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Second primary uterine malignancies after radiation therapy for cervical cancer

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Abstract

Purpose Radiation exposure has long been established as a risk factor for cancer development. The purpose of this study is to assess the risk of uterine malignancy in patients previously treated for cervical cancer with radiation therapy.

Methods A population-based cohort of 9092 patients diagnosed with cervical cancer who did not undergo surgery and received radiation therapy between 1973 and 2008 was identified from the Surveillance, Epidemiology and End Results Program database (SEER 9). Patients in this cohort who developed endometrial cancer after treatment of cervical cancer were identified. 55,140 patients with endometrial cancer were also identified. The distribution of the different histologic types of endometrial cancer was determined for each of these cohorts.

Results 54 patients (0.6%) were diagnosed with an endometrial cancer more than 12 months after diagnosis of cervical cancer. The average latency to endometrial cancer diagnosis was 160 months, with a range of 14–374 months. The average age of cervical cancer diagnosis was 52 years and the average age at subsequent endometrial cancer diagnosis was 66 years. Only 40% of the endometrial cancers diagnosed following treatment of cervical cancer were endometrioid. The majority were clear-cell adenocarcinomas (42%), 9% were carcinosarcomas and 5.5% were leiomyosarcomas. Of the 55,140 endometrial cancer patients in the database, a vast majority were endometrioid adenocarcinomas (91%), and only 2.3% clear-cell adenocarcinoma, 2.3% carcinosarcoma and 0.5% leiomyosarcoma. The difference in histologic type distribution between these two cohorts is highly significant ($p < 0.01$).

Conclusion A small proportion of women who receive radiation for cervical cancer go on to develop endometrial cancer. These are predominantly of the more aggressive histologic types when compared to primary endometrial cancers. The latency from cervical cancer diagnosis to endometrial cancer diagnosis is over a decade. In a patient who still has a uterus after receiving pelvic radiation, vaginal bleeding should be investigated.

Keywords Second malignancies · Radiation-induced malignancies · Cervical cancer · Endometrial cancer · Cancer epidemiology · Radiation therapy

Introduction

The mainstay of treatment for locally advanced cervical cancer is definitive radiation therapy, which consists of brachytherapy and external beam pelvic radiotherapy with concomitant chemotherapy. Patients with multiple medical comorbidities or with poor baseline functional status may also receive primary radiation therapy rather than surgical management of their early-stage cervical cancer [1].

A key principle of radiation therapy is that it targets rapidly dividing cells. Unfortunately, this does not spare non-cancer cells, and patients often have acute reactions due to effects of radiation on rapidly dividing cells in the skin, hair, gastrointestinal and reproductive tracts, and the bone

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marrow. In gynecologic cancer patients, acute side effects include nausea, fatigue, and diarrhea [2]. Late complications, defined as those seen 90 days or more following therapy, are thought to be related to the dose per fraction, total dose, and the volume irradiated. Observed late complications include cystitis, proctitis, enteritis, fistula formation, vaginal apex agglutination, and second radiation-associated cancers [2].

Radiation exposure has long been established as a risk factor for cancer development. Much of what we know regarding the risk of exposure to ionizing radiation comes from studying survivors of the atomic bombs in Hiroshima and Nagasaki [3]. According to the Biological Effects of Ionizing Radiation Report (BEIR VII), there is a linear association between increasing radiation dose exposure and subsequent solid cancer development [3]. Excess cancers above those observed in the general population have been observed with whole-body radiation doses between 100 and 4000 mSV, or the equivalent of about 4 Gy, of radiation energy [3].

In general, exposure to ionizing radiation induces cell death via both mitosis and apoptosis. In mitotic cell death, interaction of charged particles with intracellular water leads to the production of free radicals, which in turn creates complex DNA strand breaks [3]. This DNA damage causes activation of cell cycle checkpoints. At these checkpoints, the cell cycle will either pause to repair the DNA damage or will permanently arrest, causing cell death [4]. Given the complexity of these breaks, inherent DNA-repair mechanisms are often times unable to accurately repair the breaks, leading to DNA mutations. When the affected cell attempts to divide during mitosis, it is unable to complete the process due to the unrepaired DNA and thus undergoes necrosis. In apoptotic cell death, radiation triggers a cascade of events that leads to nuclear DNA and plasma membrane damage. Ultimately, the cancer cells lose their reproductive capability, also known as "clonogenic capacity" [3, 4]. The DNA damage that leads to tumor initiation has been shown to be dose-dependent [3].

Kamran et al. reviewed the literature on second malignancies after radiation therapy for primary breast, hematologic, gynecologic, and pediatric cancers. Along with an overall increased risk of secondary cancers among all of these groups, the authors also found that this risk was associated with a number of other factors, including hormonal factors, use of chemotherapy, age, genetic factors, infection, and immunosuppression [5].

Specific to the pelvis, Wright et al. identified patients in the Surveillance, Epidemiology and End Results (SEER) database between 1973 and 2005 who received pelvic radiotherapy for uterine, vulvar, cervical, anal, and rectosigmoid cancers. Given that a large portion of functional bone marrow is within the pelvis, the authors aimed to identify risks of leukemia and multiple myeloma due to pelvic irradiation. Their study showed only an increased risk of leukemia (HR 1.72, 95% CI 1.37–2.15). This risk peaked between 5 and 10 years post-treatment and persisted even after 15 years [6].

A number of large database studies have been performed to better quantify the risk of second primary malignancies after radiation therapy. A 2011 SEER database study by Berrington de Gonzalez et al. analyzed 647,672 5-year cancer survivors in the adult United States population. Patients identified included those who had cancers that are traditionally treated with radiation. The patients were followed for an average of 7 years, and 7% ($n=60,271$ patients) developed a second cancer. Of this group, an estimated 3266 developed a second malignancy that could have been caused by radiation. The relative risk was highest when greater than 5 Gy of total radiation was received [7].

Burt et al. similarly used the SEER database to identify second primary malignancies in women who received radiation for primary breast cancer. Of the 154,697 patients who received radiation, 13% ($n=49,867$) went on to develop a secondary malignancy, and 3.4% developed cancers attributable to radiation. This risk was most significant in patients diagnosed with breast cancer at a young age and who had longer latency to second cancer diagnosis [8].

A meta-analysis by Rombouts et al. showed that regardless of primary tumor site, radiation to the pelvis led to an increase in rectal cancer (RR 1.43, 95% CI 1.18–1.72). In particular, an increased risk was seen after radiation for prostate cancer (RR 1.36, 95% CI 1.10–1.67) and cervical cancer (RR 1.61, 95% CI 1.10–2.35) [9]. In keeping with these findings, Warschkow et al. showed that patients who receive radiation after resection for local or locally advanced rectal cancer went on to have an increased risk of endometrial cancer (HR 1.95, 95% CI 1.49–2.56), and bladder cancer (HR 1.54, 95% CI 1.31–1.80) [10].

When looking at gynecologic cancers specifically, the risk of second malignancies after pelvic radiation has long been a source of scrutiny. One of the earliest case reports from 1982 reported on 15 patients who developed endometrial cancer more than 10 years after pelvic radiation with external beam and radium implants for cervical squamous cell carcinoma (13/15 patients) and ovarian cancer (2/15 patients). About 66% of the second malignancies were endometrioid adenocarcinomas and the remaining one third (33%) were carcinosarcomas. The interval to second cancer from initial radiation was 17.2 years [11]. The authors concluded that although the incidence of second malignancies is low, long-term gynecologic cancer survivors should be closely watched for the interval development of second malignancies, particularly after radiation therapy [11].

This case series has been followed by a number of institutional and database studies on secondary malignancies after radiation. A 2010 SEER database study by Lonn

et al. investigated second cancer risks among patients who received brachytherapy and external beam radiation therapy (EBRT) for uterine corpus cancer. Patients who had received surgery and radiation therapy were compared with patients who received surgery alone. Among patients who received radiation along with surgery, the incidence rate ratios (IRR) were highest for combination radiotherapy (IRR 1.26, 95% CI 1.16–1.36), followed by EBRT (IRR 1.15, 95% CI 1.08–1.22), and brachytherapy alone (IRR 1.07, 95% CI 1.00–1.16) [12]. The organs at highest risk included the colon, rectum, and bladder. Leukemia was also observed in patients who had received EBRT. Patients who had survived 10 or more years after uterine corpus cancer were at the highest risk of developing second solid cancers after radiation [12].

A randomized study in Norway investigated long-term outcomes of vaginal brachytherapy alone vs. brachytherapy with EBRT in stage I endometrial cancer patients who underwent primary surgery. The study concluded that while there was no statistically significant difference in overall survival, women younger than 60 years old had higher mortality rates after receiving brachytherapy and EBRT combined. Furthermore, there was an overall increased risk of second cancers after EBRT, particularly in women less than 60 years old (HR 2.02, 95% CI 1.30–3.15) [13]. Similarly, Kumar et al. in 2009 evaluated second primary cancers after radiation therapy for endometrial cancer. Patients who received radiation for primary endometrial cancer were compared to those who did not. The absolute excess risk of developing a second primary cancer after radiation was 17.11 [14]. The relative risk of developing a secondary cancer increased with latency, with a peak risk at 10 or more years after radiation therapy ($p < 0.001$) [14].

In contrast, Wiltink et al. investigated the risk of second malignancies among patients enrolled in the Dutch total mesorectal excision (TME) trial as well as patients enrolled in the post-operative radiation therapy in endometrial carcinoma (PORTEC) 1 and 2 trials. The authors found that there was no increased risk of second malignancies among patients who received EBRT or vaginal brachytherapy after surgery for rectal or endometrial cancers [15]. However, rectal and endometrial cancer survivors both had an increased lifetime risk of developing a second cancer when compared to the general population [15].

In our clinic, we have treated several patients who developed endometrial cancer of aggressive histologic types many years after receiving radiation therapy for cervical cancer. The purpose of our study is to further quantify the risk of endometrial malignancy in patients previously treated with radiation therapy for cervical cancer and to investigate if these patients are more at risk for developing high-risk histologies when compared to primary endometrial cancers.

Methods and materials

All patients were identified using the National Cancer Institute's SEER database. This database includes incidence and population data stratified by race, sex, year of diagnosis, geographic area, and age. The collected data are thought to be representative of the general United States population. The SEER 9 data set contains the most longitudinal data and includes approximately 9.4% of the entire United States population based on 2010 census data. Regions covered include San Francisco-Oakland, Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, and Atlanta.

Using the SEER*Stat software program (Surveillance Research Program, National Cancer Institute, Bethesda, MD), a population-based cohort of 9092 patients diagnosed with cervical cancer who did not undergo surgery and who received radiation therapy between 1973 and 2008 was identified. *International Classification of Diseases for Oncology* third edition site and morphology classification codes for endocervix [C53.0], exocervix [C53.1], and cervix uteri [C53.9] were used to identify primary site of malignancy. Additional parameters included not having undergone surgery and having received either "beam radiation, radioactive implants, or combination of beam with implants or isotopes." Cases reported on death certificate or autopsy, as well as those with unknown age at diagnosis were excluded.

A second cohort of 55,140 women with primary endometrial cancer from this database was also identified. *International Classification of Diseases for Oncology* third edition histology codes for endometrial stromal sarcoma [8930/3], adenosarcoma [8933/3], stromal sarcoma not otherwise specified (NOS) [8935/3], carcinosarcoma, NOS [8310/3], clear-cell adenocarcinoma, NOS [8310/3], leiomyosarcoma, NOS [8890/3], serous cystadenocarcinoma, NOS [8441/3], and endometrioid carcinoma [8380/3] were utilized to identify the distribution of the different histologic types of primary endometrial cancers.

A multiple outcome analysis was then performed to identify second malignancies among patients with primary cervical cancer treated with radiation. A latency of 12 months to second primary diagnosis was required to exclude synchronous malignancies. Analysis was limited to uterine cancer events only. Selected events included cancers of the corpus and uterus (NOS), corpus uteri, and uterus (NOS). The same endometrial cancer histology codes as above were utilized to determine the distribution of endometrial cancer histologies among patients previously treated with radiation for primary cervical cancer. The distribution of endometrial cancer histologies was then compared between the two cohorts to determine if

patients previously treated with radiation for cervical cancer are more likely to experience more aggressive histologic types.

Results

54 patients (0.6%) were diagnosed with an endometrial cancer more than 12 months after diagnosis of cervical cancer. The average latency to endometrial cancer diagnosis was 160 months, with a range of 14–374 months. The average age of cervical cancer diagnosis was 52 years and the average age at subsequent endometrial cancer diagnosis was 66 years. Only 40% of the endometrial cancers diagnosed following treatment of cervical cancer were endometrioid. The majority were clear-cell adenocarcinomas (42%), 9% were carcinosarcomas and 5.5% were leiomyosarcomas. These results are summarized in Table 1. The bolded rows indicate the main purpose of the study, i.e. to compare the proportion of patients who develop endometrioid vs. non-endometrioid endometrial cancer histologies.

Of the 55,140 primary endometrial cancer patients in the database, a vast majority were endometrioid adenocarcinomas (91%), and only 2.3% clear-cell adenocarcinoma, 2.3% carcinosarcoma and 0.5% leiomyosarcoma. These results are shown in Table 2. Similar to Table 1, the bolded rows indicate the main purpose of the study, i.e. to compare the proportion of patients with endometrioid vs. non-endometrioid endometrial cancer histologies. The difference in histologic type distribution between these two cohorts is highly significant ($p < 0.01$).

Table 2 Primary endometrial cancer histologies in the SEER database

Endometrial cancer histologies	#	% of endometrial cancers (total = 55,140)
Endometrial stromal sarcoma	838	1.52
Adenosarcoma	392	0.71
Stromal sarcoma, NOS	65	0.12
Carcinosarcoma, NOS	1296	2.35
Clear-cell adenocarcinoma, NOS	1247	2.26
Leiomyosarcoma, NOS	291	0.53
Serous cystadenocarcinoma, NOS	875	1.58
Endometrioid adenocarcinoma	**50,136**	**90.9**
Non-endometrioid histology	**5004**	**9.1**

Discussion

There have been a number of suggested risk factors for the development of second malignancies among cancer survivors, including genetic risk factors, lifestyle factors, chemotherapy, and radiation [7]. The role of radiation therapy in particular has been the source of much debate.

The results of our study appear to be congruent with previous studies that show an increased risk of endometrial cancers after radiation therapy. In a large international study of 19 population-based cancer registries, cervical cancer patients across the globe were analyzed to determine the effect of radiation dose on second cancer risk [16]. Radiation doses at each organ site were determined by reconstructing the patient's original radiotherapy regimen. A total of 4188 women with second cancers were identified. Doses of radiation greater than several hundred Gray were associated with an increased risk of cancers of the bladder (RR 4.0), rectum (RR 1.8), vagina (RR 2.7), bone (RR 1.3), uterus (RR 1.3), cecum (RR 1.5), and non-Hodgkin's lymphoma (RR 2.5).

Table 1 Second primary endometrial cancers among cervical cancer survivors in the SEER database

Endometrial cancer histologies	#	% of primary cervical cancer survivors (total = 9092)	% of secondary uterine malignancies (total = 54)
Endometrial stromal sarcoma	0	0	0
Adenosarcoma	0	0	0
Stromal sarcoma, NOS	0	0	0
Carcinosarcoma, NOS	5	0.05	9.26
Clear-cell adenocarcinoma, NOS	23	0.25	42.6
Leiomyosarcoma, NOS	3	0.03	5.55
Serous cystadenocarcinoma, NOS	1	0.01	1.85
Endometrioid adenocarcinoma	**22**	**0.24**	**40.7**
Non-endometrioid histology	**32**	**0.35**	**59.3**
Total second primary uterine cancers	54	0.59	–

For second gynecologic malignancies in particular, a sharp increase in risk (more than fivefold) was identified for radiation doses greater than 150 Gy [16].

Kumar et al. utilized the SEER database to identify endometrial cancers that were diagnosed after radiation for genitourinary, colorectal, cervical, vulvar, and vaginal cancers. These cases were compared to "sporadic" cases of endometrial cancer among patients who did not receive radiation for their primary cancers. Similar to our study, the radiation-associated endometrial cancers were more likely to be of more aggressive histologies (76.2% non-endometrioid vs. 51%, $p < 0.001$), poorly differentiated (58% vs. 28%, $p < 0.001$), and of advanced stage (43% vs. 16%, $p < 0.001$) [17]. These subtypes included squamous cell carcinoma (2%), mixed cell carcinoma (4.9%), adenocarcinoma NOS (30.3%), endometrioid (16.6%), clear-cell carcinoma (2.9%), uterine papillary serous carcinoma (17.1%), and sarcoma (26.3%) [17]. In contrast to this study, the rate of clear-cell carcinoma observed in our data set was much higher (42% vs. 2.9%).

A retrospective cohort study from Memorial Sloan Kettering and MD Anderson Cancer Centers revealed similar results. Twenty three patients developed endometrial cancer or carcinosarcoma after having received radiation for cervical cancer. Sixteen of these cases were high-risk histologies, including serous, clear cell, carcinosarcoma, and undifferentiated. These cases were then compared to sporadic endometrial cancer cases at Sloan Kettering. High-risk histologies made up 70% of all second endometrial cancers as compared to 15% in the sporadic group [18]. An additional study of the same subjects showed that the mean age of endometrial cancer diagnosis was 64.4 years with a range of 53–80 years, and the average latency period between time of radiation and diagnosis of endometrial cancer was 14 years [19].

A more recent study by Matsuo et al. in 2018 evaluated second primary uterine cancers after radiation for cervical cancer. A total of 5277 women who did not undergo hysterectomy and received pelvic radiation therapy for cervical cancer were analyzed. Among the study population, only 22 women went onto develop metachronous uterine malignancies, of which the most common was endometrial cancer (95.5%), followed by uterine sarcoma (4.5%) [20]. Similar to our study, a majority of the metachronous endometrial cancers were non-endometrioid in histology (59.1%) [20]. In contrast to our findings, however, patients were more likely to develop endometrial serous carcinoma rather than clear-cell carcinoma [20].

Thus, along with prior studies, our study shows an increased risk of second endometrial malignancies after radiation therapy for cervical cancer. This becomes more clinically significant as the treatment and overall survival of cervical cancer patients improve given the long latency to second endometrial cancer development.

There are a number of limitations to our study. The SEER database is thought to be representative of the general United States population. However, the database is limited to its contributing registries. This may lead to a selection bias among patients who did or did not receive radiation based on geographic location or proximity to gynecologic oncologists and tertiary care centers. Furthermore, the SEER database does not include data on important risk factors for endometrial cancer such as body mass index (BMI), exposure to hormones, or other co-morbid conditions [10]. Future studies should seek to identify and assess the role of these factors when analyzing risk of metachronous endometrial cancer among cervical cancer survivors who had been treated with radiation.

Conclusion

A small proportion of women who receive radiation for cervical cancer go on to develop endometrial cancer. However, these are predominantly of the more aggressive histologic types when compared to primary endometrial cancers. The latency from cervical cancer diagnosis to endometrial cancer diagnosis is over a decade. In a patient who still has a uterus after receiving pelvic radiation, vaginal bleeding should be investigated. Furthermore, the risk of second malignancies should be discussed with patients when counseling them on radiation therapy for inoperable primary cervical cancer.

Author contributions KP: project development, data collection, data analysis, manuscript writing. KLH: data analysis, manuscript editing. EH: project development, data analysis, manuscript editing. CC: project development, data analysis. SR: project development, data analysis.

Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest. No financial disclosures.

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