Second Primary Malignancy in Anal Carcinoma –A US Population-based Study

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Abstract. *Background/Aim: To our knowledge, there are no data on second primary malignancies in anal cancer. This study was conducted to evaluate the risk of second primary malignancies in patients with anal carcinoma. Patients and Methods: We selected adult patients diagnosed with anal cancer from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) 13 database. We calculated the risk of second primary malignancies in these patients using multiple primary standardized incidence ratio (MP-SIR) session of SEER statistical software. Results: Among 7,661 patients, 675 (9.07%) developed 747 second primary malignancies, with an observed/expected ratio of 1.41 (95% confidence interval=1.32-1.52, p<0.001), and an absolute excess risk of ~55 per 10,000 population. Significant excess risks were observed for tumors of the oral cavity and pharynx, rectum and anal canal, larynx, lung and bronchus, ovary, vagina, and vulva, and Kaposi's sarcoma and hematological malignancies. The risk of specific second primary malignancies was related to the age of patients, exposure to radiotherapy and latency period. Conclusion: The risk of second primary malignancies in adult patients with anal cancer is significantly increased compared to the general population.*

Anal carcinoma constitutes only 2.5% of all digestive system malignancies with approximately 7,210 new cases in the United States in 2014 (1). The number of new anal cancer cases has been rising (2). Most patients with anal cancer present with localized (49%) or regional (32%) disease (2). The five-year disease-free survival for patients with non-metastatic anal cancer is more than 60% (2). It is important to investigate the long-term complications, including second primary malignancies (SPMs), in cancer survivors. The rate of SPMs in patients with anal cancer is unknown. In the present study, we analyzed the risk of SPMs in adult patients with anal carcinoma from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database.

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Patients and Methods

About the SEER database. The SEER program collects comprehensive cancer data from hospitals and cancer treatment centers and maintains high quality data from defined geographical areas. The SEER program collects data on primary tumor site, stage of the tumor, patient demographics, surgery and/or radiotherapy, survival of patients. The SEER 13 is a population-based cancer database sponsored by the National Cancer Institute. SEER 13 covers the following geographical area: San Francisco-Oakland SMSA, Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan), San Jose-Monterey, Los Angeles, Alaska Natives, and Rural Georgia which is 13.8% of the US population.

Study participants. We selected adult patients with anal carcinoma aged 18 years or older diagnosed during January 1992 to December 2011 from SEER 13 Regs Research Data, Nov 2013 Sub (1992-2011) database (3). We excluded cases diagnosed at autopsy and those who were lost to follow-up. Patients were followed-up from the diagnosis of anal carcinoma to the date of last known vital status, death, or the last point of data collection. SPM was defined as metachronous malignancy developing six months or more after an index anal carcinoma based on the Warren and Gates criteria (4), as modified by the NCI (5).

Statistical analysis. We used the multiple primary standardized incidence ratio (MP-SIR) session of SEER stat software Version 8.1.5 March 26, 2014 for statistical analysis. We calculated the SIR, absolute excess risk and confidence interval for SPM in patients with anal carcinoma by age (18-59 *versus* ≥60 years), latency (6-59 *versus* ≥60 months) and receipt of therapeutic radiation. The SIR is also known as the relative risk. It is a relative measure of the strength of association between first primary and second primary malignancies It is calculated by dividing the observed incidence of SPM by the expected incidence of SPM (O/E ratio) for the general population (6). Person-years of observation in the cohort, stratified by age, sex, calendar year, etc. are used to estimate the expected incidence of second cancer based on the cancer incidence rate in the general population. Absolute excess risk (AER) is an absolute measure of the clinical burden of

Table I. *Demographics of the patients indeed in this study.*

Characteristic	N (%)/median (range)
Total number of patients	7661
Gender	
Male	3196 (41.71%)
Female	4465 (58.28%)
Race	
White	6442 (84.08%)
Black	885 (11.55%)
Other	334 (4.35%)
Total number of SPM	747
Total number of patients with SPM	675 (9.07% of the study population)
Total number of patients with 1 SPM	
Male	244 (40%)
Female	366 (60%)
White	522 (85.57%)
Black	66 (10.82%)
Other	22 (3.61%)
Total number of patients with ≥2SPM	
Male	35 (53.85%)
Female	30 (46.15%)
White	62 (95.38%)
Black	22 (33.85%)
Other	0
Age at time of diagnosis of SPM, years	69.33 (34-103)
Latency to developing SPM, months	52 (6-219)
Follow up time, months	87 (7-239)

additional cancer occurrence in a given population. The AER is estimated by subtracting the expected number of second cancer cases from the observed number, dividing by the person-years at risk, and then multiplying by 10,000. Confidence intervals were calculated using Poisson distribution assumption.

Results

A total of 7,661 patients with a diagnosis of primary anal carcinoma were reported in the SEER 13 registry during January 1992 to December 2011. The median age (range) at diagnosis of anal cancer was 62.16 years (31-99 years) and the median duration of follow-up of patients was 87 months (7-239 months). The patient demographics are summarized in Table I.

A total of 675 patients (9.07%) developed 747 SPMs, with an O/E ratio of 1.41 (95% CI=1.32-1.52, $p\leq0.001$), and an absolute excess risk of 55.36 per 10,000 population (Table II). The median age at the time of diagnosis of SPM was 69.33 years (34-103 years). A significant excess risk of SPMs was observed for malignancies of head and neck, rectum, anus, lungs and bronchus, skin (excluding basal cell and squamous cell), vagina, vulva, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, and Kaposi's sarcoma (Table II). There was a significantly lower risk of malignancy of the ovary and prostate in comparison to the general population.

In the younger age group (18-59 years), 212 patients developed a total of 227 SPMs (O/E ratio of 2.51, $p\leq0.001$). These patients had a significant increase in the risk of malignancies of urinary bladder (N=7, O/E=3.10, $p\leq0.01$), non-Hodgkin's lymphoma (N=17, O/E=4.68, $p\leq0.05$), acute lymphoblastic lymphoma (N=3, O/E=21.8, $p\leq0.05$), acute myeloid leukemia (N=6, O/E=11.45, $p\leq0.05$), and Kaposi's sarcoma (N=5, O/E=20.18, $p\leq0.001$).

In the older age group (≥60 years), 463 patients developed 520 SPMs (O/E ratio 1.09, $p\leq0.001$). Skin cancer (excluding basal cell and squamous cell) incidence was significantly increased (N=26, O/E=1.61, $p=0.03$) while that of ovarian cancer (N=2, O/E=0.28, $p=0.05$, AER=−2.28) was significantly lower compared to the general population.

SPM and latency. The median latency period for development of all types of SPM in patients with anal carcinoma was 52 months (6-219 months). Skin cancer (excluding basal cell and squamous cell (N=19, O/E=1.74, $p=0.03$) and acute myeloid leukemia (N=7, O/E=3.44, $p=0.01$) were increased within the first five years of diagnosis of anal carcinoma.

Malignancies of bones/joints (N=2, O/E=7.81, $p=0.01$) and vagina (N=4, O/E=15.09, $p\leq0.05$) were increased and of kidney (N=1, O/E=0.15, $p=0.02$, AER=−3.24) were reduced 5 years after of diagnosis of anal carcinoma

Malignancies at all sites, of the head and neck, rectum, anus, vulva and prostate, non-Hodgkin's lymphoma and Kaposi sarcoma were increased both during first the five years and after 5 years of diagnosis of anal carcinoma.

SPM and radiation exposure. Out of 7,661 patients, 5,934 were exposed to radiotherapy (RT). There was a significantly increased risk of SPMs in both groups (RT group: N=533, O/E=1.35, $p\leq0.05$; no RT group: N=199, O/E=1.58, $p\leq0.05$). In the RT group, malignancies of bones and joints (N=3, O/E=8.04, $p=0.01$), vagina (N=5, O/E=11.41, $p\leq0.05$), acute myeloid leukemia (N=10, O/E=3.47, $p\leq0.05$) were significantly increased. In the group without RT, the incidence of skin cancer (N=11, O/E=2.14, $p=0.03$) was significantly higher compared to the general population. The risk of ovarian cancer (N=1, O/E=0.14, $p=0.01$, AER=−2.11), however, was lower compared to the general population.

Malignancies at all sites, the head and neck, anus, rectum, lung and bronchus, vulva and prostate, and non-Hodgkin's lymphoma and Kaposi sarcoma were increased in both groups.

Discussion

The number of cancer survivors is increasing (7). The Center for Disease Control's report on Cancer Survivorship estimates that the number of cancer survivors in the US is

Table II. *Second primary malignancy (SPM) inpatients withanal carcinoma.Total population: persons at risk: 7661; person-years at risk:39561.19.*

Site of SPM	Observed	Expected	O/E	*p*-Value	95% CI	Excess risk
All sites	747	527.97	1.41	<0.05	1.32-1.52	55.36
Head and neck	41	14.65	2.8	<0.05	2.01-3.8	6.66
Digestive system‡	161	79.28	2.03	<0.05	1.73-2.37	20.66
Colon excluding rectum	48	43.95	1.09	0.58	0.81-1.45	1.02
Rectum and rectosigmoid junction	40	14.78	2.71	<0.05	1.93-3.69	6.38
Anus, anal canal and anorectum	56	1.81	30.87	<0.05	23.32-40.09	13.7
Pancreatohepatobiliary	26	26.84	0.97	0.97	0.63-1.42	–0.21
Respiratory tract except larynx	175	75.88	2.31	<0.05	1.98-2.67	25.06
Lung and bronchus	172	75.01	2.29	<0.05	1.96-2.66	24.52
Bones and joints	3	0.5	6	0.03	1.24-17.54	0.63
Skin excluding basal/SCC	32	20.98	1.52	0.03	1.04-2.15	2.78
Breast	73	84.55	0.86	0.23	0.68-1.09	–2.92
Female genital system	50	32.85	1.52	0.01	1.13-2.01	4.34
Ovary	2	9.14	0.22	0.01	0.03-0.79	–1.8
Vagina	5	0.56	8.98	<0.05	2.92-20.95	1.12
Vulva	19	1.82	10.45	<0.05	6.29-16.32	4.34
Male genital system	27	76.33	0.35	<0.05	0.23-0.51	–12.47
Prostate	25	75.35	0.33	<0.05	0.21-0.49	–12.73
Penis	1	0.34	2.93	0.58	0.07-16.33	0.17
Urinary system	45	40.72	1.11	0.54	0.81-1.48	1.08
Urinary bladder	34	24.79	1.37	0.09	0.95-1.92	2.33
Kidney	10	13.6	0.74	0.41	0.35-1.35	–0.91
Ureter	1	0.73	1.37	1.04	0.03-7.61	0.07
Brain and other nervous system	2	5.41	0.37	0.19	0.04-1.34	–0.86
Thyroid	7	7.19	0.97	1.14	0.39-2.01	–0.05
All lymphatic and hematopoietic diseases	71	45.09	1.57	<0.05	1.23-1.99	6.55
Hodgkin lymphoma	3	1.33	2.26	0.3	0.47-6.61	0.42
Non–Hodgkin lymphoma	43	22.4	1.92	<0.05	1.39-2.59	5.21
Acute lymphocytic leukemia	3	0.46	6.51	0.02	1.34-19.03	0.64
Chronic lymphocytic leukemia	1	6.06	0.17	0.03	0-0.92	–1.28
Acute myeloid leukemia	11	3.92	2.81	<0.05	1.4-5.02	1.79
Chronic myeloid leukemia	2	1.74	1.15	1.04	0.14-4.15	0.07
Kaposi sarcoma	5	0.47	10.57	<0.05	3.43-24.66	1.14
Other	29	16.72	1.73	0.01	1.16-2.49	3.1

‡Except pancreaticohepatobiliary tumors; SCC: squamous cell carcinoma.

more than 13 million today, and is increasing as a result of early diagnosis and improvement in effective treatment (8). In fact, approximately 18 million cancer survivors are expected by 2022. Several factors including cancer type, pre-existing conditions and therapeutic interventions lead to increased risk of long-term morbidity and premature mortality in cancer survivors (9-11). Improved understanding of long-term complications of cancer and its treatment is necessary to guide post-treatment surveillance of patients. The 2005 Institute of Medicine report recommends use of evidence-based clinical practice guidelines to identify and manage long-term effects of cancer and its treatment (12). Unfortunately, due to lack of high-quality evidence, there are no standardized practice guidelines for management of adult cancer survivors. There is little research on survivors with recurrent disease or second cancer.

In this population-based study, we report on the risk of SPMs in patients with anal cancer. Our study shows that patients with anal carcinoma have 41% increase in risk of SPMs with an AER marginally higher than 55 per 10,000 population. Lung and bronchial cancer accounted for the largest proportion of excess second cancer burden and was the most common SPM associated with anal cancer. Lung and bronchial carcinoma in patients with anal carcinoma may be due to shared risk factors of smoking, human papilloma virus infection (HPV) (13). RT for anal carcinoma may also predispose to development of lung carcinoma in this sub-group of patients (14, 15). There was also a significantly increased risk of malignancies of the head and neck, vagina and vulva. HPV has been linked with these tumors as well as anal carcinoma (16-18). Kaposi's sarcoma is common in patients with human immunodeficiency virus infection and acquired

immune deficiency syndrome (HIV/AIDS). HIV is also a risk factor for anal carcinoma (13). Shared etiology might be implicated for development of Kaposi's sarcoma in patients with anal carcinoma. Risk of SPM in anal cancer differs by age of the patient, exposure to RT and latency period. Interestingly, we found that there was decreased risk of malignancies of ovary and prostate compared to the general population.

Strengths of our study include its large sample size, high level of quality control of the SEER program, and 98% case completeness. Limitations of our study are specific to use of a population-based registry. The SEER program does not collect data on co-morbidities, chemotherapy treatment or risk factors such as history of smoking, alcohol use, HPV status, family history of cancer. Similarly, a small number of recurrences in certain anatomical locations may be misclassified as SPM. Migration of patients out of a SEER geographic registry may lead to underestimation of SPM risk.

In summary, our study showed that risk of SPM is significantly increased in patients with anal cancer. The risk of specific SPM depends on patient's age and latency period. These findings suggest that evaluation for SPMs should be an important aspect of follow-up examination of anal cancer survivors.

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