



Five-year outcomes of an oropharynx-directed treatment approach for unknown primary of the head and neck



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ABSTRACT

Purpose: Squamous cell carcinoma of unknown primary (SCCHNUP) is commonly treated with comprehensive radiation to the laryngopharynx and bilateral necks. In 1998, we established a departmental policy to treat SCCHNUP with radiation directed to the oropharynx and bilateral neck.

Methods: From 1998–2011, 60 patients were treated – N1: 18%, N2: 75% and N3: 7%. 82% underwent neck dissection. 55% received IMRT and 62% underwent concurrent chemoradiotherapy.

Results: At median follow-up of 54 months, 5 patients failed regionally and 4 emerged with a primary (tongue base, hypopharynx and thoracic esophagus). Five-year rates of regional control, primary emergence, distant metastasis, disease-free survival and overall survival were 90%, 10%, 20%, 72% and 79%, respectively. The 5 year rate of primary emergence in a non-oropharynx site was 3%.

Conclusion: This is the first demonstration that an oropharynx-directed approach yields low rates of primary emergence in SCCHNUP with excellent oncologic outcomes.

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Introduction

Squamous cell carcinoma of unknown primary (SCCHNUP) accounts for less than 5% of cancers of the head and neck yet its treatment is controversial with multiple established approaches [1]. If managed by surgery alone, primary emergence occurs in up to 25–30% with high rates of regional failure [2]. Two common treatment approaches have evolved which focus either on (1) managing regional disease with unilateral treatment or (2) treatment of the neck bilaterally with comprehensive elective irradiation of potential mucosal sites of the aerodigestive tract from the nasopharynx to the hypopharynx. The unilateral approach is

associated with higher risk for contralateral neck failure [2–4] and potentially higher rates of emergence of primary depending on treatment technique while comprehensive radiation of the pharyngeal axis is associated with a halving of primary emergence to 8–10% [5,6], excellent regional control but increased morbidity. Despite different treatment aims, these approaches show comparable survival albeit the data are retrospective from single institutions or pooled results from a few centers. A joint European Organisation for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) randomized trial comparing unilateral versus comprehensive treatment was attempted but closed due to poor accrual.

Newer conformal radiation techniques and widespread availability of functional imaging have created a significant opportunity to better individualize treatment and improve the therapeutic ratio. Currently, despite comprehensive mucosal treatment, the

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most common site for a primary to emerge is the oropharynx [1,7]. To maintain excellent regional control and to address the most common site of occult primary while sparing patients the toxicity and functional morbidity of comprehensive mucosal irradiation, we report an oropharynx-directed approach with comprehensive nodal treatment.

Methods

Beginning in 1998, our department established a prospective policy to treat patients presenting with squamous cell carcinoma of the neck with unknown primary with an oropharynx-directed approach sparing the majority of the laryngopharynx while treating bilateral necks. All patients were evaluated and treated by two radiation oncologists specializing in head and neck cancer at Beth Israel (LBH and KH). With institutional board approval, sixty patients were identified who were treated from 1998–2011 for SCCHNUP in this manner. During this period no patients were treated with other approaches including comprehensive aerodigestive irradiation or regional only treatment.

Patient characteristics

Demographics and treatment characteristics are outlined in Table 1. Males comprised 45 of the patients. The median age was 55 years (range 21–83yo). Ethnicities of patients were as follows: Caucasian 51, Hispanic 4, black 4 and Asian 1. Tobacco status was available in 93% (55/60) with 56% (31/55) having greater than a 10 pack-year history and 45% (25/55) having less than a 10 pack-year history.

Nodal staging was as follows: N1 18% (n = 11), N2a 25% (n = 15), N2b 38% (n = 23), N2c 12% (n = 7) and N3 7% (n = 4). Two of the four

N3 patients were deemed unresectable prior to treatment). The nodal station was identified in 82% (49/60) of patients. Fig. 1 Level II involvement occurred in 62% (37/60) with isolated level II in 28% (17/60). Level III involvement was present in 40% (24/60) with isolated level III in 7% (4/60); level IV was present in 10% (6/60) and isolated in 2% (1/60) and Level I was involved in 8% (5/60) with isolated involvement in 7% (4/60). One patient had level V involvement in the context of other positive nodal levels Fig. 1.

Workup

Patient workup included anatomic imaging comprised of computerized tomography (CT) or magnetic resonance imaging (MRI), nasopharyngoscopy and exam under anesthesia with directed biopsy of abnormal-appearing mucosal sites. Positron emission tomography-computed tomography (PET/CT) was routinely performed beginning in 2003 and overall 72% patients had one performed prior to treatment. Surgical evaluation included fine needle aspiration, neck dissection or excision along with elective tonsillectomy. Molecular testing for p16 was not done for the majority of patients as its prognostic significance was not appreciated until the very end of the study period [8].

Treatment

Neck dissection was performed in 82% of patients, primarily as upfront management usually at time of tonsillectomy and directed biopsies of any abnormal appearing mucosal areas of the aerodigestive tract. Two patients with N3 disease had planned neck dissection after initial treatment to a dose of 60 Gy. Two patients with N3 were deemed unresectable and were treated to 70 Gy. Concurrent chemotherapy was delivered in 62% (n = 37) primarily platinum based regimens (high dose cisplatin given every 3 weeks n = 30, weekly carboplatin n = 2 or weekly carboplatin/Taxotere n = 1) cetuximab = 2 and 2 unknown. Induction Taxotere, cisplatin, 5-Fluorouracil (TPF) was given in 6 patients followed by concurrent chemotherapy. Radiation therapy was delivered with an intensity-modulated radiation therapy (IMRT) technique in 55% and two-dimensional/three-dimensional technique in the remainder. In general the involved neck and gross tumor volume were treated to a dose of 60–70 Gy with elective treatment of the node negative neck to 54 Gy and the oropharynx to 54–60 Gy. With IMRT treated patients, care was taken to spare the salivary glands and swallowing structures including constrictors and esophagus. Clinical Target Volume (CTV) margins ranged from 5–10 mm with Planning Target Volume (PTV) margins of 3–5 mm. The retrostyloid nodes were spared in a clinically node negative neck Fig. 2.

Statistics and Ethical guidelines

Data were analyzed using SPSS statistical software (Version18.0, Chicago: SPSS Inc.). All statistical tests were based on a 2-sided significance level, and a P value of ≤ 0.05 was considered statistically significant. Tables of measures of association in frequency were assessed with Pearson's χ^2 test or Fisher's exact test. Survival analysis was carried out using the Kaplan-Meier method and the equality of survival across groups was assessed with log-rank test. The Cox proportional hazards model was used for univariate and multivariate analyses to assess the impact of radiation therapy technique, patient characteristics, and other prognostic factors on oncologic and quality of life endpoints. Data collection and reporting procedures were done in accordance with Helsinki Declaration guidelines.

Table 1
Demographics and treatment characteristics (n = 60) IMRT: Intensity-modulated radiation therapy; TPF: Taxotere, Platinum, 5-Fluorouracil.

Characteristic	No. of patients (%)
Sex	
Female	15 (25%)
Male	45 (75%)
Ethnicity	
Caucasian	51 (85%)
Hispanic	4 (7%)
African American	4 (7%)
Asian	1 (1%)
Tobacco use >10 yr-pack	
Yes	31/55 (56%)
Nodal stage	
N1	11 (18%)
N2a	15 (25%)
N2b	23 (38%)
N2c	7 (12%)
N3	4 (7%)
Neck dissection	
Yes	49 (82%)
Radiation	
2D/3D	27 (45%)
IMRT	33 (55%)
Chemotherapy	
Induction	6 (10%)
TPF	6 (10%)
Concurrent	37 (62%)
Cisplatin	30 (81%)
Carboplatin	2 (5%)
Cetuximab	2 (5%)
Carboplatin/taxotere	1 (3%)
Unknown	2 (5%)

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