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Dysphagia

Dose to the inferior pharyngeal constrictor predicts prolonged gastrostomy tube dependence with concurrent intensity-modulated radiation therapy and chemotherapy for locally-advanced head and neck cancer

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ABSTRACT

Background and purpose: To determine if dose and/or dose-volume parameters to anatomic swallowing structures are predictive of gastrostomy tube (PEG) dependence from chemotherapy-intensity modulated radiotherapy (IMRT) in locally advanced head and neck cancer (LAHNC).
Methods and materials: A retrospective study was performed on 141 consecutive patients with LAHNC (squamous cell) treated with definitive chemoIMRT with weekly concurrent carboplatin and paclitaxel. Late dysphagia was assessed by length of PEG requirement. Analysis of IMRT dose was retrospectively performed for critical swallowing structures.
Results: Approximately 62% of patients required PEG, the majority placed during treatment. Mean and median time for PEG was 7.7 and 4.4 months respectively (range 1.4–43.8). Only IMRT dose to the inferior constrictor was significantly associated with length of PEG. Mean dose (of individual mean doses) was 47 Gy for prolonged PEG use versus 41 Gy for PEG $\leqslant$12 months. V_{40} to the inferior constrictor also correlated with PEG >12 months ($p = 0.02$) with a mean V_{40} of 48% versus 41% for PEG $\leqslant$12 months.
Conclusions: IMRT dose to the inferior constrictor correlated with persistent dysphagia requiring prolonged PEG use. Maintaining mean inferior constrictor dose to $\leqslant$41 Gy and V_{40} to $\leqslant$41% may help minimize gastrostomy tube dependence.
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In the treatment of squamous cell locally advanced head and neck cancer (LAHNC), concurrent chemoradiation improves overall survival and rates of local control at the expense of increased toxicity [1,2]. A common toxicity is acute and late dysphagia, which is associated with worse quality of life as well as an increased incidence of aspiration and percutaneous endoscopic gastrostomy (PEG) tube dependency [3,4].

A trend toward the use of intensity modulated radiation therapy (IMRT) over conventional 3D radiotherapy for LAHNC has developed over the past decade in part to help minimize high dose to critical normal structures, thus minimizing toxicity. The benefit of IMRT in minimizing late xerostomia has been confirmed by the prospective randomized PARSPORT trial [5]. For treatment-induced dysphagia, the potential benefit of IMRT has involved both identifying critical, at-risk swallowing structures and attempting to identify key dose or dose-volume thresholds for toxicity. Critical anatomic structures involved in deglutition under both voluntary and involuntary control are well-established, however damage to the larynx (supraglottic and glottic) and pharyngeal constrictor muscles in particular have been implicated in persistent dysphagia with chemoradiation [6,7]. Concurrent chemoIMRT for oropharyngeal tumors prospectively planned to avoid high dose to these swallowing structures was shown to be feasible and did not compromise rates of locoregional control [8,9]. More specific dose or dose-volume parameters were predictive of late dysphagia in numerous studies, however the critical structure(s) varied between cohorts as did the metric for evaluating swallowing dysfunction [6,8,10–16]. In general, larynx and pharyngeal constrictor (one, two, or all three constrictors) dose thresholds have been the most commonly identified critical structures, but threshold values have varied between studies complicating the general applicability of these results. In particular, analysis of dysphagia-related dose parameters in a large cohort of patients undergoing concurrent chemoradiation with a common platinum-based chemotherapy regimen and modern radiation techniques has been lacking.

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We previously published our multi-institutional experience utilizing concurrent chemoIMRT with weekly carboplatin and paclitaxel showing improved feasibility and tolerability over concurrent cisplatin monotherapy [17]. Among these patients, the majority required PEG placement but few required PEG for more than 12 months. In this current study, we utilize this same group of consecutively treated patients to examine the underlying cause of this persistent PEG requirement by evaluating which dose and/or dose-volume parameters to critical swallowing structures is predictive of prolonged, severe dysphagia as measured by PEG dependence. Our objective was to identify potential structure(s) as well as patient or tumor characteristics most associated with PEG dependence with the ultimate goal of determining specific dose or dose-volume constraints to help reduce rates of dependency among future patients.

Methods

Patients

Between September 2003 and October 2007, consecutive patients with LAHNC receiving definitive chemoradiotherapy were evaluated. Patients received radiation therapy at Vanderbilt University Medical Center or the Vanderbilt–Ingram Cancer Center at Franklin. Eligibility included biopsy-proven AJCC Stage III, IVA, or IVB squamous cell carcinoma of the head and neck for which curative surgical resection was not indicated or recommended by a comprehensive multi-disciplinary head and neck tumor board. Acceptable subsites included nasopharynx, oropharynx, paranasal sinuses, oral cavity, hypopharynx, larynx, and localized unknown primary of the head and neck. Patients were at least 18 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients were excluded if they had prior surgery (other than biopsy), prior chemotherapy or radiation, or a synchronous active malignancy at another site. After completing therapy, patients had follow-up examinations every 6–8 weeks for the first year, every 3 months for the second year, and every 4–6 months thereafter until 5 years. This study was approved by the institutional review board of the Vanderbilt University Medical Center.

Radiation therapy

Radiation was delivered using IMRT as described previously [17]. Briefly, primary gross tumor volume (GTV) and grossly involved lymph nodes were delineated by physical examination and imaging studies. GTV was expanded by 1.0–1.5 cm to account for areas of subclinical disease and daily setup error. Lymph node levels were contoured bilaterally based on the Radiation Therapy Oncology Group (RTOG) consensus guidelines [18]. A single differential fractionation IMRT regimen was then employed where prescribed dose to the gross disease (primary and nodal) was 2.1 Gy/fraction to 69.3 Gy while dose to prophylactic nodal levels was 1.7 Gy/fraction to 56.1 Gy (5 fractions/week). Dose-volume histograms for each treatment plan were evaluated prior to starting radiation therapy. Prospective normal tissue constraints included maximum spinal cord and brain dose of <45 Gy, individual mean parotid dose of <20 Gy, and $\leqslant$20 Gy to 50% of the laryngeal volume and maximal dose of <50 Gy for non-laryngeal primary tumors.

Swallowing structures

Anatomical structures implicated in normal swallowing function [19] were retrospectively contoured for each patient. Specifically, the base of tongue, soft palate, esophagus, larynx, and superior, middle, and inferior pharyngeal constrictors were contoured as previously described [6,13,15] (representative contours in Supplemental Fig. 1). For laryngeal and base of tongue tumors respectively, the larynx and base of tongue swallowing structures included the entire anatomic structure, which could contain areas involved and uninvolved with tumor. Maximum, mean, and median dose as well as V_{10}, V_{20}, V_{30}, V_{40}, V_{50}, V_{60}, and V_{70} were then determined for each structure based on the original IMRT plan.

Chemotherapy

Induction chemotherapy was used at the discretion of the treating medical oncologist, typically for bulky primary or advanced nodal disease, and consisted of 9 weekly cycles of paclitaxel 60 mg/m^2 and carboplatin AUC 2. Chemotherapy concurrent with radiation consisted of weekly paclitaxel 30 mg/m^2 and carboplatin AUC 1.

Percutaneous Endoscopic Gastrostomy (PEG) placement

PEG placement was performed during or after concurrent chemoradiation when patients lost 10% or more of their pre-IMRT weight. PEG was not routinely placed prior to starting therapy except when the patient demonstrated considerable weight loss from tumor-induced dysphagia. If placed, PEG was removed by a physician when weight was maintained by PO intake for at least 3 weeks. The duration of PEG use was defined as the documented date of insertion to the documented date of removal.

Statistical methods

Linear regression analysis was utilized to determine which dose or dose-volume parameters correlated with length of PEG placement. Logistic regression analysis was utilized to determine which dose or dose-volume parameters were predictive of PEG requirement >12 months as compared to PEG $\leqslant$12 months. Disease-free survival was defined as the time from treatment to any type of recurrence (local, regional, or distant) and was estimated using the Kaplan–Meier statistical method. Univariate analysis with Log–Rank tests was used to identify significant prognostic variables for disease-free survival, and Fine and Gray's proportional subhazards competing risk model analysis was performed on those variables when appropriate to confirm significance. Multivariate analysis was performed using the Cox proportional hazards model. p values <0.05 were considered statistically significant.

Results

Patient characteristics

One hundred and forty-one patients who received concurrent chemoradiation with IMRT and weekly carboplatin/paclitaxel were analyzed for this study. Patient characteristics are shown in Table 1. The median age is 57.5 (range, 37.6–88.5) with a median follow up of 42 months (range, 6 to 99 months for surviving patients with 96% followed for >12 months). The majority of patients were male (87%) with stage IVA disease (57%), an ECOG performance status of 1 (70%), and primary oropharyngeal tumors (58%).

PEG placement and dependency

A total of 88 patients (62%) required PEG placement. The majority of patients (77 patients, 55% of total) underwent placement during concurrent chemoradiation, while 2 patients (1% of total) required PEG after completing radiation. Nine patients (6% of total) required PEG prior to starting concurrent chemoradiation due to tumor-related dysphagia. Of patients who required PEG, the mean