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Phase II Trial of Induction Chemotherapy Followed by Surgery for Squamous Cell Carcinoma of the Oral Tongue in Young Adults

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Abstract

Background—We conducted a phase II clinical trial of induction chemotherapy followed by surgery ± radiotherapy for squamous cell carcinoma of the oral tongue (SCCOT) in young adults.

Methods—From September 2001 to October 2004, 23 patients aged 18–49 years with clinical T2–3N0–2M0 SCCOT and no prior radiotherapy, chemotherapy, or neck dissection underwent induction chemotherapy (paclitaxel, ifosfamide, and carboplatin) followed by glossectomy and neck dissection ± radiotherapy and chemotherapy.

Results—On final surgical pathology, 9 (39%) patients had a complete/major (2 complete) histologic response at the primary tumor site; 8 (35%) had no response or progression. Similarly, 9 (39%) patients had a complete response in the neck or remained node negative; 6 (26%) had an increase in nodal category. No treatment-associated deaths occurred, and toxicity was modest. At a median follow-up from the end of treatment of 52 months (minimum, 23 months), 10 (43%) patients developed recurrence, and all 10 died of cancer. Crude recurrence/cancer death rates were associated with a partial response at the tongue ($P = .029$), poor histologic differentiation ($P = .012$), and multiple adverse features on final surgical pathology ($P = .040$).

Conclusions—Response rates and overall survival with this induction chemotherapy regimen were limited, but complete/major response at the tongue was associated with excellent prognosis. Additionally, improved patient selection and predictive tumor biomarkers will be needed for induction chemotherapy to be routinely incorporated into the treatment of oral tongue cancer in young adults.

Keywords

Oral tongue cancer; Young adults; Induction chemotherapy

INTRODUCTION

In the United States, squamous cell carcinoma of the oral tongue (SCCOT) is the most common oral cavity cancer, and in 2010, there were approximately 10,990 new cases of tongue cancer and 1,990 deaths from this disease.¹ SCCOT typically occurs in men in their 50s and 60s with a history of cigarette smoking and alcohol abuse. Nevertheless, the incidence of SCCOT in young adults, often without significant tobacco and alcohol exposures, is rising.²

Local-regional control of oral cavity cancers has been enhanced in recent decades most likely in part because of more aggressive surgical resections facilitated by modern reconstructive methods and advances in radiotherapy. Additionally, concomitant chemotherapy added to postoperative radiotherapy may improve local-regional control in patients with oral cavity cancers possessing high-risk features such as extracapsular extension.³⁻⁴ However, despite improved local-regional control, survival rates for oral cavity cancer have improved only modestly over the last 3 decades, and distant recurrences remain a problem.⁵

In theory, the higher chemotherapy doses typically used for induction regimens may be more effective at preventing later distant metastases than chemotherapy given at lower doses concurrent to postoperative radiotherapy. Furthermore, induction chemotherapy has the potential to reduce the extent and morbidity of subsequent local-regional treatments (surgery and radiotherapy), which can be functionally debilitating and subject the young patient to years of adverse quality of life.

Previously, we reviewed the records all patients younger than 45 years of age with incident SCCOT treated at our multidisciplinary cancer center between July 1995 and August 2001.⁶ Of the 49 patients identified, 15 received induction chemotherapy with taxane-based regimens before undergoing glossectomy and neck dissection. All 15 patients experienced at least a partial response to chemotherapy at the primary tumor site (1 with complete histologic response), and postoperative radiotherapy was needed for only 9 patients even though 13 had stage III or IV disease. Additionally, only 2 of the 15 patients died of recurrent cancer, and none suffered a local-regional recurrence. Consequently, we conducted a phase II clinical trial to systematically document toxicity, cancer response, and survival in a series of patients with SCCOT who are younger than 50 years of age undergoing induction chemotherapy (paclitaxel, ifosfamide, and carboplatin) followed by surgery. Our goal was to report the results of this phase II trial (in effect, a prospective case series undergoing a standardized and consistent treatment approach), including the clinical response rate, toxicity, survival, and radiotherapy use.

PATIENTS AND METHODS

Patients with SCCOT not previously treated with chemotherapy, radiotherapy, or neck dissection were entered into this phase II trial at our institution between September 2001 and October 2004. To be eligible for the trial, patients had to have pathologically confirmed squamous cell carcinoma, an intermediate-clinical-stage primary tumor of the oral tongue (T2-3 N0-2 M0), and age 18–49 years. While patients with the highest T and N stage are at the greatest risk of distant metastases and morbidity of local therapy, we chose not to

include such patients because our multidisciplinary group felt that T4 (typically bone invasion) and N3 (high volume nodal disease) oral tongue cancer in young adults was extremely rare, of particularly poor prognosis, and would require postoperative radiation (and often chemotherapy) regardless of response to induction chemotherapy. Patients also could not have significant peripheral neuropathy, serious intercurrent medical illness, major cardiopulmonary illness or history, or life expectancy < 12 weeks. Patients with recurrent cancer were eligible if prior treatment had been limited to surgery on the tongue alone. The trial was approved by our Institutional Review Board (IRB), and all patients completed an IRB-approved informed consent form.

All patients were evaluated in a multidisciplinary setting. The staging evaluation included contrast-enhanced head and neck computed tomography (CT), chest radiography, and a standard laboratory evaluation. Eligible patients who consented to enrolment received induction chemotherapy (paclitaxel 175 mg/m² on day 1, ifosfamide 1000 mg/m² on days 1–3, and carboplatin AUC 6.0 on day 1) repeated every 21–28 days for 3 cycles. If there was concern about disease progression or excessive toxic effects at the end of the second cycle, patients underwent repeat CT imaging. If progressive disease was demonstrated or if significant toxic effects precluded additional chemotherapy, the patient proceeded to surgical resection. Otherwise, patients received a third cycle of chemotherapy prior to repeat CT imaging and surgical resection.

Toxic effects associated with induction chemotherapy were categorized and graded according to the Common Toxicity Criteria scale. Additionally as we reported elsewhere, patients underwent a standardized speech and swallowing evaluation before induction chemotherapy and after induction chemotherapy prior to surgical resection.⁷ Patients who had smoked fewer than 100 cigarettes in their lifetime were classified as never smokers; all others were classified as ever smokers. Tumor grade according to the initial biopsy specimens was assessed and recorded.

Surgical resection consisted of glossectomy at the primary tumor site with the intent of complete resection of the original tumor and a neck dissection. Glossectomies were classified as partial glossectomy (removal of less than half of the oral tongue), hemiglossectomy (removal of approximately half of the tongue), or subtotal glossectomy (removal of more than half of the tongue). All patients underwent, at minimum, ipsilateral selective (levels I, II, and III) neck dissection.

Upon review of surgical pathology, patients with clear histologic margins at the primary tumor site without lymph node involvement or perineural invasion received no additional treatment, while patients not meeting these criteria received standard postoperative adjuvant radiotherapy. Those with extracapsular nodal extension or multiple other adverse pathologic features (poorly differentiated tumor, perineural invasion, multiple positive nodes, or close margins) received concomitant chemotherapy along with postoperative radiotherapy.

Response to induction chemotherapy was evaluated on the basis of the final surgical pathology review. Response of the primary tumor was defined as complete (no residual cancer), major (only microscopic residual tumor), partial (gross residual tumor but tumor smaller than at presentation), no response (no change in size of tumor), or progression (tumor larger than at presentation). Response in the neck was defined as complete (N+ at presentation and N0 on final surgical pathology), NA (N0 at presentation and N0 on final surgical pathology), no response (N+ at presentation and the same N category on final surgical pathology), or progression (increase in N category between presentation and final surgical pathology review). Follow-up data obtained included the date and type of any

recurrences (local, regional, distant) and the date of last contact and disease status at that time.

Additionally, the records of all patients with clinical T2-3 N0-2 M0 SCCOT younger than 50 years of age who chose not enroll in this trial but who received treatment at our institution during the same period (September 2001–October 2004) were reviewed to explore potential differences between those choosing and not choosing to participate in this protocol.

The primary objective of the study was to determine the overall histologic response rate to this induction chemotherapy regimen. A Bayesian study design was used, with plans for early stopping with evidence that the induction chemotherapy was ineffective. Response rates were monitored in groups of 5. Specifically, the plan was to discontinue the trial if the total partial and complete response rate was unlikely to be higher than 60%. The maximum number of patients would be 71. The predictive probability of concluding a positive trial was as follows: A response rate of 60% indicated that the treatment was not effective with a type 1 error rate 0.11. If the response rate was 75%, the probability of accepting the treatment as effective was 0.90 corresponding to the power of the study.

Fisher's exact test was used to compare categorical variables between groups. Because follow-up was relatively complete, crude relative risks for recurrence and death were calculated and presented. Outcomes were also compared using Kaplan-Meier estimates and the log-rank test for equality of survival curves. For overall survival, follow-up time was calculated from date of initial diagnosis to date of last clinic visit or death. For disease-specific survival, follow-up time was calculated from date of initial diagnosis to date of last clinic visit or death with cancer. For disease-free survival, follow-up time was calculated from date of completion of treatment to date of recurrence or last clinic visit or death. Death was categorized as death due to SCCOT or overall death (any cause). All tests were 2-sided, and $P = .05$ was set as the level of statistical significance. Calculations were completed using STATA software (version 7.0; STATA Corporation, College Station, TX) and Statistical Analysis System software (Version 9.1; SAS Institute Inc., Cary, NC).

RESULTS

During the 3-year study period, 37 patients 18–49 years of age who had newly diagnosed T2-3 N0-2 M0 SCCOT and met the other eligibility criteria for this induction chemotherapy trial were treated at our institution. Twenty-three of these 37 patients were enrolled in the trial and comprise the case series presented here. The accrual goal was 71. The histologic response rate at the tongue was 65% after the 20th patient (4th interim evaluation). While this response rate was just above the designed early stoppage rule, we chose to close the study after the 23rd patient because of slow accrual and the low/borderline observed response rate.

Pretreatment Demographic and Clinical Variables

The mean age was 38 years (median, 39 years; range, 22–48 years). Thirteen patients (57%) were women, and 11 (48%) were never smokers (Table 1). No patient had significant comorbidities, and all had normal nutritional and immunologic profiles as measured by routine laboratory screening. The staging evaluation showed that 4 (17%) of patients had TNM stage II disease, 10 (44%) of patients had TNM stage III disease (T2N1 – 3 patients, T3N0 – 6 patients, and T3N1 – 1 patient), and 9 (39%) patients had TNM stage IV disease (T2N2B – 5 patients, T2N2C – 1 patient, T3N2A – 1 patient, and T3N2B – 2 patients). Of the 13 patients with clinical evidence of nodal metastases, 7 had fine-needle aspiration biopsy performed, and in all 7 the results confirmed metastatic carcinoma. Nine (39%) tumors were described as poorly differentiated.

Recurrence and Survival by Pretreatment Demographic and Clinical Variables

With a median follow-up from the end of treatment for those still living of 52 months (range, 23–84 months; only 1 patient had < 30 months of follow-up), 10 (43%) patients had developed recurrence (mean, 4.6 months; median, 3.5 months; range, 1–11 months). The most common type of recurrence was distant metastasis (7 of 10). All distant metastases were to the lung, and the mean time to detection of lung metastases was 4 months (median, 2 months; range 1–9 months). All recurrences occurred within the first year after completion of treatment, and all 10 patients with recurrence died of cancer within 9 months of detection of the recurrence. Two additional patients died of other causes at 69 and 82 months after completing SCCOT treatment, and both were without evidence of disease when last seen in follow-up in the Head and Neck Center (at 54 months and 82 months, respectively). Crude disease-free survival and disease-specific survival rates were each 57%, and the crude overall survival rate was 48% (Figure 1). The risk of recurrence or cancer death did not appear to be associated with age, sex, or smoking status (Table 1). While recurrence/cancer death was more common in patients with T2 cancers, N1-2 cancers, TNM stage IV disease, and poorly differentiated tumors, these trends were not significant (Table 1). However, in comparison of survival curves those with TNM stage IV disease appeared to have worse disease-free and disease-specific survival ($P = .054$ and $.027$, respectively).

Response to Induction Chemotherapy

Six patients did not receive the complete induction chemotherapy sequence—3 because of progression of the primary tumor and 3 because of toxicity. One additional patient received only paclitaxel and carboplatin for the third cycle. All patients had surgery within 3 months of beginning induction chemotherapy and within 6 weeks of completing induction chemotherapy.”

Rates of response to induction chemotherapy at the tongue and the neck segregated by pretreatment demographic and clinical variables are presented in Table 2. On the basis of pathologic review of the surgical specimen, 9 (39%) patients had a complete or major response at the tongue (2 with complete histologic response, ie. no residual tumor identified), and 8 (35%) patients had no response or had progression of the primary tumor. Similarly, 9 (39%) patients had a complete response in the neck or remained node negative, and 6 (26%) patients had an increase in nodal category. No patient with a complete or major response at the tongue had progression in nodal category, as compared to 6 of 14 patients with less than a complete/major response at the tongue ($P = .048$). Rates of response/progression did not appear to be associated with age, smoking status, or grade (Table 2). Response rates at both the primary tumor and the neck were higher for those with lower N category and lower TNM stage (Table 2). As expected, response rates were lower for patients who received only 2 cycles of induction chemotherapy than for patients who received the planned 3 cycles; however, these differences were not statistically significant (Table 2).

As compared to pre-treatment CT, CT imaging after chemotherapy and before surgery was performed in 21 patients and correctly predicted a major/complete histologic response at the tongue in 8 of 9 patients having such a response. In 2 of the 12 additional patients undergoing repeat CT following induction chemotherapy, the CT showed no residual abnormality or only vague enhancement in the tongue, but final pathologic evaluation indicated only a partial response.

Recurrence and Survival by Treatment and Pathologic Variables

Cancer recurrence/death was more common (though not significantly so) in patients who completed only 2 induction chemotherapy cycles or had less than a complete/major response at the tongue (Table 3, Figure 2).

Extent of surgery in this series was considerable: 5 patients underwent subtotal glossectomies, 6 patients underwent hemiglossectomies, 17 (74%) patients required flap-based reconstructions, and 8 (35%) patients had bilateral neck dissections. No radical neck dissections were performed.

While no patient had a positive margin on final pathology, 2 had a close margin on final pathology, and 3 had a positive margin on frozen section but a clear margin on final pathology. Adverse pathologic features on the final surgical specimen (poorly differentiated tumor, perineural invasion, multiple positive nodes, extracapsular extension, and/or close margins) were common; 16 (70%) patients had at least 1, and 13 patients had 2 or more. Consequently, adjuvant postoperative radiotherapy was recommended for 16 patients, in 11 cases together with concomitant chemotherapy. (One patient did not receive recommended radiotherapy with concurrent chemotherapy because distant metastases were detected 1 month postoperatively, just before radiotherapy was planned to start. Of the other 7 patients without adverse surgical pathology and thus not receiving postoperative radiotherapy, only 3 had possible pre-induction chemotherapy indications for postoperative radiotherapy- one with focal perineural invasion in the initial biopsy and 2 with clinical N-stage = N1. None of these 3 patients recurred.) Adjuvant radiotherapy was recommended for only 3 of 9 patients with complete/major response at the tongue and for 13 of 14 patients with less than a complete/major response at the tongue ($P = .005$). Cancer recurrence/death was more common for those with adverse features on final surgical pathology, particularly for those with poorly differentiated tumors (Table 3). The cancer recurrence/death rate rose incrementally with the number of adverse features on final surgical pathology (14% for patients with none, 33% for those with 1 or 2 adverse features, and 70% for those with 3–5 adverse features). Furthermore, having 3–5 adverse pathologic features was associated with a 3-fold ($P = .040$) elevated risk of cancer recurrence/death as compared to having 2 of these features (Table 3).

Toxic Effects of Induction Chemotherapy

Toxic effects associated with induction chemotherapy are presented in Table 4. There were no treatment-associated deaths. Ten episodes of grade 4 toxic effects were recorded, 9 of which reflected expected bone marrow suppression; similarly, of the 19 episodes of grade 3 toxic effects, 12 were cytopenias. Of the grade 1 and 2 toxic effects, the most common, in decreasing order of frequency, were gastrointestinal-related events, somatosensory effects, dermatologic effects, and generalized symptoms.

Protocol Versus Nonprotocol Patients

Between September 2001 and October 2004, 14 patients aged 18–49 years who had T2-3 N0-2 M0 SCCOT and met the other selection criteria for this induction chemotherapy trial were treated at our institution but chose not to participate in the trial. Compared with patients treated on protocol, the patients who chose not to participate were slightly older (mean age, 42 years, $P = .114$), were more commonly male (64%, $P = .219$), and were more likely to have T2 tumors ($P = .027$), N0 nodal status ($P = .173$), and TNM stage II-III disease ($P = .056$). All 14 nonprotocol patients received traditional treatment consisting of partial glossectomy and neck dissection, plus adjuvant postoperative radiotherapy for patients with adverse pathologic features (57%). Such features were less common in the nonprotocol group; for instance, only 2 patients in the nonprotocol group had evidence of

extracapsular extension ($P = .084$). While only 4 (29%) of the nonprotocol patients suffered recurrence, 3 of these recurrences were local-regional, and all 4 patients with recurrence ultimately died of cancer.

DISCUSSION

In this prospective phase II trial of induction chemotherapy for SCCOT in young adults, we found that our regimen consisting of paclitaxel, ifosfamide, and carboplatin had modest activity. We chose this regimen based on our retrospective experience with induction chemotherapy for young adults with oral tongue cancer⁶, in which this particular regimen was the most common utilized and resulted in the one complete histologic response reported. Furthermore, at the time of the design of this trial, we had early phase II experience demonstrating high complete response rates with the use of this regimen for locally advanced head and neck cancer⁸. While the majority of patients had oropharynx and hypopharynx/larynx cancer with high complete response rates at the primary (78% and 48%, respectively), 3 of 7 oral cavity cancers also had a complete response⁸. In the present study, histologic assessment showed that almost 40% of patients had a complete/major response at the tongue, and none of these patients had an increase in the nodal category. While it remains an investigational concept, achievement of a major response may lead to modifications of local therapies and less morbidity with greater quality of life. We have a small experience with intermediate stage laryngeal cancers avoiding morbid local therapies with the use of induction chemotherapy⁹. Only 3 of the 9 complete/major responders in this trial required adjuvant radiotherapy, and only 1 of the complete/major responders died. Furthermore, we are enthusiastic that 2 patients actually had a complete histologic response in the tongue (another 7 with only microscopic residual) and feel that this could certainly be built upon if pretreatment indicators (biomarkers) could be found to reliably predict such responses. Additionally as we have reported elsewhere, patients with response reported dramatic subjective improvements in pain and swallowing.⁷ However, despite an expectation that induction chemotherapy should help to lower distant recurrence risk, we observed a distant recurrence rate of 30% in this trial and 20% in our prior retrospective series⁶. This does raise a theoretical possibility that induction chemotherapy could select for aggressive subpopulations leading to subsequent distant recurrence, though it also appears that these patients presented with more aggressive disease than the overall eligible cohort. Knowing which patients will respond to induction chemotherapy could lead to more sophisticated and individualized treatment decisions with improved survival and perhaps more selected use of radiotherapy with better quality of life.

Comparable published reports of induction chemotherapy for specifically for oral cavity cancer are limited, with none limited to young patients. This is chiefly because squamous carcinoma of the head and neck has traditionally been considered a single disease entity. However, the medical community dedicated to the treatment of head and neck cancer is now well aware that admixture of oral cavity (an HPV-unrelated and surgically treated tumor site) and oropharynx (an HPV-related and radiation treated tumor site) cancer patients in the same clinical trial prevents clear conclusions and definitive treatment recommendations from such trials and/or secondary meta-/pooled-analyses. The recent Cochrane review¹⁰, "Interventions for the Treatment of Oral Cavity and Oropharynx Cancer: Chemotherapy" recognizes this problem, and we completely agree with their statement "...that trials on the two specific cancer sites, or combined trials where the data are reported separately by primary tumour site, would yield much better information to guide clinical practice in these two conditions which have important differences in aetiology, presentation and management." In 2003, Licitra et al reported a randomized controlled trial of induction chemotherapy (3 cycles of cisplatin and fluorouracil) for resectable oral cavity cancer (98 patients in the treatment group and 97 patients in the control group).¹¹ Three chemotherapy-

related deaths were reported, and an additional 3 patients could not undergo surgery because of severe toxic effects associated with chemotherapy. Compared to the patients in our study, the patients in the Licitra study were older (mean age 55 years) and had earlier-stage disease; in addition, only 43% had primary tumors of the oral tongue. Similar to our results, the 5-year overall survival rate in the induction chemotherapy arm was 55% (48% in our study), and (excluding second primary malignancies) the 5-year recurrence-free survival and disease-specific survival rates were both 63% (57% in our study). Furthermore, the rate of pathologic complete/major response at the primary tumor was 45% (39% in our study), and when the neck was included, 33% of patients had a complete/major response (30% in our study). While there was no evidence of improved survival for the induction chemotherapy arm in the Licitra study, only 33% of patients who received induction chemotherapy needed postoperative radiotherapy, and it also appeared that less invasive surgery was possible. In contrast, in our study, 70% of patients required postoperative radiotherapy. While we did not modify surgeries based on the response to chemotherapy, 39% of patients in our series had only microscopic residual or no detectable tumor remaining on pathologic evaluation of the tongue specimens, suggesting that modification of the extent of surgery may be an appropriate subject for study.

As the options for cancer treatment become more complex, the goal of personalized care and the search for potential tumor markers to guide such care will become increasingly important. In a recent follow-up to their clinical trial of induction chemotherapy for oral cavity cancer¹¹, Perrone et al. reported on one such potential tumor marker.¹² They demonstrated that loss-of-function *p53* mutations in these oral cavity cancers was a predictor of poor response to cisplatin-based induction chemotherapy and poor survival.¹² In our study, patients presenting with TNM stage IV disease or poorly-differentiated tumors had more than a 2-fold increased risk for cancer recurrence/death, although this association was not statistically significant in this small cohort and only TNM stage at presentation seemed to predict response to induction chemotherapy. Identification of biomarkers predictive of response to induction chemotherapy in patients with SCCOT is urgently needed.

Our study has several limitations. First, it was a single-arm phase II study, and direct comparisons to standard therapy (surgery with postoperative adjuvant radiotherapy) are limited. Second, 38% of eligible patients did not agree to participate. It is possible that biases of treating physicians toward standard therapy for patients with more favorable features influenced our participation, response, and survival rates. Nonparticipants tended to have lower-stage disease. Third, while we are very pleased to have completed a prospective trial for a rare disease, our sample size was too limited to realistically permit multivariate analyses. Similarly, this limited sample size precluded more substantive exploration of predictors of response to induction chemotherapy. Because complete/major response to induction chemotherapy appeared to be associated with excellent prognosis, we remain optimistic about the role of induction chemotherapy in selected patients and hope that biomarkers will be identified that can be used to determine which patients are most likely to benefit. However, our data do not support the routine use of induction chemotherapy with this regimen for SCCOT in young adults.

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Figure 1. Disease-free survival (dashed line) and disease-specific survival (solid line) of young adults with SCCOT treated on a phase II trial of induction chemotherapy followed by surgery (September 2001–October 2004).

a.

b.

Figure 2. Disease-free survival (A) and disease-specific survival (B) of young adults with SCCOT treated on a phase II trial of induction chemotherapy followed by surgery, by response at the tongue. Solid line indicates complete/major response at tongue; dashed line indicates partial response at tongue. (A) Log-rank $P = .011$. (B) Log-rank $P = .011$.

Table 1

Recurrence and disease-specific outcomes segregated by pretreatment demographic and clinical variables.

Variable	Total no.	Recurrence/cancer death			Log-rank test for equality of survival curves		
		No.	(Rate)	P*	Relative risk (95%CI)	Disease-free	Disease-specific
Entire group	23	10	(43.5)				
Age at presentation							
22–39 years	12	5	(41.7)				
40–48 years	11	5	(45.5)	1.0	1.1 (0.4–2.8)	.912	.783
Sex							
Male	10	4	(40.0)				
Female	13	6	(46.2)	1.0	1.2 (0.4–3.0)	.742	.907
Smoking status							
Never	11	5	(45.5)				
Ever	12	5	(41.7)	1.0	0.9 (0.4–2.3)	.944	.865
Clinical T category							
2	13	7	(53.8)				
3	10	3	(30.0)	.402	0.6 (0.2–1.6)	.295	.307
Clinical N category							
0	10	3	(30.0)				
1–2	13	7	(53.8)	.402	1.8 (0.6–5.2)	.199	.136
TNM stage							
II–III	14	4	(28.6)				
IV	9	6	(66.7)	.102	2.3 (0.9–6.0)	.054	.027
Grade							
Well or moderately differentiated	14	4	(28.6)				
Poorly differentiated**	9	6	(66.7)	.102	2.3 (0.9–6.0)	.082	.091

* Fisher's exact test.

** Includes 1 patient with a tumor classified as "moderately-poor".

Table 2

Induction chemotherapy response at the tongue and neck segregated by pretreatment demographic and clinical variables.

Variable	Total no.	Primary CR/MR			Neck CR/N0			Primary CR/MR & neck CR/N0		
		No.	(Rate)	P*	No.	(Rate)	P*	No.	(Rate)	P*
Entire group	23	9	(39.1)		9	(39.1)		7	(30.4)	
Age at presentation										
22–39 years	12	6	(50.0)		5	(41.7)		4	(33.3)	
40–48 years	11	3	(27.3)	.400	4	(36.4)	1.0	3	(27.3)	1.0
Sex										
Male	10	2	(20.0)		2	(20.0)		1	(10.0)	
Female	13	7	(53.8)	.197	7	(53.8)	.197	6	(46.2)	.089
Smoking status										
Never	11	5	(45.5)		5	(45.5)		4	(36.4)	
Ever	12	4	(33.3)	.680	4	(33.3)	.680	3	(25.0)	.667
Clinical T category										
2	13	5	(38.5)		5	(38.5)		3	(23.1)	
3	10	4	(40.0)	1.0	4	(40.0)	1.0	4	(40.0)	.650
Clinical N category										
0	10	6	(60.0)		7	(70.0)		6	(60.0)	
1–2	13	3	(23.1)	.102	2	(15.4)	.013	1	(7.7)	.019
TNM stage										
II–III	14	8	(57.1)		9	(64.3)		7	(50.0)	
IV	9	1	(11.1)	.040	0	(0)	.003	0	(0)	.019
Grade										
Well or moderately differentiated	14	6	(42.9)		6	(42.9)		4	(28.6)	
Poorly differentiated**	9	3	(33.3)	.691	3	(33.3)	.691	3	(33.3)	1.0
No. of induction chemotherapy cycles										
3	16	7	(43.8)		7	(43.8)		6	(37.5)	
2	7	2	(28.6)	.657	2	(28.6)	.657	1	(14.3)	.366

Abbreviations: CR, complete response; MR, major response; N0, node-negative at presentation.

* Fisher's exact test.

** Includes 1 patient with a tumor classified as "moderately-poor".

Table 3
Recurrence and disease-specific outcomes segregated by treatment and pathologic variables.

Variable	Total No.	Recurrence / Cancer death			Log-rank test for equality of survival curves		
		No.	(rate)	P ^a	Relative risk (95%CI)	Disease-free	Disease-specific
Entire group	23	10	(43.5)				
No. of induction chemotherapy cycles							
3	16	5	(31.3)				
2	7	5	(71.4)	.169	2.3 (1.0–5.4)	.155	.156
Response at tongue							
Complete/major	9	1	(11.1)				
Partial	14	9	(64.3)	.029	5.8 (0.9–38.2)	.011	.011
Response at neck							
Complete/N0	9	2	(22.2)				
Partial	14	8	(57.1)	.197	2.6 (0.7–9.5)	.095	.069
Response at tongue and neck							
Complete at tongue and neck	7	1	(14.3)				
Partial at tongue and/or neck	16	9	(56.3)	.089	3.9 (0.6–25.4)	.060	.060
Grade on surgical pathology							
Well or moderately differentiated [†]	12	2	(16.7)				
Poorly differentiated	11	8	(72.7)	.012	4.4 (1.2–16.3)	.003	.003
Perineural invasion							
No	12	3	(25.0)				
Yes	11	7	(63.6)	.100	2.4 (0.9–7.5)	.060	.069
Multiple positive nodes							
No	13	4	(30.8)				
Yes	10	6	(60.0)	.222	2.0 (0.7–5.1)	.141	.096
Extracapsular extension							
No	13	5	(38.5)				
Yes	10	5	(50.0)	.685	1.3 (0.5–3.3)	.559	.398
Margin status							
Negative	18	8	(44.4)				

Variable	Total No.	Recurrence / Cancer death			Log-rank test for equality of survival curves		
		No.	(rate)	P*	Relative risk (95%CI)	Disease-free	Disease-specific
Close	5	2	(40.0)	1.0	0.9 (0.3–3.0)	.984	.870
Number of adverse features [‡]							
0–2	13	3	(23.1)				
3–5	10	7	(70.0)	.040	3.0 (1.0–8.9)	.015	.014
Postoperative treatment							
None	8	2	(25.0)				
Radiotherapy ± chemotherapy	15	8	(53.3)	.379	2.1 (0.6–7.8)	.193	.191

* Fisher's exact test.

[†] Includes 9 patients with no or minimal residual disease at the tongue.

[‡] Adverse features were poorly differentiated tumor, perineural invasion, multiple positive nodes, extracapsular extension, and close margins.

Table 4

Selected toxic effects of induction chemotherapy.*

Toxicity	Number (%) of patients			
	Grade 1	Grade 2	Grade 3	Grade 4
Alopecia	11 (47.8)	4 (17.4)	1 (4.3)	0
Anemia	0	0	2 (8.7)	0
Anorexia	4 (17.4)	1 (4.3)	0	0
Constipation	5 (21.7)	1 (4.3)	0	0
Cough	0	1 (4.3)	0	0
Dehydration	0	0	1 (4.3)	0
Dizziness	1 (4.3)	1 (4.3)	0	0
Fatigue	10 (43.5)	2 (8.7)	0	0
Febrile neutropenia	0	0	0	1 (4.3)
Granulocytopenia	0	0	5 (21.7)	6 (26.1)
Hematuria	0	1 (4.3)	0	0
Infection	0	0	1 (4.3)	0
Insomnia	1 (4.3)	0	1 (4.3)	0
Leukopenia	2 (8.7)	0	5 (21.7)	0
Myalgia	6 (26.1)	1 (4.3)	0	0
Nausea	13 (56.5)	1 (4.3)	1 (4.3)	0
Pain	3 (13.0)	0	1 (4.3)	0
Rash	3 (13.0)	1 (4.3)	0	0
Stomatitis	0	0	0	1 (4.3)
Thrombocytopenia	0	0	0	2 (8.7)
Thrombophlebitis	0	1 (4.3)	0	0
Vomiting	6 (26.1)	0	1 (4.3)	0
Weight loss	1 (4.3)	1 (4.3)	0	0

* All grade 2–4 toxic effects are shown.