Tumor Response, Toxicity, and Survival After Neoadjuvant Organ-Preserving Chemotherapy for Advanced Laryngeal Carcinoma

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Purpose: **In 1984, the Department of Veterans Affairs Cooperative Studies Program began a trial in which patients with resectable squamous cell carcinoma of the larynx were randomized to receive standard surgery followed by radiation therapy or to receive neoadjuvant therapy with cisplatin and fluorouracil (5-FU) followed by radiation therapy for those achieving a greater than 50% tumor response to chemotherapy. This analysis reviews the tumor responses, toxicity, compliance, and long-term survival for those patients randomized to the chemotherapy arm.**

Patients and Methods: **One hundred sixty-six patients were randomized to the chemotherapy arm. Standard tumor response data, chemotherapy toxicity, and survival have been examined using standard statistical methods.**

Results: **The high response rates and acceptable toxicity to cisplatin and 5-FU of previously untreated patients were confirmed. Long-term disease-free survival was more likely to occur in patients who achieved a complete response to chemotherapy, particularly in those who had a confirmed histologic response to chemotherapy. Pretreatment histologic growth patterns were highly predictive of responses to chemotherapy.**

Conclusion: **Neoadjuvant chemotherapy was well tolerated and did not negatively affect the definitive treatment that followed. The survival of nonresponding patients who underwent prompt salvage surgery was also not impaired. The role of organ preservation should be explored in other head and neck sites.**

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IN 1984, the Department of Veterans Affairs Cooperative Studies Program initiated a multiinstitutional randomized trial for patients with advanced resectable squamous cell carcinoma of the larynx. This was a combined modality trial comparing two therapeutic approaches for patients with advanced laryngeal carcinoma: a standard treatment of surgical resection followed by radiation therapy, and an experimental treatment in which induction or neoadjuvant chemotherapy was followed by irradiation to the larynx and neck for responders. The goal of the study was to determine whether the larynx could be preserved in those patients who responded to chemotherapy without compromising survival. The laryngeal preservation results of this trial have been previously published.[1] In this report, a detailed analysis of chemotherapy results in terms of overall and complete response rate, compliance, and toxicity are presented, and correlation with survival is analyzed.

PATIENTS AND METHODS

Four hundred seventy-nine patients with laryngeal carcinoma were screened for study participation by a multidisciplinary group, which included a head and neck surgeon, medical oncologist, radiation therapist, and study nurse. One hundred forty-seven were deemed ineligible because of poor medical condition (n = 68), patient refusal (n = 61), or unreliability (n = 18). Eligibility criteria included advanced (stage III and IV), resectable, squamous cell carcinoma of the larynx, Karnofsky performance status ≥ 60, adequate bone marrow function as judged by a WBC count greater than 3,000/μL and platelet count of 150,000/μL, creatinine clearance ≥ 60 mL/min, normal hearing in at least one ear according to an audiometric examination, and no other major illnesses that would potentially shorten survival. Three hundred thirty-two patients (70%) were enrolled onto the trial, with 166 randomized to the experimental chemotherapy arm (Fig 1).

After informed consent had been obtained, patients randomized to the experimental arm began their chemotherapy regimen. After overnight hydration with 2 L of 5% dextrose/$^1/_2$ normal saline (NS) supplemented with 40 mEq KCl/L, the patients received a bolus of 12.5 g of mannitol, followed by cisplatin (100 mg/m^2) mixed in 200 mL of NS and administered over 20 minutes. This was followed by a 4-hour infusion of an additional 1 L of 5% dextrose/$^1/_2$ NS to which 40 mEq of KCl and 25 g of mannitol had been added. A continuous infusion of 5 fluorouracil (5-FU; 1 g/m^2/d) mixed in 2 L 5% dextrose/NS followed. Potassium chloride 80 mg and magnesium sulfate 8 mEq were added to the infusate daily. Complete blood cell counts, and creatinine, electrolytes, and magnesium levels were checked twice weekly during chemotherapy and once weekly between courses.

Courses were administered at 3-week intervals on days 1, 22, and

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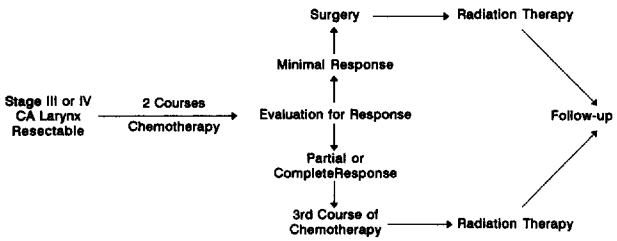

Fig 1. Patients received two courses of chemotherapy before response evaluation by physical examination including endoscopy. Those with a < 50% tumor response underwent immediate surgery. Responding patients (> 50% response) received a third course of chemotherapy followed by radiotherapy.

43 with delays when necessary for resolution of signs and symptoms of previous toxicity. The WBC count was to ≥ 3,000/μL, platelet count greater than 150,000/μL, and serum creatinine level less than 1.5 mg/dL or creatinine clearance greater than 60 mL/min before treatment was resumed. If toxicity had not resolved after 6 weeks, the patient was referred to the next treatment as appropriate for the study, ie, surgery if a less than 50% tumor response, radiation therapy if a greater than 50% tumor response. Dose modifications for toxicity were based on nadir laboratory data and clinical evaluation. Table 1 lists these modifications. Cisplatin was reduced to 80 mg/m^2 for an increase in the serum creatinine level between 2 and 4 mg/m^2. No further cisplatin was administered if the serum creatinine level increased to greater than 4.0 mg/m^2. The dose of 5-FU was reduced by 25% for a nadir WBC count less than 2,000/μL and/or platelet count less than 75,000/μL and/or grade 3 to 4 mucositis or diarrhea. The 5-FU dose was also reduced by 25% for moderate to severe dermatitis.

The initial tumor response evaluation was performed after two courses of chemotherapy. The examination was performed in the outpatient department and included indirect or fiberoptic endoscopy.

Table 1. Modifications for Toxicity

Variable	CDDP	5-FU
For nadir counts		
WBCs > 3,000/μL	NC	NC
WBCs 2,000-2,900/μL	NC	25% decrease
WBCs < 2,000/μL	80 mg/m^2	25% decrease
Platelets > 75,000/μL	NC	NC
Platelets 75-50,000/μL	NC	25% decrease
Platelets < 50,000/μL	80 mg/m^2	25% decrease
For mucositis, diarrhea		
Grade 1-2	NC	NC
Grade 3-4	NC	25% decrease
For severe dermatitis	NC	25% decrease
Renal impairment (nadir)		
Cr < 2 mg/dL or CrC > 60 mL/min		
Cr 2-4 mg/dL or CrC 40-60 mL/min		
Cr > 4 mg/dL or CrC < 40 mL/min		

NOTE. No chemotherapy is started until toxicity associated with the previous course is resolved.

Abbreviations: CDDP, cisplatin; Cr, creatinine; CrC, creatinine clearance; NC, no change in chemotherapy dose.

Table 2. Chemotherapy Toxicity

Toxicity	Two Cycles (n = 155)*	Three Cycles (n = 116)†
Renal impairment		
Grade 2 (Cr < 4 mg/dL)	12	5
Grade 3 (Cr > 4.9 mg/dL)	1	0
Myelosuppression		
Grade 1-2 (WBCs > 2,000 < 3,000/μL)	101	86
Grade 3 (WBCs > 1,000 < 2,900/μL)	12	9
Grade 4 (WBCs < 1,000/μL)	4	2
Mucositis		
Grade 1-2 (patchy)	72	52
Grade 3 (confluent)	6	9
Grade 4 (hemorrhagic)	2	4
Gastrointestinal toxicity		
Grade 1-2 (occasional vomiting, < 4 BM/d)	104	79
Grade 3 (3-4 emesis/d, > 4 BM/d)	25	23
Grade 4 (requires IV hydration)	2	1

Abbreviations: BM, bowel movements; IV, intravenous.

*Includes all assessable patients who received chemotherapy.

†Includes only those patients who received 3 courses.

Response was described separately for the primary tumor site and the cervical nodes. Patients who failed to have at least 50% tumor shrinkage at the primary tumor site and those with evidence of disease progression in the neck received no further chemotherapy and underwent immediate surgical resection. Other patients received a third course of chemotherapy, although responding patients who had significant toxicity or who refused a third course of chemotherapy began radiation therapy. A second response evaluation was performed after completion of all chemotherapy and included endoscopy under anesthesia with a biopsy of the primary tumor site. A final tumor response under anesthesia was performed 12 weeks after completion of radiation therapy. If biopsy-proven tumor persistence was found, a salvage laryngectomy was performed. All patients were monitored for recurrence and survival. The median follow-up duration of surviving patients is 60 months.

Differences in chemotherapy response by categorical variables were examined using the χ^2 test for homogeneity. Survival and disease-free survival were estimated using Kaplan-Meier techniques; the log-rank test was used to detect differences between curves. Survival and disease-free interval were measured from the date of randomization, with a disease-free interval of zero assigned to patients who had no response to chemotherapy and could not be rendered disease-free by salvage surgery. Unless otherwise specified, survival analyses are based on the 158 chemotherapy patients who were assessable for response. For each analysis, an alpha level of 0.05 was considered statistically significant.

RESULTS

Toxicity

Toxicity from the chemotherapy is listed in Table 2. Overall only one patient was removed from the study for renal impairment. Twelve patients had transient increases in the serum creatinine level (2 to 4 mg/dL) and received a reduced dose of cisplatin (80 mg/m^2) in subsequent courses. Fifty-two additional patients had mild renal impairment with a

maximum serum creatinine level of 2.0 mg/dL, which corrected with fluid hydration and required no modification of the cisplatin dose. One patient died of a suspected electrolyte imbalance. No patient had hypomagnesemia and there was no peripheral neuropathy recorded.

Four patients had grade 4 myelotoxicity, four with WBC counts less than 1,000/μL. Two of these developed pulmonary infections that resulted in the patients' death. Four patients had grade 4 mucositis that required intravenous hydration, and six had grade 3 mucositis. Nausea, vomiting, and diarrhea were classified as gastrointestinal toxicity and were severe in 27 patients, with three requiring intravenous hydration. Three patients were not assessable for toxicity. In addition, two patients did not complete the study because of angina-like chest pain occurring during the 5-FU infusion. Another was removed from study because of seizures of unknown etiology. There were a total of four deaths during chemotherapy, one due to hemorrhage from an unexpected gastric carcinoma, and one of pneumonia that developed during a period of leukopenia. Two patients died at home of unknown causes, although one presumably died of hypokalemia noted on blood drawn before his hospital discharge. Overall, 78% of the patients completed therapy with minimal toxicity ($\leq$ grade 2).

Response to Chemotherapy

Although 166 patients were randomized to the chemotherapy arm, only 163 actually started chemotherapy. Two refused the assigned treatment after randomization and one, although initially eligible, became leukopenic and no longer fit the criteria for treatment. Five patients were not assessable for response: four who died before response assessment and one who refused postchemotherapy endoscopy. Of the 158 assessable patients, 134 (84%) responded to two courses of chemotherapy, including 40 with complete disappearance of all measurable tumor. Forty-nine patients (31%) had a complete response at their primary tumor site. Twenty-four patients (14%) who failed to have at least a partial response at their primary tumor site were referred for standard therapy (surgical resection).

One hundred seventeen patients received a third course of therapy. One refused evaluation after therapy. Forty-nine (42%) had a complete response at both the primary tumor site and cervical nodes. Fifty-two patients had a complete response at the primary tumor site only, with persistent cervical adenopathy. Two patients were felt to have tumor progression during the third course and were referred for surgical salvage. The chemotherapy responses are listed in Table 3.

Table 3. Response Evaluation After Two and Three Courses

	Primary Tumor		Nodes		Overall	
Response	No.	%	No.	%	No.	%
After 2 courses						
Complete	49	31.0	35	45.5	40	25.3
Partial	85	53.8	26	33.8	94	59.5
None	24	15.2	16	20.7	24	15.2
After 3 courses						
Complete	57	49.1	30	52.9	49	42.2
Partial	57	49.1	19	33.3	65	56.0
None	3	1.8	8	14.1	2	1.8

A logistic regression analysis was performed to determine if response to chemotherapy was associated with clinical tumor or patient characteristics. Although a variety of pretreatment factors were related to clinical tumor response as single variables, stepwise regression showed that only tumor size and histologic growth pattern were significant predictors of complete tumor regression (Table 4). Tumors of smaller size showed complete responses more frequently than smaller tumors. Cancer that had histologic growth patterns characterized by blunt, thick invading fingers of tumor responded less frequently than tumors with thin irregular cords or rests of cells. Regional nodal status, tumor site, patient age, and other histologic tumor characteristics including differentiation were unrelated to tumor response.

There were 16 responders who started radiotherapy without a third course of chemotherapy. Five refused further chemotherapy because of side effects that were intolerable to them, and seven had delayed recovery from the toxicity of their previous chemotherapy. Four started the third course but had adverse events that precluded completion of the chemotherapy (angina, food poisoning, pneumonia, and myopathy). In addition, one patient developed a progressive lung infection with abscess formation and died without further treatment and another patient was lost to follow-up.

Histologic Response to Chemotherapy

One hundred seventeen patients received three courses of chemotherapy. One hundred one underwent posttreatment endoscopy and biopsy of their primary tumor site. The results of this biopsy are listed in Table 5. Sixty-four patients had no tumor in their biopsy specimen: 38 of 42 patients (88%) with a complete clinical response and 26 of 58 (45%) with a partial clinical response.

Postchemotherapy Treatment

The incidence of complications in patients who received the planned surgery was compared with those pa-

Table 4. Prognostic Factors for Clinical Complete Tumor Regression After Induction Chemotherapy in Advanced Laryngeal Carcinoma (logistic regression)

Variable	Single	Multivariable	Stepwise
T-class (T1-3 v T4)	.0191	.1880	
Karnofsky PS (< 80 v > 80)	.0967	.0929	
WBC count (< 5,000, 5,000-10,000 > 10,000/μL)	.0741	.1175	
Hgb (< mean v > mean)	.0741	.6342	
T size (> 4, 4-9, 10-14, > 15 cm)	.0103	.0421	.0075
Growth pattern (1, 2 v 3, 4)*	.0205	.0115	.0093

NOTE. Not significant variables were as follows: nodes, age, site, other histology, tumor grade.

Abbreviations: T, tumor; PS, performance status; Hgb, hemoglobin.

*1, 2 = pushing borders or well-formed infiltrating cords; 3, 4 = thin, irregular infiltrating cords or groups of cells or dissociated cells.

tients who underwent surgery after failure to respond to chemotherapy. The incidence of wound infections, fistulae, hematomas, wound dehiscence, and other complications was actually reduced in those receiving chemotherapy. These differences were not significant (Table 6). Similarly, there was no increase in the incidence of acute complications related to radiation therapy in those who had received prior chemotherapy compared with those who received this treatment after surgical resection (Table 7).

Survival and Disease-Free Survival

Patients have been monitored for a minimum of 34 months, with a mean follow-up duration of 46 months. Figure 2 shows the survival of all patients randomized to the experimental arm according to their response to chemotherapy at their primary tumor site. The overall survival rate at 3 years was 53% (45: 95% confidence interval, 45% to 61%) for the chemotherapy group. Survival of complete responders and nonresponders (who underwent surgical resection after two courses) was similar and improved compared with patients who had a partial response only (P = .068).

There were 53 patients who had a complete clinical response at both their primary tumor site and cervical nodes (Fig 3). These patients had a significantly better disease-free survival than patients with any clinical evidence of residual disease (P = .003); this would include patients with a complete response at the primary tumor site but with clinical evidence of persistent nodal disease.

Table 5. Response to Chemotherapy

	Positive Biopsy		Negative Biopsy	
Response (N = 101)	No.	%	No.	%
Complete response (n = 43)	5	12	38	88
Partial response (n = 58)	32	55	26	45
	37	37	64	63

Table 6. Effect of Chemotherapy on Surgical Complications

Complication	Surgery (n = 122)	Chemotherapy + Surgery* (n = 22)
Wound infections	3	1
Other infections	5	1
Fistula	14	0
Delayed healing/wound dehiscence	4	2
Hemorrhage/hematoma	4	0
Other	9	0
Total		
No.	39	4
%	24.4	18.2

*Two patients refused the recommended surgery.

Figure 4 includes only those patients (n = 101) who underwent endoscopy and biopsy of their primary tumor site before starting radiotherapy. Disease-free survival is significantly better in patients who had no histologic evidence of tumor after completion of chemotherapy (P = .0001). Overall survival is also improved in patients with a clinical complete response and a histologic complete response when compared with clinical and histologic partial responders.

DISCUSSION

In 1984, when the Veterans Administration Cooperative Studies Program planned this randomized trial, there

Table 7. Complications After Radiotherapy

	Postsurgery (n = 151)		Postchemotherapy (n = 126)	
Type Toxicity	No.	%	No.	%
Skin toxicity				
None	9	6	10	8
Mild/moderate	131	87	107	85
Severe	11	7	9	7
Pharyngeal toxicity				
None	19	13	11	8
Mild/moderate	130	86	113	89
Dehydration				
None	121	80	106	85
Mild/moderate	30	20	20	15
Pain				
None	85	56	49	39
Mild/moderate	66	44	73	58
Severe	0	0	4	3
Other				
None	133	88	122	97
Mild/moderate	15	10	2	1.5
Severe	3	2	2	1.5

NOTE. Not all criteria were recorded on all patients.

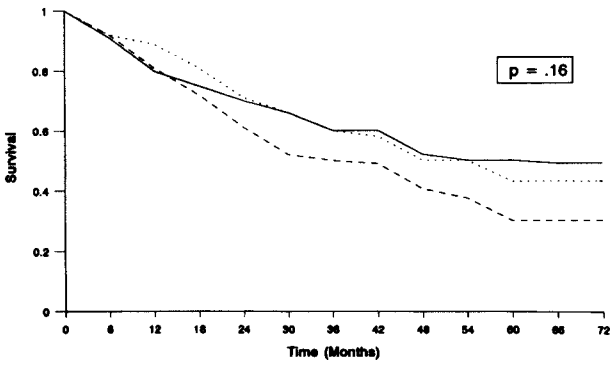

Fig 2. Those patients who failed to respond to two courses of chemotherapy underwent immediate surgery. Their survival was similar to those patients who had had a complete clinical response to chemotherapy. (—) Complete response, (···) no response, (---) partial response.

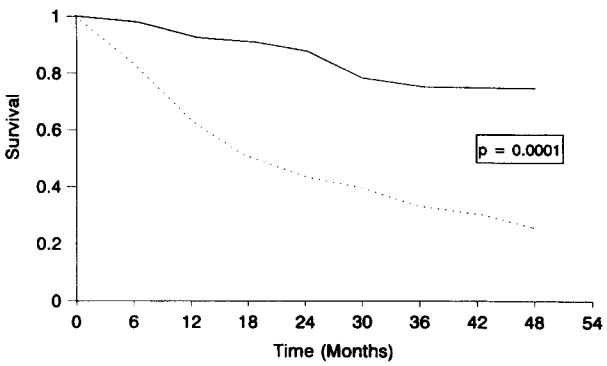

Fig 4. Patients underwent endoscopy with biopsy of their primary tumor site before starting radiation therapy. Those with no histologic evidence of tumor (—) had a better disease-free survival than those with histologic evidence of persistent disease (···), P = .0001.

was far less experience with cisplatin and 5-FU than now exists. To this date, the three-course regimen used here is the most widely used and investigated chemotherapy drug combination for squamous cell carcinoma of the head and neck region. Overall response rates in the literature have been consistently greater than 80% since the first report of this regimen's efficacy from investigators at Wayne-State University.[2] Most other trials have included patients with primary tumors at all sites in the head and neck; however, the response rates observed in this trial, which included only patients with advanced laryngeal carcinoma, are consistent with results from other studies. After two courses of chemotherapy, 84% of our patients had responded, including 25% complete responders. This is comparable to the initial report by Kish et al,[3] who observed an 89% response rate with 19% complete responders using a similar two-course regimen.

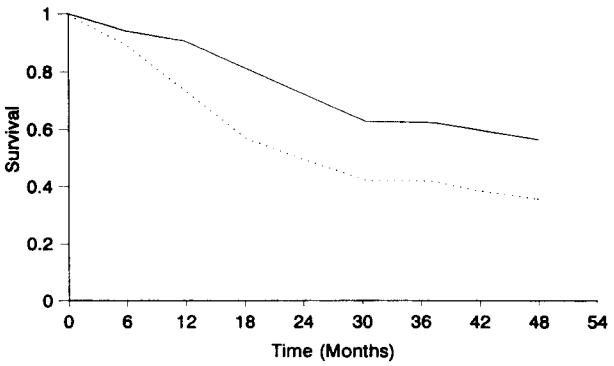

Fig 3. Those patients with complete disappearance of tumor at both the primary tumor site and regional lymph nodes (—) had a better disease-free survival than partial responders (···), P = .003.

Since only responders to chemotherapy received a third course, we cannot compare the results of those who received three courses with any other group currently in the literature. Ninety-eight percent of the patients classified as responders after two courses of chemotherapy continued to respond during their third course, with only two patients having tumor progression. One of the potential disadvantages of neoadjuvant chemotherapy is the concern that patients would become ineligible for curative therapy if tumor progressed during treatment. Because of the repeated evaluations in this study, no patients became unresectable while receiving chemotherapy.

The toxicity associated with this drug regimen was acceptable. Concerns about renal toxicity were not realized, indicating that with careful attention to prehydration and diuresis, cisplatin can be given safely to most patients. None of the patients enrolled onto this trial were eligible to participate in other experimental trials ongoing at the time of the study; thus, none of these patients received odonsetron, a drug that might have alleviated nausea and emesis better than the standard antiemetic regimens used. Management of these symptoms varied between institutions, but such tested antiemetics as metoclopramide, dexamethasone, or lorazepam were used aggressively. Nevertheless, the nausea and vomiting associated with cisplatin were a significant problem. Those symptoms, along with the nonspecific symptoms of malaise, fatigue, and anorexia also attributable to the drug, led to a refusal of further chemotherapy by five patients.

All patients received daily intravenous supplements of magnesium and potassium during therapy, and the incidence of electrolyte problems was low. There were no episodes of hypomagnesemia, although this complication has been relatively common in similar platinum-based

trials.[4,5] One patient did have severe hypokalemia, which may have contributed to his death. We likewise did not observe the peripheral neuropathy that has been reported in patients treated with cisplatin. The frequency of this side effect appears to be dose-related and is rarely seen at doses less than 350 mg/m^2.[6] The three-course limit of the induction regimen kept the maximum dose at 300 mg/m^2. Patients underwent audiograms before enrollment, and those with bilateral hearing impairment were not eligible for randomization. Although some patients complained of mild tinnitus, we also noted no hearing loss.

A quarter of the patients did have significant mucositis and/or diarrhea during chemotherapy attributable to the infusion 5-FU. These symptoms required intravenous hydration for a minority and were life-threatening for five. Ten patients also had significant myelosuppression, and in two patients this may have contributed to their death. Although the incidence of these problems was most common during the first course of chemotherapy and was less likely with subsequent dose reductions, they still occurred. Despite appropriate dose reductions, 11 patients had grade 3 or 4 myelosuppression during the third course of therapy.

Whether the use of neoadjuvant therapy in carcinoma of the head and neck does or does not add to the complications of subsequent surgery has been controversial. Corey et al[7] reported a randomized trial in which half of the patients received preoperative methotrexate and the other half underwent surgery without chemotherapy. They reported a higher incidence of complications in the patients who received methotrexate. The Head and Neck Contracts Program noted no increase in complications when patients undergoing standard surgery were compared with a group receiving a single course of neoadjuvant cisplatin and bleomycin.[8] Loré et al[9] found that the risk for fistula formation was less and postoperative infections rare in patients who received preoperative chemotherapy. In these studies, it should be noted that observations about the incidence of complications were made in patients undergoing surgery after chemotherapy to which many of the patients had responded. In our study, it was the nonresponders who underwent surgery, a population that might have been negatively affected by the prior administration of chemotherapy. However, when these patients were compared with the larger group undergoing standard surgery, there was no difference in the incidence of complications. Although the number of nonresponders is small, this finding provides support for further trials of this nature in which nonresponders can be treated by a standard surgical modality without a negative impact on survival.

Similarly, acute complications due to radiotherapy were not significantly different whether patients received postsurgical or postchemotherapy treatment. Posner et al[10] reviewed the incidence of acute radiation-related complications in their patients receiving induction chemotherapy and also found no increased risk, which parallels results in our randomized trial.

In the initial pilot study of organ preservation reported by Jacobs et al,[11] patients with a complete clinical response after three courses of chemotherapy underwent a biopsy of their primary tumor site. Only patients who had a histologic complete response were treated by radiotherapy. Our study was more inclusive and all patients who exhibited at least 50% tumor shrinkage at their primary site as judged by clinical examination were treated by radiotherapy. The majority of patients who were treated by radiotherapy underwent repeat endoscopy and biopsy of the primary tumor site before treatment was started. Eighty-eight percent of the patients felt to have a clinical complete response had no identifiable tumor in their biopsy specimen, confirming the clinical impression. The incidence of recurrence has been lowest in this patient group, as shown in Fig 4. A negative biopsy does suggest a greater degree of tumor cell kill by chemotherapy than does a positive biopsy and, in this study, did translate into improved disease-free survival and laryngeal preservation.

It was not surprising to find that tumor size was significantly associated with achievement of a complete clinical tumor regression. Smaller tumors were more likely to disappear than larger tumors. The finding that the histologic pattern of tumor growth and infiltration was predictive of a complete tumor response is a new and exciting observation. Highly infiltrative tumors were found previously in this study to correlate with decreased disease-free survival.[12] The current analysis was based on pretreatment tumor biopsies that categorized patients as having tumors with infiltration by thick cellular cords versus thin infiltrating cords or single dissociated cells. Thin irregular cords and single-cell infiltration at the tumor-stromal margin was the most significant predictor of complete tumor response. This probably reflects a rapidly growing tumor with high proliferative rates. The fact that if these patients responded then survival was increased suggests that the chemotherapy added benefit compared with similar patients treated with conventional therapy. These data suggest that simple pretreatment biopsy and histologic analysis could be a useful selection factor for induction chemotherapy. Prospective study and confirmation of these results will be needed in the future.

Sixty-four of 101 patients who underwent endoscopy

and had a biopsy of their primary tumor site after three courses of chemotherapy had no evidence of residual tumor at their primary tumor site. This included 26 of 58 patients (45%) judged clinically to have had a partial response only. This was a surprisingly high number; however, the criteria for having a complete clinical response to chemotherapy were strict. Any suggestion of induration, swelling, or discoloration at the primary tumor site placed a patient in the partial responder category. We do not believe it was a sampling error due to a biopsy of a noninvolved area, because all patients had careful diagrams at diagnosis and investigators were to make certain that a biopsy was performed on the original tumor site.

A retrospective evaluation of patients treated with one of three neoadjuvant regimens by investigators at Wayne-State had previously shown that patients who achieved a histologic complete response had better survival than those with a partial or no response.[13] In that study, 32 patients who had a complete clinical response underwent a resection and 13 had no evidence of viable tumor in the resected specimen. These 13 patients had a prolonged disease-free survival and none had relapsed with a 36-month follow-up duration. All of the complete responders, some of whom received radiotherapy rather than surgery, had a better survival than did non–complete responders. Our study also shows that patients with a complete clinical response have had a lower rate of recurrence. There were 53 patients with an overall complete clinical response (primary tumor and neck) after chemotherapy. Their prognosis for survival and laryngeal preservation was excellent. When compared with the control group, their disease-free and overall survival continues to be better than for patients treated by standard surgery and radiotherapy.

It is important to note that nonresponders to two courses of chemotherapy who underwent immediate planned laryngectomy had survival rates comparable to complete responders. This contrasts to earlier studies in which nonresponders were reported to have dismal survival rates.[13,14] These findings suggest that the timing of this resection and the appropriate wide surgical resection may be critically important to optimize cure rates. This is further supported by the lower survival rates in partial responders and is particularly true for patients with neck disease that persists after induction chemotherapy.[15] Patients with residual cervical adenopathy after chemotherapy had a high incidence of relapse after radiotherapy. Surgery at the time of that relapse was unlikely to result in disease control.

In conclusion, this large study of induction chemotherapy in patients with advanced laryngeal cancer confirms the high response rate of these squamous cell tumors to cisplatin and infusion 5-FU. Toxicity was significant, but tolerable, with 78% having grade 1 or 2 toxicity only. Nonetheless, some patients dropped out of the study because of intolerable toxicity, and others had significant complications, including renal impairment, dehydration requiring intravenous fluids, infections, electrolyte abnormalities, and death. There is a need for a less toxic regimen. Patients who achieved an overall complete clinical response to the chemotherapy had a better outcome than those with a partial response, particularly if there was no residual disease in the neck. Patients who achieved a biopsy-confirmed complete response at the primary tumor site after chemotherapy had a better prognosis than did those with persistent disease. Future chemotherapy combinations should continue to aim for a high percentage of histologic complete responders. Pretreatment histologic pattern of tumor growth and invasion was highly predictive of subsequent complete tumor response to chemotherapy. Induction chemotherapy did not impair the ability to administer definitive therapy, whether full-course radiation or salvage surgery for nonresponders. A failure to respond to chemotherapy did not impair survival when prompt and appropriate salvage surgery was performed. This finding should promote further organ-preservation trials.

APPENDIX

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