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# EATING ABILITY IN HEAD AND NECK CANCER PATIENTS AFTER TREATMENT WITH CHEMORADIATION: A 12-MONTH FOLLOW-UP STUDY ACCOUNTING FOR DROPOUT

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**Abstract:** *Background.* Head and neck cancer patients treated with chemoradiation have difficulty eating a normal diet. This study was designed to characterize eating ability over 12 months after chemoradiation treatment. Analyses take patient dropout into account.

*Methods:* Two hundred fifty-five patients with head and neck cancer treated with chemoradiation were followed for 12 months. Eating ability was analyzed using generalized linear model methods that accounted for non-ignorable dropout.

*Results.* Eating ability was compromised immediately after treatment and improved over 12 months to near pretreatment

levels. Ability to eat at most 50% of the diet orally did not return to baseline levels ( $p < .05$ ). However, the percent of patients eating a normal diet did return to baseline levels. Accounting for dropout modified the results, but the pattern of significance was similar.

*Conclusions.* Treatment of head and neck cancer with chemoradiation has a significant effect on eating ability, which improves after 12 months after treatment. © 2003 Wiley Periodicals, Inc. *Head Neck* 25: 1034–1041, 2003

**Keywords:** chemoradiation; dropout; dysphagia; generalized linear models; head and neck cancer

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**L**ongitudinal studies of functional outcome after treatment for head and neck cancer are necessary to determine the type and level of eating dysfunction to expect as a result of the disease and its

treatment. Chemoradiation in studies with small numbers of patients has been reported to negatively affect the ability to eat orally.<sup>1</sup> Dysfunction also occurs after treatment with surgery or with a combination of surgery and radiation. Pauloski et al<sup>2</sup> analyzed 38 patients with head and neck cancer who were treated primarily with surgery and who had near complete data for several evaluation points over a 12-month follow-up period. Swallowing function did not improve progressively between 1 month and 12 months after treatment. Beeken and Calman<sup>3</sup> reported deficits related to eating ability after a mean of 3.5 years after curative treatment for oral cancer. Moore et al<sup>4</sup> reported satisfactory eating ability in base of tongue cancer patients treated with radiation and neck dissection. However, survivor bias might have resulted in a selected sample in that study.

Patient dropout among head and neck cancer patients over the follow-up period is a common occurrence that threatens the validity of any formal attempt to characterize the time course of an outcome measure. In the absence of a defined study protocol, the rate of regular follow-up in patients with oral cancer is low.<sup>5</sup> In research studies with a specified follow-up protocol, some dropout is expected and not preventable, such as dropout caused by treatment complications, disease recurrence, or death. Other dropout is potentially preventable, such as dropout caused by patient desire to discontinue follow-up for reasons such as inconvenience or disinterest. Statistically, any dropout results in unobserved missing data, which must be accounted for in the statistical analysis. Little and Rubin<sup>6</sup> have classified missing data into three categories. "Missing completely at random" (MCAR) means the reason for missing data (ie, "missingness") is unrelated to either the observed or unobserved data. The missing data are a random sample of all data, and no bias would be incurred if data were analyzed without regard for the fact that some data are missing. "Missing at random" (MAR) means that missingness is dependent on the observed data but unrelated to the unobserved data. The missing data are a partially selected sample of all data, and bias could be incurred if data were analyzed without regard for the fact that some data are missing. Missing data are nonignorable (NIM) or informatively censored if missingness depends on the unobserved data. In this case, the missing data are a selected subset of all data, and

ignoring the fact that some of the data are missing could result in biased conclusions. In follow-up studies after treatment for cancer, it is likely that missing data are nonignorable, because patients who drop out probably are those who would have had poor function had they remained in the study.

Several alternative strategies exist for the analysis of data from follow-up studies with patient dropout. One option is to restrict the analysis to patients who have complete data at all follow-up points. Colangelo et al<sup>7</sup> indicated that swallowing and speech function is better in head and neck cancer patients who complete a 12-month follow-up period after primary surgical treatment for head and neck cancer compared with patients who drop out 1 month, 3 months, or 6 months after treatment. Therefore, restricting the analysis to completers might present a more optimistic picture of the time course of longitudinal outcome than is actually true.

Another option for analysis is to use all available data at all time points. If patients with poorer function drop out, this type of analysis could also present a more optimistic picture of the functional time course, especially for later time points when patients still in the study would have better function. Although generalized linear models<sup>8,9</sup> and generalized estimating equations (GEE) in particular<sup>10</sup> are flexible methods that can analyze all available data, these methods generally require restrictive assumptions about the randomness of the missing data. For example, Liang and Zeger<sup>11</sup> indicate that GEE analysis requires that data are missing completely at random.

A third option is to use statistical methods that attempt to account for dropout. Wu and Bailey<sup>12</sup> use a conditional linear model in which the time course of an outcome is modeled as a function of time on study. Follmann and Wu<sup>13</sup> extend this model to a shared parameter model, in which time to dropout is considered a random variable and is modeled jointly with the outcome variable.

The primary objective of this study was the characterization of the functional ability to eat over a period of 12 months after chemoradiation treatment in patients with head and neck cancer. Because such a longitudinal study is subject to patient dropout, another objective of this study was to use statistical methods that account for dropout, so that the resulting time course of func-

tional data could be presented in as unbiased a manner as possible. In the process of achieving these objectives, data are provided on the extent and nature of patient dropout.

## METHODS

Patients with head and neck cancer whose lesions were to be treated with radiotherapy ± chemotherapy were approached, and informed consent was obtained from those agreeing to be in the study. Patients had no prior treatment for head and neck cancer or any otolaryngologic or neurologic disorder affecting swallow and no preexisting swallowing or speech disorder unrelated to their cancer. Cooperating radiation oncologists and head and neck surgeons worked with speech language pathologists to identify patients suitable for study. Data on the ability to eat were obtained during patient clinic visits at five time points: pretreatment and 1, 3, 6, and 12 months after the completion of the chemoradiation treatment. At each point of contact, patients were asked to specify the approximate percent of nutrition taken orally. They were also asked to indicate which of the following food consistencies they were currently eating in their regular diet: thin liquids, thick liquids, paste/pureed, soft masticated, and crunchy masticated. Patients also indicated whether they were eating a normal diet, in which a normal diet was one in which all food consistencies could be eaten.

Off-study reason was documented. If all evaluations up to and including 12 months were completed, then the reason was given as “protocol complete.” For patients who did not complete the 12-month follow-up, the specific reason for early termination or dropout was documented. Study participants were observed at five visits: pretreatment and 1, 3, 6, and 12 months after treatment. They were classified into five groups according to their last or terminal visit. These groups were (1) baseline visit only; (2) 1-month visit was terminal visit; (3) 3-month visit was terminal visit; (4) 6-month visit was terminal visit; and (5) protocol complete. Although visits might have been missed before their terminal visit, patients were only considered dropouts at baseline, 1 month, 3 months, or 6 months if they did not return for any more visits. Such dropout is called monotone dropout.<sup>14</sup> Time on study was defined as the point midway between the time of the last evaluation and the time of last patient contact.

**Statistical Analysis.** Patient, disease, and treatment characteristics were compared across the groups determined by terminal visit using either one-way analysis of variance (for age and radiation dose) or the  $\chi^2$  test (for percent men, percent oropharyngeal site, or percent stage IV disease). Statistical analysis of outcome focused on two dependent variables, the percent of patients with oral intake of 50% or less and the percent of patients who could not eat a normal diet.

Longitudinal data analysis of the dependent variables was done using a GEE approach<sup>10</sup> using an exchangeable correlation structure for the repeated measures over time. For valid inference, this method requires the most restrictive assumption that the data are missing completely at random. This method does not account for nonignorable missing data.

To test the assumption that the data were missing completely at random, Ridout's test<sup>15</sup> was used. Then, outcomes were analyzed using two methods that allow for nonignorable missing data. The first of these methods is a GEE analysis that includes as conditional covariates time on study and a dichotomous variable indicating whether the patient completed the study. This method closely resembles the conditional linear model (CLM) approach of Wu and Bailey<sup>12</sup> and is described in detail in Follmann and Wu.<sup>13</sup> If the terms for time on study or completion of study are significant in the model, then there is evidence that missing data are nonignorable. The second method entails using a shared parameter model (SPM) as described by Follmann and Wu.<sup>13</sup> This method jointly models the dependent variable using mixed effects binary logistic regression and the time to dropout using Weibull regression. The Weibull hazard rate is modeled as a function of gender, age, race, and the patient-specific random effect. This method accounts for nonignorable missing data by a random effect that indirectly accounts for patient-specific trends that are not directly observable but that might be associated with the underlying dropout process. If the term for the patient-specific random effect is significant in the Weibull model, that is evidence of nonignorable missing data. Although the CLM uses the time to dropout as a fixed covariate, the SPM is a more general model, which assumes time to dropout is a random variable with a likelihood function. For each method (GEE, CLM, SPM), population-averaged estimates of the dependent

variable were obtained for each visit. All three methods include terms for patient age, gender and race, and site of disease, as well as for time of visit.

The use of three methods will allow a comparison of results by using methods that take into account nonignorable missing data (CLM, SPM) and a method that assumes that the data are missing completely at random (GEE).

## RESULTS

A total of 255 patients was observed, with a mean age of 59 years (range, 24–80 years). There were 196 men (77%) and 59 women (23%). There were 192 Caucasian (75%) and 54 African American (21%) patients. The stage distribution was stage II (16, 6%), stage III (48, 19%), or stage IV (187, 73%). Sites of primary tumors were oropharynx (118, 46%), larynx (59, 23%), oral cavity (25, 10%), hypopharynx (22, 9%), nasopharynx (13, 5%), and unknown location (18, 7%). Patients were accessed from eight cooperating medical centers. Two hundred forty-three or 95% of the patients were accessed from four centers. The percentage of patients with gastric tubes in place was 12% at baseline, 48% at 1 month, 36% at 3 months, 24% at 6 months, and 14% at 12 months.

A total of 255 patients was included in the analysis. Although the intent was to follow each patient for five evaluation points from before treatment to 12 months after treatment, not all patients came for all evaluation points. Moreover, some patients missed some evaluation points and returned for subsequent evaluations. The last evaluation that a patient came to was considered to be their terminal evaluation. Table 1 describes the number of patients at each evaluation point. n1 indicates the number of patients who have a terminal evaluation at that point. n2 indicates the number of patients who are still in the study at that point. n3 indicates the number of patients

who came for a clinic visit at that point. n3 is no greater than n2, because patients missed evaluations intermittently before their terminal evaluation. n3 is the number of patients available for analysis at each time point. The retention rates over the posttreatment course of this study were 73% at 1 month, 58% at 3 months, 49% at 6 months, and 35% at 12 months.

Table 2 gives a summary of the off-study reasons. Thirty-five percent of the patients completed the protocol for the 12-month follow-up. Twenty-eight percent of all patients were off-study as a result of treatment complication, disease recurrence, or death. These could be considered nonpreventable reasons for early study termination. Thirty-seven percent were off-study as a result of patient decision to withdraw, loss to follow-up, ending of study funding, or other reasons. These could be considered to be potentially preventable early terminations. Of the 165 patients who terminated the study early, 43% could be considered nonpreventable and 57% potentially preventable.

Table 3 compares baseline patient, disease, and treatment characteristics by length of follow-up. There were no differences in age, gender, and presence of stage IV disease according to length of follow-up. There were more oropharyngeal lesions in patients who remained in the study the longest. Mean radiation dose was lowest in the group observed only at baseline, because seven of these patients did not receive any radiation treatment.

Table 4 gives a longitudinal summary of oral intake over the 12-month follow-up period. Most measures of oral intake (mean, percent of patients with no oral intake, percent of patients with 100% oral intake, or percent of patients with at most 50% oral intake) indicate that oral intake decreased sharply immediately after chemoradiation treatment and improved to near baseline levels after 12 months of follow-up. Depending on the time of evaluation, the percent of patients

**Table 1.** Sample sizes at each evaluation point.

Evaluation point	n1	n2	n3
Pretreatment (tx)	69	255	255
1 month post-tx	38	186	165
3 months post-tx	22	148	122
6 months post-tx	36	126	116
12 months post-tx	90	90	90

*n1 = number of patients for which this is the terminal evaluation; n2 = total number of patients who have not reached terminal evaluation; n3 = number of patients observed at this evaluation and available for statistical analysis.*

**Table 2.** Disposition and off-study reason.

Disposition or off-study reason	Number (%)
Treatment complication	6 (2)
Disease recurrence	43 (17)
Death	22 (9)
Withdraw/lost	63 (25)
Study funding ended	25 (10)
Other	6 (2)
Study complete	90 (35)
Total	255 (100)

**Table 3.** Pretreatment patient, disease, and treatment characteristics by length of follow-up (terminal evaluation point).

Terminal evaluation	<i>n</i>	Mean age	% male	% oropharyngeal	% stage IV	Mean, median (range) RT dose
Pretreatment (tx)	69	57.8	83	39	71	6151, 7000 (1200–7500)*
1 month post-tx	38	59.0	71	37	84	6839, 7000 (3000–7570)†
3 months post-tx	22	61.0	77	45	82	6903, 7000 (5000–7800)
6 months post-tx	36	59.2	78	69	81	6944, 7350 (1250–7809)
12 months post-tx	90	58.4	74	47	66	7027, 7010 (5000–7920)
<i>p</i> value		.46	.68	.03	.13	.0001

\**n* = 58; 7 patients had no radiation and 4 had missing data on dose.

†*n* = 36; 2 patients had missing data on dose.

with either 0% or 100% oral intake ranged from 75% to 98%. Therefore, percent oral intake was dichotomized at 50%, which essentially divides patients into those who cannot eat orally ( $\leq 50\%$ ) and those who can eat all their food orally ( $>50\%$ ). The percent of patients with at most 50% oral intake was 7% before treatment, rose to 39% immediately after treatment, and declined to 11% 12 months after treatment. GEE analysis provided similar estimated percentages over time, with all time points having a significantly greater percentage than baseline. When Ridout's test was applied to oral intake, dropout was significantly related to a lower oral intake at the visit before dropout ( $p = .004$ ), indicating that the data were not missing completely at random. When analyzed by CLM and SPM, the estimated percentages of patients who could take no more than 50% of their food orally were slightly higher than the observed percentages and the GEE percentages. The pattern of statistical significance was the same for CLM and for SPM as it was for GEE. On the basis of the effects for the missing data mechanisms in the models, the evidence that missing data was nonignorable was absent in the CLM model and present in the SPM model.

Patient weight was reduced from baseline to

posttreatment time points. The preceding models were analyzed with and without weight as a covariate. In each model, weight was not a significant factor, indicating that after adjusting for other covariates, weight was not related to oral intake. The results that are reported do not use weight as a covariate.

Table 5 presents a longitudinal summary of the percent of patients who could not eat a normal diet. This percentage begins at 44% at baseline, rises sharply immediately after treatment, returning to baseline levels at 12 months. GEE analysis provided similar estimated percentages over time, with all time points having a significantly greater percentage than baseline except for the 12-month time. When Ridout's test was applied to this percent, dropout was significantly related to the occurrence of a non-normal diet at the visit before dropout ( $p = .03$ ). When analyzed by CLM or SPM, the estimated percentages of patients who could not eat a normal diet were slightly higher than observed percentages, especially for the later follow-up times where there are more missing data. However, the pattern of statistical significance over time was the same for CLM and SPM as it was for GEE. The evidence that missing data were nonignorable was absent

**Table 4.** Statistics on percent oral intake by evaluation and the estimated percent of patients with oral intake  $\leq 50\%$  using generalized estimating equations (GEE), the conditional linear model (CLM), and the shared parameter model (SPM). All available data at each evaluation are used.

Evaluation	<i>n</i>	Mean	Median	% of patients with percent oral intake			% of patients with oral intake $\leq 50\%$		
				0	100	<50	GEE	CLM	SPM
Pretreatment (tx)	255	93	100	5	93	7	7	7	4
1 month post-tx	165	64	100	18	57	39	39	43	40
3 months post-tx	122	76	100	14	67	25	28	33	29
6 months post-tx	116	81	100	9	76	21	22	26	21
12 months post-tx	90	89	100	8	89	11	14	18	14

For GEE, CLM, and SPM,  $p < .001$  for differences across all evaluations. For all three methods,  $p < .0001$  comparing pretreatment with each of 1, 3, and 6 months posttreatment. Comparing pretreatment with 12 months posttreatment,  $p = .007$  for GEE,  $p < .001$  for CLM, and  $p = .001$  for SPM.

**Table 5.** Statistics on percent of patients who could not eat a normal diet, by evaluation, and the estimated percent using generalized estimating equations (GEE), the conditional linear model (CLM), and the shared parameter model (SPM). All available data at each evaluation are used.

Evaluation	<i>n</i>	Observed	GEE	CLM	SPM
Pretreatment (tx)	255	44	44	44	42
1 month post-tx	165	78	78	79	82
3 months post-tx	122	66	69	70	73
6 months post-tx	116	59	62	64	66
12 months post-tx	90	44	50	53	52

For GEE, CLM, and SPM,  $p < .001$  for differences across all evaluations. For all three methods,  $p < .001$  comparing pretreatment with each of 1, 3, and 6 months posttreatment. Comparing pretreatment with 12 months posttreatment,  $p = .24$  for GEE,  $p = .10$  for CLM, and  $p = .09$  for SPM.

in both the CLM and SPM models, although marginally so in the SPM model ( $p = .07$ ).

Table 6 gives the observed percentages of patients who could not eat each of five different food types. Thin liquids were easiest to eat, as indicated by the lowest percentages in this table. Thick liquids, pudding, and soft masticated foods indicated similar levels of dysfunction over time. Crunchy boluses were the most difficult to eat. The last column in Table 6 indicates the percent of patients who could not eat all bolus types. This is the same data, by definition, as the observed column in Table 5. The inability to eat all food types is driven by the inability to eat crunchy foods, because the percentages for these two columns are similar.

## DISCUSSION

This study demonstrated that eating ability is severely compromised in head and neck cancer patients immediately after primary chemoradiation treatment for their disease. Function gradually improves over a 12-month follow-up period. For oral intake, the 12-month levels do not return to pretreatment levels. For eating a normal diet, there is no significant difference between pre-

treatment and 12-month levels. Similar results have been seen in studies of patients with oral or oropharyngeal cancer. Beeken and Calman<sup>3</sup> observed that 29% of patients could eat a normal diet after a mean of 3.5 years of follow-up after treatment for oral cancer. Zuydam et al<sup>16</sup> indicated that most of 13 patients who were treated primarily with surgery (some also had radiation) for oropharyngeal cancer had impaired swallowing at 3 months. Moore et al<sup>4</sup> found that after a median follow-up of about 5 years, 49 patients who were treated with radiation alone for base of tongue cancer had a reasonably normal diet, with larger tumors faring worse. However, this study represented a survivor subsample of about 30% of all patients treated in this manner from 1964 to 1992.

We observed a dropout rate of 64% over the 12-month follow-up period in our study for all patients registered in the study. Of the 165 patients who did not attend the 12-month evaluation, 71 or 43% dropped out for health-related reasons. Close to half the dropout seen in our study is disease or treatment related and could be expected to occur as part of any study. The remainder is potentially preventable, and efforts to retain patients should be targeted at patients who would drop out for reasons of withdrawal or loss to follow-up. Gellrich et al<sup>5</sup> observed a follow-up rate of 42% after 1 year in a sample of 143 patients treated with surgery for oral cancer. The purpose of follow-up was the early detection of recurrent lesions. This compares with a follow-up rate of 35% in our study. Our patients were required to undergo a videofluorographic evaluation (data not reported here) at their clinic visits. Our higher 1-year dropout rates could be a result of more intensive protocol requirements.

The primary dependent variables in this study were the percent of patients who could eat no more than 50% of their diet orally and the percent of patients who could not eat a normal diet. These

**Table 6.** Statistics on ability to eat various bolus consistencies, using all available data at each time point. Numbers reported are the percent of patients who could *not* eat that consistency at that evaluation.

Evaluation	<i>n</i>	Thin	Thick	Paste	Soft	Crunchy	All
Pretreatment (tx)	255	11	19	19	15	43	44
1 month post-tx	165	24	44	44	42	74	78
3 months post-tx	122	17	36	32	29	62	66
6 months post-tx	116	16	27	26	24	53	59
12 months post-tx	90	13	19	17	14	42	44

are distinct variables, representing different dimensions of eating. It is likely that patients could take all their food orally, but they could not eat a normal diet, meaning that there were food consistencies such as crunchy food that they could not eat. In our study, depending on the time of observation, the percent of patients who had greater than 50% oral intake but could not eat a normal diet ranged from 33% to 42%, indicating a high degree of nonoverlap between the two variables.

Reporting crude outcome percentages for dichotomous variables can result in biased results, because a large number of patients drop out over the follow-up period. In this study, the process of dropout itself was investigated. First, retention rates dropped considerably over the follow-up period, indicating that dropout is a serious problem in longitudinal studies of function in cancer patients after treatment. Second, these analyses indicated that dropout could be related more to disease and treatment than to demographic characteristics. Radiation dose and stage of disease differed across the groups classified by time on study, but age and gender did not. Finally, we have confirmed in these analyses that data are not missing completely at random, because the SPM analysis indicates a significant association between the patient-specific random effect, which describes patient function for both the observed and unobserved time points, and the time to dropout.

Although the significance of Ridout's test indicates that the data are not missing completely at random, that test does not indicate that the alternative explanation—missing at random or nonignorable missing—is the plausible explanation. Therefore, it is wise to model the most extreme type of missingness—nonignorable missing data—in the analyses. When nonignorable missing data are modeled in our analyses using either the CLM or the SPM, then the estimated percentages of dysfunction are higher than the observed percentages. This is to be expected, because patients with missing data might have greater dysfunction, so that the more accurate summary of dysfunction in the entire group should have higher rates than observed. However, the rates are not very different than when no adjustment is made, and they are very close to the GEE results, which do not account for nonignorable missing data. It might be expected that a statistical model that accounts for nonignorable missing data and demonstrates statistically that the missing data are nonignorable would result in a time course

that is different from that observed when no adjustment is made. Because the SPM model is a complex model with a large number of individual effects representing patient characteristics, outcome time course, and dropout mechanism, it is likely that individual effects can be statistically significant, but that this significance might have a minimal effect on the predicted values obtained from the overall model.

For both dependent variables, the trend across time was consistent for all three methods and was not sensitive to the various analyses. The trend for a reduction in eating ability immediately after treatment, with the subsequent improvement over the 12-month follow-up period, was still found to be tenable even after correcting for the effects of nonignorable missing data.

In summary, the time course of eating ability over a 12-month posttreatment period has been documented in patients treated with chemoradiation for head and neck cancer. By accounting for patient dropout and by analyzing the data under different assumptions for patient dropout, the time course for eating ability has been well characterized. Implementation of these statistical models is complex, and simpler mathematical models might need to be developed that can adequately account for all factors yet be accessible to a wide range of researchers.

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