Function Preservation in Stage III Squamous Laryngeal Carcinoma: Results With an Induction Chemotherapy Protocol

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Until recently, standard treatment for stage III laryngeal carcinoma (LC) was total laryngectomy and radiotherapy. Recent data suggest that induction chemotherapy (ICH) plays a role in preserving function in advanced head and neck cancer. No reports to date prospectively evaluate ICH exclusively in stage III LC. The authors designed a sequential phase II trial to assess if ICH allowed a conservative treatment in this disease. The objective of the first part of the study was to rule out a complete response rate with ICH below 30% with $P<.05$. ICH protocol consisted of three courses of cisplatin 100 mg/M_2 on day 1 and 5-fluorouracil 5000 mg/M_2 continuous infusion over 120 hours. Radiotherapy was administered to patients who attained a complete response (CR). Functional surgery (FS) was planned for patients with partial response. A total laryngectomy followed by radiotherapy was performed when FS was not feasible. Fifty-two previously untreated patients (all males) with squamous stage III LC were diagnosed in our institution, and 46 were entered in the ICH trial. After 9 patients were included, data showed 7 (78%) CR, ruling out a CR rate of less than 30%. After ICH, a CR was achieved in 29 (63%) of 46 patients. At the end of treatment, 35 patients (76%) had a functioning larynx. With a median follow-up of 3 years, larynx function was preserved in 26 (57%) of 46 patients and in 64% of survivors. Four-year actuarial larynx function preservation, overall survival, and disease-free survival were 55%, 77%, and 67%, respectively. Karnofsky performance score over 80% was the only significant prognostic factor in overall survival (94% at 4 years) and disease-free survival (78% at 4 years). In conclusion, the authors believe that ICH followed by response-related second treatment is safe and effective in preserving laryngeal function in stage III LC. There is no evidence of worsening survival.

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INTRODUCTION

Until recently total laryngectomy and radiotherapy was the standard treatment for stage III laryngeal carcinoma (LC), which is probably the most feared of all head and neck operations. McNeil showed that many patients would prefer a lesser operation than total laryngectomy with less likelihood of cure, if it would preserve their ability to speak.[1] In recent years, considerable efforts have been put into developing treatment strategies that would result in voice preservation. Data reported include multiple localizations, nonstratification, or results not separately reported by stage (III and IV).[2] Only retrospective studies using radiotherapy alone in stage III LC have been reported.

Analysis of historical experience in our institution showed no statistical differences in actuarial survival among stage III LC (60 patients) treated with total laryngectomy and postoperative radiotherapy and T4N0-1 LC (85 patients) treated with induction chemotherapy (ICH); the 3-year actuarial survival rates were 60% and 55%, respectively. Moreover, in the latter group it was possible to preserve laryngeal function in some patients (unpublished data). Thus, exploring the role of induction chemotherapy in laryngeal preservation in stage III LC was justified.

Since the standard nonconservative treatment of stage III LC has reported 5-year survival rates ranging from 60% to 80%,[3] any conservative treatment approach is acceptable if laryngeal function is maintained without jeopardizing patient survival. Ethical issues regarding the proposal to obtain patient consent to participate in a study with randomization to either laryngectomy or conservative treatment makes the phase III methodology unfeasible. With the aim of assessing whether ICH followed by response-related second treatment could achieve local control, allowing laryngeal function preservation, a sequential phase II trial was designed. The results of this trial applied to stage III LC patients diagnosed in our institution are reported.

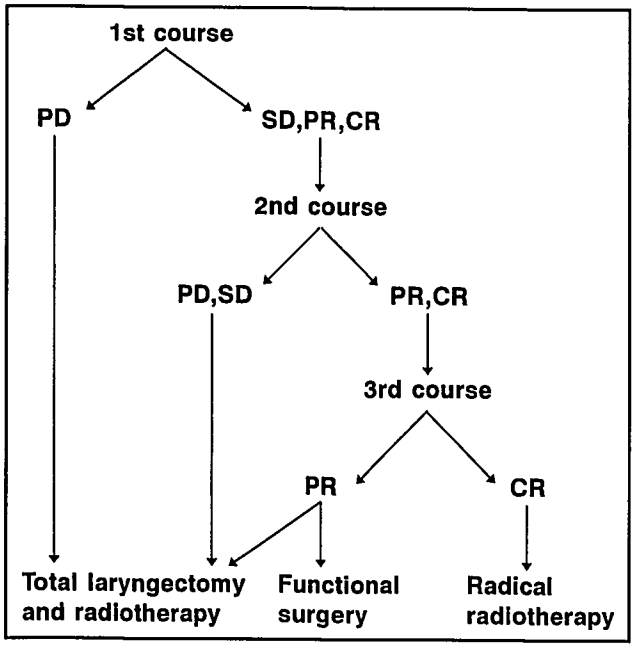

Fig. 1. Treatment schedule. PD = progression of disease; SD = stabilization; PR = partial response; CR = complete response.

MATERIALS AND METHODS

Inclusion Criteria

All patients diagnosed in our institution who were untreated, had histologically proven squamous cell laryngeal carcinoma, and were classified as a stage III (Union Internationale Contre le Cancer [UICC] 1989) were considered candidates for the conservative treatment trial. To assess extension, a physical examination, chest radiograph, indirect laryngoscopy, flexible direct laryngoscopy, and a cervical computed tomography (CT) scan were performed. Patients were required to be under 70 years old, to have a Karnofsky performance score over 60%, and normal liver, renal, and hematological function. Informed consent was obtained from all patients.

Study Design

The authors hypothesize that a complete response (CR) to ICH allows a successful conservative treatment in stage III LC with the addition of radiotherapy. For the safety of this approach a rate of CR that is too low with ICH must first be ruled out. For this reason, a sequential phase II trial was set up.[4] The first part of the study was designed to include nine patients in order to discard a CR rate below 30% with a $P<.05$. If no CR was attained, the trial would be stopped. Otherwise, the study would continue to assess the CR rate with an acceptable confidence interval and with the safety and effectiveness of the conservative approach. Patients would then be followed for a median of 3 years to verify that the recurrences and survival may be comparable to standard treatment. The study was begun in January 1990.

Treatment Definitions and Schedule

Induction chemotherapy consisted of cisplatin 100 mg/M_2 and day 1 and 5-fluorouracil 5000 mg/M_2 continuous infusion over 120 hours. All patients were treated with cobalt 60. The larynx and neck were irradiated by two lateral parallel opposed fields. The low neck was treated in all patients with an anterior field. Treatment was administered 5 days a week by continuous-course radiotherapy. Tumor doses were 65 to 70 Gy for radical radiotherapy and 50 to 60 Gy for postoperative radiotherapy. Radiotherapy had to be initiated no later than 3 weeks after third-course response assessment. Functional surgery consisted of supraglottic laryngectomy and cervical node dissection and was planned in patients with a partial response (PR) on the basis of extension at the time of surgery. The treatment schedule is shown in Figure 1.

Assessment of Response and Toxicity

Response was assessed 3 weeks after each course using a flexible laryngoscope with image recordings; a CT scan was taken after the third course. Joint evaluation was made by a medical oncologist, a radiotherapist, and an otorhinolaryngologist. Response and toxicity were evaluated according to the World Health Organization (WHO) criteria.

Statistical Analysis

Survival and larynx function preservation probability were calculated using the actuarial Kaplan-Meier method. Laryngectomy and uncontrolled local disease were the events for larynx function preservation analysis. The comparison of survivals was made by the nonparametric method of Peto and Peto.[16]

RESULTS

In the first part of the study, a CR was obtained in seven (78%) of the nine patients (confidence interval, 50% to 100%) and none experienced progression; this ruled out a CR rate less than 30% with a $P<.05$. The study was then continued. Incidences in follow-up were updated in June 1994 to assess the long-term evolution. The last patient included in this analysis was recruited in December 1992. Median follow-up was 36 months (range, 18 to 54 months).

Within the study period, 52 patients (all males) with stage III LC were diagnosed in our institution. Their characteristics are summarized in Table I. ICH was planned in 49 of the 52 patients; 2 patients were too old and 1 patient had low performance score. As 3 of 49 patients refused chemotherapy, a total of 46 were included in the ICH trial.

Chemotherapy Response and Second Treatment

Forty-three patients completed the three planned courses: 1 patient refused further treatment after the first course and died of progression 9 months later, 1 patient died of baseline disease nonrelated to chemotherapy, and 1 patient died of ICH toxicity. All 46 patients were evaluated for response (Table II). No progression was observed during ICH. After three courses, 29 (63%) of the patients attained a CR and radiotherapy was administered. Fourteen (30%) of the patients attained a PR: 6 underwent functional surgery (4 had no evidence of tumor in the surgical specimen, increasing the CR rate to 72%) and 8 underwent

TABLE I.
Patient Characteristics (n = 52).

	n (%)
Karnofsky performance score	
60%	1 (2%)
70%	1 (2%)
80%	12 (23%)
90%	38 (73%)
Alcohol intake>100 g/day	16 (30%)
Cigarettes smoked>20/day	35 (68%)
Associate diseases	32 (60%)
Localization	
Supraglottis	39 (75%)
Glottis	7 (13%)
Overlapping	6 (12%)
TNM	
T2N1	5 (10%)
T3N0	36 (69%)
T3N1	11 (21%)
Tumor differentiation	
Well	5 (10%)
Moderate	42 (80%)
Poor	5 (10%)

Note: Mean age of patients = 63 y (range, 38–78 y); two patients were older than 70 y and were not included in ICH protocol.

TABLE II.
Clinical Response to Induction Chemotherapy.

	Complete Response	Partial Response	Stabilization
First course (n = 46)	4	34	8
Second course (n = 44)	21	23	0
Third course (n = 43)	29	14	0

TABLE III.
Induction Chemotherapy Toxicity (n = 46).

	WHO Toxicity Grade			
	1	2	3	4
Renal	7 (15%)	0	0	0
Nausea/vomiting	6 (13%)	15 (33%)	6 (13%)	0
Mucositis	9 (20%)	12 (26%)	4 (9%)	0
Hematological	6 (13%)	8 (17%)	4 (9%)	1 (2%)

WHO = World Health Organization.

total laryngectomy and postoperative radiotherapy.

Survival and Laryngeal Function Preservation

All 46 patients were included in the survival and laryngeal function preservation analysis. No patient was lost to follow-up. Actuarial 4-year overall survival was 77% (Fig. 2). There were 6 deaths, 3 of them due to a second recurrence. At the end of treatment 35 (76%) of the 46 patients had a functioning larynx. During follow-up, 11 patients relapsed (10 had received radiotherapy and 1 had undergone functional surgery); 9 of these patients relapsed at the local level and 2 relapsed as pulmonary metastasis. All patients having local recurrence could be salvaged with laryngectomy;

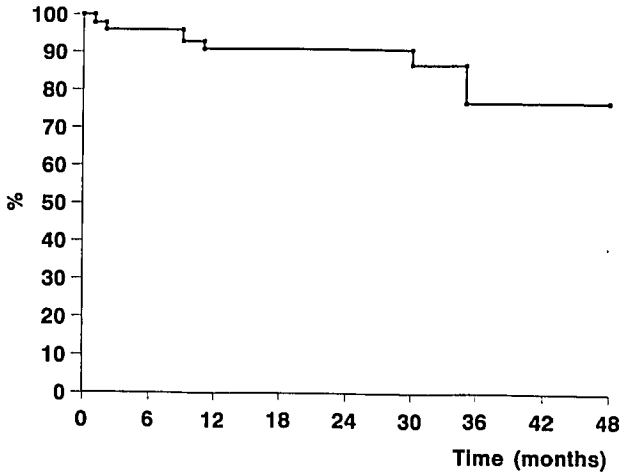

Fig. 2. Overall survival.

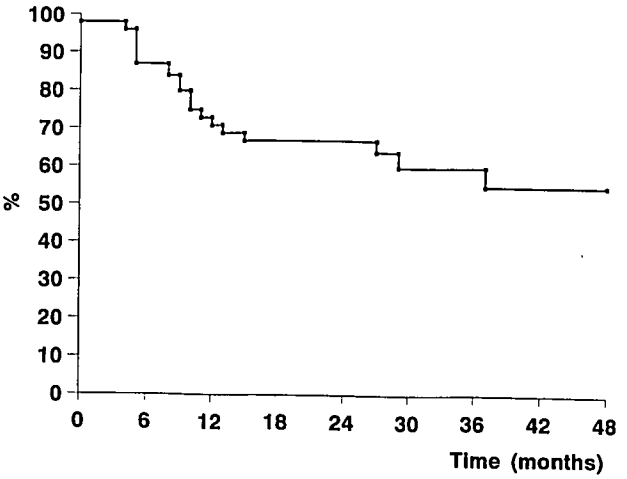

Fig. 3. Actuarial larynx function preservation.

2 of these patients had a second recurrence (local and metastatic, respectively) and died. A total of 64% of survivors therefore had preserved laryngeal function. Actuarial laryngeal function preservation probability (Fig. 3) and disease-free survival were 55% and 67%, respectively. Only a Karnofsky score over 80% was a significant prognostic factor ($P<.001$) for overall (94% at 4 years) (Fig. 4) and disease-free survival (78% at 4 years) in the univariate analysis that also included localization and tumor and node extension according to UICC.

Chemotherapy Toxicity

WHO toxicity grades are shown in Table III. Toxicity was generally mild, with nausea/vomiting being the most frequent. All grade 1 renal toxicities were reversible. There was one treatment-related death. This patient had poor medical and social conditions, grade 4 hematological toxicity was detected, and he died due to septic shock.

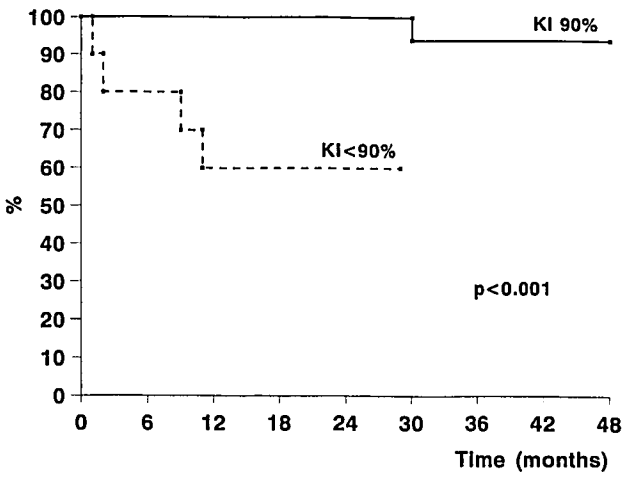

Fig. 4. Overall survival according to Karnofsky performance score. Continuous line: Karnofsky score of 90%. Discontinuous line: Karnofsky score under 90%.

DISCUSSION

To our knowledge, this is the first trial evaluating a conservative treatment with induction chemotherapy exclusively in stage III laryngeal carcinoma. Results of the trial demonstrate that ICH can achieve high CR rates allowing good local control with the addition of radical radiotherapy. It is of interest that functional surgery could be performed in 6 (43%) of 14 patients with PR. Salvage laryngectomy was effective as only 1 of the 9 patients who recurred after a conservative procedure experienced a late local second recurrence. We think that these results are attributable to the early diagnosis of recurrences obtained with a close laryngoscopic follow-up. These issues reinforce the role of surgery in the conservative approach treating laryngeal carcinoma. There is no evidence of worsening survival when compared to our previous experience and the literature[3] with nonconservative treatments.

In spite of having highly effective combinations, chemotherapy, used in a neoadjuvant or adjuvant site, has failed to increase survival, at least in randomized trials.[5,6] Chemotherapy agents have substantial toxicity making their use difficult in this neoplasm where most patients have poor medical and social conditions. Thereafter, an improvement in survival might be observed in low stages (as stage III LC) and in patients having a high Karnofsky performance score as our results (95% 4-year actuarial survival) and others[7] suggest.

Stage III laryngeal carcinoma can be managed by different approaches. Some surgical series have reported survival rates of 80% in T3N0 glottic cancers with some patients treated by vocal cord sparing techniques. In spite of this, function was lost in more than 80% of patients.[8] In selected patients, vocal cord sparing surgical techniques may preserve 40% of functions.[9] Definitive radiation with laryngectomy reserved for recurrence has been advocated by many authors. The Princess Margaret Hospital[10] reported survival rates of 69% at 5 years with function preserved in 45% of patients (65% of survivors) in T3N0 glottic cancers. Only patients having completed the planned treatment were included in this analysis. Similar results were reported by Croll, *et al.* in selected T3-T4 N0 laryngeal tumors.[11] Twice-a-day radiation therapy might improve these results.

Wang, *et al.*[12] reported survival and local control rates of 75% and 66%, respectively, in T3-T4 supraglottic carcinomas. Using this approach, the University of Florida group obtained a 65% 5-year larynx preservation in T3 glottic carcinomas. The same authors also reported these results with radiotherapy compared to laryngectomy.[13] Similar rates of local-regional control and survival were found in the two treatments, but the patients were not randomized and the criteria for choosing a conservative approach were not well defined. Other authors have failed to achieve these results, obtaining low survival rates as few patients in recurrence could be salvaged.[14,15] Combined therapies that include local treatment by surgery have obtained survival rates within the range of 60% to 80%, but nearly all patients had no voice.[2,3] Combined therapies with a conservative approach have widely been used in advanced head and neck cancers, and recently in randomized trials. Most reports include multiple head and neck localizations, and results on survival and organ preservation are not stratified into localization and stage, thus complicating comparisons with our results. In the Veterans Trial[5] the larynx was preserved in 39% of all patients treated with a conservative approach (64% of survivors) and salvage laryngectomy requirements were more frequent in stage IV than in stage III patients.

From the published results, it seems clear that a conservative approach can be performed in patients with stage III LC. Clinical trials are needed to determine which is the best approach. The 4-year actuarial survival and larynx function preservation of 77% and 55% obtained in our trial indicate that ICH followed by response-related second treatment is safe and effective. The treatment was offered to 94% of all patients with this disease diagnosed at our institution, and all the patients entered in the trial were included in survival and larynx preservation analysis. Finally, we should emphasize the importance of a motivated patient, close interdisciplinary cooperation, and careful follow-up in order to guarantee an effective salvage treatment.

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