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ORIGINAL REPORT

Durable Long-Term Remission With Chemotherapy Alone for Stage II to IV Laryngeal Cancer

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A B S T R A C T

Purpose
For patients with stage II to IV laryngeal cancer, radiation therapy (RT) either alone or with concurrent chemotherapy provides the highest rate of organ preservation but can be associated with functional impairment. Thus, we studied the use of induction chemotherapy with or without conservation laryngeal surgery (CLS). Our objectives were to study the sensitivity of laryngeal cancer to platinum-based chemotherapy alone and to highlight the efficacy of CLS in this setting.

Patients and Methods
Thirty-one previously untreated patients with laryngeal cancer (T2-4, N0-1, M0), who were resectable with CLS, were enrolled. Patients received three to four cycles of paclitaxel, ifosfamide, and cisplatin (TIP) chemotherapy, and response was assessed histologically. Patients with partial response (PR) proceeded to CLS. Patients achieving pathologic complete response (pCR) received an additional three cycles of TIP and no other treatment.

Results
Thirty patients were assessable for response. With TIP chemotherapy alone, 11 patients (37%) achieved pCR, 10 of whom (33%) remain alive with durable disease remission and no evidence of recurrence over a median follow-up time of 5 years. Nineteen patients (63%) treated with TIP alone achieved PR. The overall laryngeal preservation (LP) rate was 83%, and only five patients (16%) required postoperative RT. No patient required a gastrostomy tube or tracheotomy.

Conclusion
Chemotherapy alone in selected patients with T2-4, N0-1 laryngeal cancer can provide durable disease remission at 5 years. For patients with PR, CLS provides a high rate of LP. This prospective study suggests that chemotherapy alone may cure selected patients with laryngeal cancer, warranting further prospective investigation.

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INTRODUCTION

Historically, the role of surgery for patients with T2-3 laryngeal cancer was limited to a few select patients amenable to vertical partial laryngectomy or supraglottic laryngectomy. Thus, for decades, total laryngectomy (TL) was considered the only curative option for most intermediate- to advanced-stage laryngeal cancers. Radiation therapy (RT) alone provided an important alternative, but local control rates for T2 cancers of the glottic and supraglottic larynx ranged from 62% to 92%.[1] Worse still, 70% of patients who experienced treatment failure with RT required TL.[2,3]

In 1991, the Veterans Affairs Laryngeal Cancer Study demonstrated equivalence in overall survival (OS) between patients treated with TL followed by postoperative RT (PORT) compared with patients treated with induction chemotherapy and RT.[4] In 2003, the randomized prospective Radiation Therapy Oncology Group 91-11 study demonstrated that laryngectomy-free survival was superior for patients treated with either concurrent chemotherapy and RT (cRT) or induction chemotherapy followed by RT, compared with RT alone.[5,6] However, RT with or without chemotherapy can be associated with significant long-term morbidity. An important minority of patients have an anatomically preserved organ[7-9] but significant functional compromise, sometimes necessitating tracheotomy and/or gastrostomy. For patients treated with cRT who later require salvage surgery, postoperative complications are increased, and survival is significantly diminished.[10]

Recently, a variety of conservation laryngeal surgery (CLS) techniques have emerged.[11] The

functional compromise sometimes seen with primary RT and organ preservation approaches has led some centers to take a different approach, relying on induction chemotherapy followed by CLS. Laccourreye et al[12] reported that platinum-based chemotherapy alone could achieve long-term locoregional control in selected patients with laryngeal squamous cell carcinoma (SCC). In a subset of patients who achieved a clinical complete response after induction chemotherapy, selected patients were treated with three more cycles of chemotherapy without surgery or RT. Follow-up publications confirmed a high rate of laryngeal preservation (LP) in larger cohorts.[13,14] However, this experience has never been validated prospectively in another institution.

We evaluated this novel approach in patients with intermediate- to advanced-stage laryngeal SCC using a novel regimen of paclitaxel, ifosfamide, and cisplatin (TIP) or paclitaxel, ifosfamide, and carboplatin (TIC) developed at The University of Texas M. D. Anderson Cancer Center (M. D. Anderson).[15-17] The primary objective was to determine whether chemotherapy either alone or followed by CLS would achieve long-term, durable remission for selected patients with laryngeal cancer, without compromising LP or OS.

Fig 1. Treatment schema for laryngeal preservation. TIP, paclitaxel, ifosfamide, and cisplatin; CT, computed tomography; EUA, examination under anesthesia; CR, complete response; PR, partial response; NR, no response; PD, progressive disease; XRT, radiotherapy.

PATIENTS AND METHODS

Eligibility Criteria

From 1997 to 2004, patients with histologically proven laryngeal SCC were screened for study eligibility by multidisciplinary evaluation and endoscopic staging via direct laryngoscopy. Patients selected for this study had stage II to IVa (T2-4, N0-1, M0) glottic or supraglottic SCC that was surgically resectable via CLS. Patients with T2 tumors were included when the tumor was considered unfavorable[18] by the multidisciplinary tumor board (ie, at high risk for local failure with altered-fractionation RT alone).

Eligible patients had favorable performance level (Eastern Cooperative Oncology Group performance status of 0 or 1) and normal hematopoietic, hepatic, and renal function. Patients with nodal metastasis classified as N2 or greater and patients with distant metastatic disease were ineligible. The study protocol was approved by the M. D. Anderson Institutional Review Board. Eligible patients were required to sign an informed consent form approved by the Human Subjects Review Board.

Treatment and Chemotherapy Regimens

The treatment schema is shown in Figure 1. Patients received three to four cycles of TIP chemotherapy (paclitaxel 175 mg/m^2 on day 1, ifosfamide 1,000 mg/m^2 with mesna 420 mg/m^2 on days 1 through 3, and cisplatin 60 mg/m^2 on day 1). All patients received at least three cycles of chemotherapy before biopsy, and nine patients received four cycles. If, after three cycles, the patient had a good clinical partial response (PR), as defined by greater than 90% tumor reduction, a fourth cycle could be administered before rebiopsy at the discretion of the treating physician.

Dose modifications were allowed (specified with the full regimen in Appendix Table A1, online only). If irreversible grade 2 nonhematologic toxicity, grade 4 hematologic toxicity for ≥ 7 days, or neutropenic fever with or without infection occurred, the next dose was reduced one level. The protocol was amended to allow for a change from cisplatin (60 mg/m^2) to carboplatin (area under the curve 6) in subsequent cycles in case of the following adverse events: neuropathy ≥ grade 2; nausea or vomiting ≥ grade 3 to 4; or renal failure ≥ grade 2.

Clinical and Histologic Assessment of Pathologic Response

After high-resolution computed tomography (CT) scanning, patients returned to the operating room for operative direct laryngoscopy, tumor mapping, and biopsy of any residual abnormality. If no gross residual tumor was present, biopsies w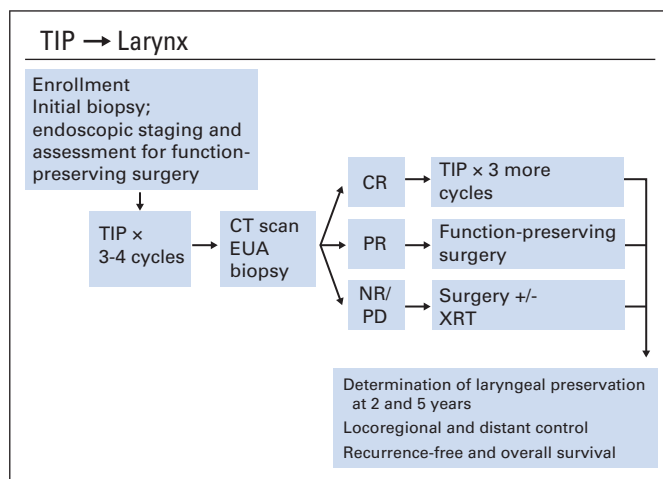ere taken at the site of the tumor epicenter (based on pretreatment videostroboscopy) and adjacent mucosa. For patients with an endoscopic and histologic complete response (CR), three additional cycles of chemotherapy were administered, followed by repeat endoscopy to confirm a final histologic CR. For patients with histologic residual disease, CLS was performed.

CLS

The surgical technique was determined by the location of the primary tumor. Patients with glottic cancers had transoral laser microsurgery, vertical partial laryngectomy, or supracricoid partial laryngectomy with cricohyoido-epiglottopexy. Patients with supraglottic cancers underwent transoral laser microsurgery, supraglottic horizontal partial laryngectomy, or supracricoid partial laryngectomy with cricohyoidopexy. Margin control was confirmed by frozen section to ensure complete tumor removal.

Follow-Up and Tumor Surveillance After Induction Chemotherapy

Patients with a pathologic CR (pCR) underwent monthly videostroboscopic examination for the first year after treatment and then fiberoptic laryngeal examination every 3 months in the second year and every 6 months during years 3 to 5. Patients with PR underwent laryngeal examination every 3 months after CLS for the first 2 years and every 6 months thereafter. CT scan of the head and neck was also performed every 3 months for the first 2 years after treatment and then yearly thereafter.

Statistical Analysis

An intent-to-treat analysis was performed. The primary end point of the study was LP, which was defined as native laryngeal speech and swallowing without TL 2 years after initiation of chemotherapy. Per protocol, if the treatment gave an LP rate of 60% or lower,[1] it was considered a failure; otherwise, the regimen was considered a success. Exact binomial test was used to test the significance of the observed LP rate. The secondary end point was the response rate (clinical and pathologic) of TIP induction chemotherapy. Other end points were local, regional, and distant control; time from initiation of chemotherapy to TL; OS; and recurrence-free survival (RFS). OS and RFS were defined as the time from initiation of chemotherapy to death and disease recurrence, respectively (patients who had no disease recurrence but died of an unrelated cause were censored from the RFS function). The distribution of RFS and OS and the time to TL were estimated using the Kaplan-Meier method. Log-rank test was performed to test differences in survival between patients with different characteristics.[19]

RESULTS

Patients

Thirty-one patients were enrolled; the median age was 58 years (range, 20 to 79 years). Table 1 lists the clinicopathologic characteristics of the study population. The majority of patients were staged as T2 (n = 23) and N0 (n = 26). Nine patients were classified as T3 (n = 6) or T4 (n = 3), but all were amenable to LP via CLS before induction chemotherapy. Mean follow-up time was 65 months (median, 64 months; range, 26 to 108 months).

Response to TIP Chemotherapy and Toxicity

The total number of TIP/TIC cycles administered was six in nine patients, five in one patient, four in nine patients, and three in 12 patients. No patient received more than six cycles of chemotherapy. Four patients changed their platinum regimen from TIP to TIC. Granulocyte colony-stimulating factor was not used prophylactically and was restricted to abrogating neutropenic fever with and without infection. Patients underwent a detailed endoscopic, radiographic, and pathologic assessment of response after three (n = 22) or four (n = 9) cycles of chemotherapy.

Of 31 eligible patients, 30 had assessable tumor response after study treatment; a single patient could not be evaluated secondary to a cerebrovascular event and could not undergo anesthesia. A

Table 1. Demographic and Clinical Characteristics

| Characteristic	Patients	
	No.	%
Sex		
Female	9	29
Male	22	71
Race		
Hispanic	3	10
White	28	90
Zubrod score		
0	11	35
1	20	65
Primary site		
Supraglottic larynx	17	55
Supraglottic larynx, NOS	7	23
Epiglottis	9	29
False cord	1	3
Glottic larynx	14	45
Tumor classification		
T2	22	71
T3	6	19
T4	3	10
Node classification		
N0	25	81
N1	6	19
TNM stage		
0-I	0	0
II	19	61
III	9	23
IV	3	16

Abbreviation: NOS, not otherwise specified.
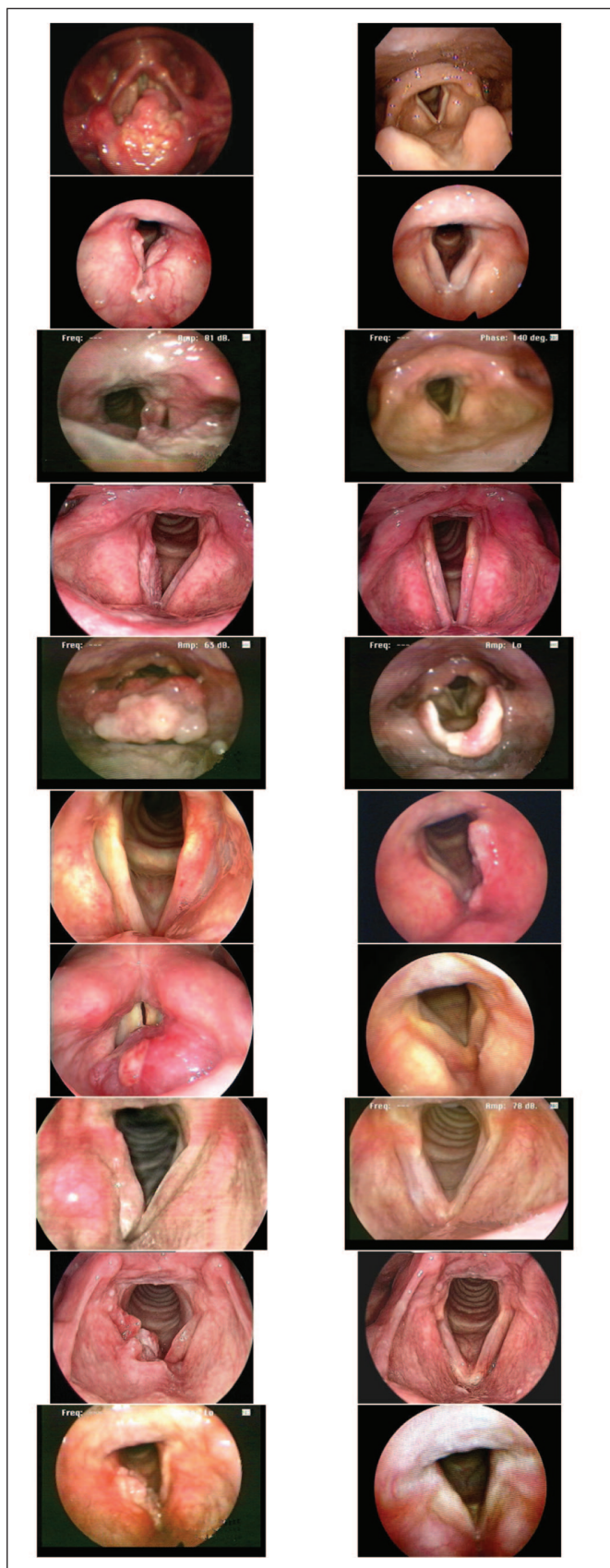
Fig 2. Pre- and postchemotherapy endoscopic tumor staging imaging for the 10 long-term complete responders.
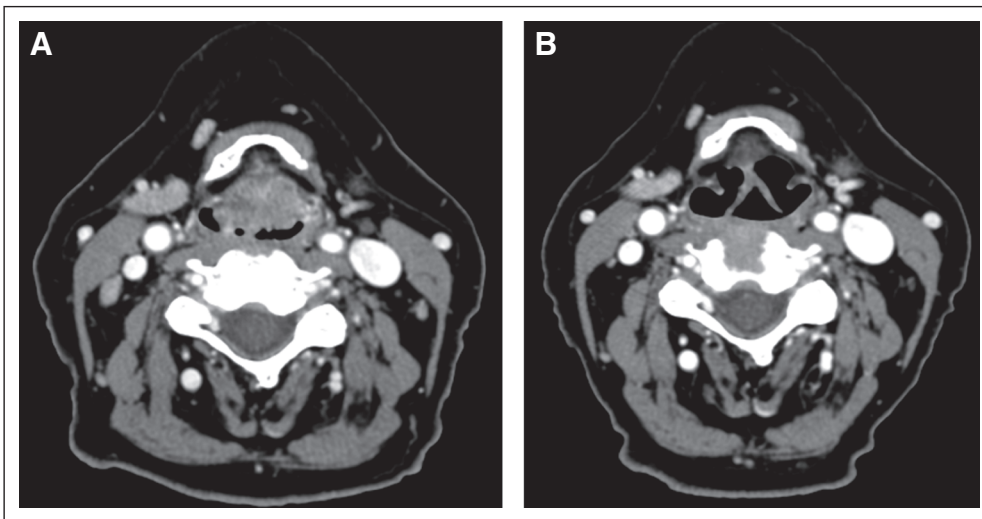
Fig 3. Pre- and postchemotherapy computed tomographic imaging of a complete response in a patient with a T3 supraglottic tumor.

small residual focus of tumor was suspected but not documented histologically.

Of all assessable patients (n = 30), 11 patients (37%) had a pCR, and 19 patients (63%) had a PR. There were no patients with stable or progressive disease. There was no significant association between the clinically observed response to chemotherapy and demographic, clinical, or baseline pathologic factors. Figure 2 shows pre- and postchemotherapy endoscopic tumor staging imaging for the 10 patients with long-term CR. Figure 3 shows CT imaging of CR after six cycles of chemotherapy in a patient whose primary supraglottic tumor was radiographically staged as T3.

Table 2 lists the distributions of response to chemotherapy and T classification. Three patients with T4 tumors were accrued before 2002, staged according to American Joint Committee on Cancer 1997 criteria, and had thyroid cartilage invasion. Two of these patients had pCR and achieved long-term remission without surgery or RT. The third patient had a PR and underwent supracricoid laryngectomy with cricohyoidopexy. All three patients had LP.

TIP/TIC chemotherapy was generally well tolerated. Table 3 lists the adverse events encountered. Dose reductions were made for five patients. Four patients required a one-level dose reduction, three patients had a two-level dose reduction, and one patient had a three-level reduction in the dose of paclitaxel for neuropathy. The major reasons for dose modification included neurotoxicity (n = 4), renal toxicity (n = 3), neutropenic fever (n = 1), intractable nausea and vomiting (n = 1), and generalized weakness and malaise (n = 1).

LP

The LP rate 2 years after initiation of chemotherapy was 83% (95% CI, 65% to 94%), which is significantly higher than 60% (P = .01). None of the 11 patients with pCR required TL. Six patients underwent TL. Of these, four patients with PR required TL for local disease recurrence after chemotherapy and CLS. One patient requested cRT instead of CLS. Six weeks after the completion of cRT, persistent disease was noted, and the patient underwent TL. Finally, one patient had TL for subglottic spread of tumor. This patient's original diagnostic biopsy demonstrated subglottic spread of disease, which regressed clinically but was histologically present on postchemotherapy biopsy and was not considered suitable for partial laryngeal surgery after endoscopy after a third course of TIP.

Functional Outcomes

All 25 patients with LP had native speech and swallowing. None required a gastrostomy tube for nutrition or a tracheostomy for airway protection. However, 3 years after induction chemotherapy and supracricoid laryngectomy, a single patient required both gastrostomy and tracheostomy as a result of adverse effects from cRT for a metachronous thoracic esophageal neuroendocrine carcinoma.

Management of the Neck

No patients with CR had neck dissection, and none had delayed recurrence in the neck. Four of the 11 patients with CR had clinical N1 disease. Twelve of 19 patients who underwent CLS also underwent selective neck dissection; eight of these patients had primary tumors arising from the supraglottis, and four had tumors arising in the glottic larynx with transglottic spread. Three patients (cN0, n = 2; cN1, n = 1) had histologic evidence of regional metastasis. Two of these patients had only one pathologic node. The third patient was found to

Table 2. Tumor Classification and Response to Chemotherapy

Larynx Subsite and T Stage*	Response Status (No. of patients)		Total No. of Patients
	CR†	PR	
Glottic larynx	4	10	14
T2	3	9	12
T3	0	1	1
T4	1	0	1
Supraglottic larynx	7	9	16
T2	5	4	9
T3	1	4	5
T4	1	1	2

Abbreviations: CR, complete response; PR, partial response.
*T stage by American Joint Committee on Cancer.
†All patients with CR had a mean follow-up time of greater than 5 years.

Table 3. Adverse Event Reporting

Adverse Event	All Grades		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Anemia	23	74.2	11	35.5	11	35.5	1	3.2				
Anorexia	9	29.0	7	22.6	1	3.23	1	3.2				
Dehydration	3	9.7			2	6.5	1	3.2				
Diarrhea	7	22.6	4	12.9	3	9.7						
Dysphagia	18	58.0	14	45.2	4	12.9						
Fatigue	24	77.4	12	38.7	7	22.6	5	16.1				
Granulocytopenia	21	67.7	3	9.7	2	6.5	7	22.6	9	29.0		
Fever, neutropenic	1	3.2					1	3.2				
Hearing	14	45.2	9	29.0	1	3.23	3	9.7				
Leukopenia	20	64.5	6	19.4	4	12.9	9	29.0	1	3.2		
Nausea	23	74.2	8	25.8	14	45.2	1	3.2				
Peripheral neuropathy	18	58.0	11	35.5	6	19.4	1	3.2				
Thrombocytopenia	9	29.0	4	12.9	2	6.5	2	6.5	1	3.2		
Vomiting	13	41.9	8	25.8	3	9.7	2	6.5				
Xerostomia	5	16.1	3	9.7	2	6.5						

have a contralateral nodal metastasis without extracapsular spread and had PORT.

RT

Only five patients (16%) underwent RT. A single patient who refused surgery after three cycles of TIP had primary cRT. Three patients (with PR and CLS) had PORT after TL for surgical salvage. The patient with a cerebrovascular accident shortly after induction chemotherapy received RT for disease control.

Survival and Disease Control

OS rates at 2 and 5 years were 97% (95% CI, 91% to 100%) and 83% (95% CI, 70% to 98%), respectively (Fig 4A). RFS rates at 2 and 5 years were 77% (95% CI, 64% to 94%) and 73% (95% CI, 58% to 91%), respectively (Fig 4B). All 31 patients were included in time-to-event analysis.

Eight patients experienced recurrences (local, n = 5; regional only, n = 1; local and regional, n = 2). Only one patient (9%) with pCR experienced a local recurrence and underwent salvage treatment with endoscopic CLS and PORT. Six patients with PRs experienced recurrences (local, n = 4; local and regional, n = 1; regional, n = 1). The patient who was not assessable for response developed regional recurrence. No patient developed distant metastasis. Metachronous primary tumors were found in two patients (papillary thyroid carcinoma and neuroendocrine carcinoma of the thoracic esophagus).

DISCUSSION

We report that selected patients with T2-4, N0-1 laryngeal cancer treated with induction chemotherapy, with or without CLS, achieve a high rate of LP (83%), meeting the primary end point of the study. More than one third of patients (11 of 30 patients; 37%) had a clinical, radiographic, and pathologic CR after three to four cycles of induction TIP chemotherapy alone. After receiving three additional cycles of TIP without surgery or RT, 10 of 11 patients had no local or regional

recurrence over a median follow-up time of 5 years. No patient had more than six cycles of chemotherapy. Patients were observed by a multidisciplinary team and assessed monthly for evidence of tumor recurrence.
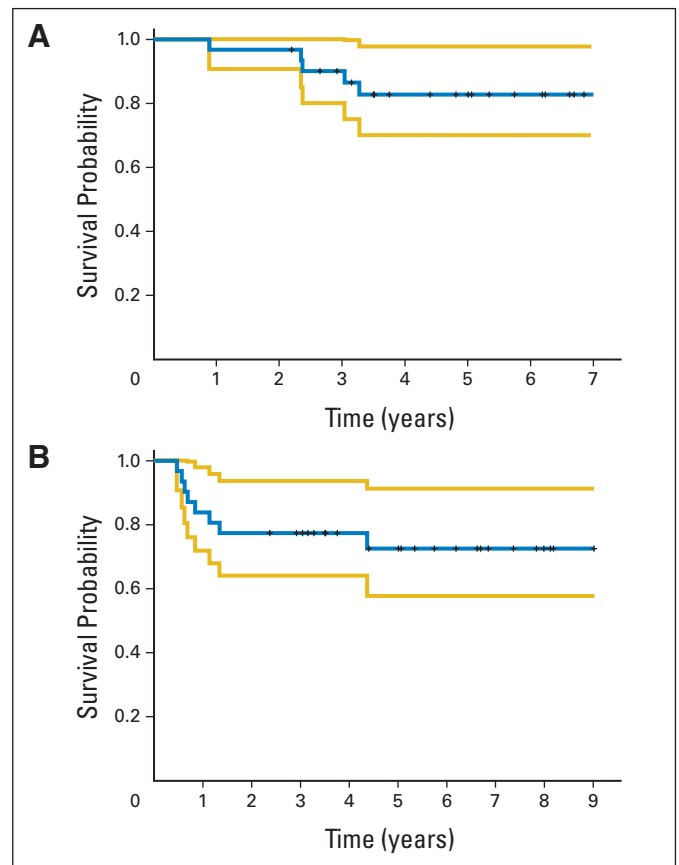

Fig 4. (A) Overall survival. (B) Recurrence-free survival. The blue line represents the Kaplan-Meier estimate of survival (overall or recurrence free) and the yellow lines represent the 95% CI limits.

All patients with a PR who had CLS had excellent functional outcomes; none required a gastrostomy tube for nutrition or a tracheotomy for airway protection. RT was not needed for 84% of patients.

To achieve these results, patients in this prospective study were carefully selected. All patients underwent operative endoscopy to ensure that the laryngeal cancer could be resected via CLS. Eligibility was restricted to patients with stage N0-1 based on the experience of Laccourreye et al,[12-14] which indicated that primary tumors may respond differently than nodal metastasis to chemotherapy. These rigorous selection criteria likely accounted for the slow rate of accrual over 7 years. Post-treatment follow-up and tumor surveillance were similarly fastidious. Monthly follow-up with laryngoscopy and CT scanning of the head and neck every 3 months for the first year were mandatory.

Despite an aggressive regimen, patient compliance with therapy was high, and toxicity was manageable with dose modification and close patient monitoring (Table 3). There were no grade 5 events. Grade 4 events were restricted to effects on the marrow, mainly neutropenia and neuropathy. Dose reduction was needed in only five patients. Four patients underwent a shift from cisplatin to carboplatin because of peripheral neuropathy and/or ototoxicity.

Most patients (71%) in this study had T2 laryngeal cancers. The recent American Society of Clinical Oncology Clinical Practice Guidelines for Larynx Preservation highlighted the difficulties in treating certain unfavorable T2 supraglottic and glottic laryngeal cancers.[18] Hinerman et al[20] reported a local control rate of 85% for T2 supraglottic carcinoma, but the vast majority of their patients had normal mobility of the vocal cords, suggesting, in general, a more favorable presentation. Reported control rates for T2 glottic tumors range from 70% to 80%, with control rates at the lower end of this range for patients with impaired vocal cord mobility.[1,21]

Although a widely used approach for patients with intermediate- to advanced-stage laryngeal cancer, the routine use of RT and the toxicity of platinum-based concurrent chemotherapy may result in a significant minority of patients with severe delayed toxicity,[22] which may have a greater impact on long-term speech and swallowing function. Permanent tracheotomy and gastrostomy are not often necessary for patients treated with RT only or the smaller fields commonly used for T2 glottic cancer, but the incidence of debilitating late complications increases with larger fields used for supraglottic and advanced glottic SCC. In our study, all 25 CLS patients with LP had native speech and swallowing, without gastrostomy or tracheostomy.

In this study, 10 patients were treated exclusively with chemotherapy and remain alive with no evidence of recurrence after 5 years. This notable achievement probably relates in part to our selection criteria, which included only patients with laryngeal cancer amenable to CLS and with N0 or N1 regional disease and excellent performance status. Our data demonstrate proof of principle that selected squamous cancers of the head and neck may be cured with chemotherapy.

However promising these results are, we wish to emphasize that further multi-institutional phase III validation is required before such an approach is widely used. This single-institution phase II study was performed in a large quaternary referral center with expertise in CLS where close multidisciplinary follow-up is possible. Furthermore, it is important to stress that the use of this approach for the larynx or other head and neck tumor sites should be done with great care and only in the setting of a clinical trial.

Laryngeal SCC may be more sensitive to cytotoxic drug therapy than some SCCs arising in the hypopharynx or oral cavity. Indeed, our experience suggests that this approach is an effective technique for achieving functional LP in centers with appropriate surgical expertise. Such an approach may obviate the need for concurrent chemoradiotherapy for unfavorable[18] T2N0 and T3N0 laryngeal tumors.

The TIP regimen is highly active, but the development of more profoundly active, novel systemic approaches is currently under intense study. Randomized trials show increased activity for the traditional cisplatin and fluorouracil platform after the addition of a taxane.[23-25] TIP was chosen as the regimen for this trial because of promising activity and tolerable toxicity in our previous phase I and II trials in patients with recurrent or metastatic head and neck cancer.[15-17] In contrast to the potent triple-drug regimen of docetaxel, cisplatin, and fluorouracil, which was then being refined at the Dana-Farber Cancer Institute,[26,27] our TIP regimen was efficient and effective, and most critically, repeated doses were tolerated by patients who were considered amenable to an organ preservation approach.

Future studies of chemotherapy in patients who are candidates for CLS should seek to identify biomarkers that predict which patients will benefit from chemotherapy alone as definitive treatment. The recent introduction of fiberoptic endoscopy will facilitate research biopsies.[28] Microarray-based biomarker approaches can predict outcomes in other tobacco-related cancers such as lung cancer, even in the earlier stages of the disease.[29] Identifying predictive biomarkers may enable us to move toward a model of personalized cancer medicine, in which the selection of therapy will be based on individual patient and tumor characteristics.[30]

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