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Clinical Investigation: Head and Neck Cancer

Active Tobacco Smoking and Distant Metastasis in Patients With Oropharyngeal Cancer

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Summary

Distant metastasis is the first site of relapse in one-third of all locally advanced oropharyngeal cancer patients. Human papillomavirus, though predictive for survival, has shown not to be predictive of distant metastasis. We evaluated the risk factors associated with distant metastasis in patients with oropharyngeal cancers. We found that active tobacco smoking was the strongest predictive factor for increased risk of distant metastasis, independent of nodal category and pack-years of tobacco smoking.

Purpose: Distant metastasis is the site of first relapse in approximately one-third of patients with locally advanced oropharyngeal carcinoma, irrespective of human papillomavirus status. Yet the risk factors associated with distant metastasis are not well characterized. We sought to characterize the relationship between smoking status and distant metastasis.

Methods and Materials: We evaluated the association between tobacco smoking status and distant metastasis in a retrospective cohort study of 132 patients who underwent definitive radiation therapy and chemotherapy for Stage III–IVA/B oropharyngeal cancer. Information on tobacco smoking was prospectively collected by patient questionnaires and physician notes at the time of diagnosis. Thirty-three percent of the patients were nonsmokers, 51% were former smokers, 16% were active smokers. The cumulative lifetime tobacco smoking in pack-years was 20 (range, 0–150).

Results: With a median follow-up time of 52 months, the overall rate of distant metastasis at 4 years was 8%. Distant metastasis was the most common first site of relapse, occurring in 56% of the patients with recurrences. Active smokers had higher rates of distant metastasis than non-active smokers (including never- and former smokers; 31% vs. 4%, $p < 0.001$) and former smokers (31% vs. 3%, $p < 0.001$). There was no statistically significant difference in the risk of distant metastasis for patients with lifetime cumulative pack-years >20 and ≤20 (10% vs. 4%, $p = 0.19$). In univariate analysis, active smoking ($p = 0.0004$) and N category ($p = 0.009$) were predictive of increased risk of distant metastasis. In multivariate analysis, active smoking was the most significant predictive factor for increased risk of distant metastasis (hazard ratio, 12.7, $p < 0.0001$).

Conclusions: This study identified a strong association between active smoking and distant metastasis in patients with oropharyngeal cancer. © 2012 Elsevier Inc.

Keywords: Cigarette, Distant metastasis, HPV, Human papillomavirus, Oropharyngeal carcinoma, Radiation, Smoking, Tobacco

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Introduction

The incidence of human papillomavirus (HPV) infection-associated oropharyngeal carcinoma has risen rapidly (1). Due to modern radiation therapy, the use of concurrent chemotherapy, and the inherent radiosensitivity of HPV-related disease (2), the overall survival and locoregional control rates in oropharyngeal cancer have increased to 80% to 85% and 90% to 96%, respectively (3–6). This high locoregional control rate has led to a shift in the pattern of failure, with increasing percentages of patients presenting with distant metastasis as the site of first failure (7). In a large national phase III randomized trial, Ang *et al*. (8) recently reported that 31.8% of HPV-positive patients had distant metastasis as the site of first relapse. As such, the ability to predict those at risk for distant failure takes on a new urgency.

The literature on risk factors specific for distant metastasis in oropharyngeal cancer is sparse. Several groups have shown that advanced primary tumor (T) (3) and nodal (N) (3, 9) categories increase the risk for distant metastasis. Despite its prognostic significance in predicting for locoregional control and overall survival, data from phase III trials did not demonstrate any statistically significant relationship between HPV status and distant metastasis (8, 10).

Several studies have shown that tobacco exposure, as defined by number of pack years or smoking status, is predictive of recurrence generally (8, 11, 12). Given the paucity of data on factors predictive of distant failure, we retrospectively evaluated our own cohort of oropharyngeal cancer patients in order to characterize the relationship between tobacco exposure and distant metastasis.

Methods and Materials

Study population

Between March 2000 and December 2009, 132 patients with newly diagnosed stage III–IVA/B oropharyngeal carcinoma were treated with radiation therapy at the Massachusetts General Hospital. The median age at diagnosis was 58 years old. The median Karnofsky performance score (KPS) at presentation was 90. Of the 38 patients for whom we had HPV data, 92% were positive. The primary sites were tonsil (48%), base of tongue (48%), and others (4%). Tumors were staged according to the American Joint Committee on Cancer Staging, with 19% of the patients having stage III disease, 65% had stage IVA, and 16% had stage IVB. The T category distribution was as follows: 24% had stage T1, 38% had stage T2, 24% had stage T3, and 14% had stage T4. The N category distribution was as follows: 9% had stage N0, 12% had stage N1, 21% had stage N2a, 33% had stage N2b, 11% had stage N2c, and 14% had stage N3.

All patients were treated definitively with radiation therapy, concomitant boost technique or intensity-modulated radiation therapy (IMRT) with simultaneous integrated boost. The median dose to the gross tumor volume was 70 to 72 Gy given over 6 to 6.5 weeks. Ninety-five percent of patients received chemotherapy. Chemotherapy consisted mainly of concurrent cisplatin, carboplatin/taxol, or cetuximab. Patient and tumor characteristics are summarized in Table 1.

Table 1 Patient, tumor, and treatment characteristics of patients in the study

Patient characteristics	No. of patients (%)
Median age in years at diagnosis (range)	58 (35–92)
Gender	
Male	109 (82.6)
Female	23 (17.4)
Race	
White	119 (90.2)
Black	4 (3.0)
Hispanic	5 (3.8)
Other	4 (3.0)
Oropharyngeal primary site	
Tonsil	64 (48.5)
Base of tongue	64 (48.5)
Others	4 (3)
AJCC stage	
III	25 (19.0)
IVA	86 (65.1)
IVB	21 (15.9)
T category	
T1	32 (24.2)
T2	50 (37.9)
T3	31 (23.5)
T4	19 (14.4)
N category	
N0	12 (9.1)
N1	16 (12.1)
N2a	28 (21.2)
N2b	44 (33.3)
N2c	14 (10.6)
N3	18 (13.7)
Radiation dose and duration	
Dose (Gy), median	70
Duration (days), median	47
Chemotherapy schedule	
None	7 (5.3)
Concurrent alone	105 (79.5)
Induction and concurrent	17 (12.9)
Induction alone	2 (1.5)
Adjuvant only	1 (0.8)

Abbreviation: AJCC = American Joint Committee on Cancer.

Tobacco history

Information on tobacco smoking was prospectively collected by patient questionnaires and physicians' notes at the time of diagnosis. Patients were categorized according to their use of cigarettes, cigars, or pipes as active, former, or never-smokers.

Patients were considered active smokers if they smoked tobacco at the time of the diagnosis. Patients who quit smoking prior to their diagnosis were considered former smokers. Never-smokers were those who had never used cigarettes, cigars, or pipes in their lifetime. Cumulative lifetime tobacco smoking was quantified in pack-years. A pack-year was defined as the equivalent of smoking one pack of cigarettes or 20 cigarettes per day for 1 year. For patients who used loose tobacco, a cigar was considered equivalent to four cigarettes, and a pipe was considered equivalent to two and a half cigarettes (13).