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The Impact of Time After Radiation Treatment on Dysphagia in Head and Neck Cancer Patients Enrolled in a Swallowing Therapy Program

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Abstract

Background—Swallowing dysfunction after radiation treatment for head and neck cancer can be devastating. A randomized control trial compared swallow exercises versus exercise plus neuromuscular electrical stimulation therapy and found no overall difference in outcomes.

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Methods—Quality of life, diet, and swallowing variables collected at discrete intervals on 117 patients were re-analyzed to test the hypothesis that shorter time between completion of radiation therapy and beginning the swallowing therapy program yielded improved outcomes.

Results—At baseline, subjects less than 1 year post radiation had significantly better function than subjects more than 2 years post RT in several measures. Over the therapy program, the early group showed significant improvement in diet and QOL. Swallowing physiology variables showed no difference between groups.

Conclusions—Beginning a swallowing therapy program within one year of completion of radiation therapy demonstrates more consistent improvement in quality of life and diet performance compared to later time periods.

INTRODUCTION

Head and neck cancers represent the seventh most common group of cancers worldwide (Rettig & D'Souza, 2015). While smoking and tobacco use remain primary risk factors, human papillomavirus (HPV) malignancies especially in the oropharynx are on the rise (Rettig & D'Souza, 2015; Pezzuto et al., 2015). Morbidity and mortality rates remain high despite aggressive multi-modality treatment protocols (Rettig & D'Souza, 2015; MacNeil et al., 2015). In particular, swallowing dysfunction, whether pre-treatment or post-treatment, (Givens et al., 2009; Ames et al., 2010; Szczesniak, Maclean, Zhang, Graham, & Cook, 2014; Kraaijenga et al., 2015) contributes significantly to both morbidity and mortality especially in older adults (O'Neill et al., 2015). Post treatment quality of life studies have identified speech and swallowing issues as well as depression as factors in poor patient scores (Gillespie, Brodsky, Day, Lee, & Martin-Harris, 2004; Lin, Starmer, & Gourin, 2012; Silveira, Dedivitis, Queija, & Nascimento, 2015).

Multiple studies have attempted to predict, prevent and/or treat swallowing dysfunction. In the hopes of targeting those with high risk of dysphagia, predictive studies have identified non-glottic cancers, advanced stage, and baseline dysphagia as factors likely to be present in long-term swallowing issues (Mortensen et al., 2013). Several types of organ sparing radiation protocols have been able to reduce but not eradicate swallow related side effects (Nuyts et al., 2013; Vainshtein et al., 2015). Protocols whereby patients undergo a speech pathology directed swallow specific rehabilitative protocol throughout the course of therapy have at best shown mild diet or quality of life benefit (van der Molen et al., 2011; Crary, Carnaby, LaGorio, & Carvajal, 2012; Duarte, Chhetri, Liu, Erman, & Wang, 2013; van den Berg et al., 2014). Specifically, tongue strengthening after treatment completion has shown improved QOL scores in eating and speech domains without strength or physiologic improvements (Lazarus et al., 2014). Respiratory muscle training is one of the few studies to show physiologic improvements (Martin-Harris et al., 2015). Percutaneous endoscopic gastrostomy (PEG) tube feeding does decline as time post-treatment continues (Setton et al., 2015), but a large cohort of patients continue to live with chronic severe dysphagia. In summary, while several studies have been able to demonstrate a mild diet or quality of life effect, studies have generally not shown a physiologic effect and no protocol has shown significant improvement in any outcome measure.

Neuromuscular electrical stimulation (NMES) has been used for decades by physical therapists to assist in skeletal muscle rehabilitation. Randomized trials for dysphagia in head and neck disease have not shown consistently positive results (Burnett, Mann, Stoklosa, & Ludlow, 2005; Carnaby-Mann & Crary, 2007; Clark, Lazarus, Arvedson, Schooling, & Frymark, 2009). Recently the authors completed a multicenter randomized controlled blinded study of swallowing exercises with active versus sham NMES in head and neck cancer subjects with moderate to severe dysphagia after treatment (Langmore et al., 2015). The study showed no benefit with the addition of active NMES to exercise. Minimal yet statistically significant improvements in several quality of life domains among all subjects over time were identified without specific improvements in physiologic measures of swallowing (Langmore et al., 2015). Within the larger study, mean time post radiation therapy between groups was included in the statistical model, but there was no attempt to stratify subjects by duration of time elapsed between when the subjects completed radiation therapy and began the swallowing therapy.

The present study represents a secondary analysis of data from the aforementioned dataset to ascertain whether the time after cancer directed radiation therapy had an effect on swallowing and non-swallowing measures at entry and at completion of the aggressive 12 week swallowing therapy program. The hypothesis to be tested was that earlier intervention after completion of cancer directed therapy would yield significantly more improvement than later intervention. Understanding how dysphagia severity changes over time as well as how a patient responds to intensive rehabilitative swallowing therapy is important for practicing clinicians so as to understand when a patient may find most benefit from dysphagia therapy.

MATERIALS AND METHODS

All protocols received approval by the appropriate human subjects institutional review board, and patients underwent a written informed consent process prior to inclusion in the protocol. Data were collected as a part of the clinical trial of NMES for rehabilitating dysphagia after treatment for head and neck cancer with primary radiation therapy (Langmore et al., 2015), and the detailed rationale for this specific protocol can be found in the original trial publication. After enrollment, the protocol included three training sessions that insured subjects could competently execute the home-based protocol, performed 2 times a day, 6 days a week, for 12 weeks. The subject returned to clinic for a face to face visit every 3 weeks to assess competence and compliance. Modified barium swallow studies [MBS], diet assessments [Performance Status Scale (PSS)] and quality of life assessments [Head Neck Cancer Inventory (HNCI)] were performed at enrollment, mid-way through the treatment (week 7) and at completion of treatment (week 13). PSS scores were calculated for each domain (diet, public, and speech) as a total score (mean of domain scores) with higher scores indicating better function. HNCI scores were similarly calculated by domain (speech, eating, aesthetics, and social disruption) and as a total score (mean domain) with higher scores indicating better function. Measures taken from the MBS evaluation included Penetration/Aspiration (PAS) Scale (Rosenbek, et al., 1996) with lower scores indicating better function, Oropharyngeal Swallow Efficiency Measure (OPSE) (Rademaker et al., 1994) with higher scores indicating better function, and maximum anterior and superior

hyoid movement (Logemann et al. 1989) with higher scores indicating better function. The PAS defines the depth of bolus misdirection into the airway, as well as the subject's ability to clear material from the airway (Rosenbek et al., 1996). The primary outcomes of interest were the PAS, PSS, and HNCI scores.

An overall Penetration/Aspiration score (PAS) was obtained across all swallows in each MBS study. The total, or composite PAS score, was the average of 14 PAS scores (one for each bolus swallowed minus the swallow in the AP projection). Mean subscale PAS scores were also computed for each consistency; thin liquid, thick liquid, pudding, banana, and cracker. OPSE is a measure of the overall timing, efficiency and safety of the oropharyngeal swallow that takes in to account oral and pharyngeal transit times, percentage residue and percentage aspiration (Rademaker, et al., 1994). OPSE scores and hyoid excursion were calculated similarly to PAS scores detailed above. Maximum superior hyoid excursion and maximum anterior hyoid excursion during the swallow were calculated relative to the resting position of the hyoid while the subject was breathing quietly.

The primary analyses showed no significant difference in the 2 treatment groups for most outcomes of interest in the already published RCT, subjects from both groups were combined for this secondary analysis. The hypothesis to be tested in this secondary analysis was that earlier intervention after completion of radiation therapy (RT) was associated with improved response to therapy. There is clinical evidence (Waters, et al, 2004; Patterson, et al., 2014) as well as physiologic evidence from the pathophysiology of radiation induced fibrosis (Yarnold & Brotons, 2010) that intervention prior to one year after completion of cancer directed therapy results in improved response to therapy compared to later time periods. There is no substantial evidence to guide division of subjects into time periods beyond one year. Because there was inadequate data to divide subjects into yearly time periods, the subjects were partitioned into three groups: those who completed RT (1) less than one year, (2) one to two years, or (3) greater than two years prior to enrollment in the study. Given subjects were assessed on a variety of performance measures prior to and immediately following treatment resulting in repeated measurements for subjects, linear mixed effects regression models were applied. Models included group (time since completion of RT therapy), time and group-by-time interaction terms. Significant overall tests for differences among the three groups over time were followed up by pairwise comparisons; the p-values for these post-hoc tests are reported unadjusted. All tests were two-sided and carried out at the 5% level of significance. The data analysis was performed using SAS v9.4 (SAS Institute, Cary, NC).

RESULTS

117 subjects were available for analysis. The minimum time from completion of radiation therapy to beginning the swallowing program was three months and the maximum was 267 months (mean $\pm$ SD, 55.8 $\pm$ 64). Other subject demographics are included in Table 1. Over half (60) of the subjects were greater than 2 years out from completion of radiation therapy, 25 were between 1 and 2 years after completion of radiation therapy, and 32 were less than 1 year. This wide range of time periods reflects not only the long term nature of swallowing dysfunction after treatment but also the challenges of recruiting large numbers of

subjects into trials into smaller time intervals. Over 40 percent of subjects had a primary oropharyngeal site. No significant treatment group differences between time since completion of RT therapy groups were evidenced.

Table 2 provides the adjusted mean and standard error for all variables pre- and post-treatment along with overall *p*-values. Given the analysis was performed with subjects in three groups (less than one year, more than one year but less than two years, and greater than two years), statistical significance in this table simply indicates there was difference somewhere among the three groups.

The pre- treatment (baseline) differences in each variable by group is reported first. The *p*-values associated with pairwise comparisons for variables with pre-treatment differences by time after radiation therapy completion and beginning of swallowing therapy (Table 2 Column 7 labeled 'Pre-Treatment') include total OPSE score ($p<0.01$) revealing better scores for the earlier time periods, total hyoid bone displacement (anterior $p=0.05$ and superior, $p=0.04$) revealing better scores for earlier time periods and PSS scores (diet $p=0.05$ and public $p=0.02$) revealing better scores in later time periods. Further analysis to break down where differences may be present among the three groups was limited to those variables with significant overall effect differences (OPSE, total hyoid bone displacement, and PSS scores) as it is unlikely that any variable would show by group effect with no overall effect.

The result from the detailed pre-treatment analysis is seen in Table 3. Significant differences were identified between subjects in groups less than one year and those greater than two years (i.e., those most recently completing radiation and those farthest out from radiation) for all variables including OPSE, total hyoid bone displacement, and PSS score. Change for some variables was associated with worse function over time (OPSE, hyoid displacement) while others were improved (PSS). No differences were noted within these variables in baseline performance for the time period less than one year and greater than one year but less than two years.

Of those variables showing pre- treatment differences, only the total OPSE score showed significant difference between subjects in groups one to two years and greater than two years after completion of radiation therapy in addition to the aforementioned difference between those less than one year and greater than two years. This indicates that unlike other variables, the OPSE had significant pre-treatment differences (better function) for patients less than two years after completion of radiation therapy compared to those greater than two years after completion of radiation therapy.

The second analysis performed was comparing pre- and post-treatment scores for variables across the trial (Table 2 Column 8). Consistent change in score over the clinical trial (pre- to post- treatment) was not identified in physiologic variables (PAS, OPSE, or hyoid bone displacement) as reflected in non-significant overall effect *p*-values. PAS scores on average were similar across all groups between baseline and end of treatment. OPSE and hyoid bone displacement had a non-significant trend toward worsening across the clinical trial. Statistically significant effects (improvement) were identified in quality of life HNCI

subscale (speech $p<0.01$ and eating $p<0.01$) as well as diet PSS subscales (diet $p<0.01$, public $p<0.01$, speech $p<0.01$, and total $p<0.01$) between pre- and post- treatment. The improvement in HNCI eating subscale scores over time can be seen graphically in Figure 1 while the PSS diet and total score improvement over time can be seen in Figures 2 and 3. These aforementioned variables were then further analyzed in detail by group (Table 4) with PSS and HNCI scores on these subscales showing improvements during the trial for all subjects in the less than one year group. The HNCI eating subscale scores also improved for the greater than one year but less than two years and greater than two years groups indicating all subjects regardless of time between beginning the trial and completion of radiation therapy had improvements on this subscale.

The final comparison to report is whether there is an interaction for each variable across the clinical trial (pre- v post- treatment) by group (less than one year, greater than one but less than two years, and greater than two years after completing radiation treatments) which is illustrated in Table 2 Column 9. Of all the variables, only PSS scores also showed a significant overall effect (diet $p<0.01$, total $p=0.02$). On further investigation (Table 5) to ascertain which group had the greater rate of change in improvement, the PSS diet subscale showed differences between groups less than one year and greater than one year but less than two years and less than one year and greater than two years. PSS total showed differences only between the less than one and greater than two years. Taken together, this indicates patients completing radiation less than one year ago experienced a significantly greater increase in PSS score change (improvement) compared to those completing radiation more than two years ago.

DISCUSSION

Swallowing dysfunction after head and neck cancer directed therapy contributes to reduced patient quality of life, increased morbidity, and increased mortality. This study analyzed subject data from an intensive 12 week home therapy course of swallow exercise (rehabilitation) with and without NMES. The dataset represents the largest cohort of subjects enrolled in a clinical trial testing an intervention for radiation induced swallowing problems. The initial study did not address the questions of optimal time post radiation treatment to intervene with swallowing rehabilitation. In particular, it did not address when intervention may be considered beneficial versus futile. These are questions, however, that must frequently be discussed when counseling HNC patients.

The results of this present study suggest, much like other studies, (Waters, et al, 2004; Patterson, et al., 2014) that earlier intervention has the potential to yield a better response to therapy for diet (PSS, Figures 2 and 3) and quality of life (HNCI, Figure 1) but the effect was not seen for swallow physiology outcomes. This finding is consistent with studies showing exercise can improve quality of life in patients after cancer directed treatment (Kalter et al., 2015) but neither study fully controls for the confounding problem of patients improving organically from the acute toxicities of treatment. Particularly for this study, initiation of the swallowing protocol prior to one year after completion of cancer directed therapy showed improved rate of change of quality of life and PSS diet scores compared to initiation one to two years or greater than two years from completion. The PSS diet subscale

also showed improvement between less than one year and greater than one but less than two year groups. While there were pre-treatment differences in PSS total and diet subscales, subjects less than one year between completion of radiation treatments and initiation of the intensive therapy showed greater improvement than other groups. The diet (PSS) score changes overall would clinically be considered as mild changes where the QOL (HNCI) would be considered more clinically relevant.

The physiologic measures did not show consistent differences in absolute change across all groups or similar rate of change across any time period. This could either be a result of multiple issues. Although the validated measures chosen (hyoid movement and OPSE) are the most commonly applied measures of swallowing function, they may have limitations in capturing with adequate sensitivity the physiology of the swallow. The physiologic measures also may lack consistent function change over time independently or among patients. The range of worsening hyoid bone movement and OPSE was not likely clinically relevant as the change was at most a few millimeters of hyoid movement and a few percentage points of OPSE which is clinically indistinguishable.

There are several limitations of this study including that it represents a secondary analysis of clinical trial data. The pre- treatment heterogeneity of the cohort is perhaps the most significant limitation, however. Substantial differences existed at baseline between the less than one year and greater than two year groups. This selection bias cannot be overcome as it was not controlled for by the original clinical trial. While this heterogeneity may reflect a natural worsening of function over time, these differences are likely at least in part due to the inherent subject selection biases of the clinical trial. A patient who is still suffering from dysphagia more than two years after completion of therapy has likely already failed one if not several rounds of traditional swallow therapy. They may have already distinguished themselves as non-responders' which was reinforced by their lack of response to the swallow therapy given to them in this trial. Contrast that to the earlier time period groups which may not have already had traditional therapy and might have responded well to either this intensive therapy or the traditional therapy. Subjects themselves are likely confounding the results as differences in motivation to stay in a swallowing program may be substantially different based upon how long the patient has been suffering from the disease.

A counter argument to this hypothesis however, is the fact that the patients in the earliest time period (less than 1 year) did not show significant improvement in any of the physiologic measures of swallowing over the trial. Only a prospective study including an observational arm which followed patients over several years, including patients without significant dysphagia at the time of entry, would be able to resolve this issue. We do not know if the diet and QOL effects we found early would be maintained later. There is also the emerging evidence of latent toxicities post RT that can further impair swallow physiology over time (Hutcheson et al., 2012).

In conclusion, the data from this cohort suggest the greatest improvement in quality of life (HNCI) and PSS diet outcomes are achieved is when an intensive program is initiated within one year of therapy completion. This upholds the original hypothesis of the study. Outside of

one year, the response to therapy is not as consistent and physiologic measures tend to worsen as the time post RT increases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Figure 2.

Figure 3.

Table 1

Subject Demographics

Variable	Subscale	N = 117	%
Treatment Group	NMES	84	71.8
	Sham	33	28.2
Gender	Male	101	86.3
	Female	16	13.7
Radiation Therapy Modality	IMRT	63	53.8
	Brachytherapy	1	0.9
	Conventional	43	36.8
	Multiple	10	8.5
Radiation Therapy site	Oral	8	6.8
	Nasopharynx	13	11.1
	Oropharynx	47	40.2
	Hypopharynx	13	11.1
	Larynx	9	7.7
	Other	9	7.7
Interval	Multiple	18	15.4
	<1 Year	32	27.3
	1–2 Years	25	21.4
	>2 Years	60	51.3

Table 2

Linear Mixed Effects Overall Results

Outcome Measure	Group	Pre-Treatment		Post-Treatment		Pre-Treatment p-value	Pre/Post Treatment p-value	Pre/Post * Group p-value
		Mean	Standard Error	Mean	Standard Error			
PAS Total	<1 Year	5.0	0.3	4.7	0.3	0.11	0.11	0.40
	1-2 Years	4.8	0.4	4.4	0.4			
	>2 Years	5.6	0.2	5.6	0.2			
OPSE Total (%)	<1 Year	44.7	3.6	47.2	3.5	<01	0.25	0.94
	1-2 Years	43.9	4.0	44.9	4.1			
	>2 Years	32.6	2.6	34.9	2.7			
Hyoid Superior Total (mm)	<1 Year	19.7	1.5	19.7	1.5	0.05	0.49	0.64
	1-2 Years	17.0	1.6	16.8	1.7			
	>2 Years	15.1	1.1	13.8	1.1			
Hyoid Anterior Total (mm)	<1 Year	8.3	0.8	7.7	0.8	0.04	0.08	0.97
	1-2 Years	6.9	0.9	6.3	0.9			
	>2 Years	5.8	0.6	5.1	0.6			
HNCL Speech	<1 Year	56.1	4.1	63.3	4.2	0.37	<01	0.68
	1-2 Years	59.8	4.8	64.2	4.8			
	>2 Years	52.0	3.0	55.8	3.0			
HNCL Eating	<1 Year	24.5	3.9	31.4	3.9	0.33	<01	0.76
	1-2 Years	27.1	4.5	36.2	4.5			
	>2 Years	31.5	2.9	37.4	2.9			
HNCL Aesthetics	<1 Year	70.0	5.6	72.1	5.5	0.89	0.79	0.61
	1-2 Years	74.1	6.1	71.3	6.2			
	>2 Years	71.5	4.0	74.2	4.0			
HNCL Social	<1 Year	62.6	4.4	65.3	4.4	0.22	0.06	0.38
	1-2 Years	74.4	5.1	75.6	5.1			
	>2 Years	67.4	3.3	74.4	3.2			
PSS Diet	<1 Year	30.3	5.3	47.5	5.3	0.05	<01	<01
	1-2 Years	40.4	6.0	44.7	6.1			
	>2 Years	46.8	3.9	48.8	3.9			

Outcome Measure	Group	Pre-Treatment		Post-Treatment		p-value	Pre/Post Treatment		p-value	Pre/Post * Group
		Mean	Standard Error	Mean	Standard Error		p-value	p-value		
PSS Public	<1 Year	39.1	6.1	52.3	6.1		0.02	< .01		0.21
	1–2 Years	49.0	6.9	58.4	7.0					
	>2 Years	60.8	4.5	63.8	4.5					
PSS Speech	<1 Year	86.7	3.2	92.2	3.2		0.81	< .01		0.82
	1–2 Years	84.0	3.6	87.9	3.7					
	>2 Years	86.7	2.4	90.0	2.4					
PSS Total	<1 Year	52.0	3.8	64.0	3.8		0.03	< .01		0.02
	1–2 Years	57.8	4.3	63.7	4.4					
	>2 Years	64.8	2.8	67.5	2.8					

Pre-Treatment p-value column indicates an overall difference among patient groups at baseline. Pre/post treatment p-value column indicates an overall difference in scores before vs. after swallow therapy across all groups; Pre/post*group p-value column indicates a difference in rate of change in scores among patient groups before and after swallow therapy

Table 3

Pairwise comparisons for variables different at baseline

Outcome Measure			P-value
OPSE Total	<1 Year	1–2 Years	0.88
	<1 Year	>2 Years	<.01
	1–2 Years	>2 Years	0.02
Hyoid Superior Total	<1 Year	1–2 Years	0.22
	<1 Year	>2 Years	0.01
	1–2 Years	>2 Years	0.34
Hyoid Anterior Total	<1 Year	1–2 Years	0.24
	<1 Year	>2 Years	0.01
	1–2 Years	>2 Years	0.27
PSS Diet	<1 Year	1–2 Years	0.21
	<1 Year	>2 Years	0.01
	1–2 Years	>2 Years	0.37
PSS Public	<1 Year	1–2 Years	0.28
	<1 Year	>2 Years	<.01
	1–2 Years	>2 Years	0.15
PSS Total	<1 Year	1–2 Years	0.32
	<1 Year	>2 Years	<.01
	1–2 Years	>2 Years	0.18

Table 4

Within-group estimated change from pre-treatment to post-treatment

Outcome Measure	Group	Estimated Change	Standard Error	P-value
HNCI Speech	<1 Year	7.2	3.2	0.02
	1–2 Years	4.4	3.7	0.24
	>2 Years	3.8	2.3	0.11
HNCI Eating	<1 Year	6.9	3.1	0.03
	1–2 Years	9.1	3.6	0.01
	>2 Years	5.9	2.3	0.01
PSS Diet	<1 Year	17.2	3.7	<.01
	1–2 Years	4.3	4.3	0.32
	>2 Years	2.0	2.7	0.46
PSS Public	<1 Year	13.2	4.8	<.01
	1–2 Years	9.4	5.6	0.10
	>2 Years	2.9	3.5	0.41
PSS Speech	<1 Year	5.5	2.7	0.05
	1–2 Years	3.9	3.2	0.22
	>2 Years	3.3	2.0	0.10
PSS Total	<1 Year	12.0	2.7	<.01
	1–2 Years	5.9	3.1	0.06
	>2 Years	2.8	1.9	0.16

Table 5

Pairwise comparisons for differences in rate of change between groups

Outcome Measure			P-value
PSS Diet	<1 Year	1–2 Years	0.02
	<1 Year	>2 Years	<.01
	1–2 Years	>2 Years	0.65
PSS Total	<1 Year	1–2 Years	0.13
	<1 Year	>2 Years	<.01
	1–2 Years	>2 Years	0.38