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Impact of neck dissection on long-term feeding tube dependence in head and neck cancer patients treated with primary radiation or chemoradiation

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Abstract

Background—The impact of post-treatment neck dissection on prolonged feeding tube dependence in head and neck squamous cell cancer (HNSCC) patients treated with primary radiation or chemoradiation remains unknown.

Methods—Retrospective cohort study using propensity score adjustment to investigate the effect of neck dissection on prolonged feeding tube dependence.

Results—A review of 67 patients with node positive HNSCC (T1-4N1-3), treated with primary radiation or chemoradiation, with no evidence of tumor recurrence and follow-up of at least 24 months was performed. Following adjustment for covariates, the relative risk of feeding tube dependence at 18 months was significantly increased in patients treated with post-treatment neck dissection (RR 4.74, 95% CI 2.07-10.89). At 24 months, the relative risk of feeding tube dependence in the patients having undergone neck dissection increased further (RR 7.66, 95% CI 2.07-10.89). Of patients with feeding tubes two years after completing treatment, 75% remained feeding tube dependent.

Conclusion—Neck dissection may contribute to chronic oropharyngeal dysphagia in HNSCC patients treated with primary radiation or chemoradiation.

Introduction

Radiation therapy for the treatment of head and neck cancer results in mucositis, odynophagia and dysphagia, and often requires the use of a feeding tube especially in the era of concurrent chemotherapy and radiation. Some patients develop persistent swallowing impairment, becoming dependent on a feeding tube for long-term nutritional support. The presence of a feeding tube has a powerful adverse effect on quality of life in otherwise

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successfully treated patients(1, 2). Risk factors for chronic dysphagia are complex and poorly understood. A number of variables have been identified as increasing the risk of swallowing dysfunction in patients treated with radiation therapy(3). Although post-radiotherapy neck dissection has been associated with increased morbidity in patients with antecedent chemoradiation, neck dissection has only recently been linked to an increased risk of chronic dysphagia(4-6). The goal of this study was to evaluate the impact of neck dissection on chronic dysphagia and feeding tube dependence in patients treated with radiation therapy with or without chemotherapy for head and neck cancer.

Patients and Methods

Patients

Between January 1993 and December 2004, 180 patients with squamous cell carcinoma of the oropharynx, larynx and hypopharynx treated definitively with external beam radiation were identified in a database from the Department of Radiation Oncology at our institution. Of 180 patients, 67 were selected for inclusion in the study, based on criteria listed in Table 1. Patients with tumor recurrence, history of esophageal cancer, preexisting feeding tube dependence and neurological problems (history of stroke or neurodegenerative disease) were excluded to minimize competing factors predisposing to feeding tube dependence. As a relatively small number of patients were treated using intensity-modulated radiation therapy (IMRT) during this period, these patients were also excluded.

Thirty three patients who underwent a neck dissection after radiation or chemoradiation represented the experimental arm while 34 patients who did not undergo neck dissection represented the control group. Regardless of treatment group, unless treated with altered fractionation, the primary site received a dose of 7000cGy. Both 2 and 3 dimensional treatment was employed. A 3 field approach was employed in nearly all patients, using a standard shrinking field technique after 50 or 60 Gy to the final dose. Two patients in the neck dissection group underwent concurrent chemoradiation with concomitant boost, while 4 patients in the control group received this regimen. Cisplatin was the radiosensitizing chemotherapeutic agent most commonly used. Carboplatin was selected in patients with contraindications to cisplatin use. Twenty four patients (71%) in the control group, and 23 (70%) in the neck dissection group received concurrent chemoradiation. Cisplatin and 5-fluorouracil were given in patients who received induction chemotherapy (2 patients in each group).

Only patients who underwent a neck dissection as part of initial multimodality treatment for head and neck cancer were included. Although a post-treatment neck dissection was generally recommended for patients with clinical N2-3 disease at our institution, patients with a complete clinical response, and the elderly and infirm were less likely to undergo neck dissection. Neck dissection was also withheld if patients refused to consent to the procedure. Neck dissection was recommended for patients classified as N1 with incomplete clinical response to treatment, and for patients who had pretreatment open neck biopsies. For the purposes of this study, the end of radiation was considered the completion of treatment.

Patients underwent placement of a feeding tube during the course of treatment as clinically indicated. Pretreatment dysphagia and weight loss, particularly in the elderly usually prompted prophylactic feeding tube placement before treatment. The decision to remove a feeding tube was most commonly made by a single surgeon (JAR), who also placed most of the feeding tubes. Feeding tubes were removed if the patients could maintain their weight for at least six weeks without using the feeding tube. Tube removal was usually undertaken during a scheduled office visit, so freedom from tube support for more than six weeks prior to removal was common.

Statistical methods

The presence of a feeding tube was evaluated at 12, 18 and 24 months following the completion of treatment in patients who underwent post-radiotherapy neck dissection and those who did not. Prolonged feeding tube dependence was defined as the presence of a feeding tube 12 months after the completion of treatment, a point in time at which residual treatment-related mucositis is distinctly uncommon (7).

In order to adjust for baseline differences between those patients who did and did not have neck dissections, we used propensity score adjustment through propensity score based weighting with doubly robust estimation (8). The propensity scores, which are the probabilities of having a neck dissection given selected key covariates, were estimated by a multiple logistic regression. The adequacy of the propensity score model was checked by examining the adjusted differences in potential confounder variables between the neck dissection and no neck dissection groups. The lack of significant differences in propensity-score adjusted averages of the confounder variables suggested that they could not be confounders after adjustment. We used t-tests and Fisher's exact tests to assess unadjusted differences. We used Wald tests with robust standard errors(9) to assess adjusted differences. The criterion for statistical significance was set as $p < 0.05$ using two-sided hypothesis tests. As a sensitivity analysis, we confirmed our findings using multiple logistic regression models of feeding tube use with neck dissection and the potential confounders entered as covariates.

Rationale for selection of covariates

Covariates were selected based on potential effects on feeding tube dependence (Table 2). Age, sex, T and N-stage, tumor site, preexisting dysphagia with weight loss (>5 lbs), non-surgical treatment approach (radiation alone, concurrent chemoradiation, induction chemotherapy followed by radiation) and presence of stricture were included. As the presence of a radiation-induced hypopharyngeal/ upper esophageal stricture, defined as a radiographically confirmed narrowing in this area, would be expected to have an impact on feeding tube dependence, the study was initially executed by balancing the presence of this covariate between neck dissection patients and no-neck dissection groups. In a subsequent analysis, patients with strictures were excluded altogether to confirm the reliability of the initial results. Patient groups were also matched for pretreatment weight loss, primary tumor site and the extent of pretreatment nodal disease. The breakdown of primary tumor site into tonsil, base of tongue and larynx/hypopharynx was based on the fact that within these categories, the primary sites receive similar radiation fields and doses. Groups were also matched with respect to nodal stage (N1-2a vs N2b-3), and length of the high-dose radiation field (i.e. cranial to caudal length in the final lateral field arrangement) used during radiotherapy treatment. Radiation field measurements were measured at the central axis, which was typically placed in the pharynx in midline. Increasing field length has been found associated with an increased risk of acute grade 4 swallowing toxicity from radiation(10, 11). The craniocaudal length of the treatment fields used to treat the upper neck and primary site has been used as a surrogate for volume of irradiated pharynx and neck(11). After adjustment by propensity score-based weighting, there were no clinically relevant or statistically significant differences between the neck dissection and no neck dissection group (Table 1).

Results

Patients and treatment

Sixty-seven patients treated at our institution between 1993 through 2004, classified T1-4N1-3, treated with definitive radiation with or without chemotherapy, without

locoregional or distant recurrence for at least 24 months, and without preexisting unrelated feeding tube dependence were included in this analysis. The median and mean follow-up for these patients was 53 and 58 months, respectively (23-163 months). Neck dissections were performed a minimum of 3 and maximum of 16 weeks after the completion of radiation (median 6.5 weeks). All patients underwent comprehensive neck dissections. Four patients underwent bilateral neck dissection.

Some baseline differences between patients who had neck dissections and those who were observed without neck dissection were identified. Patients who underwent neck dissection were younger (55.6 years) compared with those who did not undergo neck dissection (61.6 years, $p=0.011$), and were more likely to have a radiographically documented upper cervical esophageal or hypopharyngeal stricture ($p=0.054$). In contrast, patients without neck dissection were more likely to have tonsil primaries ($p=0.047$) (Table 2).

Seven patients, five of whom had a neck dissection, developed hypopharyngeal and/or upper cervical esophageal stricture confirmed by barium swallow. All patients with strictures underwent dilation if possible. Three of 7 patients with evidence of stricture had feeding tubes at 12-24 months after the completion of their treatment (one patient without neck dissection and two patients with neck dissection). However, most patients with long-term feeding tubes in place had no evidence of stricture: twenty-four months after completion of radiation, 11 of 14 patients with feeding tubes had no evidence of a stricture.

Three patients in the neck dissection group and three in the control group ultimately developed recurrence of disease. There was no significant difference in the length of the high-dose radiation field used in patients who underwent neck dissection, and those who did not. The length of the radiation field correlated most closely with tumor site and T-classification. The field length used to treat tonsil cancers was significantly shorter than those used to treat base of tongue, laryngeal or hypopharyngeal cancers (9.1 cm for tonsil cancer patients versus 11.4 cm for others, $p=0.003$ by t-test). Increasing T-stage was also associated with increased field length (9.7 cm for T1 or T2 versus 11.7 cm for T3 or T4, $p=0.02$ by t-test).

Effect of neck dissection on feeding tube dependence

In order to elucidate the effect of neck dissection on feeding tube dependence, patients who underwent neck dissection were compared to a control group with respect to ongoing feeding tube dependence. As patients who undergo a neck dissection potentially represent a clinically distinct population, a propensity score adjustment was used to normalize differences between groups and adjust for confounders. In the unadjusted cohort, patients who underwent a neck dissection were younger and more likely to have an upper cervical esophageal/ hypopharyngeal stricture, while no-neck dissection patients were more likely to have tonsil primary cancers. After propensity score adjustments, the magnitude of the differences was reduced to the point at which the adjusted groups were on average very similar. In the adjusted sample, no differences in age ($p=.99$), presence of stricture ($p=0.47$) or other variables ($p>0.82$) were detectable (Table 2).

After adjusting for baseline characteristics, the 12-month frequency of feeding tube dependence was similar between patients who underwent neck dissection, and those who did not (29% vs 24%, RR 1.19, 95% CI 0.55-2.59, $p=0.658$). Beyond 12 months, however, the risk of feeding tube dependence increased in the neck dissection group, while decreasing in the no neck dissection group. The adjusted relative risk of feeding tube dependence at 18 months was over four-fold greater in the group undergoing neck dissection (RR 4.74, 95%CI 2.07-10.89, $p=0.001$). The adjusted relative risk of feeding tube dependence 24 months after the completion of treatment was over seven-fold greater in the neck dissection group (RR

7.66, 95%CI 2.6-22.59, $p=0.001$) (Table 3). After 24 months, ongoing feeding tube dependence was observed in most patients with feeding tubes. Less than 25 % of these patients ultimately had their feeding tube removed. Due to patients loss to follow-up after 2 years, differences between groups became non-significant after the 24 month time-point, although a persistent trend was observed. Even when 7 patients with upper cervical esophageal/ hypopharyngeal strictures were excluded from the analysis, neck dissection remained a significant predictor of feeding tube dependence (RR 5.49, 95%CI 1.85-16.24, $p=0.002$). The relative risk of feeding tube dependence increased over time: from 5.49 at 18 months to 11.28 at 24 months ($p=0.005$) (Table 4). Using multiple logistic regression rather than propensity score adjustment, neck dissection remained a potent predictor of feeding tube dependence.

Other independent predictors of feeding tube dependence included pretreatment weight loss ($p=0.04$) and advanced patient age ($p=0.03$). Twenty-four months after completion of radiation, 6 of 13 patients with pretreatment weight loss remained feeding tube dependent ($p=0.018$). Patients with pretreatment weight loss were no more likely to undergo neck dissection than those without weight loss ($p=0.843$). The use of chemotherapy had no measurable effect in this study.

Discussion

Following the completion of treatment with primary radiation or chemoradiation for head and neck squamous cell carcinoma, acute toxicities such as mucositis and odynophagia resolve, but persistent swallowing impairment is common(12, 13). Advanced age, T-stage and primary tumor site have been associated with late chronic dysphagia in patients undergoing primary radiation, and post-radiation neck dissection has also been identified as a potential risk factor for poor swallowing outcome(4, 5). In this study, we hypothesize that neck dissection independently exacerbates post-radiotherapy dysphagia, increasing the risk of feeding tube dependence. Measuring the effect of neck dissection on chronic dysphagia is inherently problematic as patients who undergo neck dissection potentially represent a different population than patients who do not. Matching using propensity score adjustment has been used to minimize selection bias when a randomized clinical trial is not ethical or feasible (14). In this analysis, covariates thought to have an effect on the outcome were balanced between patients whose treatment included neck dissection and those spared a neck dissection, controlling for numerous potential confounders including advanced patient age, pre-treatment weight loss and numerous other potential factors. In adjusted analyses, the probability of feeding tube dependence increased significantly with a post-treatment neck dissection, and increased over time relative to the probability of feeding tube dependence without a neck dissection. In the present study, we present evidence supporting the notion that neck dissection contributes to chronic severe late toxicity after concurrent chemoradiation for head and neck cancer(4, 5). To our knowledge, this is the first study to use propensity score matching to investigate the effect of neck dissection on feeding tube dependence.

In order to exclude the possibility that long-term feeding tube dependence is a result of larger radiation treatment volumes used to treat patients with bulky nodal disease rather than neck dissection, the length of the high dose radiation field was measured in all patients. An increase in craniocaudal length of the radiation treatment field, used as a surrogate for radiation treatment volume, has been associated with an increased incidence of grade 4 swallowing toxicity in patients treated with radiation(11). Larger treatment fields might also be expected to contribute to chronic swallowing toxicity. In the current study, both the radiation fields used and radiation dose were essentially identical between groups, regardless of neck dissection status. Radiation field size was related to primary tumor site and T-stage

and affected little by nodal tumor bulk. Information regarding smoking history and history of depression, which could have an impact on our results, was not available and thus not included. Smoking may promote the development of fibrosis and exacerbate post-radiotherapy dysphagia. Depression has been linked to worse functional outcomes following chemoradiation due to diminished patient capacity to follow through on swallowing rehabilitation(15).

Although the use of radiation has been linked to the development of severe upper cervical esophageal/ hypopharyngeal strictures(16, 17), most patients who develop chronic dysphagia after radiation have no evidence of narrowing on imaging studies. Upper cervical esophageal and hypopharyngeal stenosis, estimated to occur in 12-21% of patients receiving aggressive chemoradiation regimens(18-20), are believed to be a sequelae of radiation, and may however secondarily exacerbate oropharyngeal dysphagia. Oropharyngeal dysphagia, characterized by inhibited tongue base retraction, laryngeal elevation and pharyngeal constriction necessary to propel the bolus through the upper aerodigestive tract(17, 21-23) may persist despite dilatation of a stricture, contributing to long-term feeding tube dependence. In our analysis, neck dissection was found to contribute to feeding tube dependence, regardless of whether patients with radiographically-confirmed strictures were included or not. We observed a slightly higher rate of stricture in patients with neck dissection. By exacerbating swallowing dysfunction, neck dissection may delay swallowing rehabilitation in a patient with a radiation-induced stricture, enabling a radiation-induced injury in the hypopharynx and upper cervical esophagus to become fixed. Nevertheless, we observed that approximately one half of patients with strictures were ultimately able to have their feeding tubes removed.

The mechanism by which a post-treatment neck dissection contributes to chronic dysphagia is uncertain. Radiation is believed to damage soft tissue by means of oxidative stress secondary to hypoxia, perpetuating tissue damage and increasing fibrosis long after radiation is completed(24). Patients treated with intense organ preservation protocols may be vulnerable to increasingly severe chronic dysphagia, as a result of cumulative side effects of treatment with multiple modalities. Radiation disrupts the coordinated activity of multiple adjacent structures and complex sensory feedback necessary for normal swallowing. Neck dissection may exacerbate post-treatment fibrosis of the neck and edema of the upper aerodigestive tract while also causing structural and sensory changes. In the present series, all patients undergoing neck dissection underwent a comprehensive dissection of levels I-V. A less extensive dissection of the neck, via a selective neck dissection of “at risk” levels, may potentially have less of an impact on swallowing by causing less tethering of the larynx and pharynx. Advances in radiation delivery may also diminish tissue fibrosis that predisposes to poor swallowing outcome, diminishing the effect of post-radiotherapy neck dissection. Results using IMRT in which uninvolved constrictor musculature is spared high dose radiation has been found to yield improved swallowing outcomes relative to traditional radiotherapy techniques(25). Neck dissection likely contributes to long-term toxicity burden in patients undergoing multimodality treatment for head and neck cancer, but remains potentially therapeutic in appropriate patients. The indications for neck dissection following chemoradiation for head and neck cancer continue to evolve.

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Table 1**Cohort exclusion criteria**

Locoregional or distant failure <2 years after treatment
Less than 24 month follow-up
Pre-existing feeding tube dependence
History of esophageal cancer
History of dementia or other neurological disorders
Use of Intensity-Modulated Radiation Therapy (IMRT)

Table 2

Distribution of patient and treatment characteristics

	Unadjusted			p-value	Adjusted		
	No	ND	ND		No	ND	ND
Number patients (N)	34		33		34		33
Age, mean (SD)	61.6 (10.7)		55.6 (7.9)	0.011	59.1 (10.7)		59.1 (8.2)
Mean Vertical Length of Radiation Field in cm (SD)	10.4 (3.0)		10.8 (3.3)	0.599	10.5 (2.8)		10.4 (2.9)
Male sex	85%		82%	0.752	89%		87%
Site							
Base of tongue	24%		42%	0.047	27%		26%
Larynx/hypopharynx	26%		36%		30%		28%
Tonsil	50%		21%		43%		46%
T-stage							
T1	15%		12%	0.950	13%		11%
T2	41%		39%		43%		47%
T3	32%		39%		32%		31%
T4	12%		9%		11%		10%
N-Classification							
N1-2a	50%		36%	0.327	51%		47%
N2b-3	50%		64%		49%		53%
Pretreatment weight loss	15%		18%	0.752	15%		12%
Stricture present	3%		18%	0.054	3%		9%
Treatment approach							
Concurrent chemoradiation	71%		70%	1.000	71%		75%
Induction chemotherapy and radiation	6%		6%		6%		5%
Radiation without chemotherapy	24%		24%		23%		20%

Abbreviations: ND neck dissection

Table 3
Risk of feeding tube dependence with and without neck dissection (N=67)

Relative Risk of Persistent Feeding Tube	No ND	ND	Relative Risk	95% CI	p-value
12 months (unadjusted)	26%	30%	1.14	0.51-2.58	0.745
12 months (adjusted)	24%	29%	1.19	0.55-2.59	0.658
18 months (unadjusted)	15%	33%	2.27	1.08-4.75	0.030
18 months (adjusted)	11%	52%	4.74	2.07-10.89	0.001
24 months (unadjusted)	9%	33%	3.78	1.72-8.30	0.001
24 months (adjusted)	7%	51%	7.66	2.6-22.59	0.001

Abbreviations: ND neck dissection, CI confidence interval

Table 4

Risk of feeding tube dependence with and without neck dissection excluding patients with stricture (N=59)

Relative Risk	Persistent Feeding Tube	No ND	ND	Relative Risk	95% CI	p-value
12 months (adjusted)		23%	25%	1.11	0.45-2.74	0.828
18 months (adjusted)		7%	41%	5.49	1.85-16.24	0.002
24 months (adjusted)		4%	40%	11.28	2.12-60.08	0.005

Abbreviations: ND neck dissection, CI confidence interval