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ORIGINAL ARTICLE

Retrospective Study

Relationship between anal cancer recurrence and cigarette smoking

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Abstract

BACKGROUND

The incidence of anal cancer has been increasing in the United States. Smoking is a well-established risk factor; however, the impact of smoking on disease recurrence and outcome has not been well studied. The aim of this study was to assess the association between anal cancer recurrence and cigarette smoking.

AIM

To investigate the relationship between cigarette smoking status and anal cancer treatment outcome.

METHODS

The cancer registry from a single, community hospital was screened for patients with anal cancer between 2010 and 2021. The following characteristics were gathered from the database: Age; sex; cigarette smoking history; American Joint Committee on Cancer Clinical Stage Group; response to therapy; recurrence; time to recurrence; mortality; time to death; and length of follow-up. Patients were divided into the following groups: Current smokers; former smokers; and never smokers. SPSSv25.0 software (IBM Corp., Armonk, NY, United States) was used for statistical analysis.

RESULTS

A total of 95 patients from the database met the screening criteria. There were 37 never smokers, 22 former smokers, and 36 current smokers. There was no difference between groups in regards to race or sex. There was no difference in the American Joint Committee on Cancer Clinical Stage Group between groups. The former smokers were significantly older when compared to never smokers and current smokers (66.5 ± 13.17 *vs* 57.4 ± 7.82 *vs* 63.7 ± 13.80, P = 0.011). Former smokers and current smokers had a higher recurrence rate compared to never smokers (30.8% and 20.8% compared to zero, P = 0.009). There was not a significant difference in recurrence between former smokers and current smokers. There was no difference in the mortality, non-response rate, or time to death

between the groups.

CONCLUSION
Our data contributes evidence that cigarette smoking status is associated with increased recurrence for patients with anal cancer.

Key Words: Anal cancer; Smoking; Recurrence; Nigro protocol; Chemoradiation; Retrospective review

Core Tip: This retrospective review examined the impact of smoking on anal cancer treatment for 95 patients. Smoking status was associated with a significantly higher rate of anal cancer recurrence after standard treatment. There was not a significant association between smoking status and anal cancer treatment non-response or mortality. Further study is needed to determine if smoking cessation would alter the course of anal cancer or if adjunct therapy would be beneficial in patients with anal cancer and a smoking history.

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INTRODUCTION

The incidence of anal cancer is increasing[1]. Several risk factors have been associated with anal cancer including human papilloma virus (HPV), HIV, age, immunosuppression, and smoking[1-3]. Although the association between anal cancer and smoking has been well-documented, the association between smoking status and recurrence is much less studied. A few prior studies have examined the impact of smoking status on anal cancer treatment, but these studies have been relatively small with the largest including 171 patients, while the other two included 64 and 68 patients[4-6]. Given smoking is a modifiable risk factor, studies examining its relationship with treatment success are important. This study aimed to contribute to the body of data examining treatments and outcomes for patients who smoke and have anal cancer.

MATERIALS AND METHODS

The study was conducted as a retrospective review of the cancer registry from a single health system. The registry was screened for patients with anal cancer between 2010 and 2020. All patients included in the registry were over the age of 18. The following characteristics were gathered from the database: Age; sex; cigarette smoking status; American Joint Committee on Cancer Clinical Stage Group; treatment pathway; response to therapy; recurrence; time to recurrence; mortality; time to death; and length of follow-up. Non-response was defined as persistent presence of disease despite completing standard chemoradiation. Recurrence was defined as the presence of disease after documentation that there was not any disease present. Unfortunately, HPV status and HIV status were not included in the database. Within the database, smoking status was divided into current smokers, never smokers, and former smokers. Smoking status was determined based on cigarette smoking alone. Current smokers were classified as any patient that reported cigarette smoking within 30 d of the time of diagnosis. Former smokers were classified as patients who had stopped smoking at least 30 d prior to diagnosis.

SPSSv25.0 software (IBM Corp., Armonk, NY, United States) was used for statistical analysis. Age and length of follow-up were analyzed between groups using single factor analysis of variance with Tukey post-hoc test. Patient race and sex were analyzed between groups using Fisher's exact test and Pearson's χ^2 test, respectively. *P* values were generated using an exact Mann-Whitney *U*-test to compare the mortality, non-response, recurrence, and time to recurrence between the current, former, and never smoker groups. In order to minimize type I error and given the small sample size, Bonferroni adjusted *z*-test was completed to compare the recurrence rate between groups. A subgroup analysis was completed to analyze time to death for the patients who did not respond using a single factor analysis of variance test.

RESULTS

A total of 95 patients were identified from the database. The patients were divided into three groups: Current smokers; former smokers; and never smokers. There was no significant difference in age, race, or sex between the groups (Table 1).

Table 1 Demographic data

Variable	Cigarette use			*P* value
	Never, *n* = 37	Former, *n* = 22	Current, *n* = 36	
Age in yr,				0.011
mean ± SD	63.70 ± 13.80	66.50 ± 13.17	57.40 ± 7.82	
Clinical stage group				0.066
1	5 (13.5)	4 (18.2)	8 (22.2)	
2	14 (37.8)	9 (40.9)	18 (50.0)	
3	14 (37.8)	9 (40.9)	8 (22.2)	
4	4 (10.8)	0	2 (5.6)	
Race				0.273
Black	2 (5.4)	0	4 (11.1)	
White	35 (94.6)	22 (100)	32 (88.9)	
Sex				0.078
Female	30 (81.1)	17 (77.3)	21 (58.3)	
Male	7 (18.9)	5 (22.7)	15 (41.7)	
Length of follow-up in d				0.759
mean ± SD	1195.10 ± 1135.96	1023.20 ± 855.35	1218.20 ± 986.20	

Data are *n* (%). SD: Standard deviation.

There was a difference in age between groups, with the former smokers being older than the smoker and never smoker groups (Table 1).

There was no significant difference in mortality or non-response between groups (Table 2). Former and current smokers did have a significantly higher recurrence rate compared to never smokers ($P = 0.009$). There was no difference in recurrence between the former and current smokers (Table 2).

Time to death was analyzed between the groups. On average, there was a shorter time to death in the current smoker arm, but this was not statistically significant (Table 3). The mortality rate between groups in the non-responder subset was also examined. Never smokers who did not respond to treatment were approximately twice as likely to die (43% *vs* 22%), but this did not achieve statistical significance (Table 3).

DISCUSSION

While three prior studies have examined the relationship between anal cancer treatment and smoking status, these studies have been small[4-6]. Our data contributes further evidence that smoking status is associated with a worse outcome and increased recurrence for patients with anal cancer. Additionally, it raises two interesting questions: (1) Should smokers and former smokers have more aggressive anal cancer treatment to reduce risk of recurrence?; and (2) Does smoking cessation result in an improvement in anal cancer outcomes? Lerman *et al*[4] raised the question of whether smokers would benefit from programmed cell death 1 inhibitors given the seemingly reduced efficacy of chemoradiation in smokers and a similar trend in non-small cell lung cancer. While our paper is limited in its evaluation, it does highlight the need for studies examining varying treatment options for smokers moving forward.

Interestingly, 14 of the never smoker patients did not respond to initial treatment. Of these patients, 43% died, with an average of 598 d after diagnosis (Table 3). This mortality rate was twice as high as the mortality rate for former and current smokers who did not respond. Although this did not achieve statistical significance due to the small numbers of this study, it is an interesting trend. One potential hypothesis is that never smokers who do not respond to initial therapy have a more aggressive tumor biology. Our data is not extensive enough to examine this further, but future research should examine this relationship. If confirmed, one could consider examining more aggressive treatment pathways for never smokers who do not respond to initial chemoradiation.

Unfortunately, the database used for this study did not include patient HPV status. This could be an important confounder that is not accounted for in this data. In similar cohorts of patients, 74%-88% of patients with anal cancer were HPV positive[1,3]. Although HPV is certainly linked to anal cancer, these same studies have shown that smoking status is an independent risk factor for anal cancer apart from HPV[1,3]. Additionally, the impact of HPV status on anal cancer outcome is not clear at this time as the two other largest studies examining anal cancer outcome and smoking status did not have HPV status collected for their cohorts either[4,5].

Table 2 Outcome data by group

Variable	Cigarette use			*P* value
	Never, *n* = 37	Former, *n* = 22	Current, *n* = 36	
Death	14 (37.8)	6 (27.3)	8 (22.2)	0.332
Non-response	14 (37.8)	9 (40.9)	14 (38.9)	0.973
Recurrence	0	4 (30.8)	5 (20.8)	0.009
Time to recurrence in d (median interquartile range)	NA	195.0 (159.0-351.0)	362.0 (214.5-1019.0)	0.413
Recurrence and non-response combined	14 (37.8)	13 (59.1)	18 (50.0)	0.264

NA: Not available.

Table 3 Mortality subgroup analysis

Feature	Cigarette use			*P* value
	Never	Former	Current	
Mortality* subgroup	*n* = 14	*n* = 6	*n* = 8	
Time to death in d, mean ± SD	598.30 ± 734.61	848.40 ± 756.83	393.80 ± 325.69	0.465
Non-responder subgroup	*n* = 14	*n* = 9	*n* = 14	
Deaths in non-responders subgroup, *n* (%)	6 (42.9)	2 (22.2)	3 (21.4)	0.285

*Death. SD: Standard deviation.

As noted before, this study is limited in its scope due to the retrospective nature and limitations of the collected data. A prospective study examining the impact of smoking cessation on anal cancer treatment would be valuable. Even without a prospective study, this study adds important data indicating an increased incidence of anal cancer recurrence in patients who smoke.

CONCLUSION

This paper highlighted the increased risk of anal cancer recurrence in patients who smoke. Although this study was small and limited in its scope, compared to current literature it is the second largest cohort of patients examining anal cancer, smoking, and recurrence. Further research is needed to examine the impact of smoking cessation on anal cancer treatment outcome and if adjuncts to standard therapy would be beneficial in patients who smoke.

ARTICLE HIGHLIGHTS

Research background

Despite the occurrence of approximately 50000 new cases of anal cancer per year and the clear link with smoking, very few studies have examined the relationship between smoking status and treatment outcome. It has already been shown that there is a link between anal cancer and smoking. This paper goes further and showed that there was an increased risk of recurrence in patients who smoke and have a history of smoking. This serves as a foundation for future research to examine modifications to the current treatment approach for patients with anal cancer.

Research motivation

Investigating the relationship between cigarette smoking status and anal cancer treatment outcome.

Research objectives

The main objective of this study was to examine the relationship between smoking status and outcomes for patients with anal cancer.

Research methods

A total of 95 patients were included in this data, making it the second largest study to examine the impact of smoking on anal cancer treatment outcomes. The patients were similar between the groups (never smokers, former smokers, and current smokers) in regards to important factors such as clinical stage group, race, and sex. Former and current smokers had a higher recurrence rate compared to never smokers. There was no difference in the mortality, non-response rate, or time to death between the groups. Unfortunately, data did not include human papilloma virus status, which would be an important area to include for future research.

Research results

There was an increased risk of anal cancer recurrence in patients who currently smoke and have a history of smoking.

Research conclusions

This study was the second largest study examining the relationship between treatment outcome and smoking status in patients with anal cancer. Although this data was limited in its scope, it contributed further to the limited body of evidence that smoking increases risk of recurrence of anal cancer.

Research perspectives

Future research should examine the impact of smoking cessation on treatment outcomes for patients with anal cancer as well as the role of adjuncts to standard chemoradiation in the treatment of anal cancer.

FOOTNOTES

Author contributions: McMahon KR designed and performed the research and wrote the paper; Gemma N helped write and revise the report; Dibello J assisted with data curation and editing of the report; Clapp M assisted with data curation and editing the report; Sanchez-Montejo P assisted with data analysis and editing the report; Laipply E designed the research and supervised the report.

Institutional review board statement: The study was reviewed and approved by the Summa Health System Institutional Review Board (Approval No. 21176).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to inclusion in the cancer registry used in this review.

Conflict-of-interest statement: All the authors report having no relevant conflicts of interest for this article.

Data sharing statement: Statistical code and dataset available from the corresponding author at kevin.mcmahon88@outlook.com. Consent was not obtained, but the presented data are anonymized and risk of identification is low.

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