ORIGINAL ARTICLE

CHEMOTHERAPY ALONE FOR ORGAN PRESERVATION IN ADVANCED LARYNGEAL CANCER

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Abstract: *Background.* For patients with advanced laryngeal cancer, a trial was designed to determine if chemotherapy alone, in patients achieving a complete histologic complete response after a single neoadjuvant cycle, was an effective treatment with less morbidity than concurrent chemoradiotherapy.

Methods. Thirty-two patients with advanced laryngeal or hypopharyngeal cancer received 1 cycle of induction chemotherapy, and subsequent treatment was decided based on response.

Results. A histologic complete response was achieved in 4 patients and were treated with chemotherapy alone. All 4 patients' cancer relapsed in the neck and required surgery and postoperative radiotherapy (RT). Twenty-five patients were treated with concomitant chemoradiation. Three patients were treated with surgery. Overall survival and disease-specific survival at 3 years were 68% and 78%, respectively.

Conclusion. Chemotherapy alone is not feasible for long-term control of regional disease in patients with advanced laryngeal cancer even when they achieve a histologic complete response at the primary site. © 2009 Wiley Periodicals, Inc. *Head Neck* **32:** 1040–1047, 2010

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The introduction of chemotherapy as part of organ-preservation strategies for treatment of advanced squamous cell carcinoma of the larynx has led to continuous refinement of the relative roles and timing of chemotherapy, radiotherapy (RT), and surgery in treatment. Chemoradiation approaches have been unsuccessful at improving overall survival compared with primary surgery[1]; however, tumor response to induction

chemotherapy has been predictive of patients with a favorable response to chemoradiotherapy. In these protocols, the highest survival rates were seen in patients experiencing a complete tumor response after 1 or 2 cycles of chemotherapy.[1,2]

Organ-preservation chemoradiation protocols continue to have a high level of associated morbidity. The addition of intensive chemotherapy to RT produces higher levels of mucositis. The long-term effects of RT that include significant fibrosis with resulting speech and swallowing dysfunction appear greater after concurrent chemoradiation compared with radiation alone.[3] Treatment of advanced laryngeal cancer with chemotherapy alone in patients with highly chemosensitive tumors would potentially result in improved voice and swallowing outcomes by avoiding both acute and late effects of radiation. Hence, based on the favorable prognosis associated with a complete response at the primary site, we designed a single-arm phase II study to determine if advanced tumors of the larynx, which completely respond to a single cycle of induction chemotherapy, could be managed with a chemotherapy-only approach.

MATERIALS AND METHODS

Eligibility. All patients had histologically confirmed, previously untreated, stage III or stage IVA squamous cell carcinoma of the larynx or hypopharynx. Patients underwent pretreatment endoscopic tumor staging, contrast-enhanced CT scanning, and tissue biopsy. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance score <3 and laboratory testing documenting eligibility for chemotherapy. This protocol was approved by the Institutional Review Board at the University of Michigan, and all patients gave documented informed consent. The study schema is shown in Figure 1.

Induction Chemotherapy. Prior to enrollment, patients underwent a history and physical examination, complete blood count with differential and platelets and serum chemistries. For patients with a creatinine clearance $\geq$60 cc/minute and hearing loss $\leq$30 dB between 500 and 2000 Hz, cisplatin (100 mg/m^2) was administered on day 1. Those with a creatinine clearance of 30 to 59 cc/minute or hearing loss $>$30 dB received carboplatin (AUC = 6) on day 1. In addition, 5-fluorouracil (1000 mg/m^2/day) was administered by continuous infusion over 5 days.

Tumor Assessment. Bi-dimensional measurements and biopsies of the primary tumor were performed by direct laryngoscopy under anesthesia pretreatment and 3 weeks after induction chemotherapy (IC). RECIST criteria were not used,[4] as repeat CT imaging was not used to assess treatment response, nor was positron emission tomography imaging. A final tumor assessment under anesthesia was performed 8 weeks after completion of definitive chemoradiation or definitive chemotherapy (cycles 2–4). If persistent residual disease was detected at the primary site or if a planned neck dissection was necessary, the appropriate salvage surgery was performed. Patients treated with chemotherapy alone or chemoradiation who were disease-free, went on to receive 2 additional cycles of adjuvant chemotherapy as detailed below.

Chemotherapy Alone. Patients who were complete clinical and histologic responders at the primary site after IC, were treated with 3 additional alternating cycles of chemotherapy. Cycles 2 and 4 consisted of cisplatin (100 mg/m^2) or carboplatin (AUC = 6) plus 5-fluorouracil (1000 mg/m^2/day $\times$ 5 days). Cycle 3 consisted of weekly docetaxel (35 mg/m^2 $\times$ 3 weeks) followed by 1 week of rest. Patients with sustained complete histologic response 8 weeks after these initial 4 cycles of chemotherapy, received an additional 4 cycles of chemotherapy. Cycles 5

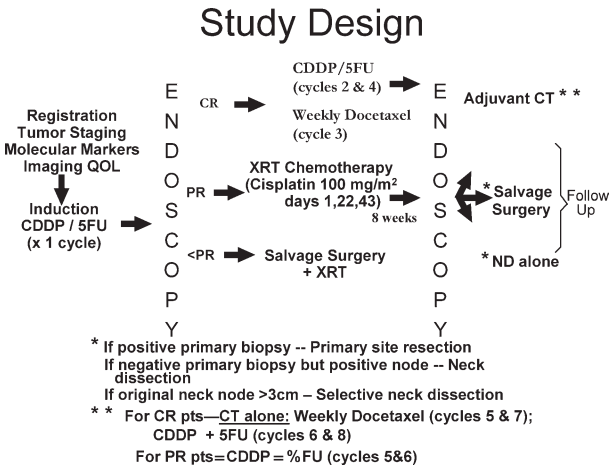

FIGURE 1. Study design.

and 7 consisted of weekly docetaxel for 3 weeks alternating with cisplatin (or carboplatin) and 5-fluorouracil for cycles 6 and 8. Patients with biopsy-proven disease at the primary site 8 weeks after completion of the initial 4 cycles of chemotherapy underwent salvage total laryngectomy. Neck evaluation was also performed and positive disease was an indication for neck dissection. Patients who had multiple positive nodes or extracapsular spread were eligible for postoperative conventional RT or concurrent cisplatin (or carboplatin) and RT treatment at the discretion of the treatment team with conventional fractionation (2.0 Gy per fraction, 5 fractions per week). The dose to the tumor bed and lymph nodes was 56 to 64 Gy, depending on extranodal extension or close surgical margins. Patients with gross residual disease or positive resection margins received a total of 66 to 70 Gy to the sites of residual disease.

Concurrent Chemoradiotherapy. Patients who did not achieve a histologic complete response (HCR) but had partial (>50% reduction of the primary tumor) following IC were treated with chemoradiotherapy. Definitive radiotherapy began within 3 weeks after IC. The targets included the primary tumor, grossly involved lymph nodes, and electively treated nodes at risk. Treatment was administered once daily, 5 days per week, at 2 Gy per fraction. Doses to elective targets were 50 to 60 Gy, and the dose to tumor and grossly involved lymph nodes was a total of 70 Gy. Patients received cisplatin 100 mg/m^2 or carboplatin (AUC = 6) on days 1, 22, and 43 concurrent with radiation with appropriate dose modifications for neutropenia, grade 2 sensory neuropathy, or other grade 3 toxicities.

Eight weeks after the completion of chemoradiotherapy, tumor evaluation was performed with both a CT scan of the neck and direct laryngoscopy. Patients with no residual disease at the primary site were eligible for 2 cycles of adjuvant chemotherapy (cisplatin/carboplatin and 5-fluorouracil).

Statistical Methods. Chi-square statistics were used to compare the frequency distribution of IC response and clinical characteristics. Kaplan–Meier analysis of survival endpoints included overall survival, cause-specific survival, disease-free survival, and laryngectomy-free survival. Overall survival considered all deaths as events. Cause-specific survival defined an event as head and neck cancer-related death. Disease-free survival was defined as the time to recurrence. Laryngectomy-free survival was defined as the time to laryngectomy, recurrence, or death. The median follow-up was 45.1 months (95% CI: 39.6–48.5). No subset analysis was planned.

The trial was designed to accrue 72 eligible patients in order to meet our objectives of assessing local control and voice-related quality of life (V-RQOL). The sample size would have been adequate to detect a 15% change in local control and a 15 unit increase in V-RQOL with 80% power compared to our previously published long term phase II study results.[2] An early termination rule was developed to stop the trial if too many of the histologic complete responders required surgery or RT at the time of the follow-up planned endoscopy or at the end of their total course of chemotherapy.

RESULTS

Patient Characteristics. Between November 1, 2002, and December 31, 2004, 33 patients were enrolled, of whom 32 were eligible. One patient was not eligible due to a second primary cancer diagnosed prior to treatment. Patient characteristics are listed in Table 1. A total of 20% of patients required pretreatment tracheostomy. A total of 69% were stage IV, and of these 73% had N2 or N3 disease. Accrual was stopped at 33 patients due to the trial's early termination criteria.

Response of the Primary Site to Induction Chemotherapy. Thirty-two patients received IC. Four patients (13%) had a complete histologic and clinical response (CR) and received chemotherapy alone, 24 patients (75%) had partial response (PR) and went on to concurrent chemoradiation, and 4 patients (13%) had <50% response (nonresponders). All patients proceeded on the protocol as originally planned with the exception of 1 nonresponder who refused laryngectomy surgery and underwent chemoradiotherapy.

Regional Failure Rate and Neck Dissection. None of the 4 patients who were histologic CRs to induction chemotherapy and treated with chemotherapy alone, were disease-free at the completion of chemotherapy. Moreover, all experienced

Table 1. Patient characteristics.

	No. of patients ($n = 32$)	%
Sex		
Male	24	
Female	8	
Age, y		
Mean	56	
Range	42–74	
Stage		
III	10	31%
IVa	21	66%
IVb	1	3%
Site		
Glottic	8	25%
Supraglottic	20	63%
Hypopharynx	4	13%
Tumor status		
T2	3	9%
T3	18	56%
T4	11	34%
Node status		
N0	10	31%
N1	6	19%
N2	15	47%
N3	1	3%
ECOG PS		
0	31	97%
1	1	3%

failure in the neck (3 had persistent disease, and 1 had local-regional progression), and all 4 received salvage therapy. Depending on the primary treatment, it could include surgery or surgery combined with radiation. The addition of radiation or chemoradiation was based on the number of nodes in the neck, presence of extracapsular spread, and whether the patient could tolerate additional chemotherapy or radiation. This varied by patient and only guidelines could be established.

Of these patients, 2 had hypopharyngeal (T4N2 and T3N1) and 2 had supraglottic (T2N2 and T3N0) primaries. Three had clinically positive nodal disease pretreatment. These 3 patients experienced persistence or progression of their disease in the neck while undergoing chemotherapy. Two of the 3 underwent salvage neck dissection and received chemoradiotherapy based on the presence of multiple positive nodes or extracapsular extension. The third failed locally and regionally after 5 cycles of chemotherapy for a supraglottic T3N0 cancer and elected to undergo radiation therapy rather than salvage surgery. This patient's disease persisted in the laryngeal cartilage after completing hyperfractionated radiation and the patient subsequently underwent salvage surgery with total laryngectomy and extended neck dissection. Direct extension of disease invading the carotid artery was found, and the patient subsequently sustained a carotid hemorrhage resulting in death. The fourth complete responder developed neck recurrence 2 months following the completion of definitive chemotherapy. This patient underwent salvage neck dissection with postoperative radiation and remained alive without disease.

In summary, all 4 of the patients who failed chemotherapy alone, received postoperative intensity-modulated radiation therapy as a part of their salvage. Doses ranged from 66 to 74 Gy delivered to high-risk volumes (positive margins, extracapsular nodal extensions found in neck dissection, or prechemotherapy extents of the gross disease), at 2 Gy/fractions, while the rest of the bilateral neck received 50 to 64 Gy concomitantly.

Of the patients with PR who were treated with chemoradiation, 6 of 24 had locoregional failures. Of those with PR and regional failures, 2 had persistent disease following chemoradiation and the third had a recurrence 6 months after completion of treatment.

A total of 15 patients (47%) underwent neck dissections. Three neck dissections were performed with total laryngectomy after nonresponse to induction chemotherapy. Five were performed as planned neck dissections based on pretreatment nodes >3 cm. Of these, 2 of 5 (40%) had positive disease on final pathology. Four neck dissections were performed with laryngectomy for primary salvage, 2 for progression of disease during treatment, and 1 for regional recurrence.

Survival. The medium follow-up time for this study was 45.1 months (95% CI, 39.6–48.5). Kaplan–Meier overall survival estimate at 3 years was 67.6% (Figure 2A). Disease-specific survival estimate at 3 years was 78.1% (Figure 2B). For the 4 with CRs after induction chemotherapy, only 1 of 4 (25%) was alive at 3 years. Of the others, 1 died from a carotid blowout following surgical salvage, 1 from distant metastases, and 1 from regional recurrence. Overall, a total of 6 patients died from disease and 4 died from other causes (carotid blowout, acute myelocytic leukemia, congestive heart failure and sepsis, and

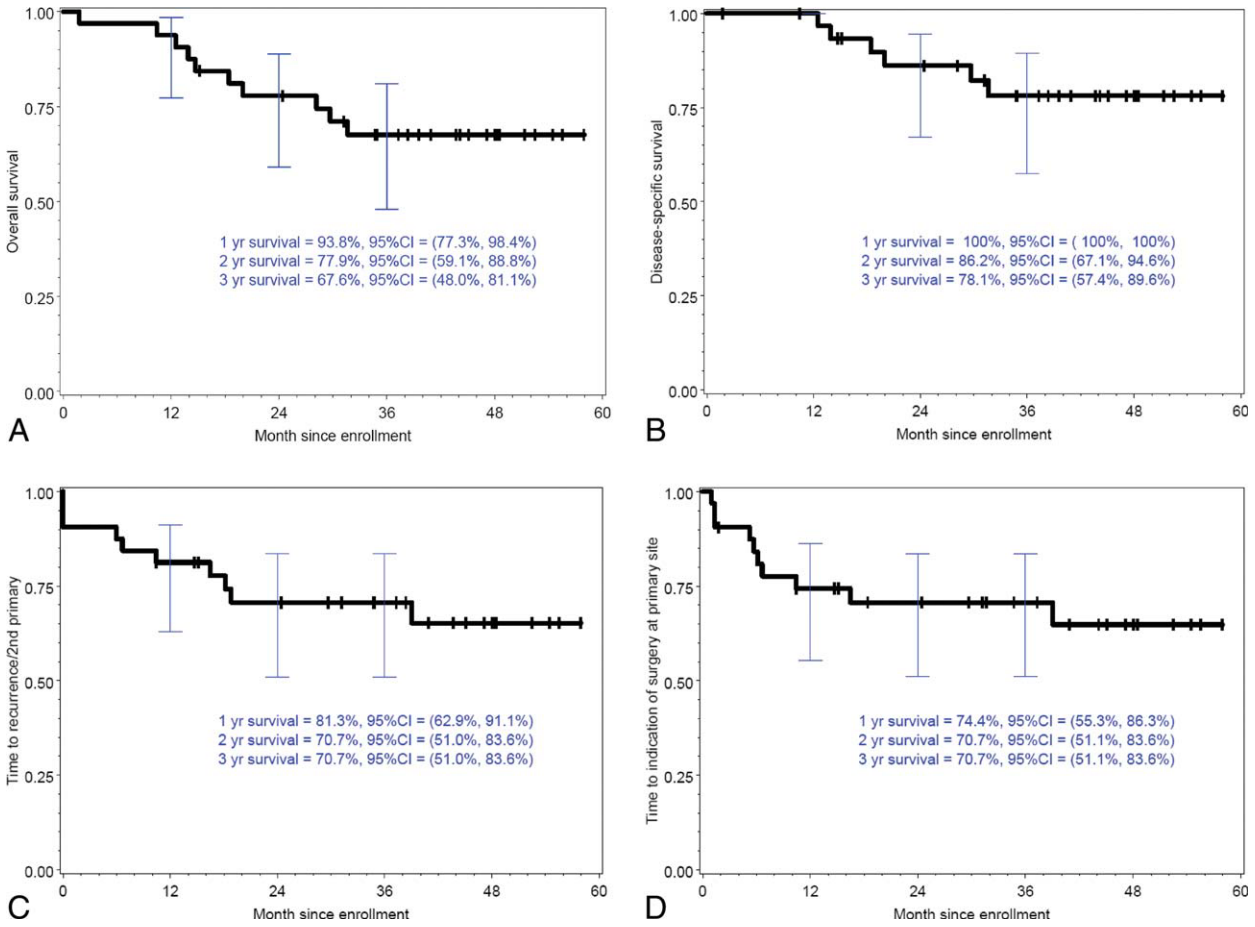

FIGURE 2. (**A**) Overall survival estimate. (**B**) Disease-specific survival estimate. (**C**) Time to recurrence or secondary primary. (**D**) Local control estimate. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

myocardial infarction). Excluding the 4 complete responders treated with chemotherapy alone, the overall survival estimate at 3 years was 74.5% (95% CI, 53.4% to 87.0%). Absence of recurrence or second primary cancer at 3 years was 70.7% for the entire cohort (Figure 2C).

Pattern of Recurrence. Regional failures occurred in 7 patients, 4 in the chemotherapy-only group and 3 in the chemoradiation group. Of the 3 regional failures in the chemoradiation group, 2 were unresectable in the neck. All patients who were nonresponders to IC survived and are disease-free. Three underwent laryngectomy and 1 who refused surgery received successful chemoradiation. Overall local control estimate at 3 years with this treatment strategy was 70.7% (Figure 2D). Three patients were never free from disease.

Larynx Preservation. Larynx preservation at 3 years was achieved in 78% overall. Seven patients underwent total laryngectomy. Three patients underwent laryngectomy after nonresponse to 1 cycle of IC, 2 patients had persistent disease, and 2 patients had a local recurrence. Two patients required laryngectomy but were found to have unresectable disease in the operating room. One patient died in hospice from a local recurrence within the larynx. Eighteen of 32 patients were alive with an intact larynx at 3 years. Functional results showed that of the patients alive with intact larynx, 2 have tracheostomies and 1 is gastric-tube dependent. Therefore, 16 patients were alive at 3 years with a functional pharyngolarynx.

Toxicity and Complications. Common grade 2 to 4 toxicities are reported in Table 2. No grade 5 toxicities occurred. Overall, a total of 11 acute and long-term complications occurred in 6 patients, consisting of carotid blowout ($n = 1$), chondroradionecrosis ($n = 3$), persistent tracheostomy ($n = 2$), persistent feeding tube ($n = 2$),

Table 2. Chemotherapy toxicities.

	Grade 2	Grade 3	Grade 4
After induction chemotherapy			
Anemia	4	0	0
Chemo mucositis	14	4	0
ChemoXRT induced mucositis	0	1	0
Diarrhea	2	1	0
Fatigue/weakness	5	0	0
Leukopenia	1	3	0
Nausea	6	3	1
Neutropenia	2	3	1
Thrombocytopenia	0	1	0
Vomiting	5	3	1
During chemoradiation			
Anemia	4	1	0
Chemo mucositis	2	0	0
ChemoXRT induced mucositis	8	5	0
Fatigue/weakness	10	1	0
Leukopenia	2	3	0
Nausea	5	5	0
Neuropathy	2	1	0
Neutropenia	3	3	0
Radiation dermatitis	10	0	0
Thrombocytopenia	4	1	0
Vomiting	4	5	0
After adjuvant therapy			
Chemo mucositis	2	0	0
Diarrhea	0	1	0
Fatigue/weakness	4	0	0
Leukopenia	2	0	0
Nausea	2	0	0
Neuropathy	2	0	0
Neutropenia	1	0	0
Radiation dermatitis	2	0	0
Vomiting	2	0	0

peripheral neuropathy ($n = 2$), and aspiration pneumonia ($n = 1$).

DISCUSSION

In this study, treatment with chemotherapy alone failed to control metastatic regional disease in patients achieving a HCR of their primary tumor. This finding suggests that the biology and chemosensitivity of a primary tumor may differ significantly between the primary tumor and metastases. This finding was also noted in the VA larynx trial when tumor response at the primary and the neck were separately assessed. A mixed response was noted almost 50% of the time. In our prior neoadjuvant studies, both greater and lesser responses in neck nodes were observed with equal frequency compared with the primary site. The risk of neck failure is likely dependent on the presence of apparent or occult regional disease with higher risk for primary sites that have high rates of metastases. The failures of the chemotherapy-alone approach in this trial occurred in patients with primary tumors of the hypopharynx or supraglottic larynx, both sites associated with high-risk of regional metastatic disease. Thus, it may be particularly important to include a surgical neck management strategy in such patients.

Patient accrual into the study was terminated early based on our stopping rule which was reached due to regional failures requiring radiation in our chemotherapy-only group which would likely eliminate any chance of overall improvement in voice functioning. Based on these results, future attempts at chemotherapy-alone treatment might consider early neck dissection as part of the treatment protocol for

patients with regional disease or at high risk of occult metastases. Only 1 of the 4 patients in the chemotherapy-alone group, failed at the primary site and this was a deep cartilage recurrence of an aryepiglottic fold primary that could have been a direct extension from the metastatic neck disease. This patient initially had N0 disease but developed needle biopsy–positive neck disease that involved soft tissues of the neck, carotid artery, and thyroid cartilage. It is unclear if earlier neck dissection would have prevented this recurrence.

Patients who rapidly achieve a complete response to IC typically represent the most favorable prognostic group. Due to the high rate of regional failure in our trial, the overall long-term survival in this usually favorable group was lower than expected. These results suggest that effective treatment for regional disease must include an additional modality, possibly early neck dissection or radiation. Treating the primary laryngeal cancer with chemotherapy-alone and regional disease with surgery might avoid the toxic effects of radiation or allow a reduced radiation dose with less morbidity and improved functional outcomes. Another approach for patients with the most responsive tumors may be treatment with radiotherapy alone or reduced doses of RT concurrent with chemotherapy or targeted agents. In our study, all 4 of the failures with chemotherapy-alone received RT with or without chemotherapy to the primary site as well as to regional lymph nodes. However, we were able to deliver less intensive doses of radiotherapy to all but 1 of these patients, which ultimately reduced the morbidity related to full-dose radiation.

Overall, the chemotherapy regimen was well tolerated by the patients. Repeated cycles (more than 3) of platinum/5-fluorouracil–based therapy may not be feasible in patients with head and neck cancer. Thus, alternative regimens with better tolerance are needed, hence our decision to alternate weekly docetaxel with platinum and 5-fluorouracil. This allowed us to deliver up to 7 cycles of chemotherapy without treatment delays, giving us the advantage of potentially overcoming platinum resistance.

A chemotherapy-only strategy using the agents currently available might be more effective in early stage patients, clinically node-negative patients, or those with a low risk of regional disease. Our results differ significantly from those reported by Laccourreye et al.[5,6] In their study, a subset of patients with early-stage squamous cell carcinoma of the glottis amenable to partial laryngeal surgery were treated with 3 cycles of induction chemotherapy. Five-year follow-up revealed that patients with T1–3N0 tumors of the glottis who achieved a clinical and HCR and were treated with additional chemotherapy alone, had a 95.2% 5-year survival rate, 70.7% local control rate, and 100% organ-preservation rate including patients who received salvage treatment.[5] Local failures were successfully managed with surgery or RT for a 100% local control rate after salvage treatment.

A subsequent study was expanded to include T1–4N0 tumors which were not limited to the glottis.[6] Overall 5-year survival was 71.1%, 5-year local control rate was 52.6%, and larynx preservation was achieved in 89% after salvage treatment. Interestingly, analysis of patients with glottic carcinoma versus other sites in the pharyngolarynx show a sharp difference between the 2 groups, with an 85.1% and 54.8% 5-year overall survival rate, respectively, and 65.7% and 37.5% 5-year local control rates, respectively. Our survival rates and rates of laryngeal preservation in patients with much more advanced disease are comparable to these results.

Holsinger et al[7] treated patients with T2–T4aN0–N1 tumors which were amenable to resection by conservational laryngeal surgery in a similar approach to Laccourreye et al.[5,6] The majority of the 30 evaluable patients had T2N0 disease. Eleven patients (37%) had a pathologic complete response after 3 to 4 cycles of chemotherapy using paclitaxel, ifosfamide, and cisplatin. These patients received 3 additional cycles of chemotherapy alone. None required a total laryngectomy, but 1 required endoscopic conservational laryngeal surgery following a local recurrence. Of the 11 CRs, 4 were N1. None required neck dissection or had any evidence of regional recurrence.[7]

The survival rate reported in our current study (68%) is slightly lower than previously reported from our institution using induction chemotherapy to select patients for chemoradiation or laryngectomy. If patients receiving chemotherapy alone are excluded, the 3-year overall survival estimate rises to 74.5%, which approximates our prior experience. Survival of patients selected for surgery after less than a partial response to a single course of neoadjuvant chemotherapy was excellent, consistent with our prior results. However, this represents an important subgroup that might benefit from newer

targeted therapy or adjuvant approaches that could result in organ preservation.

CONCLUSION

Using response to a single cycle of neoadjuvant chemotherapy to identify and select patients for organ preservation treatment approaches achieves high survival and larynx preservation rate in patients with advanced laryngeal cancer. In the same population of advanced laryngeal cancer, based on our results, it is not feasible to control disease with chemotherapy alone, even when planned neck dissections were part of the original treatment plan. Furthermore, investigations to treat patients with laryngeal cancer using chemotherapy or biologic agents should most probably be reserved for those patients with N0–1 nodal disease.

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