

CANCER: HEAD AND NECK

Clinicopathologic Characteristics of Head and Neck Squamous Cell Carcinoma in Puerto Ricans

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Objective. The purpose of this study is to characterize head and neck squamous cell carcinoma (HNSCC) in the Puerto Rican population. This is a follow-up to our initial published report on the first 134 patients. Specifically, demographic characteristics, stage at presentation, initial treatment given, and rate of recurrence were studied.

Methods. Relevant data was obtained from 445 histologically confirmed HNSCC cases identified through the University of Puerto Rico School of Medicine Otolaryngology Department Head and Neck Cancer Clinics between August 1993 and January 2003. Data collected after informed consent included demographic factors (sex, age, areas of residence, income); risk factors (occupation, alcohol intake, cigarette usage); and pathological variables (tumor location, histopathology, stage at presentation, current disease status, tumor recurrence).

Results. The average age at diagnosis was 64.0 years (range 18-98); 84.5% of the patients were male, 16% were females. The most frequent anatomical sites of the

primary tumor were the larynx (36.4%) and the oral cavity (29.9%). The majority of patients (61.1%) presented with advanced stage (III-IV) disease at the time of diagnosis and over half (55.5%) had moderately-differentiated tumors. Most patients had less than 12 years of formal education (81.2%). Prolonged use of tobacco and alcohol identified in 88.1% and 79.8% of patients, respectively. The most frequent therapeutic modality used was radiation therapy followed by the combination of radiation and surgery. Twenty five percent of the cases experienced a recurrence of disease during the follow-up period.

Conclusions. These findings emphasize the need for early detection programs for HNSCC in Puerto Rican patients given the high rate of advanced-stage disease at time of diagnosis. The key role of heavy alcohol intake and tobacco use as risk factors in the development of HNSCC is once again highlighted.

Key words: Squamous cell carcinoma, Head and neck, Puerto Rico, Epidemiology

Squamous cell carcinoma of the upper aerodigestive tract represents a devastating disease for the patient who is not diagnosed early on. In the United States, up to 60% of these tumors present as locally advanced (Stage III and IV) at time of diagnosis. Even when surgically resectable, the survival rate for this group is only 10-60% (1). Head and neck squamous cell carcinoma (HNSCC) can significantly affect three of the most basic human

functions: respiration, deglutition, and phonation, frequently leaving the patient dependent on a tracheotomy, gastrostomy, and/or artificial voice for daily living. Moreover, advances in the diagnosis and treatment strategies of this disease have not resulted in significantly improved survival rates over the past several decades (2).

In the United States and Europe, HNSCC represents 3% of all malignant tumors (2-5). There were 37,800 new cases of HNSCC with 11,1000 deaths in the United States alone in 2002. This corresponds to an age-adjusted incidence rate of 15 new cases per 100,000 people. This rate has plateaued over the past decade, but is three times as high in males as compared to females. The oral cavity and larynx account for the majority of tumors in the United States with a 2002 annual incidences of 20,300, and 8,900 cases, respectively.

Squamous cell carcinoma is the culprit in 90% of all malignancies diagnosed in the head and neck region (6,7). In Puerto Rico, there were 489 cases of HNSCC in 2000.

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This study was funded in part by the Department of Otolaryngology- Head & Neck Surgery, University of Puerto Rico School of Medicine and NIH Grant 3P30CA16672-24SI

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The annual incidence in Puerto Rico is 23 new cases per 100,000, which represents 5% of all malignant tumors (5,8). Incidence of HNSCC increases with age. The majority of oral cavity, oropharyngeal, and hypopharyngeal cancers are diagnosed between the 6th and 7th decades of life, although larynx and nasopharyngeal cancers occur in younger patients (9).

The etiology of HNSCC is currently thought to be multifactorial in nature. Numerous factors are thought to play a role in the development of HNSCC including family history, tobacco consumption, and heavy alcohol use. Tobacco and alcohol constitute the two greatest risk factors and have a synergistic effect. The excessive use of both tobacco and alcohol is associated with a 15-fold increase in the risk of developing HNSCC (10,11). Other factors that have been associated with HNSCC include betel nuts, chronic infection, poor oral hygiene, chronic local trauma from ill-fitting dentures, lichen planus, Plummer-Vinson syndrome, human papilloma virus (HPV), and Epstein-Barr virus (9). Gastroesophageal reflux is postulated to be a cocarcinogen but this is still under investigation. The presence of HPV infection in up to 25% of HNSCC specimens and its link to p53 mutations appear to play a significant role in the pathogenesis of these malignancies (12,13). Several occupational groups including wood workers, leather workers, metal and petroleum refiners, and chrome pigment manufacturers have also been found to have an increased risk of developing HNSCC (14-16).

Differences in incidence of HNSCC across the world and within the racial and ethnic groups in the United States call attention to possible geographic, cultural, genetic and socioeconomic factors. In the United States, HNSCC is less common among Native Americans and Hispanics, but more common in African-Americans than in whites (2,16,17). The reasons for these racial differences are not understood yet, but dietary, hormonal and environmental risk factors have been suggested (18).

The incidence of HNSCC in Puerto Rico is higher than that in the U.S. as a whole, although no difference in prognosis has been identified between these two populations (19). When comparing Puerto Ricans to Hispanics in the U.S., the difference in incidence is marked, as HNSCC is 2.5 times more common in the former group (4,5,17). Hispanics in the U.S. have a lower incidence (9.4 per 100,000) than the general population (4). The purpose of this study is to characterize the epidemiology, presentation, and treatment of HNSCC in Puerto Rico in order to achieve a better understanding of why this difference in incidence occurs. This is a follow-up of our initial published report on the first group of patients included in our study group (20).

Methodology

This is a descriptive study using data from the head and neck cancer longitudinal study group at the University of Puerto Rico. Patients included in this study were Puerto Rican patients with a histopathologically confirmed diagnosis of squamous cell carcinoma of the upper aerodigestive tract. Patients with skin, nasal cavity, paranasal sinus, or esophageal carcinomas were excluded. The patients were treated at the cancer clinics of the Otolaryngology-Head and Neck Surgery Department at the University District Hospital, San Juan City Hospital, and Isaac Gonzalez Martinez Oncology Hospital between August 1993 and January 2003.

Four hundred and forty-five patients were identified and included in this study. After obtaining informed consent, patients were interviewed and filled out a questionnaire detailing their employment history, family history of cancer, concurrent diseases, tobacco and alcohol use, socioeconomic data, and environmental exposure. Staging and initial treatment were noted. Patients were staged using the American Joint Committee on Cancer Tumor-Node-Metastasis (AJCC-TNM) classification. The patients were then followed prospectively at their clinic appointments to document disease status, recurrence, of disease and further treatment.

Results

Table 1 summarizes the demographic characteristics, tumor site, stage, and pathologic grade of the 445 patients. The average age at diagnosis was 64.0 years, with a minimum age of 18 years and a maximum of 98 years. The vast majority of patients (78.8%) presented between the 6th and 8th decades of life. Males accounted for 376 (84.5%) of the patients while females numbered 69 (15.5%). The average age for males and females were 63.7 and 65.3, respectively.

Of the primary tumor sites, the larynx was the most frequent, accounting for 162 (36.4%) cases, followed by the oral cavity with 133 (29.9%) cases. When analyzed by gender, there was a difference in the frequency of the site of origin. In males, there was a predominance of laryngeal tumors (39.1%), followed by oral cavity tumors (26.6%). However, in females this trend was reversed with oral cavity tumors (47.8%) more than twice as common as laryngeal tumors (20.3%).

Advanced primary site tumors larger than 4 cm. (T3, T4) predominated with 245 (55.1%) cases, being T4 the most frequent ones (33.5%). With regard to regional nodal status, 65.8% of all cases were node-free (N0) at the time of diagnosis. In patients with advanced primary tumors, 50.5%

Table 1. Demographics, staging and histopathologic characteristics of head and neck squamous cell carcinoma patients in Puerto Rico

Characteristics	Total	Percent
Number of subjects	445	100%
Gender		
Male	376	84.5%
Female	69	15.5%
Age at diagnosis		
<50 yrs	45	10.1%
50-59 yrs	123	27.6%
60-69 yrs	127	28.5%
70-79 yrs	101	22.7%
≥80 yrs	49	11.0%
Education level		
None	27	6.1%
<6th grade	140	31.5%
6th-12th grade	194	43.6%
Associate/Bachelor	28	6.3%
Post-graduate	2	0.4%
Unknown	54	12.1%
Primary tumor site		
Oral cavity	133	29.9%
Nasopharynx	8	1.8%
Oropharynx	88	19.8%
Hypopharynx	39	8.8%
Larynx	162	36.4%
Other	15	3.4%
Primary tumor status (T)		
T1	98	22.0%
T2	102	22.9%
T3	96	21.6%
T4	149	33.5%
Nodal status (N)		
N0	293	65.8%
N1	55	12.4%
N2	73	16.4%
N3	24	5.4%
Distant metastasis (M)		
M0	439	98.7%
M1	6	1.3%
Stage		
I	89	20.0%
II	84	18.9%
III	81	18.2%
IV	191	42.9%
Grade		
Well differentiated	104	23.4%
Mod. differentiated	247	55.5%
Poorly differentiated	48	10.8%
Not specified	46	10.3%

were node-positive. Distant metastases were very infrequently identified in our group with only 6 (1.3%) cases. The analysis of stage at presentation showed that most patients (61.1%) presented with advanced stage (III, IV) disease.

The distribution of tumors by pathologic grade revealed that the most common tumor classification was moderately differentiated, accounting for 55.5% of patients. The least frequent classification was poorly differentiated (10.8%). There was no difference identified between males and females with regard to histology. The educational level of the majority (81.2%) of the HNSCC patients was equal to or less than a twelfth grade equivalent. Furthermore, 37.6% of patients had less than a sixth grade education, while only 12.5% went on to associate or bachelors degrees.

Analysis of smoking and alcohol consumption characteristics is summarized in Table 2. The vast majority of patients were chronic smokers (88.1%). Males were more likely than females to be chronic smokers with 90.4% and 60.1% respectively. The source of tobacco in most patients was cigarettes (92.9%), with pipes/cigars and chewing tobacco a distant second and third (9.7% and 5.6%). The majority of patients (75.8%) smoked more than 20 cigarettes per day. Even though most patients (91.6%) had smoked for more than twenty years, a considerable proportion (79.3%) of them quit after the diagnosis of HNSCC was made.

Chronic alcohol use was also very common in our HNSCC population with 79.8% identified as chronic users. Females were much less prone to chronic alcohol use (39.1%) than males (87.2%). Most patients used a combination of hard liquor and beer regularly, while only a small minority (6.5%) drank wine. Of the population who drank, most (86.8%) had done so for more than 20 years, and more than half (56.6%) consumed more than 10 drinks per week. As with the tobacco use data, the majority of the patients (86.8%) quit drinking after the diagnosis of HNSCC was made. Of the whole HNSCC group, 324 patients (72.8%) were identified as concurrent alcohol and tobacco users.

Most patients in our study group were initially treated with surgery, radiotherapy or a combination of the two (Figure 1). As a single treatment modality, radiotherapy was the most frequently employed treatment with 173 (39.0%) patients. Surgery alone was practiced in 69 patients (15.5%), while chemotherapy alone was only used for 2 patients (0.4%). Of combination modalities, surgery plus radiotherapy was employed on 126 patients (28.4%), while radiotherapy plus chemotherapy was used in 34 patients (7.6%).

Recurrences were identified in 115 (25.9%) patients on follow-up. Of those patients with recurrences, there was

Table 2. Tobacco and alcohol consumption characteristics of head and neck squamous cell carcinoma patients in Puerto Rico

Characteristic	Total	Percent	Characteristics	Total	Percent
Tobacco exposure			Alcohol exposure		
Smoked (>6 mo.)	392	88.1%	Regularly	355	79.8%
Never smoked	53	11.9%	Not regularly	90	20.2%
Tobacco source			Alcohol source		
Cigarettes	364	92.9%	Liquor	169	47.6%
Chewing tobacco	22	5.6%	Beer	163	45.9%
Pipes/cigars	38	9.7%	Wine	23	6.5%
Current status			Current status		
Smoke after diagnosis	81	20.7%	Drink after diagnosis	57	16.1%
Quit before/at diagnosis	311	79.3%	Quit before/at diagnosis	298	83.9%
Total years tobacco use			Total years alcohol use		
≤20 yrs	33	8.4%	≤20 yrs	47	13.2%
>20 yrs	359	91.6%	>20 yrs	308	86.8%
Quantity (cigarettes/day)*			Quantity (drinks/week)**		
1-19	95	24.2%	1-10	154	43.4%
20-39	159	40.6%	>10	201	56.6%
>40	138	35.2%			

* 1 cigar = 5 cigarettes, 1 pipe = 2.5 cigarettes ** 2-oz. drink = 1 beer = 1 glass of wine

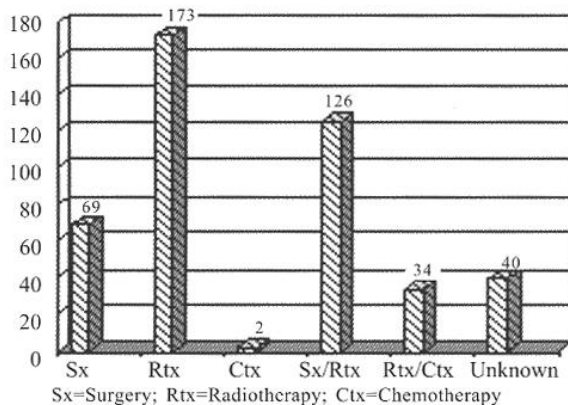


Figure 1. Initial treatment given to HNSCC patients.

no significant difference in the past or present use of tobacco and alcohol compared to the general population of HNSCC patients. On last follow-up, 45.1% of the HNSCC patients were alive and tumor free, while the rest were either alive with active tumor or deceased.

Discussion

The incidence of head and neck squamous cell carcinoma in Puerto Rico (23 per 100,000) is higher than among Hispanics living in the United States (9.4 per

100,000) (4,5). The reasons for this difference are unknown. In this study we described the clinical and pathological characteristics of a group of Puerto Rican patients diagnosed with HNSCC. Most of our findings confirm prior published data, but some new and interesting tendencies not previously described were revealed.

The oral cavity has traditionally been cited as the most common site of origin of HNSCC, and this is supported by data from current U.S. and international cancer registries (2-5). Our data was not consistent with this, as 36.4% of tumors originated in the larynx and 29.9% in the oral cavity. When analyzed by gender a difference also exists, with the larynx more common in males while the oral cavity was the most common site in females. The preponderance of laryngeal primaries in Hispanic males has previously been reported by Trapido et al. (21).

Our data confirms the prevalence of advanced stage disease at presentation with 61% of patients in Stage III or IV. This is partly due to a level of self-neglect typically present in these patients as well as a lack of training of the primary physician in the early detection of this type of cancer. Furthermore, nearly 80% of our patients had less than or equal to a 12th grade education, a factor which can significantly limit the success of early detection strategies. Despite this, nearly two-thirds of patients had no evidence of metastatic cervical disease at presentation, which is consistent with prior data. This is significant, as the presence of regional metastasis is one of the most important prognostic indicators of this disease (9,16). Distant

metastases are rare in HNSCC, although the low incidence of this presentation in our study group (1.3%) probably represents a failure of identification in some cases.

Tobacco and alcohol consumption were identified in 88% and 79% of our patients, while concomitant use was identified in three out of four patients. Tobacco exposure causes progressive and sequential morphologic changes in the mucosa with eventual neoplastic transformation. Although our study does not confirm this, prior studies show that in patients who persisted smoking after a presumed cure of an oral cancer, 40% developed a second primary tumor in the upper aerodigestive tract, compared to 6% of those who stopped smoking (22). Alcohol may act as a cocarcinogen synergistically with tobacco or it alone may be carcinogenic, causing local irritation to the mucosa, and metabolic and nutritional disorders which alter the resistance of the mucosa.

Occasionally, non-smokers and non-drinkers develop HNSCC. In our data, 12% did not use tobacco and 21% did not consume alcohol regularly. This suggests that in addition to the tobacco and alcohol, other factors such as dietary deficiencies, poor oral hygiene, viral infections, chronic trauma, genetics, and environmental exposures play a role in the development of HNSCC (23). Initial data by our group, point to a higher prevalence of HPV16 infection in HNSCC in Puerto Rican patients compared to published U.S. data (12). Whether this increased prevalence of HPV16 is the reason for the increased incidence of HNSCC in Puerto Rico is under investigation.

Radiotherapy was the most common single treatment modality, due in part to the large proportion of laryngeal primaries present in our group. In this subset of patients, organ-preserving therapy is vital for post-treatment phonation and radiotherapy is usually recommended for early cancers. Recent reports, however, have refuted this claim and phonosurgery for early tumors is gaining popularity (24). Surgery combined with radiotherapy was the most common combined treatment modality in our group. Although historically this has been the standard of care for advanced-stage tumors, this also has been changing with reports in the last decade of equivalent success using combination radiotherapy and chemotherapy for advanced laryngeal and pharyngeal tumors in Phase III trials (25,26).

In conclusion, our findings point to the need for early detection and prevention programs of HNSCC in Puerto Rico at two basic levels. At the population level, these should emphasize the critical role tobacco and alcohol play in the pathogenesis of this disease and how in the majority of cases HNSCC is mostly preventable. At the primary care physician level, early detection strategies for high-risk patients should emphasize thorough periodic

examinations of the head and neck area and familiarization with the anatomy of this complex area.

Resumen

El propósito de este estudio es caracterizar el carcinoma espinocelular de cabeza y cuello (CECC) en la población puertorriqueña. El estudio consiste de 445 pacientes con CECC confirmado histopatológicamente y tratados en las Clínicas de Cáncer del Departamento de Otorrinolaringología y Cirugía de Cabeza y Cuello de la Universidad de Puerto Rico entre agosto 1993 hasta enero 2003. El estudio es una ampliación de nuestro reporte inicial en el que se analizaron los datos de 134 pacientes. Después de obtener el consentimiento informado, se recopiló la información sobre los pacientes a través de entrevistas seriadas y análisis de los expedientes médicos. Se analizaron los datos demográficos, el estadio y clasificación patológica del tumor, exposiciones a tabaco y alcohol, el tratamiento inicial, y la incidencia de recurrencia del tumor.

La edad promedio de los pacientes fué 64.0 años y la mayoría (84.5%) eran varones. Un 81.2% de los pacientes había completado doce años o menos de educación formal. La laringe y la cavidad oral fueron los sitios de origen del tumor más comunes. Dos de cada tres pacientes se presentaron con un estadio avanzado de enfermedad (III o IV). El uso prolongado de tabaco y alcohol fué reportado en 88.1% y 79.8% de los pacientes, respectivamente. Radioterapia fué el método de tratamiento único mas usado, mientras que la cirugía con radioterapia fué el tratamiento de combinación mas común. El 25.8% de los pacientes sufrieron una recurrencia de la enfermedad.

Estos hallazgos enfatizan la necesidad que existe de implementar programas de detección temprana de CECC dada la alta incidencia de la enfermedad en estadios avanzados en Puerto Rico.

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