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Tobacco smoking and risk of recurrence for squamous cell cancer of the anus

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Abstract

Objective: Squamous cell cancer of the anus is associated with multiple risk factors, including infection with human papillomavirus, immunosuppression, chronic inflammation, and tobacco smoking, although there is little data on these factors for the prediction of recurrent disease. Here, we evaluated the risk of recurrence and mortality of anal carcinoma in association with tobacco smoking. *Methods*: We conducted a retrospective review of cases of anal carcinoma from two local hospitals. We obtained information on treatment response and cancer recurrence, as well as tobacco usage from medical records. *Results*: We identified 64 patients with squamous cell cancer of the anus, and 34 of these (53%) had a tobacco smoking history. Current smokers had higher carcinoma recurrence rates (11/34, 32%) than non-smokers (6/30, 20%). Overall mortality was 33% (21/64), and cancer-related mortality was 23% (15/64). Smokers were more likely to die from recurrence than non-smokers, with 45% of smokers dead compared to only 20% of non-smokers by 5 years after treatment. *Conclusion*: Tobacco smoking appears to be associated with anal carcinoma disease recurrence, and is related to increased mortality. This data suggests that patients should be cautioned about tobacco smoking once a diagnosis of anal carcinoma is made in attempt to improve their long-term outcome.

Keywords: Anal carcinoma; Anal cancer; Tobacco; Cigarette smoking; Squamous cell; Tumor recurrence; Multiple risk factors; HIV status; HPV status; Tumor stage; Tumor grade

1. Introduction

Squamous cell cancer of the anus is increasing in frequency in the general population in the United States, Europe and South America [1]. Between 1973 and 2000 in the United States, the incidence of anal cancer has increased 160% among men and 78% in women [2]. This increase is thought to be attributable to the corresponding increase in incidence of human immunodeficiency virus (HIV) and human papillomavirus (HPV) [3]. Overall, the development of anal cancer appears to be multifactorial. Identified risk factors include: infection with HIV and HPV, anal receptive intercourse, having more than 10 sexual partners, age over 50, immunosuppression, and tobacco smoking [1]. While many of the risk factors for the development of anal cancer have been extensively studied, little is known about their impact on recurrence. Recurrence, defined as both persistent disease and recurrence after completion of chemoradiation therapy, occurs in 10–30% of anal cancer patients [4]. Primary treatment for anal cancer is chemoradiation, with surgery reserved for incomplete response to treatment and/or recurrence. Here, we evaluated the risk of recurrence and mortality of anal carcinoma in association with tobacco smoking.

Smoking is an important risk factor for the development of several squamous cell cancers, and smokers often present with more advanced tumor stages. Smoking may confer

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a worse prognosis than non-smokers undergoing therapy for head and neck cancers [5]. However, smoking has not been evaluated as a risk for the recurrence of anal carcinoma once treatment has been initiated. We find that current smokers have higher recurrence rates of anal carcinoma than non-smokers, which contributes to their mortality.

2. Materials and methods

2.1. Patients and demographic data

A retrospective analysis of all cases of squamous cell cancer of the anus between 1999 and 2005 treated at the University of California, San Diego and Veteran's Affairs San Diego Healthcare System was performed. Patients were identified through the cancer registries and pathology databases at both institutions. Cases of transitional cell, cloacogenic or adeno-squamous cell cancers were not included. Patients with anal margin tumors were also excluded. Only patients with pathologically confirmed cases of invasive squamous cell cancer of the anal canal were included in our study. Staging was performed with computed tomography, exam under anesthesia and, when available, endoanal ultrasound, and followed American Joint Committee on Cancer (AJCC) guidelines. Upon completion of treatment, patients were followed up at 6 weeks and at 3 months with a physical exam, anoscopy and biopsy when appropriate. Thereafter, patients were followed every 3–6 months with physical exam and anoscopy, and every 6 months with endoanal ultrasound and CT scan for the first 2 years, then yearly for a total of 5 years. Incomplete response was defined by biopsy-proven residual disease that persisted at the first post-treatment examination and within 6 months of the completion the treatment. Recurrence was defined as biopsy-proven cancer 6 months after completion of treatment that had not been previously identified at post-treatment evaluation. For the purposes of our study, recurrence and incomplete response were grouped together. Treatment consisted of chemoradiation and surgical excision when indicated.

Demographics including the presence of HIV disease and smoking history were obtained from the patient's medical record. HPV infection was ascertained by extracting the patient's DNA from archived malignant formalin-fixed tissue and subjecting it to PCR and microarray analysis for conserved regions in the viral domain as previously described [6,7]. Smokers were defined as those patients with documented tobacco usage in the medical record before, during and after treatment for anal cancer. Non-smokers were defined as those patients who denied a history of tobacco usage within 5 years or greater of diagnosis of anal cancer.

2.2. Statistical analysis

To compare demographic data, smokers and non-smokers, Fisher's Exact test was used. For continuous variables minimums, median, means, maximum and standard deviations are reported by smoking status and overall. To compare smokers to non-smokers for recurrence and survival, Kaplan–Meier curves were generated and the Wilcoxon-Rank test was used. Time to recurrence and time to death was compared between smokers and non-smokers using a multivariate Cox proportional hazards model. P values ≤ 0.05 were considered significant. Statistical calculations were performed by UCSD Biostatistics Resource of the Rebecca and John Moores UCSD Comprehensive Cancer Center.

3. Results

3.1. Demographic data

A total of 80 cases were identified for inclusion in the study, and complete clinical and pathologic follow-up was available on 64 cases (80%). The mean follow-up time for the group was 35.9 months (range 1–72 months). Cases were grouped into individuals with anal cancer who smoked tobacco, and those without a tobacco history for the preceding 5 years (non-smokers). There was no significant difference between the two groups with regards to age or gender, as shown in Table 1, although there was a trend for smokers to be younger in our cohort. HIV-positive patients represented 36% of our patient population but the proportion of smokers and non-smokers with HIV did not differ significantly between the two groups (Table 1). HPV status was obtained from both pathologic reports and molecular analysis of anal cancer tissue, and was found to be positive in 46/49 (94%) cases tested. Using AJCC tumor staging guidelines, there was no significant difference between smokers and non-smokers with regards to stage of disease or histopathology (Table 1). Of those patients who received chemoradiation treatment, 84% completed the full course, which typically consisted of mitomycin C with 5-fluoruracil infusions and 50–54 Gy of radiation. There was no statistical significant difference between smokers and non-smokers with regard to completion of treatment.

3.2. Tumor recurrence

Recurrence occurred in 17/64 (26.6%) patients during our follow-up period, with most recurrences occurring within 24 months after treatment (Fig. 1). The time to recurrence trended towards a shorter time for smokers, with 11/34 (32%) of smokers with recurrence as compared to 6/30 (20%) of non-smoker showing recurrence compared to (Fig. 1). There were eight patients who underwent primary surgical resection without neo-adjuvant chemoradiation (4 smokers and 4 non-smokers), all with negative pathological margins at resection. Of these, 1/8 recurred (a smoker).