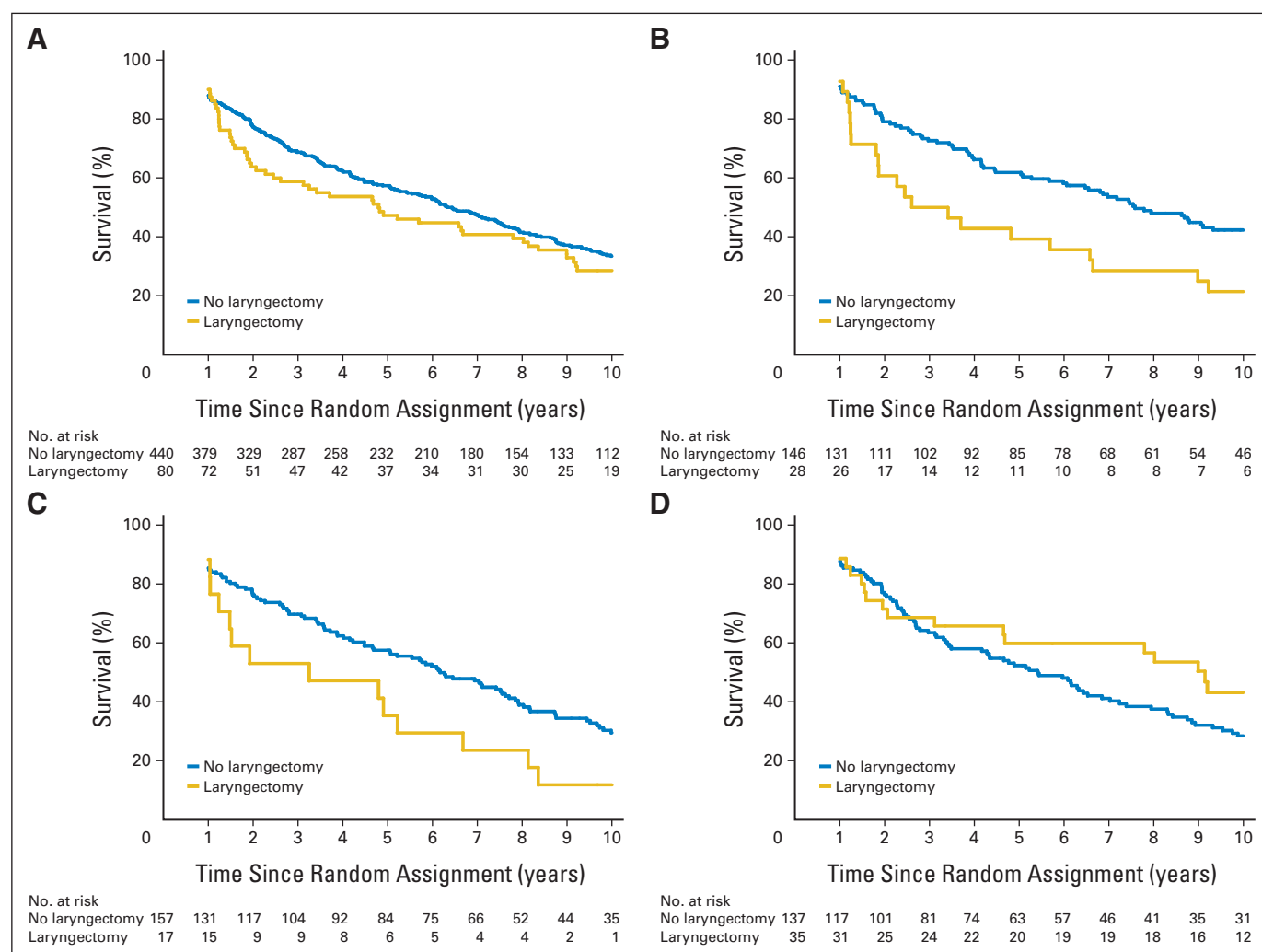


Fig 3. Survival according to whether or not a laryngectomy was performed in the first year: (A) all treatment arms combined ($P = .21$); (B) induction arm ($P = .03$); (C) concomitant arm ($P = .01$); and (D) radiation therapy-only arm ($P = .20$).

Table 3. Cause of Death

Cause of Death	RT + Induction Chemotherapy		RT + Concomitant Chemotherapy		RT Alone	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Cancer under study	45	37.5	38	29.2	60	48.4
Second malignancy	15	12.5	18	13.8	15	12.1
Complications of protocol treatment	9	7.5	9	6.9	5	4.0
Complications of other treatment	3	2.5	2	1.5	3	2.4
Unrelated to cancer or treatment	25	20.8	40	30.8	21	16.9
Unknown/not reported	23	19.2	23	17.7	20	16.1
Total deaths	120		130		124	

Abbreviation: RT, radiation therapy.

parallel those for larynx preservation. Concomitant cisplatin/RT resulted in a 41% reduction in risk of locoregional failure compared with RT alone (HR, 0.59; 95% CI, 0.43 to 0.82; $P = .0015$) and a 34% reduction compared with induction (HR, 0.66; 95% CI, 0.48 to 0.92; $P = .0037$).

Distant Metastases

Chemotherapy given concomitantly or as induction showed similar benefit for achieving distant control (7% to 8% difference compared with RT alone), but neither comparison reached statistical significance ($P = .08$ and $P = .06$, respectively). The distant recurrence rate was low, with 28, 29, and 41 patients experiencing distant recurrence in the induction, concomitant, and RT alone groups, respectively.

Cause of Death

A total of 374 patients have died. The RT alone group had the highest proportion of deaths attributed to larynx cancer, and the

concomitant group had the lowest (Table 3). More deaths were classified as unrelated to either larynx cancer or treatment in the concomitant group (30.8%) compared with the induction group (20.8%) and the RT alone group (16.9%), whereas the proportion of deaths classified as unknown/not reported was similar for all groups (17.7%, 19.2%, and 16.1%, respectively).

We conducted an exploratory analysis of death caused by study cancer and death not caused by study cancer (Figs 4A and 4B). There were no statistically significant pairwise differences between the treatment groups for death caused by the study cancer. However, for death from causes not related to the study cancer, there was a significant disadvantage for the concomitant group compared with the induction group (52.8% v 69.8%, respectively, at 10 years; $P = .03$).

DISCUSSION

Intergroup trial RTOG 91-11, designed more than two decades ago, compared concomitant cisplatin/RT and RT alone with the control group of induction PF followed by RT. The composite end point of LFS was chosen as the primary end point. For this outcome, treatment with concomitant cisplatin/RT compared with induction is not significantly different and treatment with RT alone is significantly inferior. However, when larynx preservation and survival are separately analyzed, the significant advantage of concomitant cisplatin/RT for larynx preservation and securing locoregional control is confirmed; induction PF was not better than RT alone. With longer follow-up, differences in overall survival were not statistically significant, but there was a suggestion of better survival in patients treated with induction PF. After 4.5 years, the survival curves show some separation, and the death rate in the concomitant treatment group remains constant. Deaths in later years of follow-up resulted in LFS changing from nonsignificant to significant for induction PF compared with RT alone (and obscure the significantly inferior larynx preservation achieved by induction PF compared with concomitant treatment). More deaths in the concomitant group were unrelated to larynx cancer. This occurred with no apparent increase in late effects. This raises

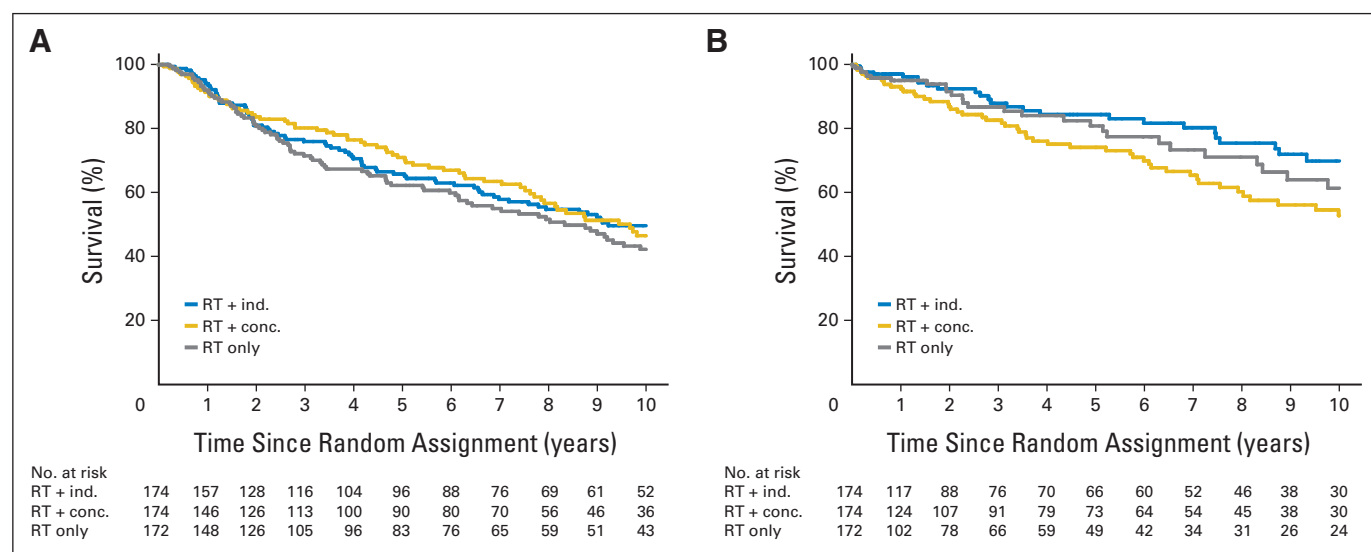


Fig 4. Survival, limited to (A) deaths from study cancer and (B) deaths not caused by study cancer according to treatment group. conc., concomitant; ind., induction; RT, radiation therapy.

the possibility of fatal treatment-related episodes not identified with the current system for monitoring and grading late effects.

Function, as assessed through patient-reported outcomes, was excellent. The results for each treatment group were consistent over time. Although we did not collect information on gastrostomy tube usage, few patients (< 5%) were limited to liquids or unable to swallow.

The composite end point of LFS was chosen as the primary end point for sample size calculation in 1990 using an estimate of 66% (based on the crude rate of 52 of 79 patients reported alive with their larynx in the Veterans Administration Laryngeal Study Group report).² However, LFS had not previously been used or reported. In this report, induction and concomitant treatments show similar LFS. This composite end point obscures the significant difference in local control and larynx preservation rates and underscores what are now recognized as significant limitations of an ill-considered end point.⁷ Evaluating each end point separately (eg, survival, larynx preservation, locoregional control) provides the clearest information and does not equally weight death and loss of one's larynx.⁸

For stage III or IV larynx cancer studied in this trial (T1 and high-volume T4 primary tumors excluded), the larynx can be preserved in the majority of patients with any of the three nonsurgical approaches tested; however, nearly twice as many patients will undergo laryngectomy if treated with induction PF or RT alone instead of concomitant cisplatin/RT. The results also suggest that improved local control and high rates of larynx preservation achievable with concomitant high-dose cisplatin/RT may be accompanied by increased risk of serious late effects perhaps as a consequence of more acute mucosal toxicity.¹ Whether that risk would be the same with today's RT techniques (three-dimensional or intensity-modulated RT), which provide much better conformality and normal tissue sparing, is unknown. Most patients in RTOG 91-11 were treated with simple two-dimensional plans. The reason for the increase in late noncancer deaths in the concomitant group remains speculative.

The finding that induction PF did not add to treatment with RT alone for achieving locoregional control or larynx preservation was consistent with previous trials of induction PF and with the updated Meta-Analysis of Chemotherapy for Head and Neck Cancer, which showed no effect of induction PF on local control, contrasted with an absolute difference in local failure of $-13.5 \pm 2.8\%$ for concomitant treatment.⁹ A phase III comparison of alternating PF and RT versus induction PF followed by RT for larynx and hypopharynx cancers postulating improved outcomes with the alternating regimen showed no difference in larynx preservation.¹⁰ Lower doses of chemotherapy and RT in the alternating treatment regimen (in an effort to reduce toxicity) may have contributed to the negative result.

Strategies for further investigation include RT with a different radiosensitizing agent (with or without a more effective induction regimen). However when compared with PF induction, no differences were detected for local, locoregional, and distant failure or (in subset analyses) for overall survival for larynx cancer, stage III cancers, T3 and T4 cancers, and N0 and N1 cancers for taxane plus PF (TPF) followed by carboplatin/RT.¹¹ The Groupe Oncologie Radiothérapie Tête et Cou (GORTEC) 2000-01¹² trial investigated TPF induction compared with PF induction followed by RT for larynx preservation in patients with T3 and selected T4 cancers of the larynx or hypopharynx. The preliminary findings showed higher rates of larynx preservation with induction TPF, likely be-

cause of the better response rate with TPF (80% v 59% for PF; $P = .002$), which was the decision point for radiation or laryngectomy. On the basis of this result, induction TPF is considered a standard treatment option by European investigators. The findings were not reported separately for these two biologically different primary sites, so the specific benefit for larynx cancer is uncertain.

A randomized trial comparing RT with or without cetuximab in patients with locally advanced, stage III or IV head and neck cancer showed significantly improved overall and locoregional failure-free survival (a composite end point) but no difference in distant metastasis.¹³ Locoregional control was not reported. Subset analyses suggested that the benefit of cetuximab was limited to patients with oropharynx cancer. The RTOG has evaluated RT/cisplatin with or without cetuximab and found no improvement in any outcome with the addition of cetuximab¹⁴; however, a direct comparison of cetuximab/RT and cisplatin/RT is only now being undertaken in patients with human papillomavirus-related cancers of the oropharynx (RTOG 1016). This is a relevant question for intermediate-stage larynx cancer, where cetuximab/RT would be an attractive alternative, if efficacy were comparable.

Integrating chemotherapy and conservation laryngeal surgery in selected patients with T3 disease warrants investigation.^{15,16} Our exploratory analysis of the outcome after salvage laryngectomy for patients receiving induction or concomitant chemotherapy suggests that early identification of patients who will eventually experience failure with nonsurgical therapy may be important for long-term survival.

In conclusion, the long-term results of Intergroup RTOG 91-11 show that for the composite end point of LFS, induction and concomitant treatments had similar efficacy. However, locoregional control and larynx preservation were significantly improved with concomitant treatment compared with induction or RT alone. No differences in late toxicity or speech or swallowing function were demonstrated, but there was an unexplained increase in deaths unrelated to cancer in patients who received concomitant cisplatin/RT. This may be responsible for the absence of a survival advantage for the concomitant treatment group. For intermediate-stage larynx cancer, new strategies focusing on improved locoregional control should be undertaken, and better assessment of late events should be performed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

Table A1. Patients With a Late Toxicity by Type and Grade

Late Toxicity	No. of Patients														
	RT + Induction Chemotherapy (n = 154)					RT + Concomitant Chemotherapy (n = 157)					RT Alone (n = 158)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematologic NOS	14	4	0	0	0	21	6	3	0	0	16	3	1	0	0
Skin (within RT field)	51	16	5	1	1	58	16	1	0	0	59	20	2	1	0
Mucous membrane/stomatitis	32	23	5	0	0	40	23	3	0	0	42	25	3	1	0
Subcutaneous tissue	33	34	11	1	0	46	34	9	1	0	40	35	9	2	0
Salivary gland	30	72	9	0	0	52	53	9	0	0	39	72	6	0	0
Pharynx/esophagus	38	19	15	3	2	39	20	22	3	1	34	30	22	2	0
Larynx	43	41	10	6	1	50	40	17	6	1	27	52	21	8	0
Upper GI	4	4	2	0	0	8	4	0	0	0	8	3	0	0	0
GU/renal	6	2	0	0	0	12	4	0	0	0	9	1	0	0	0
Spinal cord	5	0	0	0	0	11	0	0	0	0	10	0	0	0	0
Neurologic	10	6	0	0	0	20	5	3	0	0	15	3	1	1	0
Bone	2	1	1	1	0	7	0	0	0	0	7	3	0	0	0
Joint	8	0	2	0	0	11	2	0	0	0	8	3	1	0	0
Other	18	27	1	2	1	20	36	7	1	1	14	26	12	1	1

Abbreviations: GU, genitourinary; NOS, not otherwise specified; RT, radiation therapy.

Table A2. Pattern of First Failure

Treatment Failure	RT + Induction Chemotherapy (n = 144)		RT + Concomitant Chemotherapy (n = 152)		RT Alone (n = 148)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
No failure, alive	34	23.6	35	23.0	26	17.6
No failure, dead	38	26.4	60	39.5	35	23.6
Local only	45	31.3	32	21.1	45	30.4
Regional only	8	5.6	3	2.0	7	4.7
Local and regional	3	2.1	1	0.7	8	5.4
Local and/or regional, and distant	0		2	1.3	2	1.4
Distant only	15	10.4	15	9.9	20	13.5
Dead, study cancer NOS	1	0.7	4	2.6	5	3.4

NOTE. Does not include second primary tumors; includes all patients with no evidence of disease at the completion of protocol therapy. Abbreviations: NOS, not otherwise specified; RT, radiation therapy.