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Functional Swallowing Outcomes Following Transoral Robotic Surgery vs Primary Chemoradiotherapy in Patients With Advanced-Stage Oropharynx and Supraglottis Cancers

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Objectives: To evaluate functional swallowing outcomes in patients undergoing transoral robotic surgery vs primary chemoradiotherapy for the management of advanced-stage oropharynx and supraglottis cancers.

Design: Prospective nonrandomized clinical trial.

Setting: Academic research.

Patients: We studied 40 patients with stage III or stage IVA oropharynx and supraglottis squamous cell carcinoma. Group 1 comprised 20 patients who received transoral robotic surgery with adjuvant therapy, while group 2 comprised 20 patients whose disease was managed by primary chemoradiotherapy.

Main Outcome Measures: Patients completed the M. D. Anderson Dysphagia Inventory (MDADI) before treatment and then at follow-up visits at 3, 6, and 12 months. The MDADI scores were analyzed and compared.

Results: The median follow-up period for both groups was 14 months (range, 12-16 months). When comparing the median MDADI scores between group 1 and group 2, we found no statistically significant differences before treatment or at the 3-month follow-up visit. However, this difference was significant at the posttreatment visits at 6 months ($P=.004$) and 12 months ($P=.006$),

where group 1 had better swallowing MDADI scores. We also found significant differences in swallowing MDADI scores between the groups at the 6-month posttreatment visit for patients with T1, T2, and T3 disease and at the 12-month follow-up visit for patients with T2 and T3 disease, where group 1 had significantly better MDADI scores. Comparing tumor subsites, group 1 fared significantly better at the follow-up visits at 6 months ($P=.02$) and 12 months ($P=.04$) for patients with primary tumor at the tonsil. Compared with group 2, group 1 patients having base of tongue cancers exhibited significantly better swallowing MDADI scores at the 6-month follow-up visit ($P=.02$), and group 1 patients having lateral oropharynx disease had significantly better swallowing MDADI scores at the 12-month follow-up visit ($P=.04$).

Conclusion: Advanced-stage oropharynx and supraglottis cancers managed by transoral robotic surgery with adjuvant therapy resulted in significantly better swallowing MDADI outcomes at the follow-up visits at 6 and 12 months compared with tumors treated by primary chemoradiotherapy.

JAMA Otolaryngol Head Neck Surg. 2013;139(1):43-48.

Published online December 17, 2012.

doi:10.1001/jamaoto.2013.1074

OROPHARYNX AND SUPRAGLOTTIS tumors contribute to approximately one-fifth of head and neck malignant neoplasms, most of which are squamous cell carcinoma. The prognostic outcomes of these patients strongly depend on the primary location of the tumor and the initial staging and grading of the disease. The main criteria for a successful treatment are the locoregional control of the primary tumor, as well as favorable survival outcomes. To achieve these goals, surgery, ra-

diotherapy, and chemotherapy can be administered alone or in combinations. Early-stage tumors can be managed by surgery or by radiotherapy; published literature shows that local control and survival do not significantly differ between the 2 modalities.¹

Posttreatment swallowing is a vital functional health-related quality-of-life outcomes parameter from the patient's perspective, as important as survival or the absence of tumor recurrence. Patients with oropharynx and supraglottis cancers often have poor quality of life and func-

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Table. Patient and Tumor Characteristics

Characteristic	Group 1 (n = 20) ^a	Group 2 (n = 20) ^b	Total, No. (%) (N = 40)	P Value ^c
Sex				
Male	12	14	26 (65)	.51
Female	8	6	14 (35)	
Age, y				
<60	11	13	24 (60)	.52
≥60	9	7	16 (40)	
Primary tumor site				
Tonsil	6	8	14 (35)	.49
Base of tongue	10	5	15 (38)	
Lateral oropharynx	3	5	8 (20)	
Epiglottis	1	2	3 (8)	
Primary tumor T classification				
T1	6	6	12 (30)	.92
T2	8	6	14 (35)	
T3	6	8	14 (35)	
Primary tumor N classification				
N0	1	0	1 (3)	>.99
N1	8	8	16 (40)	
N2	11	12	23 (58)	
Primary tumor stage				
III	9	8	17 (43)	.75
IVA	11	12	23 (58)	

^aTransoral robotic surgery with adjuvant therapy.

^bPrimary chemoradiotherapy.

^c χ^2 Tests and Fisher exact tests (as appropriate) comparing group 1 with group 2.

tional status.^{2,3} Treatment advances in the management of oropharynx carcinoma have largely gravitated toward nonsurgical approaches, with the development of various combinations of chemotherapy and radiotherapy.^{4,5} Functional swallowing outcomes are an important factor to be considered in treatment modality selection, which should be effective not only in controlling the cancer but also in preserving function and quality of life. Postradiotherapy tissue fibrosis may alter the functional ability of the base of tongue and the epiglottis, which in turn adversely affects the pharyngeal phase of swallowing. Transoral robotic surgery (TORS) has greatly facilitated the surgical approach by providing excellent 3-dimensional visualization and magnification, with a precise maneuverability in a limited portal of exposure, along with the ability to control bleeding. All these benefits facilitate en bloc pathology-confirmed complete tumor resection, with minimal damage to the surrounding musculature. This technique also preserves motor and sensory neural innervations of the pharynx, which improves swallowing outcomes without compromising oncologic outcomes. Operative time, intensive care stay, and overall length of hospital stay are reduced after robotic procedures compared with classic open procedures.⁶

METHODS

PATIENTS

This prospective nonrandomized quality-of-life study (2011-2012) was approved by the University of Kansas School of Medicine Institutional Review Board. The study included 40 patients with biopsy-proven American Joint Committee on Cancer

stage III or stage IVA oropharynx and supraglottis squamous cell carcinoma who had not previously received definitive treatment. One cohort (group 1) of 20 was consecutively enrolled from patients who received TORS with adjuvant therapy, and another cohort (group 2) of 20 was consecutively enrolled from patients whose disease was managed by primary chemoradiotherapy with curative intent. The decision for surgical vs nonsurgical treatment of tumors was made by the patients after detailed counseling about each approach from the physician. Patients were excluded if they had recurrent or residual cancer or had preexisting swallowing difficulties.

Patient and tumor characteristics are summarized in the **Table**. No differences between the groups were statistically significant. The median ages were 54 years for group 1 and 56 years for group 2. Primary tumor T classification distributions were matched in the groups. Overall, 12 tumors were T1, 14 tumors were T2, and 14 tumors were T3. The primary tumor sites were base of tongue (n=15), tonsil (n=14), lateral oropharynx (n=8), and epiglottis (n=3). Group 1 had 10 patients with tumor of the base of tongue, while group 2 had 5 patients with tumor of the base of tongue, although the differences in overall distribution of patients by primary tumor site were not statistically significant.

All the patients in group 1 underwent TORS with modified neck dissection in the same setting. Primary tumors removed with TORS included the tonsil in 6 patients (30%), base of tongue in 10 patients (50%), lateral oropharynx in 3 patients (15%), and epiglottis in 1 patient (5%). Negative margins (frozen and permanent) were obtained in all the cases. Nodal levels 2 through 4 were removed in all dissections, with extension performed as needed. Adjuvant therapy recommendations by the multidisciplinary tumor board (T.T.T., D.A.G., and Y.S.) were based on surgical pathology and operative findings. Twelve patients received adjuvant chemoradiotherapy (based on final pathology findings of extracapsular spread in cervical nodes, with surgical margins <10 mm), while 8 patients received only adju-

vant radiotherapy (based on the findings of a T3 primary tumor or N2 disease). In 12 patients (60%), adjuvant therapy consisted of combined chemoradiotherapy (cisplatin, 100 mg/m², in 3 cycles), while 8 patients (40%) received radiotherapy alone (median dose, 56 Gy).

All the patients in group 2 received primary concomitant chemoradiotherapy (cisplatin, 100 mg/m², in 3 cycles). For patients whose primary tumor site involved neck nodes, the median chemoradiotherapy dose was 70 Gy (2.12 Gy/d for 33 days), and 54 Gy (1.63 Gy/d for 33 days) was administered to the contralateral neck. Occasionally, a low neck field to both sides with a 50-Gy dose was administered.

Patients in both groups were treated with intensity-modulated radiotherapy. Overall, 32 patients in both groups received chemotherapy. Of these, 6 patients in group 1 and 12 patients in group 2 completed all 3 cycles.

ASSESSMENTS

Swallowing assessments of the study patients were performed to evaluate the effect of treatment and to analyze the functional outcomes. Patients were asked to complete the M. D. Anderson Dysphagia Inventory (MDADI)⁷ at 4 time points (before treatment and at 3, 6, and 12 months after treatment). The MDADI has 20 questions, with responses on a 5-point Likert-type scale. A total median score was calculated, ranging from 20 to 100, with higher scores indicating better swallowing function. The MDADI scores were analyzed for variation in follow-up periods based on the effects of treatment, primary tumor site, and primary tumor T classification as independent variables.

All the statistical analyses were performed using commercially available software (SPSS, version 20.0; IBM SPSS), and significance was established a priori at $P < .05$. As appropriate, χ^2 and Fisher exact tests were used to compare the cohorts. Mann-Whitney tests were used to identify differences in MDADI scores between the groups.

RESULTS

The median follow-up period for both groups was 14 months (range, 12-16 months). All the patients from both groups were cancer free at the last follow-up clinic visit.

Twenty patients in group 1 underwent TORS with neck dissection, followed by adjuvant therapy. For the TORS resection of the primary tumor, the mean (SD) times were 32 (14) minutes for operating room setup, 40 (12) minutes for patient positioning, and 86 (36) minutes for the robotic procedure. On average, the estimated blood loss was 100 mL (range, 60-200 mL), and the overall length of hospital stay was 2 days (range, 1-4 days). All the patients tolerated oral feeds without airway compromise on discharge. These findings are consistent with previous studies⁸⁻¹⁰ of TORS for oropharynx primary tumors.

Two patients in group 1 had posterior pharyngeal wall injury, which was sutured primarily, and 1 patient had lip laceration. Ten patients remained intubated for 24 hours because of excessive base of tongue or oropharynx edema and were successfully extubated on postoperative day 1. Four patients had nasal airway tubes placed after surgery, which also were successfully removed on postoperative day 1.

In group 1, nasogastric tubes were placed in 16 patients during the immediate postoperative period, for a

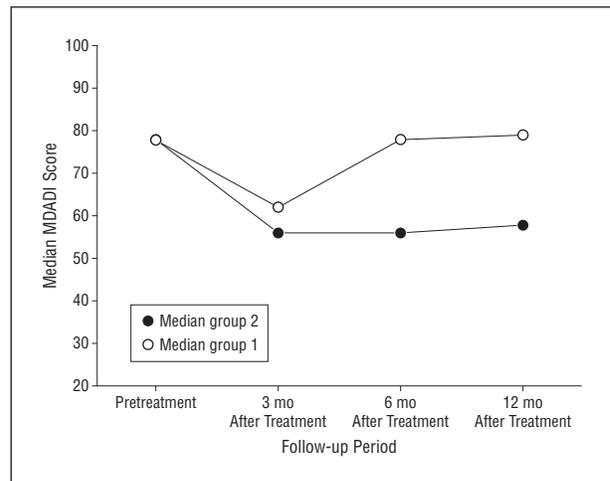


Figure 1. Overall median M. D. Anderson Dysphagia Inventory (MDADI) scores in group 1 (transoral robotic surgery with adjuvant therapy) and group 2 (primary chemoradiotherapy).

mean of 2 days before resuming oral feeds on discharge from the hospital. Six patients were discharged drinking a liquid diet; all the others went home eating a soft or regular diet. Twelve patients in group 1 who received adjuvant chemoradiotherapy had a percutaneous endoscopic gastrostomy (PEG) tube placed prophylactically at the beginning of radiotherapy. Four of the remaining 8 patients who received adjuvant radiotherapy only had a PEG tube placed during the course of treatment. Among patients in group 1, PEG tubes remained in place for a mean of 3 months after the completion of treatment. However, no patients in group 1 were dependent on the use of a PEG tube at the 6-month follow-up visit.

All 20 patients in group 2 underwent PEG tube placement before the start of chemoradiotherapy. PEG tube dependence was calculated from the date of treatment completion. Twelve patients (60%) were dependent on the use of a PEG tube at the 6-month follow-up visit, and 1 patient (5%) was dependent on its use at the 12-month follow-up visit. Soft or regular diet tolerance was documented in 6 patients (30%) at the 3-month follow-up visit, in 12 patients (60%) at the 6-month follow-up visit, and in 19 patients (95%) at the 12-month follow-up visit. One patient in group 2 was receiving a liquid diet and was dependent on the use of a PEG tube at the 12-month follow-up visit.

The median swallowing MDADI scores of patients in both treatment groups fell sharply at the 3-month follow-up visit compared with pretreatment scores, with gradual improvement noted at the follow-up visits at 6 and 12 months (**Figure 1**). Group 1 patients had a median pretreatment MDADI score of 78, which decreased to 62 at the 3-month follow-up visit, followed by gradual improvement to 76 at the 6-month follow-up visit and a return to baseline at the 12-month follow-up visit. Group 2 patients had a median pretreatment MDADI score of 78, followed by fairly constant scores of 56 at the 3-month follow-up visit and 57 at the 6-month follow-up visits, with gradual improvement to 60 at the 12-month follow-up visit. Statistical comparison of the median MDADI scores between groups 1 and 2 showed no statistically

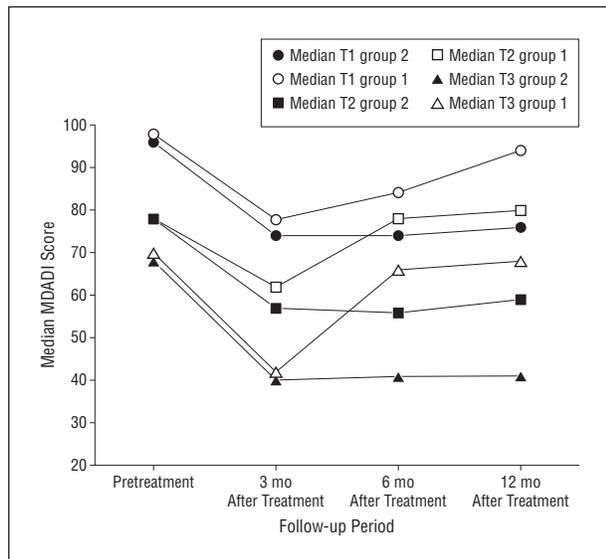


Figure 2. Median M. D. Anderson Dysphagia Inventory (MDADI) scores in group 1 (transoral robotic surgery with adjuvant therapy) and group 2 (primary chemoradiotherapy) based on primary tumor T classification (T1 to T3).

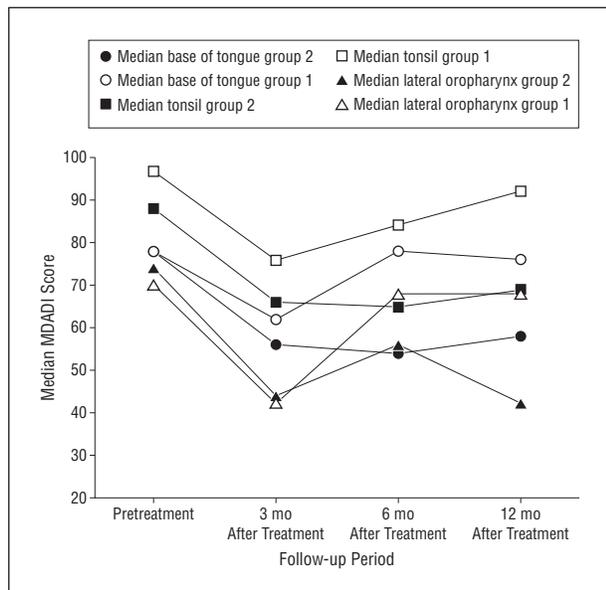


Figure 3. Median M. D. Anderson Dysphagia Inventory (MDADI) scores in group 1 (transoral robotic surgery with adjuvant therapy) and group 2 (primary chemoradiotherapy) based on primary tumor site (tonsil, base of tongue, or lateral oropharynx).

significant differences before treatment or at the 3-month follow-up visit. However, the difference in the median MDADI scores was significant at the posttreatment visits at 6 months ($P = .004$) and at 12 months ($P = .006$), where group 1 had better swallowing MDADI scores.

Overall, increases in primary tumor T classification from T1 to T3 were associated with a decrease in swallowing MDADI scores (the median pretreatment MDADI scores were 96 for patients with T1 disease, 78 for patients with T2 disease, and 68 for patients with T3 disease) (**Figure 2**). No statistically significant differences were noted comparing MDADI scores in group 1 patients vs group 2 patients based on primary tumor T

classification (T1 to T3) or primary tumor site (tonsil, base of tongue, and lateral oropharynx) at pretreatment or at the 3-month follow-up visit.

In patients with T1 disease, group 1 patients fared significantly better in swallowing MDADI scores than group 2 patients at the 6-month posttreatment visit ($P = .004$). However, no statistically significant difference was noted between the groups at the 12-month follow-up visit.

Among patients having T2 disease, statistically significant differences in swallowing MDADI scores were noted at the 6-month follow-up visit ($P = .002$) and at the 12-month follow-up visit ($P = .003$), where group 1 performed better at both time points. The same trend was noted on analyzing MDADI scores of patients with T3 disease, with significant improvements in MDADI scores among group 1 at the 6-month posttreatment visit ($P = .01$) and at the 12-month posttreatment visit ($P = .002$).

Our study included 14 patients (6 in group 1 and 8 in group 2) whose primary tumor site was the tonsil. Comparing tumor subsites, group 1 fared significantly better at the follow-up visits at 6 months ($P = .02$) and at 12 months ($P = .04$) for patients with primary tumor at the tonsil (**Figure 3**). Compared with group 2, group 1 patients having base of tongue cancers exhibited significantly better swallowing MDADI scores at the 6-month follow-up visit ($P = .02$), and group 1 patients having lateral oropharynx disease had significantly better swallowing MDADI scores at the 12-month follow-up visit ($P = .04$). However, at the 12-month surveillance, no statistically significant difference was observed between the 2 treatment groups among patients with base of tongue cancers. Patients with lateral oropharynx tumors undergoing surgical management in group 1 had significantly better swallowing MDADI scores at the 12-month follow-up visit ($P = .04$). However, because of few patients in each primary tumor site subset, the statistical power was insufficient to make reliable comparisons.

COMMENT

Traditionally, oropharynx and advanced-stage supraglottis squamous cell cancers with cervical node metastases were managed by open surgical resection and neck dissection, followed by adjuvant radiotherapy as indicated. The success of organ preservation protocols by chemoradiotherapy in the management of laryngeal squamous cell carcinoma,¹¹⁻¹³ as well as advances in the administration of chemotherapy and radiotherapy, has led to a change in the pattern of care, favoring primary treatment with chemoradiotherapy,^{4,5} replacing traditional extensive resections that compromised speech and swallowing function.⁶ Combined chemotherapy and radiotherapy is associated with significant speech and swallowing dysfunction, along with varying degrees of xerostomia and dysgeusia.¹⁴ A National Cancer Data Base analysis has shown better survival outcomes with surgery plus radiotherapy compared with radiotherapy alone or chemoradiotherapy combined.¹⁵ Combined chemoradiotherapy for advanced head and neck cancer often has significant long-term adverse effects on patients' quality of life.¹⁶

Functional outcomes of head and neck cancer treatment are as important for patients and treating physicians as survival outcomes. The transoral laser surgical approach has organ preservation rates comparable to those of chemoradiotherapy, with better functional outcomes.^{17,18} The development of the TORS approach eliminated the line-of-sight limitation of laser therapy and has demonstrated high rates of locoregional disease control and survival outcomes.⁸⁻¹⁰ TORS may possibly be used as salvage surgery in patients with previous radiotherapy and is potentially repeatable.^{19,20}

Our study shows a median length of hospital stay of 2 days for patients who underwent TORS. This study focuses on swallowing outcomes in patients with advanced-stage oropharynx and supraglottis cancers based on their management protocols. Our study reflects the analysis of swallowing function changes throughout the treatment process, with at least a 12-month follow-up period for all patients.

Overall, this study shows that a treatment approach that includes TORS, neck dissection, and adjuvant therapy results in favorable swallowing outcomes for T1 to T3 tumors of the oropharynx and supraglottic region. All of our patients who underwent TORS were discharged on oral intake. Subjectively, worsening of swallowing function (the median pretreatment MDADI score of 78 had decreased to 62 at the 3-month follow-up visit) coincides with the administration of adjuvant therapy.

Tumor board recommendations for adjuvant chemoradiotherapy among 12 patients (60%) in group 1 were based on the final pathology findings (extracapsular spread in cervical nodes, with narrow surgical margins of <10 mm); the remaining 8 patients (40%) (with advanced T3 tumor or N2 disease) received adjuvant radiotherapy only. Therefore, TORS prevented the necessity of chemotherapy in 8 patients, who may have received it if they had been treated with primary chemoradiotherapy based on primary tumor T classification of their original cancers.

Group 1 patients with adjuvant chemoradiotherapy had poorer swallowing function than group 1 patients with adjuvant radiotherapy alone. Radiotherapy has acute effects such as mucositis, edema, xerostomia, and dysgeusia that affect swallowing. Delayed effects such as fibrosis, stricture, mucosal atrophy, xerostomia, and thick secretion further add to swallowing dysfunction. Adding chemotherapy to radiotherapy seems to make swallowing dysfunction more prominent.¹⁶ Group 1 patients received a median adjuvant radiotherapy dose of 54 Gy, while group 2 patients received median primary chemoradiotherapy doses of 70 Gy to the primary site and to involved cervical lymph nodes and 54 Gy to the contralateral neck. The probability of complication with increasing radiotherapy dose is sigmoidal^{21,22}; therefore, the lower-dose or deintensified adjuvant radiotherapy lowers overall swallowing dysfunction, which may explain the higher swallowing MDADI scores noted in patients undergoing TORS with adjuvant treatment.

A primary tumor site in the tonsillar region was associated with overall better swallowing MDADI scores throughout the treatment period in both groups compared with the MDADI scores of patients with base of tongue or lateral oropharynx tumors (Figure 3). Pa-

tients undergoing TORS for tonsillar region tumors had significantly better swallowing outcomes at the 6- and 12-month follow-up visits ($P = .002$ for both) compared with patients receiving primary chemoradiotherapy. Comparing patients with base of tongue primary tumors in both treatment groups, we found no statistical difference in swallowing MDADI scores at the 12-month posttreatment visit, while group 1 patients with lateral oropharynx tumors exhibited significantly better swallowing MDADI scores only at the 12-month follow-up visit. However, because of few patients in each primary tumor site subset and the reduced statistical power, these comparisons are difficult to substantiate.

Increases in primary tumor T classification, from T1 to T3, were associated with a worsening of swallowing MDADI scores in both treatment groups (Figure 2). Patients with more advanced disease also had lower swallowing MDADI scores before treatment, most likely from the effect of the cancer on the swallowing mechanism, and this function further deteriorated after treatment in both groups. The correlation of swallowing MDADI scores with primary tumor T classification and primary tumor site may be important in pretreatment patient counseling, as well as in treatment modality selection.

This study is novel in the sense that it prospectively analyzes longitudinal swallowing function in patients who underwent TORS with adjuvant therapy, as well as in patients who underwent primary chemoradiotherapy for their advanced-stage cancers of the oropharynx and supraglottis. Our study substantiates the advantage of TORS as a viable treatment approach for advanced-stage oropharynx and epiglottis cancers by identifying better functional swallowing outcomes.

The small study population and the short (12-month) follow-up period limit our ability to draw broad conclusions, especially in the individual treatment cohorts. Overall, our study had few patients in each primary tumor anatomic subsite groups, which led to a low-power statistical analysis for swallowing outcomes comparison between treatment groups. We used a patient-reported subjective swallowing measure (MDADI score) instead of an objective swallowing study, which may not be the most accurate measure for comparing swallowing outcomes among patients, despite its validation. However, an objective radiographic swallowing assessment at frequent intervals may not be practical or cost-effective. Swallowing is a dynamic process, and a larger study population with a prospective long-term follow-up period that includes objective measures may help us better understand long-term effects of different treatment approaches on swallowing function in patients with cancer.

In conclusion, TORS with adjuvant therapy is an emerging alternative in the management of advanced-stage oropharynx and supraglottis cancers that shows superior swallowing function and reduced morbidity compared with classic primary chemoradiotherapy. Our patients undergoing TORS returned to baseline swallowing MDADI scores at about the 6-month follow-up time point, while patients receiving primary chemoradiotherapy experienced persistent decline. Higher primary tumor T classification is a predictor of worse swallowing outcomes.

Submitted for Publication: June 27, 2012; final revision received September 9, 2012; accepted October 5, 2012.

Published Online: December 17, 2012. doi:10.1001/jamaoto.2013.1074

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Author Contributions: Drs More, Sykes, and Shnayder had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* More, Tsue, Girod, and Shnayder. *Acquisition of data:* More and Williams. *Analysis and interpretation of data:* More, Tsue, Harbison, and Sykes. *Drafting of the manuscript:* More and Williams. *Critical revision of the manuscript for important intellectual content:* More, Tsue, Girod, Harbison, Sykes, and Shnayder. *Statistical analysis:* More and Sykes. *Obtained funding:* Harbison. *Administrative, technical, and material support:* More, Tsue, Girod, Sykes, and Williams. *Study supervision:* Girod and Shnayder.

Conflict of Interest Disclosures: None reported.

Previous Presentation: This study was presented at the American Head & Neck Society Eighth International Conference on Head and Neck Cancer; July 22, 2012; Toronto, Ontario, Canada.

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