Long-term Swallowing Problems After Organ Preservation Therapy With Concomitant Radiation Therapy and Intravenous Hydroxyurea

Initial Results

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Objective: To evaluate the long-term effects on swallowing function of concomitant continuous infusion hydroxyurea and hyperfractionated radiation therapy used to treat advanced head and neck carcinoma.

Design: A prospective evaluation of swallowing function was performed on an inception cohort by analyzing posttreatment videoflouroscopic swallow function studies using radiological descriptors for pharyngeal transport abnormalities and temporal measures of structural movements, as well as by conducting patient interviews to assess alimentation, more than 1 year after tumor treatment (range, 52-124 weeks; median, 70 weeks).

Setting: Academic tertiary care referral medical center.

Patients: Ten patients, aged 44 to 71 years, with stage III and IV squamous cell carcinoma of the oral cavity, oropharynx, or hypopharynx.

Main Outcome Measure: Radiographic and temporal swallow abnormalities, as well as functional status, were documented and compared with published norms and results of earlier swallowing studies when possible.

Results: Pharyngeal transport dysfunction and anterior segment abnormalities, manifested by epiglottic dysmotility, vallecular residue, laryngeal penetration, or aspiration, were evident in all 10 patients. Posterior segment abnormalities, such as pharyngeal stasis, constrictor dysmotility and piriform residue were documented in 8 patients. Three patients developed late aspiration, and the majority of patients showed persistent or worsened delay in laryngeal movement compared with their earlier posttreatment evaluations. Also, 3 patients developed a hypopharyngeal stricture, and 6 patients continued to require gastrostomy tube supplementation beyond 1 year. There was no association between site of primary, duration to swallowing evaluation, and severity of dysfunction.

Conclusion: Prolonged and debilitating functional swallowing abnormalities may occur after this aggressive concomitant chemotherapy and radiotherapy regimen.

PATIENTS AND METHODS

PATIENTS

A phase 1/2 clinical trial of parenteral hydroxyurea and external beam radiation therapy was approved by the Albert Einstein Cancer Center Review Committee and the Montefiore Medical Center Institutional Review Board, Bronx, NY, and initiated in 1995 to treat stage III or IV piriform sinus tumors or unresectable, nonlaryngeal head and neck squamous cell carcinoma. Preliminary results of this trial were previously reported.10 Twenty-six patients with advanced stage III or IV carcinoma of the oral cavity, oropharynx, or hypopharynx were included in the study. Ten patients were fully evaluated by videofluoroscopy more than 1 year after the completion of chemoradiotherapy. Ten patients were unavailable for follow-up (refusal or death); 2 patients had local failure before the follow-up swallow study was performed; and 4 patients have not yet completed 1 year of follow-up. The study group consisted of 8 men and 2 women, aged 44 to 71 years (mean age, 59 years), and all had previously untreated, nonmetastatic squamous cell carcinoma. Primary sites included the oral cavity (n = 1), oropharynx (n = 4), and hypopharynx (n = 5), with 9 patients having stage IV disease and 1 having stage III disease. All patients were treated with 74.4 Gy of external beam radiotherapy, and all but 1 received hydroxyurea at a dose of 0.313 mg/m² per minute, with patient 5 receiving 0.375 mg/m² per minute. Table 1 summarizes the characteristics of the patient group, including tumor site, clinical staging, and time from completion of radiotherapy to videofluoroscopy. All patients underwent videofluoroscopic swallow studies more than 1 year after the completion of treatment, and 8 also had early swallow studies performed within 4 months of treatment.

No patient had a medical history of neurologic disease, gastroesophageal reflux disease, other head and neck cancer, or surgical or radiation treatment in the head and neck region. No patient was taking medication that might affect swallowing function or had previously undergone swallowing therapy. Prior to treatment, all patients were eating orally; however, in this study, most patients underwent pretreatment gastrostomy tube placement because of the experience with the initial patients, who developed severe swallowing dysfunction after beginning the radiation-hydroxyurea protocol. The oral and enteral alimentation details for the patients are presented in Table 2.

VIDEOFLUOROSCOPIC EVALUATION

Videofluoroscopic swallowing function studies were performed at 3 to 15 weeks (median, 9 weeks) and then again at 1 year or more after completion of the protocol (range, 52-124 weeks; median, 70 weeks). Patient 9 underwent early and late swallowing studies, but the quality of the early video recording precluded later analysis. When multiple swallowing evaluations were performed, the one furthest from treatment completion was used in the late study group and one the nearest to completion was used in the early study group. VHS video recordings of the patients’ fluoroscopic images of the oral and pharyngeal stages of swallowing were captured in the lateral and anteroposterior planes. For the purposes of this investigation, the video recordings of each patient’s initial, standardized, small-volume (3-mL) swallow of low-density liquid barium from a cup were subjected to in-depth real-time, slow-motion, and frame-by-frame analysis by a certified speech pathologist (T.K.) using a computerized swallowing station (Kay Elemetrics Co, Lincoln Park, NJ), as previously documented.17 To describe the pharyngeal stage of the swallow, Leopold and Kagel’s20 videofluoroscopic descriptors were used to characterize pharyngeal transport abnormalities. These descriptors divide the pharynx into the anterior (laryngeal and epiglottic motility) and posterior (pharyngeal constrictor) segments and provide a language useful in describing the pharyngeal stage of swallowing. Liquid consistency swallowing analysis was performed to minimize any impact on the swallow from the oral cavity and oropharynx. Temporal measures of structural movements of the laryngeal complex, based on air column and cricoid position, as well as on epiglottic position and movement, were obtained to facilitate description of laryngeal motility.

STATISTICAL ANALYSIS

Data were analyzed to evaluate the differences between the early and late posttreatment studies, as well as between the study groups and published norms, when available. Analysis included the paired t test, Spearman rank correlation, Wilcoxon rank sum test, Wilcoxon signed rank test, 1 sample test of a mean, and Fisher exact test.

ryngal carcinomas included impaired laryngeal elevation, epiglottic movement, and pharyngeal stripping.16 Our prior investigation of early swallowing abnormalities after concomitant radiation and intravenous hydroxyurea therapy demonstrated epiglottic dysmotility, impaired laryngeal motion, pharyngeal constrictor dysmotility, and limited bolus transport and clearance.17

The long-term effects of concomitant chemoradiotherapy on swallowing function have been poorly studied, and may not be consistent with the early effects of chemoradiation. One study found marked improvement in dysphagia, despite early swallowing dysfunction, by 18 months after completion of the chemoradiotherapy, with 87% of the patients eating orally.18 The purpose of our investigation was to evaluate the long-term effects on swallowing, using objective and functional measures, through the study of patients with advanced-stage nonlaryngeal head and neck carcinoma who were treated with concomitant intravenous hydroxyurea and hyperfractionated, accelerated external radiation therapy.

RESULTS

FUNCTIONAL STATUS

The ability of our patients to tolerate oral alimentation was assessed by patient interview and correlation with the video swallow studies. The details of each patient’s oral intake and gastrostomy tube feeding requirements are presented in Table 2. Early in the posttreatment course, oral intake was poorly tolerated, as 6 (60%) of
our 10 patients could tolerate liquids, while only 2 (20%) and 1 (10%) could tolerate purees or solid foods, respectively. All patients required gastrostomy tube feeding to maintain adequate nutrition during this period. Oral intake improved after 1 year, although 6 (60%) of the 10 patients still required gastrostomy tube feeding. The ability to tolerate liquids, puree, or solid foods orally was noted in 9, 8, and 2 patients, respectively. Also, the late swallowing studies demonstrated hypopharyngeal strictures in 3 patients late in their posttreatment course (Figure 1). The strictures were located in the oral cavity (patient 2), oropharynx (patient 3), and hypopharynx (patient 7). Patients 2 and 7 had subtotal strictures that responded to dilations, while the total stenosis present in patient 3 has persisted. The presence of tracheotomy tubes did not change over the course of the study, with the same patients, Nos. 2 and 3, having tracheotomy tubes throughout.

LARYNGEAL MOTION

Laryngeal motion analysis was performed in both the early and late swallow studies. Timely initiation of the swallow response was present throughout, with a mean ± SEM onset time of laryngeal elevation of 0.078 ± 0.022 seconds (range, 0.033-0.231 seconds) in the early group and 0.053 ± 0.013 seconds (range, 0.000-0.132 seconds) in the late group. Time 0 for laryngeal motility was the initiation of laryngeal elevation, while that for triggering the swallow reflex was defined at the point at which the bolus reached the anterior faucial arches. The patients’ laryngeal elevation initiation times were all within the temporal standards reported by Logemann21 for normal adult subjects (0-0.2 seconds) and for adults older than 60 years (0.5 seconds). There was no significant difference between the early and late groups. The onset of laryngeal elevation, although within normal limits in both groups, only improved in 3 (38%) of 8 patients, while it worsened in 2 (25%) and remained the same in the other 3 (Figure 2, A).

In contrast to the onset of elevation, the duration of laryngeal motion during the swallow was impaired in both groups. The mean duration of laryngeal motion from the onset of superior movement (associated with the pharyngeal swallow response) to the maximum superior excursion and return to rest was 1.263 ± 0.132 seconds, with a range of 0.726 to 1.891 seconds, in the early studies, and 1.151 ± 0.299 seconds, with a range of 0.066 to 3.231 seconds, in the late studies. Using the Logemann standard of 0.32 seconds for pharyngeal transport of small-bolus intake, the duration of laryngeal motion was impaired in both groups.

Table 1. Patient Characteristics*

<table>
<thead>
<tr>
<th>Patient No./ Age, Sex</th>
<th>Clinical Stage</th>
<th>Early Video Swallow†</th>
<th>Late Video Swallow‡</th>
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<td>1/46/F HP T2 N1</td>
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<tr>
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<tr>
<td>10/62/M OP T4 N2c</td>
<td>12 124</td>
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</table>

*All patients received the identical radiation dose of 74.4 Gy. HP indicates hypopharynx; OC, oral cavity; OP, oropharynx; ND, not done; and NA, not able to analyze videotape because tape was damaged.  
†Numbers indicate time, in weeks, after completion of hydroxyurea and radiation treatment.

Table 2. Oral and Enteral Alimentation Characteristics of Study Group*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Liquid Intake</th>
<th>Puree Intake</th>
<th>Solid Intake</th>
<th>Gastrostomy Tube</th>
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<tr>
<td>Total Y</td>
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<td>9</td>
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<td>8</td>
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</table>

*Early indicates evaluations obtained prior to 1 year after completion of therapy; late, evaluations performed more than 1 year after completion of the chemoradiotherapy protocol; Y, ability to tolerate substance orally, or need to supplement with gastrostomy; and N, inability to tolerate substance orally, or need to supplement with gastrostomy.
volume bolus swallows, all patients receiving radiation-hydroxyurea therapy showed aberrantly increased durations of laryngeal motion during the swallow, with both groups demonstrating a significant prolongation (P<.05) on the 1-sample test of a mean. Overall, however, the duration of laryngeal movement progressed over time, with 63% (5/8) worse after 1 year and only 25% (2/8) improved over that period (Figure 2, B), which was not significant using the Wilcoxon signed rank test. This prolonged laryngeal motion correlated with an increased delay in peak laryngeal elevation using the Spearman correlation (r = 0.68; P = .06), although it was not statistically significant.

**FUNCTIONAL ABNORMALITIES**

All patients had multiple structural abnormalities leading to pharyngeal transport dysfunction. These findings were present in both the early and late posttreatment groups. Anterior pharyngeal segment dysfunction was present in all patients in both groups, while posterior pharyngeal segment abnormalities were present in all 8 patients in the early group and in 8 (80%) of the 10 patients in the late group. Radiographic examples are presented in Figure 3. Although many of our patients had oral cavity or oropharyngeal primary lesions, there was no evidence of impaired propulsion of the liquid bolus, with normal oral transit times (data not presented), and there was no residue in the lateral sulcus, in the floor of the mouth, or on the tongue. These findings may have been different if a pureed or soft solid bolus had been used in the study.

Anterior segment abnormalities included epiglottic dysmotility, vallecular residue, supraglottic penetration, and frank aspiration. Epiglottic dysmotility was present in all patients studied. The epiglottis of 1 patient in the early group was horizontally malpositioned at rest, while that of all other patients was appropriately vertically oriented, albeit abnormally enlarged. Normal epiglottic inversion, a laryngeal protective mechanism, was absent in every patient, and any movement occurred in only 2 patients (20%) in the late group. Vallecular residue was a common occurrence in both the early (88% [7/8]) and late (70% [7/10]) posttreatment groups, as was supraglottic penetration (75% [6/8] and 80% [8/10]). The Fisher exact test failed to demonstrate a significant association between either vallecular or piriform residue and supraglottic penetration. Only the patient with the oral cavity primary had no supraglottic penetration throughout his posttreatment course. Patient 1 had early aspiration, due to piriform sinus residue, which resolved over time, and patients, 3, 5, and 10 developed aspiration as a late consequence of this protocol: 1 due to piriform sinus residue; 1 due to supraglottic residue; and 1 due to premature spillage into the laryngeal vestibule.

Posterior abnormalities included pharyngeal constrictor dysmotility, pharyngeal stasis, and piriform residue, which was noted after the intake of small-volume liquid boluses. All patients demonstrated some type of posterior segment dysmotility in the early posttreatment period, while posterior segment dysmotility occurred in only 80% (8/10) of patients in the late period. Most patients had multiple abnormalities. Superior, middle, and inferior constrictor dysmotility was present in 6 (63%), 9 (100%), and 8 (88%) of the patients in the early group and in 7 (70%), 7 (70%), and 6 (60%) of the patients in the late group, respectively, as inferred from persistent residue on the appropriate segment of the posterior pharyngeal wall. All patients had 1 or more constrictor abnormalities early on, while 2 patients had resolution of their constrictor dysmotility at the time of the late swallow study. The incidence of piriform sinus residue increased slightly throughout the study period (38% early and 50% late), while that of posterior pharyngeal wall stasis and residue decreased from 100% to 80%. The
only 2 patients who did not manifest any late posterior segment dysfunction were patients 2 and 7, with an oral cavity primary and a small hypopharyngeal primary tumor, respectively.

**LOCAL CONTROL**

Local control of the cancer has been excellent in this study, with recurrence in only 4 of the 26 total patients, as shown in **Figure 4**.

**COMMENT**

As the survival rates of patients with head and neck cancer who have been treated with chemotherapy and radiotherapy have not proved superior to those of patients treated with surgery and radiotherapy, the focus of combining chemotherapy and radiotherapy has shifted to organ preservation. This change is based on the premise that preservation of structure will result in preservation of function. However, experience with radiation treatment alone reveals that this may not be the case, with the consequent xerostomia, fibrosis, edema, and mucositis all having a negative effect on swallowing function. The addition of concomitant, or adjuvant, chemotherapy may exacerbate the detrimental effects of “conservative” treatment on swallowing function.

Studies by Lazarus et al,13 Koch et al,16 and Kotz et al17 have shown severe impairment of swallowing function in patients with oral and pharyngeal cancer who were treated with chemoradiation for organ preservation. These studies focused on swallowing-related treatment sequelae that were present within the first 6 months after the completion of therapy. Lazarus and associates demonstrated reduced laryngeal elevation and a significant difference in temporal and distance measures of pharyngeal structure movement of the patients compared with normal subjects. They studied 9 patients, noting aspiration in 8 (89%) of them, and described 3 patients each who could tolerate liquids only, liquids and puree, or all bolus consistencies. They concluded that radiotherapy to the tongue base or larynx could adversely affect swallowing. Koch and colleagues also demonstrated impaired laryngeal elevation, epiglottic movement, and pharyngeal stripping. Our study of the early effects of radiation-hydroxyurea therapy confirmed significant pharyngeal transport dysfunction in all 15 patients studied.17 Abnormalities observed in the early period were characterized by a lack of epiglottic movement, significantly slowed laryngeal motility, and pharyngeal stasis.

The current long-term follow-up of 10 patients within our treatment protocol has demonstrated a persistent, severe swallowing dysfunction after radiation-hydroxyurea therapy. Laryngeal motion was significantly slowed in both the early and late posttreatment groups and was improved in only 2 patients after more than 1 year. Laryngeal motion actually worsened in 6 of the 10 patients, although the difference was not statistically significant. The increased laryngeal motion duration, with normal onset of elevation, is suggestive of fibrosis rather than of neurologic effects. There was no association between degree of swallowing abnormality and primary tumor site. Additionally, structural abnormalities, such as a lack of epiglottic movement with normal inversion, persisted throughout the duration of follow-up. Vallecular residue and supraglottic penetration of bolus remained prevalent, although decreased somewhat by 12 or more months. All patients continued to manifest some form of anterior segment abnormality over the course of their posttreatment follow-up. Posterior segment dysfunction also persisted, with most patients demonstrating altered pharyngeal constrictor function, pharyngeal stasis of the bolus, and residual bolus material in the piriform sinuses. The incidence of constrictor dysmotility decreased over time, as 2 patients resolved their constrictor motility dysfunction in the late study group, and a similar improvement in pharyngeal stasis was noted. However, the resolution of constrictor dysmotility was not associated with a greater degree of functional improvement. Piriform sinus residue, however, increased slightly over time, persisting in 5 (50%) of the patients in the late group.

The prevalence of aspiration in the organ preservation group has also been noted. Contrary to the high aspiration rate reported by Lazarus et al,13 and the decreased incidence of aspiration over time reported by Koch et al,16 we found aspiration in 1 (13%) of the patients in the early posttreatment group, with an increase to 3 (30%) of the patients in the late group. Aspiration in our patients, when present, was minimal and did not pose a significant risk or impairment. This decreased aspiration rate may be, in part, related to our low tracheotomy rate, as one of the late aspirators had a tracheotomy tube in place. However, there were 5 and 2 patients in the late group with supraglottic and piriform residue, respectively, who did not aspirate.

Subjective issues of alimentation after concomitant chemoradiation treatment, with intra-arterial cisplatin, thiosulfate, and radiation therapy, have recently been addressed.18,19 Studies of patients’ perceptions of the changes in swallowing function after undergoing such therapy showed a treatment-related decline in quality of life during therapy.21 This improved over the 6 months after treatment and was observed to vary according to disease site (oropharynx, hypopharynx, and larynx), with the greatest decline observed in the hypopharynx group. There
was a return to normal eating in 72% of patients by 18 months after treatment. Of note, however, 13% of patients continued to require gastrostomy tube feeding at the same 18-month interval.

Late consequences of treatment are also documented by functional measures of the swallowing apparatus. Although functional improvement in swallowing liquids and puree was seen after more than a 1-year interval from tumor treatment, the inability to tolerate solid food persisted in 8 (80%) of our patients. The requirement of a gastrostomy tube for adequate nutrition also decreased over the study period; however, 6 patients (60%) still required a gastrostomy tube to meet their nutritional requirements. This finding suggests that the majority of patients who feed orally do so recreationally, to satisfy emotional, but not physiological, needs. Troubling late developments were aspiration (3 patients) and hypopharyngeal stricture (3 patients). The aspiration was related to premature spillage of the bolus into the larynx in 1 patient, who was rehabilitated with aggressive swallowing therapy. The other patient developed aspiration as a result of complete hypopharyngeal stenosis and has not been rehabilitated to date. This patient requires an indwelling trachotomy tube as well as a gastrostomy tube. The dysphagia in our patients was characterized by an inability to move the bolus through the pharynx, rather than by a risk of aspiration. The 3 cases of hypopharyngeal stricture developed late in the posttreatment course and appear to have been caused by localized severe fibrosis after radiation injury and mucositis. Two of the 3 cases resolved with limited surgical intervention, and the third has not been relieved thus far. To our knowledge, these are the first documented strictures to occur after chemoradiotherapy.

The physiological abnormalities demonstrated in this study were marked when compared with previously published norms and were similar, though more pronounced, than those that occurred after radiation therapy alone. The prior studies of swallowing abnormalities after organ-sparing chemoradiation therapy have been limited by small numbers or a lack of objective findings, a reliance on subjective patient-based questionnaires, and relatively short follow-up. The current study has sought to address these issues through quantification of abnormalities using consistent timing indices and radiological descriptors, with subsequent analysis of changes over periods that have been described by others as showing resolution of most posttreatment abnormalities. Our data did not demonstrate significant improvement in swallowing at more than 1 year after initiation of therapy, although this conclusion is only preliminary, given the small number of patients analyzed.

Our findings show that significant functional consequences can result from an aggressive concomitant chemoradiotherapy protocol. Severe prolonged dysfunction may include acquired hypopharyngeal stricture or long-term gastrostomy tube feeding. The documented long-term alterations in laryngeal motion, in addition to anterior and posterior pharyngeal segment abnormalities, are likely to have a significant impact on swallowing rehabilitation and functional recovery. Such impairment may be justified by the excellent rates of locoregional control that were achieved in these patients with advanced head and neck cancer. Hopefully, systematic analyses of subjective and objective swallowing variables, as performed in the current study, will allow critical evaluation of the functional consequences of organ preservation therapies and comparison across varied treatment protocols.

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REFERENCES


