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Second primary cancer risk in cervical cancer patients after definitive radiotherapy: a nationwide population-based study

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► ***Original article***

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ABSTRACT

***Background*:** Although radiotherapy (RT) is an important treatment modality for cervical cancer, it can cause cancer. However, the risk of second primary cancer (SPC) tends to be ignored during RT for cervical cancer. We analyzed the prevalence and incidence patterns of SPC in cervical cancer patients that underwent definitive RT. ***Materials and Methods*:** The insurance claims data of cervical cancer patients that underwent definitive RT from 2007 to 2012 were analyzed. Standardized incidence ratios (SIRs) were used to estimate the relative risks of SPC. In addition, odds ratios were estimated by unconditional Poisson regression and adjusted for age at cervical cancer diagnosis, chemotherapy, and comorbidities. ***Results*:** Median patient age was 59.4 years. SIRs for bladder, ovary, and uterine cancer were 6.72 (95% confidence intervals (CI) 3.36–12.03, $p < 0.001$), 7.12 (95% CI 4.22–11.25, $p < 0.0001$), and 8.44 (95% CI 5.08–13.18, $p < 0.001$), respectively. The SIRs of all organs in the pelvic irradiation field were significantly increased. SIRs for breast and stomach cancer were 0.5 (95% CI 0.22–0.99, $p = 0.0441$) and 0.8 (95% CI 0.43–1.37, $p = 0.5331$), respectively. SIRs were not affected by chemotherapy, age, or comorbidities. ***Conclusion*:** RT increases the incidence of SPC in cervical cancer patients. In particular, SPC rates of organs in the irradiation field were higher than those of organs outside the irradiation field. If SPC risk were quantified with respect to irradiation dose, it could be utilized in clinical practice.

INTRODUCTION

Cervical cancer is a highly prevalent solid cancer among women and has a high cure rate due to recent treatment developments [1, 2]. However, some studies have reported that the rate of second primary cancer (SPC) in cancer patients is higher than in the general population [3, 4]. Genetic predispositions and lifestyles may cause other cancers in cancer patients, but several studies have reported that radiotherapy (RT) is a possible cause of SPC [5-8]. In clinics, the risk of SPC development is often not considered when deciding on a treatment modality. However, patients with cervical cancer have much longer life expectancies than patients with other organ cancers [9]. The 5-year survival rate for all stages of cervical cancer is around 63% [10]. Moreover, cervical cancer patients are relatively young at disease onset.

RT is an important treatment modality in cervical cancer and the treatment of choice in locally advanced cervical cancer when surgery is considered difficult. RT is usually used in combination with chemotherapy and regional lymph node chains are included in irradiation fields [11, 12]. Furthermore, adjacent organs such as bladder and bowel are inevitably exposed to radiation. Considering planned target volumes and penumbra areas, all organs in the pelvis are exposed to radiation to greater or lesser extents. Some studies have already been undertaken on radiation-induced SPC [13-15], but the majority are old or phantom studies and have limited relevance in terms of modern treatment techniques [16].

RT is a widely used therapeutic modality in cervical cancer, but it can cause SPC. It is known that the incidence of radiation-induced SPC increases after 5 years [17]. In cervical cancer with a long life expectancy, SPC is a topic that deserves more attention but there are few studies on SPC in cervical cancer. We analyzed the prevalence of SPC in cervical cancer patients that received definitive RT, using the database compiled by the South Korean Health Insurance Review & Assessment Service (HIRA). The effects of age, co-existent diseases, and chemotherapy were also analyzed.

MATERIALS AND METHODS

The Korean National Health Insurance (NHI) System is a national system that includes almost all residents. Data such as sex, age, diagnosis, prescriptions, and procedures for nearly all medical

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claims in South Korea are stored in the HIRA database. The present study was conducted on a nationwide cohort using this database. The subjects were 3,267 patients diagnosed with cervical cancer from January 2007 to December 2012 that underwent definitive RT and all received whole pelvic RT and intracavitary brachytherapy. Those that underwent surgery with distant metastasis or a concurrent malignancy were excluded. In the 3,267 study subjects, the occurrence of SPC was observed until April 2020. The institutional review board (IRB) of Dongguk University Gyeongju Hospital approved the present study (IRB no. 110757-202009-HR-03-02, 2/9/2020).

The study population consisted of 3,267 patients diagnosed with cervical cancer (C53) according to the Korean Classification of Disease sixth edition (KCD-6), a version of the International Classification of Disease 10 (ICD-10) modified for the Korean health care system. Cervical cancer subgroups, that is, endocervix (C530), exocervix (C531), overlapping lesion of cervix uteri (C538), and unspecified (C539), were included. The occurrences of colorectal cancer (C17, C18, C19, C20), bladder cancer (C67), ovarian cancer (C56), uterine cancer (C54), breast cancer (C50), hepatic cancer (C22), lung cancer (C34) and stomach cancer (C16) after definitive radiotherapy were monitored until December 2020. Risks associated with age at cervical cancer diagnosis, time of SPC occurrence, the presence of comorbid diseases, and chemotherapy were analyzed. Metastatic cancers were excluded. Patients were identified using procedure codes for external beam RT (HD055, HD056, HD061) and intracavitary brachytherapy (HD081, HD082).

Standardized incidence ratios (SIRs) were used to estimate the relative risks of SPC development and were calculated with respect to risks in the South Korean female population. Reference incidences of all cancers were obtained from the Korean Statistical Information Service. Expected numbers of cancer cases were calculated using reference incidence rates. SIRs were then calculated by dividing the numbers of observed SPC cases by expected numbers. The statistical significances of SIRs were determined using the exact test based on the assumption that SPC occurrences exhibited a Poisson distribution. Odds ratios (ORs) and their 95% confidence intervals (CI) were estimated by unconditional Poisson regression and adjusted for age at cervical cancer diagnosis, chemotherapy, and comorbidities. The statistical analysis was performed using R (version 3.4.2).

RESULTS

Details of the 3,267 study subjects that underwent definitive RT between 2007 and 2012 were obtained from HIRA. Median patient age was 59.4 years; the patient age distribution is provided in figure 1. Chemotherapy (e.g., cisplatin or carboplatin) was performed in 2,509 (76.8%) patients. Hypertension, diabetes, and hyperlipidemia were present in 2,134 (65.3%), 1,745 (53.4%), and 2,288 (70.0%), respectively.

SIRs of SPC 5 years after definitive RT were calculated, and for bladder, ovary, and uterine cancer were 6.72 (95% CI 3.36–12.03, $p < 0.001$), 7.12 (95% CI 4.22–11.25, $p<0.0001$), and 8.44 (95% CI 5.08–13.18, $p<0.001$), respectively. The SIRs of all organs in the pelvic irradiation field were significantly increased as were those of liver and lung cancer outside the pelvic irradiation field, though these increases were relatively small. On the other hand, SIRs for breast and stomach cancer were 0.5 (95% CI 0.22–0.99, $p=0.0441$) and 0.8 (95% CI 0.43–1.37, $p=0.5331$), respectively. Details are presented in figure 2.

Timings of SPC occurrences were analyzed for organs in the pelvic irradiation field. The incidence of SPC began to increase from about 4 years after RT, and the incidence per annum remained relatively constant, except for bladder cancer, which developed sooner than other cancers and had an inverted U-shaped incidence graph. Median time from RT to SPC occurrence for bladder, colorectal, ovarian, and uterine cancer were 5.8, 7.9, 7.8, and 7.8 years, respectively. Related information is presented in figure 3.

The crude and adjusted ORs of SPC according to age, comorbidities, and chemotherapy were analyzed. Although the ORs of colorectal and ovary cancer were increased by chemotherapy, these increases were not statistically significant. Age and comorbidities were not found to influence the ORs of SPC. Related information is presented in table 1.

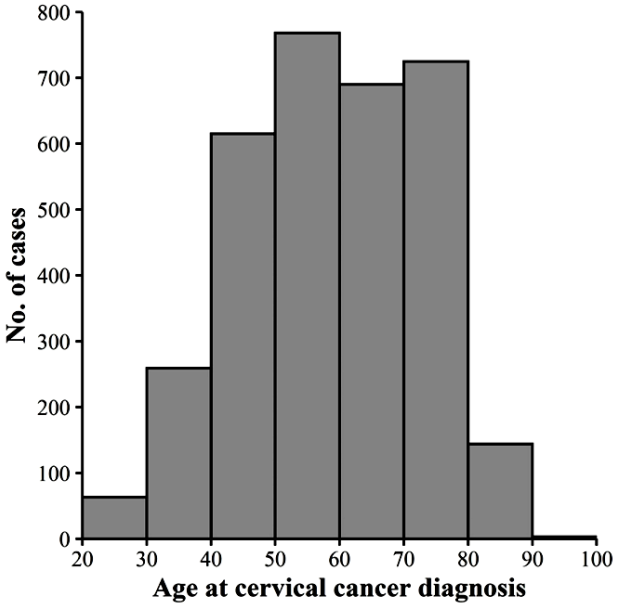


Figure 1. Age distribution of patients that underwent definitive radiotherapy for cervical cancer from 2007 to 2012 in South Korea.

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Cancer	Obs	Exp	SIR(95%CI)	P-value
Bladder	11	1.64	6.72(3.36-12.03)	<0.0001
Colorectal	42	19.04	2.21(1.59-2.98)	<0.0001
Ovary	18	2.53	7.12(4.22-11.25)	<0.0001
Uterus	19	2.25	8.44(5.08-13.18)	<0.0001
Breast	8	15.87	0.5(0.22-0.99)	0.0441
Liver	22	7.39	2.98(1.86-4.51)	<0.0001
Lung	33	13.66	2.42(1.66-3.39)	<0.0001
Stomach	13	16.22	0.8(0.43-1.37)	0.5331

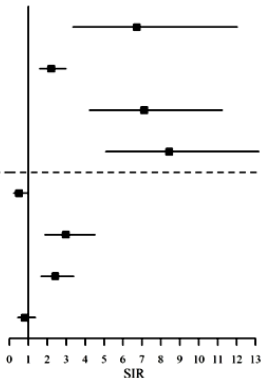


Figure 2. SIRs of second primary cancer development in cervical cancer patients after 5 years after receiving definitive radiotherapy. Obs: observed cases, Exp: expected cases, SIR: standardized incidence ratios, CI: confidence interval.

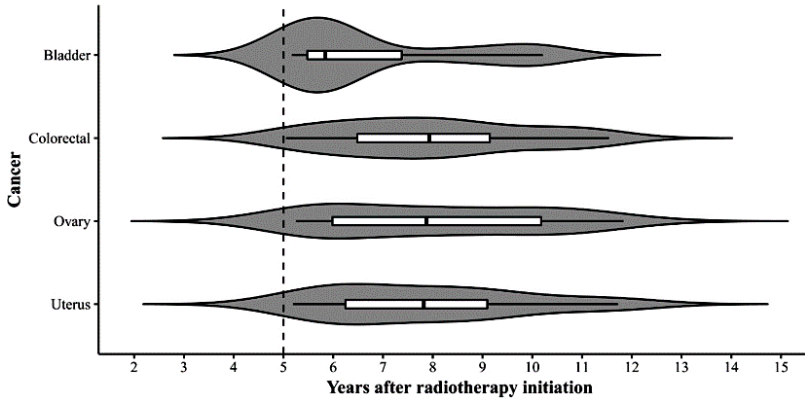


Figure 3. Incidence of second primary cancer after radiotherapy.

Table 1. Crude and adjusted odds ratios for age and chemotherapy.

	Age			Chemotherapy		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Univariate						
Bladder	0.9950	0.9519 – 1.0380	0.8190	0.7349	0.1119 – 2.8589	0.6940
Colorectal	0.9883	0.9661 – 1.0103	0.3010	1.4922	0.7467 – 2.8251	0.2340
Ovary	1.0345	1.0008 – 1.0704	0.0464	0.9454	0.2674 – 2.6446	0.9210
Uterus	1.0192	0.9869 – 1.0527	0.2460	0.3878	0.0614 – 1.3563	0.2060
Multivariate						
Bladder	0.9906	0.9396 – 1.0424	0.7209	0.6747	0.0969 – 2.9245	0.6346
Colorectal	1.0089	0.9821 – 1.0356	0.5115	1.3709	0.6534 – 2.7487	0.3860
Ovary	1.0545	1.0144 – 1.0962	0.0071	1.5113	0.4050 – 4.5573	0.4934
Uterus	1.0373	0.9981 – 1.0775	0.0600	0.4597	0.0707 – 1.7078	0.3142

OR: Odds ratio, CI: confidence interval

DISCUSSION

Since age at onset for cervical cancer is relatively low and life expectancy is long, research on SPC is essential. The curative rate of early-stage cervical cancer is known to exceed 85% [10], and in the present study, the median patient age was 59.4 years, which demonstrates that analysis of SPC rates and timings is essential. Furthermore, it has been established that the latency period of radiation-induced cancer is at least 5 years [17]. Elsamadicy *et al*. analyzed radiation-induced malignant glioma and found the latency period was more than 5 years in 88.6% of SPC cases [18]. Therefore, we only analyzed SPC cases that occurred from 5 years after RT.

A study based on the Danish Cancer Registry compared SPCs in patients with cervical cancer who received RT and those that did not. The relative risks of SPC in those that received RT were 5.5 and 2.4 for bladder and rectum, respectively. On the other hand, relative risks were 0.7 and 0.6 for breast and brain, respectively [14]. Kleinerman *et al.* analyzed SPC in 86,193 cervical cancer patients and reported that the risk of SPC was more than twice as high for heavily irradiated organs [15], which suggests risks are dependent on whether an organ is included in the irradiation field. Grantzau *et al.* reported the hazard ratios of SPC of RT-associated sites and non-RT-associated sites were 1.34 and 1.04, respectively [19]. In the present study, the SIRs of organs in the irradiation field, such as bladder and uterus, were 6.72 and 8.44, respectively. And the SIR of organs

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outside the irradiation field, such as breast and stomach, was low. This suggests a relationship between radiation exposure and the development of SPC. Therefore, organs in the irradiation field are required more careful observation of SPC.

Several recent studies have analyzed SPC incidences after RT in cervical cancer patients. Papatia et al. reported an increase in clear cell type uterine cancer in cervical cancer patients that received RT [20]. Teng *et al*. analyzed SPC risk in 35,175 patients treated for cervical cancer and found the SIR of all cancers was 1.56 and the hazard ratio of RT was 1.41 [21]. Hung et al. reported that RT increases the risk of rectal cancer in patients with cervical cancer [22]. However, no recent study has analyzed organ-specific risks according to inclusion in the irradiation field. In present study, similarly to the previous studies, increased SPC incidences were observed. Our study is different from previous studies in that it analyzed organ-specific SPC incidences in patients with cervical cancer.

SPC caused by irradiation has been reported to occur after 5-20 years. According to Zhang *et al*. in breast cancer patients, the relative risks of SPC at 5-9 years, 10-14 years, and ≥ 15 years after RT were 1.08 (95% CI 0.71–1.65), 1.34 (95% CI 0.71–2.52), and 1.13 (95% CI 0.46–2.77), respectively [23]. The maximal follow-up period in our study was 172 months, which is relatively short. The HIRA database system in Korea was started in the late 2000s, and thus, no patient was followed for more than 15 years. Furthermore, because the study was based on insurance claim codes, specific information about RT regimens, such as on planning techniques and radiation doses, was not available. Nevertheless, the present study was performed on a large number of patients, and thus, we believe our findings are statistically meaningful.

CONCLUSION

The present study shows that RT increases the incidence of SPC in cervical cancer patients. In particular, the incidences of SPC for organs inside the irradiation field were greater than those of organs outside the irradiation field. We suggest that if SPC risks were quantified with respect to irradiation dose, the risk of SPC risk could be carefully considered in clinical practice.

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***Conflicts of Interest*:** The Authors declare that they have no competing interests for this study.

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***Author contributions*:** IS and HJ contributed equally to the conception and design of the study and wrote the manuscript. HJ collected clinical data. IS analyzed the data and conducted the statistical analysis. All authors reviewed and approved the final version of the manuscript.

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