EFFECTS OF RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY ON TONGUE STRENGTH AND SWALLOWING IN PATIENTS WITH ORAL CANCER

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Abstract: Background. Oral tongue strength and swallowing ability are reduced in patients treated with chemoradiotherapy for oral and oropharyngeal cancer.

Methods. Patients with oral or oropharyngeal cancer treated with high-dose chemoradiotherapy underwent tongue strength, swallowing, and dietary assessments at pretreatment and 1, 3, 6, and 12 months posttreatment. Tongue strength was assessed using the Iowa Oral Performance Instrument (IOP). Oral and pharyngeal residue was evaluated utilizing videofluoroscopy.

Results. Mean maximum tongue strength dropped a non-significant amount immediately after treatment, and then increased significantly at 6- and 12-months posttreatment completion. Analyses were adjusted for patient dropout. Tongue strength was not significantly correlated with swallow observations of percentage oral and pharyngeal residue. Ability to eat various diet consistencies was reduced after treatment but improved over time at a rate similar to changes in oral intake and type of diet.

Conclusions. Parallel but not significant changes in oral intake, diet, and tongue strength in the first year post chemoradiation therapy need further study in a larger population.

Keywords: tongue strength; chemoradiotherapy; residue; head and neck cancer; longitudinal analysis

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A reduction in muscle strength in the tongue has been found in patients treated with primary chemoradiotherapy for oral and oropharyngeal cancer.\(^1\) This reduction in tongue strength has been found both prior to and after treatment when compared with age- and sex-matched healthy controls.\(^1\) In addition, oropharyngeal swallow function has been shown to be worse than normal in this population after treatment with primary chemoradiotherapy.\(^1-3\) Lazarus et al\(^1\) found that oral transit times during swallowing were prolonged and that oropharyngeal swallow efficiency measures were lower than normal in patients with oral and oropharyngeal cancer treated with primary chemoradiotherapy. Tongue strength was found to correlate with oral transit time and pharyngeal transit times and number of swallows.\(^1\) Patients in the Lazarus et al\(^1\) study were evaluated pre- and 2 months post-treatment. No study to date has examined tongue strength and swallowing over an extended period of time (ie, 1 year post-treatment) in oral and oropharyngeal cancer patients treated with primary chemoradiotherapy. This prospective study examined swallowing and tongue strength at pretreatment and 1, 3, 6, and 12 months posttreatment in patients with oral and oropharyngeal cancer treated with primary chemoradiotherapy.

PATIENTS AND METHODS

Subjects. Forty-six subjects with oral or oropharyngeal cancer participated in this study. The study protocol was approved by the institutional review board of Northwestern University and the institutional review board of the University of Chicago Medical Center. Written informed consent was obtained for all subjects. Individuals with newly diagnosed head and neck cancers about to undergo external beam radiation and chemotherapy protocols for cancer of the oral cavity or oropharynx who agreed to participate were accessed sequentially from Northwestern Memorial Hospital, the Lakeside (currently Jesse Brown) Veteran’s Affairs (VA) Medical Center and the University of Chicago Medical Center. An in-depth interview revealed that no individual demonstrated any history of gastrointestinal disease or surgery, head and neck injury, head and neck cancer, or swallowing problems prior to those related to the newly diagnosed oral or oropharyngeal tumor. Individuals ranged in age from 29 to 78 years, with a mean age of 59 years. Thirty-five males (age range 36–78, mean age = 59) and 11 females (age range 29–75, mean age = 57) participated in this study. Thirty-eight patients had stage IV disease, 5 had stage III disease, and 3 had stage II disease. Twenty-six patients had tongue base tumors, 2 of whom had extension of disease to include the tonsil. Thirteen patients had tumors of the tonsil, 2 of whom had extension of disease to include the palate. The remaining patients had tumor sites that included floor of mouth (n = 3), oral tongue (n = 2), retromolar trigone (n = 1), and soft palate (n = 1). Forty-five patients had squamous cell carcinoma and 1 patient had adenocystic carcinoma.

Radiation doses ranged from 5850 to 7578 cGy (mean, 7235 cGy) external beam radiotherapy for primary organ preservation treatment. Of the 46 patients, 21 underwent induction chemotherapy consisting of paclitaxel (Bristol-Myers Squibb, New York, NY) and carboplatin (Bristol-Myers Squibb, New York, NY), 19 of whom underwent 6 cycles and 2 of whom underwent 5 cycles. Forty-three patients received twice-daily radiotherapy and 3 received once-daily radiotherapy at conventional fractionation. Forty-three of 46 patients received concomitant chemotherapy with either paclitaxel, cisplatin (Bristol-Myers Squibb, New York, NY), or 5-fluorouracil (Roche, Basel Switzerland). Treatment volume included the major salivary glands. Even those subjects with anterior floor of mouth tumors received radiotherapy to the oropharynx and hypopharynx due to advanced neck disease. Thus, regardless of tumor site, patients were irradiated to similar oral and pharyngeal regions because of the advanced local and regional disease.

Videofluoroscopic Swallow Protocol. Videofluoroscopic (VFG) examination of swallowing was utilized.\(^4,5\) VFG examination of swallowing was performed and recorded with a Sony VO9600 videocassette recorder (VCR), coupled to a Thalner Electronics counter-timer that placed numbers in hundredths of a second on each video frame, in order to review swallows in slow motion and frame by frame. Subjects were seated upright and in the lateral plane. Subjects were given 3 swallows each of 1, 3, 5 and 10 mL thin liquids, 3 and 10 mL thick liquids, and 3 mL barium paste. Approximate percentage oral and pharyngeal residue was estimated by trained observers for each swallow at each time point. This procedure has been validated from scintigraphic data.\(^6\) Interobserver and intraobserver reliability measures were per-
Effects of Chemoradiotherapy in Oral Cancer

Tongue Strength Instrumentation and Protocol. All patients underwent tongue strength assessment; maximal isometric pressure generation \( (P_{\text{max}} = \text{strength}) \). Maximum tongue strength was assessed using the Iowa Oral Performance Instrument (IOPI).\(^7,8\) The IOPI is a device designed to measure pressure generated by the tongue. It consists of an air-filled bulb attached to a pressure transducer, which is connected to an amplifier, signal conditioning conduit, and digital voltmeter. The amount of pressure generated by squeezing the bulb with the tongue is displayed on a digital display readout that is calibrated in kiloPascals (kPa). A peak-holding circuit in the device displays peak pressure.

Test Protocol and Data Collection. During data collection for the tongue strength measure \( (P_{\text{max}}) \), patients were seated with the tongue pressure bulb placed against the hard palate, just behind the upper alveolar ridge. The participants were instructed as follows: “Press up on the tongue bulb with your tongue and squeeze the bulb against the roof of your mouth. Squeeze as hard as you can for 3 seconds.” Subjects performed 3 trials with 2-minute rest between trials.\(^9\) The greatest value for the 3 trials was used as \( P_{\text{max}} \). Means and standard errors were used to describe the tongue strength measures pretreatment and posttreatment.

Statistical Analysis. Mean tongue strength over time was analyzed several ways, to determine whether patient dropout affected the results. Observed data are first presented as mean and standard errors, for each time point. Mixed linear model analysis was then used to compare across time points, making no adjustment for dropout. The methods proposed by Vonesh et al\(^{10}\) were used to account for patient dropout. Two nonlinear mixed models were used to jointly model tongue strength and dropout. Each model used overall fixed effects and patient-specific random effects for the tongue strength. One model used the Weibull distribution for dropout and the other used discrete hazards for dropout. Statistical tests for change over time were done using an overall test across the 5 time points. Pairwise contrasts compared each pair of timepoints using a t test. Since a total of 10 comparisons were made (all pairwise comparisons across the 5 time points), a Bonferroni correction of \( p < .005 (= .05/10) \) was used for each pairwise comparison. Analysis of covariance and partial correlations were used to determine the relationship between tongue strength versus the ability to eat specific food types and the presence of bolus residue, adjusting for the time of observation. Fisher’s exact test was used to compare the percentage of patients who could eat specific food types across timepoints. The independent sample \( t \) test was used to compare baseline tongue strength between subgroups defined by subsequent dropout. Statistical analyses were done using SAS software.\(^11\)

RESULTS

Of the 46 patients evaluated for pretreatment, 35 underwent 1-month posttreatment tongue strength assessment, 22 underwent 3-month posttreatment assessment, 24 underwent 6-month assessment, and 16 underwent 12-month posttreatment assessment. One patient had a tracheostomy tube in place at the pretreatment evaluation. This same patient had the tracheostomy tube in place 1 month posttreatment. One other patient had a tracheostomy tube in place at the 6-month posttreatment evaluation.

Table 1 shows mean maximum tongue strength measures for all time points across subjects. Results revealed that mean maximum tongue strength differed significantly among the evaluation points \( (p < .002 \text{ for all analyses}) \). For all statistical models, pairwise comparisons revealed that the drop in mean maximum tongue strength was not significant immediately after treatment, but then increased significantly at 6- and 12-month posttreatment completion. While adjustment for dropout tended to decrease the estimates of mean tongue strength for the 3- and 6-month posttreatment times, the changes over time remained similar to the unadjusted results. When baseline mean tongue strength was compared between the 24 patients with 6-month data and the 22 patients without 6-month data, there were no significant differences \( (51.0 \text{ vs } 43.0, p = 0.22) \). Similar nonsignificant comparisons of baseline data occurred between subgroups having and not having data at 1 month \( (p = .39) \), 3 months \( (p = .46) \), and 12 months \( (p = .66) \). Tongue strength measures were less than those found in the healthy middle-aged and elderly population (ie, approximately 60 kPa)\(^{12,13}\) at the pretreatment, 1-, and 3-month posttreatment time points. Tongue strength measures at 6 and 12 months
Table 1. Mean (standard error) maximum tongue strength in kiloPascal for oral and oropharyngeal cancer patients by evaluation point.

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Pretreatment (n = 46)</th>
<th>1-month posttreatment (n = 35)</th>
<th>3-month posttreatment (n = 22)</th>
<th>6-month posttreatment (n = 24)</th>
<th>12-month posttreatment (n = 16)</th>
<th>p value*</th>
<th>Pairwise tests†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed‡</td>
<td>47.0 (3.1)</td>
<td>41.7 (2.6)</td>
<td>51.0 (3.2)</td>
<td>57.5 (3.2)</td>
<td>54.7 (2.7)</td>
<td>&lt;0.005</td>
<td>6, 7</td>
</tr>
<tr>
<td>Predicted-none§</td>
<td>47.0 (2.5)</td>
<td>43.0 (2.7)</td>
<td>49.3 (3.1)</td>
<td>55.0 (3.0)</td>
<td>55.3 (3.4)</td>
<td>&lt;0.0005</td>
<td>6, 7</td>
</tr>
<tr>
<td>Predicted-Weibull**</td>
<td>47.0 (2.5)</td>
<td>43.0 (2.7)</td>
<td>49.3 (3.1)</td>
<td>55.0 (3.1)</td>
<td>55.3 (3.5)</td>
<td>&lt;0.005</td>
<td>6, 7</td>
</tr>
<tr>
<td>Predicted-discrete**</td>
<td>46.9 (2.4)</td>
<td>42.6 (2.7)</td>
<td>49.1 (3.2)</td>
<td>44.9 (3.1)</td>
<td>55.0 (3.6)</td>
<td>0.002</td>
<td>6, 7</td>
</tr>
</tbody>
</table>

Note: n, number of subjects at each timepoint for observed data.
*p value is for a significant difference across all timepoints.
‡Statistical significance of pairwise comparisons: 1 = p < .005 for pre versus 1 month; 2 = p < .005 pre versus 3 months; 3 = p < .005 pre versus 6 months; 4 = p < .005 pre versus 12 months; 5 = p < .005 1 month vs. 3 months; 6 = p < .005 1 month vs. 6 months; 7 = p < .005 1 month vs. 12 months; 8 = p < .005 3 months vs. 6 months; 9 = p < .005 3 months vs. 12 months; 10 = p < .005 6 months vs. 12 months.
§The observed data.
*Predicted values using Weibull adjustment for dropout.
**Predicted values using discrete hazard for dropout.

DISCUSSION

This study revealed that mean maximum tongue strength did not drop significantly immediately after treatment and then increased significantly at 6- and 12-month posttreatment completion. The lack of significant tongue strength decrease posttreatment may be due to the fact that the tumor bulk was not present following treatment. Presence of tumor pretreatment likely contributed to pain, soreness, and reduced tongue strength due to its presence. Posttreatment, although mucositis and soreness might have been present and might have contributed to reduced

Table 2. Number (percent) of patients who could eat each diet type at each evaluation point for oral and oropharyngeal cancer patients treated with primary chemoradiotherapy.

<table>
<thead>
<tr>
<th>Diet type</th>
<th>Pretreatment</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>46</td>
<td>35</td>
<td>22</td>
<td>24</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Thin liquid</td>
<td>45 (98%)</td>
<td>29 (83%)</td>
<td>19 (86%)</td>
<td>21 (88%)</td>
<td>14 (88%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Thick liquid</td>
<td>37 (80%)</td>
<td>14 (40%)</td>
<td>11 (50%)</td>
<td>18 (75%)</td>
<td>13 (81%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Pureed</td>
<td>41 (89%)</td>
<td>23 (66%)</td>
<td>16 (73%)</td>
<td>19 (79%)</td>
<td>15 (94%)</td>
<td>0.052</td>
</tr>
<tr>
<td>Soft masticated</td>
<td>38 (83%)</td>
<td>20 (57%)</td>
<td>17 (77%)</td>
<td>20 (83%)</td>
<td>15 (94%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Crunchy masticated</td>
<td>31 (67%)</td>
<td>7 (20%)</td>
<td>7 (32%)</td>
<td>11 (46%)</td>
<td>10 (63%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Normal diet</td>
<td>31 (67%)</td>
<td>5 (14%)</td>
<td>5 (23%)</td>
<td>8 (33%)</td>
<td>9 (56%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Oral intake &gt; 50%</td>
<td>45 (98%)</td>
<td>22 (63%)</td>
<td>18 (82%)</td>
<td>19 (79%)</td>
<td>16 (100%)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Numbers in parentheses denote percentage of the patients.
*p value is for a significant difference across all timepoints.
tongue strength, tumor bulk was not present, perhaps contributing to improved lingual strength. Therefore, the side effects of radiotherapy and chemotherapy may have been countered by the lack of tumor bulk and greater ease of performing the tongue strength task posttreatment. In addition, it is likely that the mucositis experienced by these patients resolved over time, and why, in addition to resolution of tumor bulk, pretreatment tongue strength was significantly lower than the 6- and 12-month posttreatment tongue strength measures. For the observed data (Table 1), there was a slight worsening of tongue strength from pretreatment to 1 month posttreatment. It is likely that worsening in mean maximum tongue strength was due to the early side effects of chemoradiotherapy, including mucositis, pain, and soreness and may also be due to patients’ overall fatigue and weakness after treatment. Improvement in tongue strength is likely due to lessening of early side effects and improvement in physical status. Although a previous study found no significant differences in maximal tongue strength from baseline to 2 months post-baseline, this may be due to the smaller mean number of subjects (n = 13). In addition, there may have been some decrement in tongue function in these same patients at 1 month posttreatment that might not have been appreciated at 2 months posttreatment.

Fewer patients underwent tongue strength assessment post-treatment as compared with pretreatment, with the number of patients seen for tongue strength evaluations dropping over the course of the year. Drop-out is a common problem in conducting prospective studies. Colangelo et al showed that patients who were treated surgically for oral and oropharyngeal cancer, and who had poorer swallowing performance early in follow-up, tended to drop out at a higher rate later in follow-up. On the other hand, Rademaker et al found that in patients treated primarily with chemoradiation, adjustment for dropout had little effect on the final results. In the present study, comparisons of baseline mean tongue strength between patients who did or who did not drop out subsequently did not reveal any significant differences. This indicates that there is no initial bias in tongue strength that is introduced by dropout. This is supported by the similar results between the models adjusting and not adjusting for dropout. Even with adjustment for dropout, the significant differences between immediate posttreatment values and those at 6 and 12 months were still observed.

Percent of oral intake and type of diet in these patients shifted in the same direction as did tongue strength over the course of the year, though this relationship was not statistically significant. Specifically, ability to handle oral intake worsened at the 1-month evaluation (as did maximum tongue strength), with fewer patients able to manage some sort of oral diet, and improved over time (as did maximum tongue strength), with fewer patients receiving primary nutrition via PEG and more patients taking at least a soft diet over the course of the year. Tongue strength may have played a key role in ability to handle some types of oral diet in these patients, although since this study was not designed to detect the nature of this role, the potential key role of tongue strength in the ability of patients to consume more viscous consistencies is speculative. This relationship needs further investigation in a larger number of patients. Posttreatment xerostomia also likely played a role in type and ability to take oral nutrition, since xerostomia is known to increase oral transit time and result in increased oral residue.

The tongue motion and tongue pressures involved in swallowing for oral intake may serve as a strengthening exercise in and of themselves, as viscosities are expanded in the diet. While tongue strength was generally higher in patients who could eat specific food types, and this held for most food types and most timepoints. With several statistical tests being performed for this analysis alone, the presence of one significant result for soft foods may result from chance. Of greater interest is the result that tongue strength was directly related to the patient’s ability to eat >50% of their food orally.

In this study, there was no relationship between tongue strength and residue in the oral cavity or pharynx. Tongue strength was measured with the IOPI as an isolated task, and not in the context of swallowing. A follow-up study should examine tongue strength during swallow and its relationship to oral residue, as well as the relationship between tongue base strength and pharyngeal residue. In addition, tongue base strength, as determined by measuring tongue base to pharyngeal wall pressures manometrically, might be a more useful measure to compare to bolus clearance through the pharynx and pharyngeal residue.

The late effects of radiotherapy on tissues can occur long after treatment and can include capillary occlusion, soft tissue and muscle fibrosis, and collagen replacement. Tissue and muscle fibrosis are believed to result in swallowing prob-
lems that can occur long after treatment completion in irradiated individuals.27,28 A recent pilot study by Lazarus (2005)26 found tongue strength decrements (mean maximum tongue strength = 35 kPa) in 12 head and neck cancer patients treated with primary radiotherapy +/- chemotheraapy to a variety of sites, including nasopharynx, tongue base, tonsil, oropharynx, hypopharynx, and larynx. All subjects demonstrated reduced tongue base function for swallowing on videofluoroscopic examination. Time from radiotherapy to tongue strength and videofluoroscopic swallow assessment ranged from 1 month to 15 years, with a mean of 73 months. Ten of these 12 patients never underwent a swallow exercise program, with or without tongue strength exercises, during or after treatment completion. Thus, it appears that tissue fibrosis continues over time, particularly in the lingual musculature.

Whether or not these patients might benefit from tongue strengthening exercises to maintain tongue strength and swallow function over time cannot be determined from the data in this present study. However, tongue strengthening exercises have been found to increase tongue strength in other studies of normal and patient populations.27,28 Future studies will examine the effects of prophylactic swallow exercises on tongue strength and swallowing in oral and oropharyngeal cancer patients treated with primary chemoradiotherapy.

REFERENCES