Pharyngeal Transport Dysfunction Consequent to an Organ-Sparing Protocol

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Objective: To investigate the effects of a protocol of concomitant intravenous hydroxyurea and hyperfractionated, accelerated, external-beam radiation therapy on the swallowing mechanism of patients with advanced-stage head and neck cancer.

Design: Posttreatment videofluoroscopic swallow function studies, using images of single-bolus swallows of low-density liquid barium, were analyzed in real time, slow motion, and frame by frame using an integrated system that allows objective analysis of video recordings through image processing and digitization (Kay Elemetrics Computerized Swallowing Station). Radiological descriptors were used for pharyngeal transport abnormalities, and temporal measures were obtained of structural movements.

Setting: Academic, tertiary care, referral medical center.

Patients: Fifteen consecutive patients with previously untreated, stages III and IV, nonmetastatic squamous cell carcinoma of the head and neck who underwent a phase 1 study of prolonged infusion hydroxyurea therapy in combination with hyperfractionated, accelerated external-beam radiation therapy for their disease.

Results: All patients had anterior pharyngeal segment dysfunction, characterized by no epiglottic movement and slowed laryngeal motility (1.011 ± 0.379 seconds [mean ± SD]). Anterior pharyngeal dysfunction was more severe in patients with primary tumors of the hypopharynx than in those with cancer of the oropharynx. Twelve (80%) of our patients demonstrated posterior pharyngeal segment dysfunction characterized by impaired pharyngeal constrictor motility. All 15 patients displayed pharyngeal stage abnormalities that limited bolus transport and clearance.

Conclusions: Severe pharyngeal physiological abnormalities were present that led to impaired bolus transport and that were frequent and debilitating consequences of this organ-sparing protocol. Long-term follow-up of this group will be required to assess the permanence of the abnormalities.


Severe dysphagia is a frequent and debilitating consequence of head and neck cancer resection.1-7 Patients who have undergone major resections for cancer of the oral cavity, oropharynx, hypopharynx, and larynx experience varying degrees of swallowing difficulty. The nature and extent of the swallowing disability are related to the site and size of the tumor and the method of treatment,8 with increasing size of the resection being associated with a greater impairment of swallowing.5,9 The type and method of reconstruction also have a substantial effect on deglutition and associated neurologic deficits.

Although radiation therapy does not result in the removal of structures necessary for effective swallowing, it impairs swallowing ability.10 Specifically, irradiation causes fibrosis of the pharyngeal muscles, with resultant impairment of pharyngeal contraction, and fibrosis of the soft tissues, which impairs laryngeal elevation.11 When the salivary glands are included in the radiation field, the resultant xerostomia and hyposalivation further impair mastication and the initiation of the swallowing reflex.12

The role of combined-modality treatment with chemotherapy and radiation therapy in an organ-sparing context has recently been investigated as an alternative to ablative surgery for advanced-stage disease. The effects of combined-modality therapy on swallowing have not been frequently evaluated.13-17 Among patients with oral and pharyngeal tumors treated with external-beam irradiation and adjuvant chemotherapy, reduced swallowing efficiency and tongue base and laryngeal movement...
PATIENTS AND METHODS

ADMINISTRATIVE

This study was correlated to a prospective, single-institution phase 1 trial of a regimen of concomitant prolonged-infusion hydroxyurea therapy with hyperfractionated, accelerated, external-beam irradiation. This trial was approved by the Albert Einstein Cancer Center Review Committee and the institutional review board of Montefiore Medical Center, Bronx, NY.

PATIENTS

Twenty-four patients have been entered into a phase 1 study of XRT-HU. Fifteen patients with advanced stage III or stage IV carcinoma of the oral cavity (n = 1), oropharynx (n = 7), or hypopharynx (n = 7) were enrolled in this portion of the study. Seven patients have not yet had posttreatment swallowing studies, 1 patient’s study was performed more than 1 year following the treatment, and 1 other patient’s study was not available for review. The patient group included 12 men and 3 women, ages 40 to 68 years (mean, 56 years), and all had previously untreated, locally advanced squamous cell carcinoma. The Table summarizes characteristics of the patient group, including tumor site and American Joint Committee on Cancer stage, hydroxyurea dosage, and the time from the completion of radiation therapy to videofluorography. All patients underwent videofluorographic swallow studies within 1 year of the completion of treatment.

All patients were treated with 74.4 Gy of external-beam irradiation using 1.2-Gy twice-a-day fractionation. No patient had a medical history of neurologic disease, gastroenterologic dysfunction, previous head and neck cancer, or surgical or radiation treatment to the head and neck region. No patient was taking medication that might affect swallowing function or had previously undergone swallowing therapy. Before treatment, all patients were eating orally, although 6 patients had pain and swallowing difficulty and 3 patients experienced weight loss. In this study, most patients underwent pretreatment gastrostomy tube placement, based on the initial patients who had severe swallowing dysfunction following the initiation of the XRT-HU protocol. At the time of the videofluorographic swallowing study, all but 1 patient were dependent on enteral feedings as their primary means of nutrition and hydration. Ten of the patients tolerated oral liquids on a nonnutritive basis.

VIDEOFLUOROSCOPIC EVALUATION

Fifteen patients with late-stage head and neck cancer who received the XRT-HU protocol underwent a complete videofluoroscopic swallowing function study, which was evaluated for the current report. Studies were performed between 3 and 45 weeks after the completion of the protocol, with patients’ medical status dictating the timing of the study. Videotape (General Electric wide band super VHS cassette recorder XR70; General Electric Co, Chicago, Ill) recordings of the fluoroscopic images of the patients’ oral and pharyngeal stages of swallow were captured in the lateral and anteroposterior planes. For the purposes of this investigation, the videotape recordings of each patient’s initial, small-volume swallow of low-density liquid barium from a cup were subjected to in-depth analysis in real time, slow motion, and frame by frame, using an integrated system that allows objective analysis of video recordings through image processing and digitization (the Kay Elemetrics Computerized Swallowing Station; Kay Elemetrics Co, Lincoln Park, NJ). Features of the treated patients’ pharyngeal stage motility were described using Leopold and Kagel’s20 videofluoroscopic descriptors of pharyngeal transport abnormalities, which divide the pharynx into the anterior (laryngeal and epiglottic motility) and the posterior (pharyngeal constrictor motility) segments. Temporal measures of structural movements were obtained to facilitate the description of laryngeal motility. Subsequent to data collection, motility descriptors of patients treated with XRT-HU, temporal data, and feeding status were analyzed using visual inspection, descriptive statistics, nonparametric 1-sample χ² test, 2-sample related Wilcoxon tests, and Spearman rank correlations.

RESULTS

PHARYNGEAL TRANSPORT

All 15 patients treated with XRT-HU demonstrated abnormal pharyngeal transport for liquid bolus swallows following completion of their therapy. All presented with multiple pharyngeal stage abnormalities affecting bolus transport through, and clearance from, the pharynx. Furthermore, all patients displayed anterior pharyngeal segment dysfunction with impairment of both epiglottic and laryngeal motility. Of the 15 patients, 12 (80%) had posterior pharyngeal segment dysfunction with impairment of pharyngeal constrictor motility.

All 15 patients had anterior segment dysfunction. All of the study patients demonstrated epiglottic dysmotility, defined as restricted or limited range of motion. Fourteen (93%) patients had normal vertical positioning of the epiglottis at rest, and 1 had horizontal epiglottic malpositioning at rest. No epiglottic movement from a vertical or horizontal resting position to partial or complete inversion was evidenced during the swallows in all 15 patients. Twelve (80%) of the 15 patients treated with XRT-HU had vallecular residua after the swallow study, and this was in concordance with supraglottic laryngeal stasis (χ² = 12.86;
An evaluation of laryngeal motility demonstrated adequate timing of the start of laryngeal elevation associated with the swallow response. In contrast, the speed of laryngeal motion during swallowing was impaired, with a mean (SD) onset time of laryngeal elevation of 0.146 (0.169) seconds and a range of 0.033 to 0.528 seconds. The patients' onset times of laryngeal elevation were within the temporal standards reported by Logemann\textsuperscript{21} for normal adult subjects (up to 0.2 seconds) and for adults older than 60 years (0.5 seconds). The mean (SD) duration of laryngeal motion from the start of superior movement (associated with the pharyngeal swallow response) to maximum superior excursion and return to rest for the group was 1.011 (0.379) seconds, with a range of 0.429 to 1.792 seconds. Using Logemen's standard of 0.32 seconds for pharyngeal transport of small-volume bolus swallows,\textsuperscript{21} all patients had an increased duration of laryngeal motion during the swallow study. Patient subgrouping was then performed according to the site of tumor and a maximum pharyngeal transport time of 1 second.\textsuperscript{21} Wilcoxon signed rank testing revealed significant differences in duration between tumor site subgroups, with patients with supraglottic penetration having a significantly longer duration of laryngeal motion during the swallow study than those with oropharyngeal cancer ($P = .03$).

Table 1: Characteristics and Anterior Segment Abnormality of Patients Receiving Concomitant Radiation Therapy and Hydroxyurea Therapy (XRT-HU)

<table>
<thead>
<tr>
<th>Patient No./Sex/Age</th>
<th>Site†</th>
<th>Clinical Stage‡</th>
<th>Hydroxyurea Dose, mg/ (m²·min)</th>
<th>Time to Videotaped Swallow Study After XRT-HU, wk</th>
<th>Laryngeal Elevation, s§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/50 HP T3 N2b</td>
<td>250</td>
<td>44</td>
<td>1.066</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/F/53 HP T4 N2c</td>
<td>250</td>
<td>23</td>
<td>0.429</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/M/59 OP T4 N3</td>
<td>375</td>
<td>3</td>
<td>0.627</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/M/49 OP T4 N2c</td>
<td>375</td>
<td>12</td>
<td>0.792</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/M/50 OP T4 N2b</td>
<td>375</td>
<td>34</td>
<td>1.429</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/M/40 HP T4 N1</td>
<td>375</td>
<td>19</td>
<td>1.792</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/F/45 HP T4 N0</td>
<td>313</td>
<td>15</td>
<td>1.495</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/M/57 OP T4 N2c</td>
<td>313</td>
<td>12</td>
<td>0.891</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/M/54 OP T4 N3</td>
<td>313</td>
<td>40</td>
<td>0.594</td>
<td></td>
<td></td>
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<tr>
<td>10/F/69 HP T2 N1</td>
<td>313</td>
<td>13</td>
<td>1.099</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/M/67 HP T4 N2b</td>
<td>313</td>
<td>9</td>
<td>1.066</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/M/62 HP T4 N3</td>
<td>313</td>
<td>7</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13/M/64 OC T3 N2c</td>
<td>313</td>
<td>5</td>
<td>0.693</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14/M/61 HP T4 N2b</td>
<td>313</td>
<td>35</td>
<td>0.825</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15/M/59 OP T4 N2c</td>
<td>313</td>
<td>9</td>
<td>1.363</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All patients received the identical irradiation dose of 74.4 Gy.
†HP indicates hypopharynx; OP, oropharynx; and OC, oral cavity.
‡The TNM staging system of the American Joint Committee on Cancer.\textsuperscript{17}
§The duration of the laryngeal elevation measured from the onset of superior movement of the larynx to its return to rest (mean ± SD, 1.011 ± 0.379). Historical norms of laryngeal elevation are all <0.32 seconds (from Logemann\textsuperscript{21}).

P = .005) and pharyngeal stasis ($\chi^2 = 16.29; P = .001$), but not pyriform sinus residua ($\chi^2 = 8.29; P = .04$). The epiglottis was enlarged in 14 (93%) of 15 patients, with normal epiglottic sizing observed in only the 1 patient with cancer of the anterior tongue and floor of mouth.

**LARYNGEAL MOTILITY**

The surgical approach to the treatment of advanced-stage head and neck cancer can be influenced by the resultant severe impairments of swallowing function. Investigation of combined-modality chemotherapy and radiation therapy is based on the premise that the preservation of structure will result in the preservation of function. Our experience with radiation treatment alone reveals that serious functional consequences may arise following nonoperative therapy. The xerostomia, fibrosis, edema, and mucositis caused by radiation treatment all have an adverse effect on swallowing function. With concomitant chemotherapy, the detrimental effect on swallowing function may be even greater and must be closely examined.

Studies by Lazarus et al\textsuperscript{13} and Koch et al\textsuperscript{16} have shown severely impaired swallowing function in patients with oral and pharyngeal cancers that were treated using chemotherapy and radiation therapy for organ preservation. The use of XRT-HU produced similar results of debilitating pharyngeal dysphagia, characterized by the inability to successfully transport a small-volume liquid bolus through the pharynx into the esophagus due to multiple pharyngeal stage abnormalities. Specifically, epiglottic dysmo-

**LARYNGEAL PENETRATION**

Ten (67%) of 15 patients displayed supraglottic penetration, defined as entry of the material into the laryngeal vestibule but not below the true vocal cords.\textsuperscript{22} Delayed closure of the laryngeal vestibule was the predominant causative factor for penetration. This finding was consistent with patients' increased laryngeal motion time during the swallow ($\chi^2 = 19.14; P < .001$). Glottic aspiration, defined as entry of the material below the true vocal cords,\textsuperscript{22} was observed in 4 of 10 patients with supraglottic penetration. Spillage of the postswallow residua from the pyriform sinus into the airway was the primary cause of aspiration.

**MOTILITY STUDIES**

Posterior pharyngeal segment dysfunction was also evident in most patients. Of the 15 patients, 12 (80%) showed dysfunction of pharyngeal constrictor movement. Dysmotility of the superior, middle, and inferior constrictors was most frequent, observed in 8 (53%) of 15 patients. Middle or inferior constrictor dysmotility was evident in 2 (13%) of 15 patients, with the remaining 2 (13%) displaying superior or medial pharyngeal constrictor dysmotility. Pharyngeal constrictor dysmotility was associated with pharyngeal stasis ($\chi^2 = 17.43; P = .006$), but not pyriform sinus residua ($\chi^2 = 3.71; P = .29$).

Swallowing function was defined as the ability to tolerate nonnutritive oral intake at the time of the videofluorography and analyzed by the time from the end of the treatment to the date the study was performed and by the dose of hydroxyurea. There was no significant correlation between the timing of the swallow study (ie, number of weeks after the completion of treatment) and level of swallowing dysfunction ($r = -0.15; P = .49$) or between chemotherapy dosage and level of swallowing dysfunction ($r = 0.24; P = .78$) using Spearman rank correlation.

**COMMENT**

The surgical approach to the treatment of advanced-stage head and neck cancer can be influenced by the resultant severe impairments of swallowing function. Investigation of combined-modality chemotherapy and radiation therapy is based on the premise that the preservation of structure will result in the preservation of function. Our experience with radiation treatment alone reveals that serious functional consequences may arise following nonoperative therapy. The xerostomia, fibrosis, edema, and mucositis caused by radiation treatment all have an adverse effect on swallowing function. With concomitant chemotherapy, the detrimental effect on swallowing function may be even greater and must be closely examined.

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tality was seen in all patients, with all but 1 patient showing epiglottic enlargement. The duration of laryngeal motion on bolus swallows was increased for all patients, but those with hypopharyngeal tumors showed substantially longer durations of laryngeal motion during the swallow than patients with oropharyngeal tumors. Consistent with patients' increased laryngeal motion time was delayed closure of the laryngeal vestibule, resulting in supraglottic penetration. Glottic aspiration, however, was observed in only 4 (27%) study patients and was not responsible for the patients' inability to tolerate oral feeding. Most of the patients showed dysfunction of the pharyngeal constrictors, the muscles primarily responsible for moving a bolus through the pharynx and clearing it. Ideally, all patients would have been analyzed within the first 3 to 4 months following therapy, to identify the short-term effects of the treatment regimen. In some patients, however, the dysphagia was so pronounced that an earlier evaluation could not be performed, and patient compliance issues required delay in others. Swallowing often improves over time, or stabilizes rather than worsens, and our data show no association between the timing of the study and the severity of abnormalities.

An objective and standardized evaluation of the swallowing function is necessary not only to clearly describe the effects of combined-modality treatment but also to provide as a basis for appropriate comparison with other treatment modalities, including conventional surgical resections. This has become even more important as recent investigations of the chemoradiotherapy approach to the treatment of head and neck cancer have not consistently demonstrated increased survival rates. Quality-of-life issues will play an even greater role in determining treatment. In a study to assess patients' perceptions of the changes in swallowing function after undergoing concurrent chemotherapy and irradiation for the treatment of head and neck cancer, Murry et al.17 noted that a treatment-related decline in quality of life was observed that varied according to disease site (oropharynx, hypopharynx, and larynx), with the greatest decline observed in patients with hypopharyngeal carcinoma. This is consistent with our finding of a greater impairment of laryngeal motion among patients with hypopharyngeal primary tumors and validates the relationship between impairment of swallowing function and the perception of swallowing dysfunction.

The physiological abnormalities demonstrated in this study, both anterior and posterior segment, were marked when compared with previously published norms and were similar, though more pronounced, than those observed with radiation therapy alone. The prior studies of swallowing abnormalities following organ-sparing chemoradiotherapy have been limited by small numbers or a lack of objective findings and a reliance on subjective patient-based questionnaires, and these studies have demonstrated less severe abnormalities than those described in the present study. This may be due to the different treatment regimen used, both in the type of chemotherapy and the more aggressive radiation therapy regimen used or to the bulky tumors present in these patients. The conclusions that can be drawn from this study are limited by the lack of pretreatment swallowing stud-ies; however, all patients were swallowing before their therapy. Increased abnormalities were seen in those patients with hypopharyngeal carcinomas, which may have long-term quality-of-life effects in these patients. These findings suggest that the preservation of structure by itself does not guarantee the preservation of function and that further studies on these important quality-of-life issues are clearly indicated. A randomized trial would eliminate any patient selection factors.

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REFERENCES