

Multiple primary malignancies in patients with anal squamous cell carcinoma

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Abstract: Prior studies examining the risk of second primary malignancy (SPM) after a first primary cancer generally have used large datasets such as the Surveillance, Epidemiology, and End Results (SEER) registry and excluded survivors of previous primaries and developers of synchronous primaries. The goal of this study was to provide a more complete representation of multiple cancer risk in squamous cell carcinoma of the anus (SCCA) patients. A single-institution retrospective study of 46 patients treated definitively for SCCA between January 2006 and July 2017 was conducted. Of the 46 patients, 18 (39%) had either a primary malignancy before SCCA (n=9) or SPM after an index SCCA (n=9). Six patients had ≥ 3 total malignancies. In our cohort, patients without SPMs tended to die from SCCA recurrence, while patients with SPMs were more likely to die from their SPM than from SCCA. Our study suggests that patients with SCCA are often either survivors of previous cancers or develop later malignancies. Several risk factors may play a role including HPV infection, HPV-related or treatment-related immunosuppression, somatic mutations due to chemotherapy, and genetic factors. Patients with SCCA require lifelong surveillance given their elevated risk of malignancy. Future work should focus on identifying genomic or immunologic factors that may predispose SCCA patients to develop multiple primary malignancies.

Keywords: Anal cancer; second primary malignancy (SPM); chemoradiotherapy

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Introduction

Improvements in early intervention and treatment modalities have led to a 26% decline in cancer death rates in the United States (US) in the past two decades (1). This has resulted in about 15 million cancer survivors alive in the US in 2016, a number expected to rise to 20 million by 2026 (2). However, cancer survivors are predisposed to develop new cancers due to risk factors such as genetic disorders and somatic mutations resulting from prior chemotherapy or radiotherapy (3,4). Cancer survivors are now a significant subset of patients presenting with new cancers, accounting for 17% of new

cancer cases in the US. An analysis of 10 high-incidence cancer sites using the Surveillance, Epidemiology, and End Results (SEER) registry showed that 55% of patients with two cancers died of their second primary malignancy (SPM), a greater percentage than patients with only a single primary who died of that cancer (5).

Patients with squamous cell carcinoma of the anus (SCCA) are at risk of SPM development due to favorable long-term survival, high association with human papillomavirus (HPV) (6), and receipt of chemoradiotherapy. A recent study found the 5-year age-standardized relative survival of SCCA patients to be 65.9%. Furthermore, half of SCCA

patients present with localized disease which portends a 5-year relative survival rate of approximately 80% (7). After an index SCCA, the rate of developing an HPV-related SPM is significantly increased (8). A study from France found an increase in global SPM in men but not women after index SCCA, hypothesized to be due to the higher prevalence of human immunodeficiency virus (HIV) in men (9).

Prior studies examining the risk of SPM after an index SCCA have used large datasets such as the SEER registry and excluded survivors of previous primaries and developers of synchronous primaries. By contrast, we conducted a single-institution study to provide a more complete representation of survivorship status, survival trends, and multiple cancer risk in SCCA patients.

Materials and methods

Study participants

An IRB-approved retrospective review identified 46 patients with SCCA treated with curative intent at Robert Wood Johnson University Hospital (RWJUH) and Rutgers Cancer Institute of New Jersey from January 2006 to June 2017. Additional malignancies were recorded through chart review and the RWJUH tumor registry. Multiple malignancies in a single patient were biopsy-proven to be morphologically and histologically different. Per National Comprehensive Cancer Network guidelines, patients were tested for HIV at time of SCCA diagnosis.

Patients received definitive chemoradiotherapy, with the exception of one patient treated with curative local excision. Standard of care consisted of 2 cycles of mitomycin-C (10–15 mg/m² on days 1 and 29) and 5-fluorouracil (5-FU) (1,000 mg/m² continuous infusion on days 1–4 and 29–32) with radiotherapy to 50.4–54 Gy to the pelvic lymph nodes and primary tumor. T3–T4 tumors received a boost to 60 Gy. For five patients, daily capecitabine was substituted for infusional 5-FU (10).

Definitions

We defined an “index primary malignancy” (IPM) as the first diagnosed cancer. A “second primary malignancy” (SPM) was defined as a biopsy-confirmed biologically distinct primary cancer that developed after IPM diagnosis. An SPM is “synchronous” if diagnosed <6 months after IPM diagnosis and “metachronous” if diagnosed ≥6 months after IPM diagnosis.

Data analysis

Patients were classified into one of three groups: prior IPM, SCCA-only and SPM after an index SCCA. Summary statistics of baseline characteristics and details of additional malignancies were provided for each group. Univariate logistic regression was used to assess associations between baseline characteristics [gender, age, race (white *vs.* non-white), stage (III/IV *vs.* others), smoking status (ever smoked *vs.* never smoked)] and either presence of ≥2 malignancies among all patients or development of SPM among index SCCA patients. Overall survival was estimated with the Kaplan-Meier method, measured from end of radiotherapy to date of death or last known follow-up. *P* < 0.05 was considered statistically significant. Analyses were performed using SAS version 9.4 (Cary, NC, USA).

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Results

Of the 46 patients treated definitively for SCCA, a total of 18 (39.2%) patients had multiple primary malignancies. Nine (19.6%) patients had a prior IPM, 9 (19.6%) developed SPMs after an index SCCA, and 28 (60.9%) had SCCA only. Six patients had ≥3 total malignancies. No baseline characteristics (*Table 1*) correlated with presence of ≥2 malignancies (among all patients) or development of SPM (among index SCCA patients).

Prior IPM patients

Among the 9 patients with a prior IPM, 7 were female. The median latency from IPM to SCCA diagnosis was 141.6 months (range, 20.5–296.7 months). All patients had a latency period of >120 months except for two who developed SCCA after 20 and 30 months. Of note, these two patients also developed third cancers within three months of SCCA diagnosis.

The most common IPMs were breast (n=4) and gynecologic cancers [endometrial (n=2) and vulvar (n=1)] (*Table 2*). Malignancies in the pelvic radiation field (gynecological and rectal) did not receive radiation, so subsequent development of SCCA was not clearly related to radiotherapy.

Table 1 Baseline characteristics of patient population

Characteristic	All patients No. [%]	Patients with prior IPM, N [%]	Patients with SCCA only, N [%]	Patients with SPM after index SCCA, N [%]
Total number of patients	46	9	28	9
Gender				
Male	14 [30]	2 [22]	9 [32]	3 [33]
Female	32 [70]	7 [78]	19 [68]	6 [67]
Race				
White	33 [72]	9 [100]	20 [71]	4 [44]
Black	6 [13]	0	4 [14]	2 [22]
Hispanic	7 [15]	0	4 [14]	3 [33]
Age (mean \pm SD)	58 \pm 9.2	63 \pm 8.7	58 \pm 9.6	56 \pm 7.3
Stage of SCCA at diagnosis				
Tis	1 [2]	1 [11]	0	0
I	3 [7]	1 [11]	1 [4]	1 [11]
II	21 [46]	5 [56]	12 [43]	4 [44]
III	18 [39]	2 [22]	12 [43]	4 [44]
IV	3 [7]	0	3 [11]	0
Smoking status				
Active smoker at SCCA diagnosis	8 [17]	1 [11]	6 [21]	1 [11]
Former smoker	16 [35]	3 [33]	9 [32]	4 [44]
Never smoked	22 [48]	5 [56]	13 [46]	4 [44]

IPM, index primary malignancy; SCCA, squamous cell carcinoma of the anus; SPM, second primary malignancy; SD, standard deviation.

Index SCCA patients

Of the 37 total patients with an index SCCA, 9 (23.7%) patients had ≥ 1 SPM (Table 2). The median latency from an index SCCA to first SPM diagnosis was 36.3 months (range, 1–146.1 months). Two patients had synchronous SPMs. None of the SPMs were found to be in the pelvic radiation field or HPV-related.

Median follow-up for SCCA-only patients and SPM patients was 45 and 102 months, respectively. Of the 28 SCCA-only patients, 6 died of SCCA within 10 months of treatment (Figure 1). Of the 9 SPM patients, 4 died from their SPM 12–36 months after diagnosis of their SPM. Three of these deaths were from stage IV lung cancer and one was from stage IV pancreatobiliary adenocarcinoma. There were not enough death events to correlate SPM status to survival.

Of the 9 patients who developed SPMs, 6 (67%)

developed lung cancers. Three of these patients had no smoking history, of which 2 developed multiple lung primaries. Non-small cell lung cancer (NSCLC) (n=6) and SCLC (n=2) accounted for 46% and 15% of the total number of SPMs, respectively. Four lung primaries were diagnosed at or progressed to stage IV.

Four patients were HIV positive with undetectable viral load while on antiretroviral medication. Of these four patients, one developed SCLC and NSCLC, and one developed 2 primary breast cancers.

Discussion

We discovered an elevated rate of multiple primary malignancies in SCCA patients. Of 46 total patients, 9 (19.6%) had prior IPMs and 9 (19.6%) developed SPMs after an index SCCA. The study is limited by lack of genomic analysis data and small sample size. However, several risk

Table 2 Distribution of SCCA patients with and without multiple malignancies

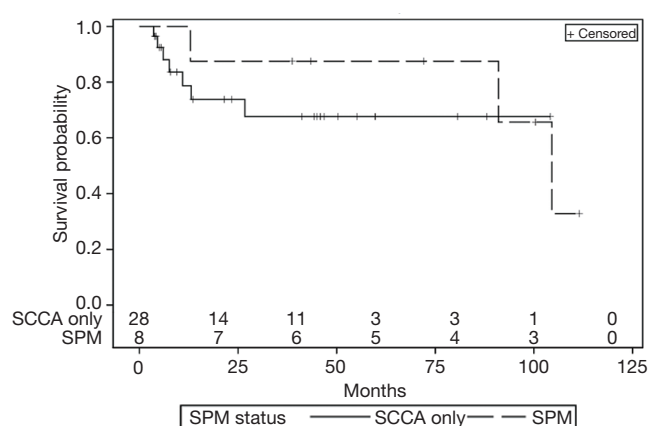
Characteristics	Number
Total number of patients	46
Patients with prior IPM	9 ^a (19.6%)
Total prior malignancies	14
Breast	4
Colorectal	3
Endometrial	2
Vulvar	1
Hepatocellular	1
Chronic lymphocytic leukemia	1
Multiple myeloma	1
Pancreatic	1
Patients with SCCA only	28 (60.9%)
Patients with SPM after index SCCA	9 ^b (19.6%)
Total subsequent malignancies	12
Lung	8
Non-small cell	6
Small cell	2
Breast	2
Pancreatohepatobiliary	1
Thyroid papillary	1

^a, one patient had 4 cancers prior to their SCCA diagnosis [colon (IPM), uterine, rectal, chronic lymphocytic leukemia]. Two patients with a prior IPM had a third cancer, within three months of SCCA diagnosis [patient 1: endometrial (IPM) and multiple myeloma; patient 2: vulvar (IPM) and pancreatic];

^b, two patients had two metachronous SPMs (patient 3: 2 breast primaries; patient 4: 2 NSCLC primaries). One patient had one synchronous and one metachronous SPM (patient 5: synchronous NSCLC and metachronous small cell lung cancer). One patient had one synchronous SPM (NSCLC). IPM, index primary malignancy; SCCA, squamous cell carcinoma of the anus; SPM, second primary malignancy.

factors may play a role including HPV infection, HPV-related or treatment-related immunosuppression, somatic mutations due to chemotherapy, and genetic factors.

HPV-related and treatment-related general immunosuppression may predispose patients to second cancers in our IPM and SPM cohorts. HPV16-specific T-cell frequency lowers dramatically after radical/curative

**Figure 1** Overall survival of patients with SCCA only versus patients with at least one SPM after an index SCCA. There were 7 deaths and 21 patients censored after last known follow-up in the SCCA only cohort, and 4 deaths and 5 patients censored in the SPM cohort. SCCA, squamous cell carcinoma of the anus; SPM, second primary malignancy.

treatment in oropharyngeal cancer patients (11). While information on HPV status was limited, HPV prevalence in anal cancer populations can be as high as 90% (6). Among patients with a prior IPM, we hypothesize that treatment-induced immunosuppression of previous cancers could lead to HPV persistence after infection, thus increasing risk of SCCA development (12). Though HPV infection is a risk factor for developing HPV-related SPMs after an index SCCA (8), there were none in our SPM patient cohort. However, virally-induced immunosuppression can indirectly promote tumor development (13); combined with treatment-induced immunosuppression, the risk for multiple cancers may increase.

The most common SPM was lung cancer, aligning with a SEER analysis which found increased risk of lung cancer after an index SCCA (14). One study suggests lung cancer is the most common SPM in survivors of common cancers, and suggested risk factors include exposure to etiological agents such as tobacco smoke and chemotherapy (5). However, 3 of the 6 patients who developed lung cancer never smoked, and 2 of the never-smokers developed multiple lung SPMs. Risk factors remain uncertain, but immunosuppression, somatic mutations from chemotherapy, or genetic factors may play a role.

SCCA-only patients were more likely to die soon after treatment from SCCA progression, whereas SPM patients tended to die soon after their SPM diagnosis. While

survival of the SCCA-only group stabilizes after about one year, survival of the SPM group worsens (*Figure 1*). SPM patients were cured of SCCA, but their SPMs generally had a worse baseline prognosis.

In conclusion, SCCA patients are often either survivors of previous cancers or develop later malignancies. As SCCA outcomes continue to improve and incidence rises (1,15), patients will be at increased risk for developing SPMs, an area which has not garnered sufficient study. We believe our findings provide a basis for examining these trends in a larger cohort. There is a possible genetic link between SCCA and lung cancer SPMs that should be investigated further. Identifying factors predisposing SCCA patients to SPMs may aid in the development of screening or surveillance tools, particularly for patients who respond to initial treatment.

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Footnote

Conflicts of Interest: Salma K. Jabbour has received research grants from Merck and Nestle. The other authors have no conflicts of interest to declare.

Ethical Statement: This retrospective study was conducted at the Rutgers Cancer Institute of New Jersey and approved by the Rutgers Institutional Review Board (Pro20170001775). Informed consent was waived, as this was a retrospective study.

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