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Patterns of Prophylactic Gastrostomy Tube Placement in Head and Neck Cancer Patients: A Consideration of the Significance of Social Support and Practice Variation

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Abstract

Objective—The purpose of this study is to examine factors associated with prophylactic placement of feeding tubes in head and neck cancer patients receiving radiation therapy as part of treatment using multi-level models that account for patient-, physician-, and institution-level sources of variation.

Study Design—A retrospective analysis using binary logistic regression and hierarchical linear models were run to evaluate independent predictors of prophylactic feeding tube placement.

Methods—The Surveillance, Epidemiology, and End Results-Medicare Data (SEER-Medicare) were used. Head and neck cancer patients diagnosed with locoregionally advanced stage disease from 2000-2005 were included in this study (N=8,306).

Results—Across all models, prophylactic gastrostomy tube placement was found to be more likely in patients who had cancer of the larynx or oropharynx compared with those with cancer of the nasopharynx or oral cavity; had regional instead of local cancer; who did not receive surgery as part of treatment, but did receive chemotherapy; and who were divorced, separated, or widowed. Additionally, while practice variation is observed to occur, its' overall contribution in predicting prophylactic gastrostomy tube placement is minimal.

Conclusions—As healthcare enters an era of patient-centered care, further investigation of the potential role of social support (or lack of social support) in influencing treatment decisions of head and neck cancer patients and providers is warranted.

Keywords

Head and Neck Cancer; Gastrostomy Tube; Social Support; Practice Variation

Introduction

Head and neck cancer patients are at high risk for experiencing nutritional problems caused by both their cancer and the toxic side effects of its treatment. Recent advances in treatments have resulted in maintenance of organ anatomy, increased tumor control, and prolongation of life; but not without considerable concomitant severe toxic oral side effects. These side effects, which can include severe mucositis and difficulty swallowing, contribute to poor nutrition which may contribute to poor outcomes or poor quality of life. Percutaneous endoscopic gastrostomy (PEG) tubes are sometimes placed prophylactically prior to treatment in patients without existing nutritional problems in anticipation of problems that may arise, in particular for those undergoing more aggressive therapies. Recent research has found that head and neck cancer patients who received nutritional support prior to treatment experienced significantly less weight loss, but inferior tumor control compared with all other patients.¹ Thus, the authors suggest based upon evidence from the basic sciences literature that while patients may have benefited in that weight was maintained and interruptions in treatment did not occur; theoretically, the addition of nutritional support may have also supported tumor cell growth and contributed to negative outcomes. Despite the importance of this matter in providing care for head and neck cancer patients, data-based evidence regarding a full appraisal of the benefits and risks associated with prophylactic PEG tube placement has not been established.^{2,3} The present study is an examination of factors associated with prophylactic placement of feeding tubes in head and neck cancer patients.

While numerous studies have examined predictors of long-term dependence on feeding tubes following treatment, few have focused on predictors of initial placement, and none have focused on prophylactic PEG tube placement. Several that have examined factors associated with initial feeding tube placement have relied upon retrospective chart reviews within single practice locations. Factors identified as being associated with initial feeding tube placement in these studies have included: tumor site (oropharynx, hypopharynx and oral cavity), tumor stage (higher T classification and N status, as well as overall American Joint Commission on Cancer stage), initial presentation with significant pretreatment weight loss, and poor performance status.^{1, 4, 5, 6} However, one study found that no variables predicted initial placement.⁷ A limitation of these studies is that they rely upon single practice locations. By contrast, a recent report using the Longitudinal Oncology Registry of Head and Neck Carcinoma (LORHAN) database, which is a cancer registry for patients receiving radiation therapy both in academic and community settings, Murphy and her colleagues found that feeding tube use was higher in academic centers (59%) in contrast with community settings (48%).⁸

None of these studies have evaluated the role that social support might play in additionally predicting placement of a feeding tube; and, with the exception of the LORHAN study, none have evaluated the role of either physician or institutional level characteristics that may also predict placement of a feeding tube. With respect to social support, there is a growing body of literature demonstrating that social support (particularly, spousal caregivers) may be associated with better nutritional support and improved cancer control outcomes for head and neck cancer patients.^{9, 10, 11} Further, numerous reports in the literature suggest that physicians rely upon individual judgment and prevailing institutional custom to make clinical decisions regarding appropriate placement of feeding tubes in this vulnerable population.^{4, 5, 7, 12, 13} As Wennberg has observed in regard to many treatment decisions, uncertainty is one of the principal drivers of practice variation.¹⁴ Thus, the purpose of this study is to examine various factors associated with prophylactic placement of feeding tubes in head and neck cancer patients using multi-level models of patient-, physician-, and institution-level sources of variation using the SEER-Medicare Data.

Materials and Methods

Patients and Databases

SEER-Medicare Data from the 2009 merge, in which cancer cases diagnosed from 1973-2005 and Medicare claims through 2006, were used in this study.¹⁵ We obtained only data for head and neck cancer cases diagnosed from 2000-2005 (N = 31,627). The SEER 17 registry captured in this merge was comprised of 26.2% of the United States population. The SEER Data are highly valid and the program's standard for completeness is 98%. Ninety-three percent of persons aged 65 and older in the SEER files were matched to the Medicare enrollment file.

Consistent with other studies using the linked SEER-Medicare Data, persons were excluded if they were either not covered by Medicare Parts A and B (n = 9,817) or enrolled in managed care (n = 5,352). We extended these exclusion criteria to the six month period prior to month of diagnosis in order to identify patients who prior to treatment already had either existing nutritional deficits or a gastrostomy (PEG) tube already in place. We additionally excluded patients from our analyses who were not diagnosed with locally or regionally advanced stage disease, who were diagnosed with lip cancer, or who did not receive radiation therapy because they are much less likely to have feeding tubes placed prophylactically. Finally, we excluded patients who had a tube placed prior to treatment who also had corresponding Medicare claims for nutritional support before the onset of radiation therapy. Such patients could not have feeding tubes placed prophylactically because they were using them therapeutically before experiencing any treatment-related nutritional deficits. This resulted in 8,306 patients included in the final sample.

Variables

The SEER registry and Medicare National Claims History (NCH) and outpatient files for multiple years were used to identify and classify study variables.

Placement of gastrostomy tubes—Placement of gastrostomy tubes were identified using appropriate Current Procedural Terminology (CPT) and International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM) codes described previously.^{3,16, 17, 18}

Possible use of gastrostomy tubes—Because actual use of feeding tube is not captured in administrative claims files, we identified one indicator of possible use by examining the Medicare Durable Medical Equipment file for claims indicating receipt of

nutritional support. Because Medicare only provides reimbursement for nutritional products and supplies associated with enteral feeding tubes only, use of supplements consumed orally is not captured in claims files. A previous paper has described in depth the rationale and appropriateness of our methods for determining placement and use of gastrostomy tubes.³

Cancer site and SEER Historic Stage—We used the ICD-O-3 codes for head and neck cancer to categorize patients into meaningful groupings based upon anatomical location, clinical presentation, and standard treatment described previously.³

Treatment characteristics—We used Medicare Claims files to identify receipt of surgery, chemotherapy, and radiation therapy for cancer treatment. These codes are numerous and are available upon request from the first author.

Sociodemographic characteristics—Age, gender, race, and marital status were identified from the SEER data files.

Statistical Analyses

We first used descriptive statistics to characterize differences observed between patient groups based upon timing of feeding tube placement relative to beginning of radiation treatment. Three patient groups were identified for descriptive purposes: prophylactic (gastrostomy tube placed before treatment), reactive (gastrostomy tube placed after treatment), and none (no claims evidence of gastrostomy tube placement). Descriptive group differences were examined using the chi-square statistic for categorical variables and oneway analyses of variance for continuous variables.

Next, we performed a multivariable binary logistic regression analysis to evaluate patient-level variables associated with prophylactic gastrostomy tube placement. Patients were categorized into two groups, with the “reactive” and “none” groups combined to form a single referent condition for the “prophylactic group”. Arguably, we could have analyzed the predictors of prophylactic tube placement separately comparing those who had tubes placed reactively and those who never received a feeding tube; however, this analysis focused on the clinical decision of whether a feeding tube ought to be placed prior to the beginning of radiation treatment for prophylactic purposes. Thus, it would be inappropriate to include information on the subsequent need for tube placement that was not available to clinicians (or patients) at the time the decision was made. Because it is possible that patients receiving surgical treatment for HNC differ from those who do not receive surgery, we conducted additional analyses including only non-surgical patients.

Finally, in order to take into account the possible clustering of cases and to examine higher-order predictors, we conducted two multilevel or hierarchical logistic regression models, one to model the hospital- or institution-level factors and a second to examine physician-level factors. Our institution definition refers specifically to radiation therapy delivered in facilities affiliated with a hospital and billing under the “Outpatient Hospital” standard analytic files. This means that we are unable to include facility characteristics for care provided in freestanding facilities. We included ownership status, bed size, urban vs. rural, and medical school affiliation of the institution in our institution-level analysis, and we included physician age and years since completion of specialty training in the physician-level analysis. In order to test the clustering of patients in higher-order units, we had to be able to observe multiple cases within both institutions and physicians. Consequently, our institution-level hierarchical analysis was limited to institutions with at least 10 patients in our sample, and our physician-level analysis was limited to radiation oncologists with at least 5 patients in our sample. This resulted in smaller sample sizes of 5,148 patients in 202

institutions for the first analysis, and 5,514 patients treated by 473 physicians in the second model.

Results

Table 1 displays the descriptive characteristics of the sample. Because of the large sample size, statistically significant differences were observed between all groups for all variables. Table 2 displays the percentage of patients who had prophylactic gastrostomy tubes placed according to institution-level characteristics. None of these institution-level associations with prophylactic placement were statistically significant when examined with simple, unadjusted chi-square tests. In addition, the bed size of the institutions ranged from 32 to 1175 (Mean = 321.9, SD = 163.5). For the physician-level analysis, 473 physicians were included with mean age of 47.8 years (SD = 9.1 years) and a mean experience level of 15.0 years (SD = 9.2 years).

The results of our standard (non-hierarchical) logistic regression analysis using the full sample are summarized in Table 3. Prophylactic gastrostomy tube placement was found to be more likely in patients who were minorities; not married; had regional instead of local cancer; and who did not receive surgery as part of treatment. Using cancer of the larynx as the referent point, prophylactic placement was also more likely in patients who had cancer of the hypopharynx, but less likely in patients who had cancers of the nasopharynx and oral cavity. The sub-analysis performed on non-surgical patients was similar to the full sample.

Unconditional multilevel models without any predictor variables revealed that patient clustering of prophylactic placement within higher-order units was statistically significant but minimal at both the institution and physician levels. Approximately 1.8% and 1.5% of total variance in prophylactic placement was observed to be clustered in these higher-order units, respectively. Among physicians included in the analysis, the median proportion of patients receiving prophylactic tube placement was 10% (Interquartile range: 7.7% – 16.7%, Minimum, 2.1% and Maximum, 42.8%). Among hospitals, the median proportion of patients receiving prophylactic tube placement was 7.0% (Interquartile range: 4.4% - 10.3%, Minimum, 1.6% and Maximum 30.8%).

The results of the hierarchical models for both the institution- and physician-level models presented in Table 4 were similar to that observed for the overall logistic regression model with a few differences. In the physician-level model, prophylactic gastrostomy tube placement was no longer more likely in those who were African American or in those who were single, but was still more likely in those who were separated, divorced, or widowed compared to those who were married.

Discussion

Across all models, prophylactic gastrostomy tube placement was found to be more likely in patients who had cancer of the larynx or oropharynx compared with those with cancer of the nasopharynx or oral cavity; had regional instead of local cancer; who did not receive surgery as part of treatment; and who were divorced, separated, or widowed. Additionally, while practice variation is observed to occur, its' overall contribution in predicting prophylactic gastrostomy tube placement is minimal.

That patients who had cancers of the larynx, hypopharynx or oropharynx and those who had more advanced stage disease were more likely to have prophylactic gastrostomy tubes placed is not unexpected and is consistent with previous reports in the literature. These primary sites encompass anatomic structures critical for effective and safe swallowing. Primary disease in the oropharynx and larynx impacts the swallowing mechanism directly,

often causing more severe dysphagia at presentation. Additionally, radiation treatment targeting the pharyngeal musculature is expected to cause more treatment-related dysphagia than fields targeting the oral cavity or nasopharynx. Additionally, frequently the radiation oncologist can spare the larynx from receiving treatment for tumors occurring in the primary sites of the oral cavity and nasopharynx. Finally, patients with regional disease compared to those with localized cancer are more likely to require more comprehensive radiation therapy that includes all swallowing apparatus, including the larynx and constrictors.

Treatment-related factors also predicted prophylactic placement. Across all models, patients who received surgery as part of treatment were less likely to have a gastrostomy tube placed prophylactically. This may be related to the lower doses of radiation used for post-operative therapy and the decreased likelihood of use of chemotherapy with surgery. This is borne out in the hierarchical models wherein in the physician-level model, only patients receiving chemotherapy as part of treatment were more likely to have a prophylactic gastrostomy tube placed. Because it may be advantageous to place a PEG tube before treatment when the procedure and sedation is safer to perform before onset of severe mucositis, especially for patients undergoing combined chemoradiation therapy, this finding makes sense.¹⁹ Additionally, it is the case that for patients receiving chemotherapy, we would expect the radiation reaction to be more intense. We speculate that two other factors may be associated with the decreased likelihood of a gastrostomy tube being placed prophylactically for those who receive surgery as part of therapy. First, it may be more convenient to place a feeding tube at the time of surgery, rather than schedule a separate earlier procedure simply for insertion. Second, it is possible for surgeons to observe that some of cancerous lesions may be small or situated in a location that does not necessarily require a feeding tube. For these reasons, we additionally conducted our analyses separately on patients who did not receive surgery as part of treatment. Unexpectedly, the results stayed almost exactly the same as for the full sample except for wider confidence intervals attributable to smaller sample sizes which rendered some results no longer significant. However, the direction and magnitude of the relationships remained the same. This is consistent with the interpretation that the initiation of chemoradiation therapy is driving the decision to place a feeding tube.

Patients who were divorced, separated, or widowed were more likely to receive prophylactic gastrostomy tubes placed compared with patients who were married. To our knowledge, no study has investigated the important role that social support in the form of partner status may play in the initial decision to place a feeding tube. Previous work has found that not having a partner is associated with long term dependence on percutaneous gastrostomy tubes following treatment.²⁰ In the absence of spousal caregivers who may provide different forms of social support related to eating behavior, prophylactic gastrostomy tube placement may provide needed nutritional support for a vulnerable subset of patients. Such support may include encouragement to eat as well as to seek treatments that may facilitate oral intake. Both patients and physicians may make decisions to place a feeding tube based upon expectations for such behavior. Unfortunately, one cannot ascertain the intent of either patients or clinicians under these circumstances through use of the SEER Data. Future work is warranted to investigate precisely what the role of social support may be, as well as what the intentions of patients and clinicians are. It is also the case that people who are more likely to receive a prophylactic tube have increased long-term requirements for a feeding tube for reasons that we cannot observe in our data. It is also the case that patients without partners are more likely to present with advanced stage disease. In a post-hoc Chi-square analysis, we explored this possibility. It was the case that persons with partners were less likely to present with advanced stage disease compared with those with partners (54% versus 62%, respectively, $p < .001$). This certainly may help to explain some of the observed differences between those with and without partners, but not all.

Unexpectedly, practice variation, while statistically significant, did not explain much of the variation in prophylactic gastrostomy tube placement in our models. It may be that in general, health care providers look for similar signs (such as nutritional risk and social support) when determining who would be a reasonable candidate for prophylactic gastrostomy tube placement. A noteworthy limitation of this study is the necessity to exclude low volume providers from our analysis of the effects of hospital and physician characteristics. In order for an assessment to be made of these effects, providers had to have some minimum number of patients for variances to be meaningful. This requirement, however, means that large numbers of patients treated by low volume providers are excluded from the analysis, affecting both the power and generalizability of our results. Thus, it may be that our analyses underestimate the extent of practice variation. Of note, we did relax our assumptions regarding the requirement that institutions treat at least ten patients to the requirement that institutions treat at least five patients and the findings were essentially the same. Additionally, a limitation of our institutional level analysis is that we are precluded from including facilities that are not hospital affiliated.

Another limitation of this study is the lack of reliable data on tumor size. Even in limiting the analysis to local and regional disease stages, 50% of the tumor size variables were coded as missing. We did, however, run our analyses excluding those cases with missing values for tumor size and obtained very similar results on all of the other explanatory variables. We do not report those results as we believe the data are not missing at random and thus would produce biased estimates of tumor size effects.

African Americans were more likely to have gastrostomy tubes placed only in our standard logistic regression model. Differences in models could be due to many factors, including smaller sample sizes of the hierarchical models, the nature of the cases deleted, higher-order clustering that is ignored in the ordinary least squares model, and correlations that may exist across patient-level and institution-level analyses. We conducted some post-hoc analyses by race to explore this matter further. It appears as though the main difference is the nature of the cases deleted because African Americans are not more likely to have prophylactic gastrostomy tubes placed in the standard model with the 5,514 for the physician-level analysis. Additionally, similar to partner status, whites were less likely to present with regional stage disease (57%) compared with blacks and others (64%, $p < .01$).

Conclusion

Most studies examining gastrostomy tube placement and use have focused on tumor and treatment related factors. Our study contributes to the literature by simultaneously exploring multiple patient, physician, and institution level characteristics that might influence prophylactic gastrostomy tube placement. Consistent with a growing body of work emanating from our own and other institutions, the potential role of social support in influencing treatment decisions of patients and providers is emphasized. Our study is limited in that we had one single indicator of social support—namely, marital status. Future work with clinical databases may more precisely define the mechanisms by which social support, as well as living arrangements, operates to influence treatment and supportive care decisions.

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Table 1

Gastrostomy Tube Placement

Patient-level Characteristics	None (N=4,882)		Prophylactic (N=428)		Reactive (N=2,996)		P-value
	N	%	N	%	N	%	
Socio-demographic							
Gender							0.0067
Male	3461	70.9	300	70.1	2023	67.5	
Female	1421	29.1	128	29.9	973	32.5	
Age (years)	72.5		70.6		71.5		<0.0001
Race							
Black	400	8.2	69	16.1	342	11.4	<0.0001
White	4180	85.6	318	74.3	2439	81.4	
Other	302	6.2	41	9.6	215	7.2	
Marital Status							
Single	531	10.9	68	15.9	372	12.4	<0.0001
Married	2565	52.5	163	38.1	1533	51.2	
Separated	41	0.8	11	2.6	31	1.0	
Divorced	436	8.9	59	13.8	326	10.9	
Widowed	1028	21.1	104	24.3	608	20.3	
Unknown	281	5.8	23	5.4	126	4.2	
Disease-specific							
Tumor Site							
Hypopharynx	254	5.2	54	14.6	274	9.1	<0.0001
Larynx	2505	51.3	142	38.3	866	28.9	
Nasopharynx	184	3.8	*	*	134	4.5	
Oral Cavity	912	18.7	*	*	652	21.8	
Oropharynx	1027	21.0	175	47.2	1070	35.7	<0.0001
Stage at Diagnosis							
Localized	2600	53.3	81	18.9	805	26.9	
Regional	2282	46.7	347	81.1	2191	73.1	
Treatment-related							

Patient-level Characteristics	None (N=4,882)		Prophylactic (N=428)		Reactive (N=2,996)		P-value
	N	%	N	%	N	%	
Surgery (yes)	3168	64.9	137	32.0	1901	63.5	<0.0001
Chemotherapy (yes)	1207	24.7	184	43.0	1413	47.2	<0.0001
Charlson Comorbidity Score							0.0337
0	4263	87.3	355	82.9	2561	85.5	
1-2	311	6.4	37	8.6	227	7.6	
3+	308	6.3	36	8.4	208	6.9	

* Per NCI policy, in order to eliminate the possibility that individuals with cancer may be identified, investigators may not publish or present findings in which the number of cases in a cell is less than eleven. In instances where cell findings are suppressed, the same patterns observed for other cancer sites and stages are similarly observed.

Table 2

Institutional Characteristics

	N	Number of Patients	% of Patients with Prophylactic PEG Tube
Urban vs. Rural Location			
Urban	118	2990	5.1
Rural	10	251	6.4
Unspecified	74	1907	4.9
Teaching Status			
Some	120	3204	5.0
None	77	1843	5.4
Unknown	5	101	3.0
Ownership			
Voluntary non-profit-church	40	1066	4.2
Voluntary non-profit-private	66	1715	5.4
Voluntary non-profit-other	58	1486	4.2
Proprietary	6	129	7.0
Government-federal	1	23	8.7
Government-state	11	353	6.9
Government-local	4	92	4.4
Government-other	16	284	8.5

Table 3

Logistic Regression Results

Dependent Variable: Prophylactic Tube Placement		All Radiation Tx Cases N = 8,306		Excluding Surgical Cases N = 3,100	
	OR	95% CI	OR	95% CI	
Socio-demographic factors					
Age	0.99	0.98 - 1.00	*	1.00	0.98 - 1.01
Gender					
Male	(Referent)				
Female	0.93	0.73 - 1.18		0.89	0.67 - 1.19
Race					
White	(Referent)				
Black	1.40	1.05 - 1.87	**	1.34	0.96 - 1.87
Other	1.84	1.29 - 2.63	***	1.28	0.79 - 2.07
Marital Status					
Married	(Referent)				
Single	1.51	1.11 - 2.06	***	1.69	1.17 - 2.44
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Disease-specific					
Tumor Site					
Larynx	(Referent)				
Hypopharynx	1.39	0.98 - 1.96	*	1.42	0.96 - 2.09
Nasopharynx	0.45	0.23 - 0.88	**	0.47	0.20 - 1.13
Oral Cavity	0.67	0.47 - 0.95	**	0.55	0.33 - 0.91
Oropharynx	1.19	0.93 - 1.52		1.06	0.80 - 1.43
Stage					
Localized	(Referent)				
Regional	2.55	1.96 - 3.32	***	2.63	1.89 - 3.67
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Treatment-related					
Separated	3.55	1.78 - 7.08	***	2.91	1.14 - 7.44
Divorced	1.55	1.12 - 2.13	***	1.60	1.10 - 2.34
Widowed	1.68	1.27 - 2.24	***	1.55	1.10 - 2.20
Unknown	1.47	0.92 - 2.33		1.58	0.92 - 2.69

<u>Dependent Variable: Prophylactic Tube Placement</u>		All Radiation Tx Cases N = 8,306		Excluding Surgical Cases N = 3,100	
		OR	95% CI	OR	95% CI
Surgery		0.33	0.27 - 0.41	***	NA
Chemotherapy		1.22	0.99 - 1.51	*	0.87 - 1.44
Comorbidity	0	(Referent)			
	1-2	1.33	0.92 - 1.90		0.68 - 1.75
	3+	1.21	0.84 - 1.74		0.70 - 1.67

* p < 0.10

** p < 0.05

*** p < 0.01

Table 4

Hierarchical Modeling Results

Dependent Variable: Prophylactic Tube Placement		Hospital Hierarchical Model (N = 5148)		Physician Hierarchical Model (N = 5514)	
	OR	95% CI	OR	95% CI	
Socio-demographic factors					
Age	1.00	0.98-1.01	0.99	0.98-1.01	
Gender	(Referent)		(Referent)		
Male	0.81	0.59-1.11	0.95	0.71-1.26	
Female	(Referent)		(Referent)		
Race	1.57	1.06-2.33	**	0.94-1.91	
White	1.90	1.19-3.05	***	1.17-2.90	***
Black	(Referent)		(Referent)		
Other	1.73	1.16-2.60	***	0.90-1.93	
Marital Status	5.90	2.67-13.01	***	2.02-10.16	***
Married	2.22	1.50-3.28	***	0.96-2.11	*
Single	1.70	1.16-2.48	***	1.13-2.22	***
Separated	1.71	0.91-3.24	*	1.03-3.11	**
Divorced	(Referent)		(Referent)		
Widowed					
Unknown					
Disease-specific					
Tumor Site	(Referent)		(Referent)		
Larynx	1.40	0.90-2.18	1.40	0.93-2.12	
Hypopharynx	0.39	0.16-0.93	**	0.19-0.96	**
Nasopharynx	0.57	0.35-0.91	**	0.40-0.96	**
Oral Cavity	1.16	0.84-1.59	1.15	0.86-1.55	
Oropharynx	(Referent)		(Referent)		
Stage	3.02	2.10-4.33	***	2.09-4.05	***
Localized					
Regional	0.38	0.29-0.51	***	0.25-0.41	***
Treatment-related					
Surgery					

<u>Dependent Variable: Prophylactic Tube Placement</u>		Hospital Hierarchical Model (N = 5148)		Physician Hierarchical Model (N = 5514)	
		OR	95% CI	OR	95% CI
Chemotherapy		1.26	0.96-1.66	1.30	1.01-1.68
Comorbidity	0	(Referent)		(Referent)	
	1 to 2	1.02	0.62-1.70	1.25	0.81-1.94
	3+	1.15	0.72-1.85	1.13	0.73-1.75

* p < 0.10
 ** p < 0.05
 *** p < 0.01