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Original Article



# Radiotherapy combined with chemotherapy increases the risk of herpes zoster in patients with gynecological cancers: a nationwide cohort study

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## ABSTRACT

**Objective:** This study aimed to determine the effect of radiotherapy (RT) on the risk of herpes zoster (HZ) in patients with gynecological cancers via a nationwide population-based study.
**Methods:** Based on patient data obtained from the National Health Insurance Research Database, 1928 gynecological cancer patients were identified with 1:1 matching for RT and non-RT cohorts by age, index date, and cancer type. Another cohort consisting of 964 non-cancer individuals matched was used as normal control. The incidence of HZ was compared between cancer patients with and without RT. Age, comorbidities, cancer-related surgery and chemotherapy (CT), and cancer type were adjusted as confounders.
**Results:** The risk of HZ in cancer patients was higher than that of non-cancer individuals (14.23 versus 8.34 per 1,000 person-years [PY], the adjusted hazard ratio [aHR]=1.38, p=0.044). In the cancer population, the incidence of HZ for the RT and non-RT cohorts was 20.55 versus 10.23 per 1,000 PY, respectively (aHR=1.68, p=0.009). Age >50 years was an independent factor for developing HZ. The 5-year actuarial incidence for patients receiving neither RT nor CT, RT alone, CT alone, and combined modalities was 5.4%, 6.9%, 3.7%, and 9.9%, respectively (p<0.001). In the RT cohort, the risk rose rapidly in the first year, becoming steady thereafter.
**Conclusion:** This population-based study showed that gynecological cancer patients receiving RT combined with CT had the highest cumulative risk of HZ. Health care professionals should be aware of the potential toxicities.

**Keywords:** Gynecologic Neoplasms; Herpes Zoster; Cohort Study; Radiotherapy; Chemotherapy

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**Conflict of Interest**
No potential conflict of interest relevant to this article was reported.

**Author Contributions**
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## INTRODUCTION

Herpes zoster (HZ) is a disease stemming from reactivation of endogenous and latent varicella-zoster virus [1], and it is associated with immunosuppressed conditions including aging, organ transplants, human immunodeficiency virus infection, or cancer-related treatment such as radiotherapy (RT) or chemotherapy (CT) [2]. The estimated incidence is 10–20% in the general population, rising to 50% in some high-risk groups [3]. Generally, HZ presents as a dermatomal unilateral vesicular rash, known as shingle, often with preceding pain and hypersensitivity [4]. Long-term sequelae, such as postherpetic neuralgia, could impact the patient's quality of life, with a minority of the infected patients experiencing serious complications such as neuropathy, vasculopathy, retinal necrosis, and encephalitis. Moreover, several studies have indicated that the incidence of HZ is higher in cancer patients [5-8], in particular, the risk in patients with hematological malignancies was higher than that in those with solid tumors [5-7]. However, the contribution of a specific treatment on the HZ risk for an individual cancer population has not been well studied [8-10].

With the rapid evolution of medical care in female cancers, the quality of life has become an important issue worldwide. To date, RT or CT have been proven to play an imperative role across definitive therapy, adjuvant treatment, or palliative care for patients with gynecological cancers. However, it remains difficult to quantify the sole impact of RT on the HZ risk because the study populations in several studies comprised heterogeneous patients and treatment modalities, lacking a well-controlled comparison [10,11]. Since limited evidence is available regarding the contribution of RT on the HZ risk in patients with gynecological cancers, we conducted a nationwide population-based study to evaluate the risk of patients with and without RT adjusting for other cancer-related treatments and comorbidities.

## MATERIALS AND METHODS

### 1. Data source

The National Health Insurance Research Database (NHIRD) established by the Taiwanese government in 1995 was used for this population-based study. The NHI program is a compulsory and single-payer system containing health care data for most Taiwanese citizens. A subset of NHIRD, the Longitudinal Health Insurance Database 2000, contains medical claim data from one million beneficiaries who were randomly selected in 2000, including a registry of beneficiaries, disease registry profile, drug prescriptions, and other medical services, with cohort members followed up since the construction of the database. The disease history for each insured individual was recorded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). This study has been approved by the Research Ethics Committee at China Medical University Hospital (CMUH104-RECX-XXX-CR-X).

### 2. Study participants

The inclusion criteria were female patients aged >30 years with at least one diagnosis of gynecological cancer (ICD-9-CM code: 179 malignant neoplasms of the uterus, part unspecified, 180 malignant neoplasms of cervix uteri, 182 malignant neoplasms of the body of the uterus, 183 malignant neoplasms of ovary and other uterine adnexa, and 184 malignant neoplasms of other and unspecified female genital organs) from 2000 to 2012. We regarded ICD-9-CM code 180 as cervical cancer, 182 as endometrial cancer, 183 as ovarian cancer, and

179 and 184 as other cancers. All study patients were linked to the registry of the Catastrophic Illness Patient Database to confirm the cancer diagnoses. They were divided into two groups, namely RT and non-RT cohorts, depending on whether they had received RT after diagnosis (ICD-9-CM treatment code 36011B and 36012B). The initial date of RT was defined as the index date, with patients with HZ before the index date or with a history of any other cancer (ICD-9-CM code 140-208) excluded. Subjects in the non-RT cohort were randomly selected from the target population for the same criteria and frequency-matched by age (every 5 years), the index date, and cancer type in a 1:1 ratio (**Supplementary Fig. 1**). Another reference cohort with the same number of non-cancer female individuals matched for age was used as normal control.

### 3. Outcome and comorbidities

The study outcome was the onset of HZ (ICD-9-CM code 053) after the diagnosis of gynecological cancer. All study participants were followed from the index date until the onset of HZ, withdrawal from the NHI program, or the end of 2013, whichever occurred first.

The history of comorbidities was considered potential confounding factors, which included hypertension (HTN, ICD-9-CM code401-405), diabetes (DM, ICD-9-CM code 250), hepatitis B (HBV, ICD-9-CM code 070.20–070.33), hepatitis C (HCV, ICD-9 code 070.41, 070.44, 070.51, 070.54, 070.70, and 070.71), systemic lupus erythematosus (SLE, ICD-9-CM code 710.0), rheumatoid arthritis (RA, ICD-9-CM code 714), human immunodeficiency virus infection (HIV, ICD-9-CM: 042), and chronic obstructive pulmonary disease and allied conditions (COPD, ICD-9-CM code 490-496). In addition, records of gynecological surgery and CT drugs used during the study period were also assessed.

### 4. Statistical analysis

The distribution of age, baseline comorbidities, gynecological surgery, and the use of CT between the two cohorts were compared. The chi-square test and the independent t-test were used to examine differences in categorical variables and continuous variables, respectively. The Cox proportional hazards regression model was used to estimate the hazard ratio (HR) with accompanying 95% confidence interval (CI) to analyze the incidence of HZ in the RT and non-RT cohorts, with stratification of age, comorbidities, gynecological surgery, the use of CT, and follow-up period. The multivariable model was adjusted for age, comorbidities, gynecological surgery, and CT. Differences in the cumulative incidence of HZ between the two cohorts were measured using the Kaplan-Meier method and the log-rank test. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, NC, USA). A two-tailed p-value less than 0.05 was considered as statistically significant.

## RESULTS

In total, 3,741 patients with gynecological cancer were identified. Among them, 972 patients underwent RT (RT cohort). Another 964 patients who did not receive RT were matched by age, the index date, and cancer type (non-RT cohort); therefore, there were 964 patients in both groups, respectively. The demographic and clinical characteristics are presented in **Table 1**, showing the median age for RT and non-RT cohorts of 57 and 56 years, respectively (p=0.421). Regarding cancer type, the distribution between the two cohorts was equal, and the most common type was cervical cancer, followed by endometrial cancer, ovarian cancer, and others. There was no statistical significance between the two cohorts with regard to the

**Table 1.** Demographic and clinical characteristics among gynecological cancer patients with and without radiotherapy

| Characteristics | Non-radiotherapy cohort* (n=964) | Radiotherapy cohort (n=964) | p-value |
|---|---|---|---|
| Age (yr) | | | 0.995 |
| <50 | 273 (28.32) | 275 (28.53) | |
| 50–65 | 372 (38.59) | 371 (38.48) | |
| >65 | 379 (33.09) | 318 (32.99) | |
| Median (IQR) | 56.4 (48.87, 67.43) | 58 (49.03, 68.53) | 0.421 |
| Cancer type | | | 0.803 |
| Cervical cancer | 687 (71.27) | 679 (70.44) | |
| Endometrial cancer | 165 (17.12) | 179 (18.57) | |
| Ovarian cancer | 61 (6.33) | 61 (6.33) | |
| Others | 51 (5.29) | 45 (4.67) | |
| Comorbidity | | | |
| Hypertension | 387 (40.15) | 400 (41.49) | 0.547 |
| Diabetes mellitus | 194 (20.12) | 206 (21.37) | 0.500 |
| Hepatitis B | 28 (2.9) | 28 (2.9) | 1.000 |
| Hepatitis C | 14 (1.45) | 14 (1.45) | 1.000 |
| Systemic lupus erythematosus | 1 (0.10) | 6 (0.62) | 0.058 |
| Rheumatoid arthritis | 28 (2.9) | 37 (3.84) | 0.256 |
| COPD | 233 (24.17) | 246 (25.52) | 0.493 |
| Gynecological surgery | | | 0.002 |
| No | 749 (77.70) | 690 (71.58) | |
| Yes | 215 (22.30) | 274 (28.42) | |
| Chemotherapy drugs | | | <0.001 |
| No | 858 (89.00) | 348 (36.10) | |
| Yes | 106 (11.00) | 616 (63.90) | |
| Follow-up (yr), Median (IQR) | 6.18 (3.14, 9.22) | 3.47 (1.84, 6.35) | <0.001 |

Data shown as number (%) or median (IQR).
IQR, interquartile range.*Using 1:1 frequency matching by age, the index date, and cancer type.

proportions of patients with and without comorbidities. For treatment-related factors, more patients in the RT cohort were exposed to CT and underwent cancer-related gynecological surgery than those in the non-RT cohort. The percentage were 63.9% vs. 11% (p<0.001) and 28.42% vs. 22.3% (p=0.002), respectively.

As shown in **Supplementary Table 1**, the incidence of HZ in the 964 non-cancer female individuals and all of the 1,928 patients with gynecological cancer was 8.34 and 14.23 per 1,000 person-years (PY) (adjusted HR [aHR]=1.38; 95% CI=1.02–1.65, p=0.044), respectively. When compared to non-cancer individuals, the RT cohort had a significantly higher risk of HZ (aHR=1.89, 95% CI=1.22–2.93, p=0.004), however, there was no statistical difference between the non-RT cancer cohort and non-cancer normal control (aHR=1.19, 95% CI=0.82–1.74, p=0.362) (**Fig. 1**). The 5-year actuarial incidence of HZ for patients with and without RT was 8.8% and 5.3% (p<0.001) (**Supplementary Table 2** and **Fig. 1**). With a median follow-up of 3.47 and 6.18 years, the cumulative incidences of HZ for the RT and non-RT cohorts were 20.55 and 10.23 per 1,000 PY, respectively (p=0.009).

**Table 2** summarizes the risk of HZ development in the studied cancer population. After adjusting for potential confounders, the RT cohort had a 1.68-fold higher risk of HZ than the non-RT cohort (95% CI=1.16–2.36, p=0.009). Additionally, to clarify the respective impact of adjuvant or primary RT, we defined these settings according to the interval between surgery and RT since the treatment intent is not available in the NHIRD. Those who underwent surgery followed by RT within 6 months were considered as adjuvant group, while those who did not meet this criterion were considered as primary group. The patients receiving primary RT had significantly higher risk of HZ than the non-RT cohort (aHR=1.52, 95% CI=1.03–2.33,


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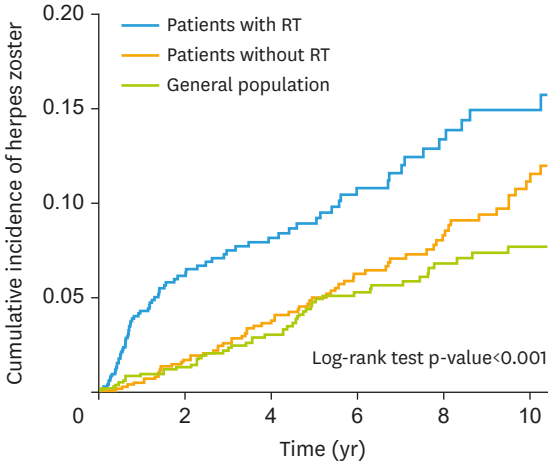


**Fig. 1.** Kaplan Meier curves of cumulative incidence of herpes zoster in RT and non-RT cohorts, and non-cancer general population.
RT, radiotherapy.

p=0.033), and those with adjuvant RT had a higher trend of HZ development (aHR=1.87, 95% CI=0.89–3.93, p=0.091). As to the effect of CT, there was a higher trend of HZ risk in those exposed to CT than those without CT. The incidence rates were of 21.30 and 11.35 per 1,000 PY, respectively (aHR=1.41, 95% CI=0.94–2.10, p=0.094). In addition, using the patients aged <50 years as a reference, the risk of HZ was significantly higher in patients older than 50 years (aHR=1.56, p=0.045 for age 50–65 years, aHR=1.75, p=0.023 for age >65 years). Undergoing cancer-related surgery was not associated with HZ risk. Moreover, there was no significant difference in HZ risk between patients with and without comorbidities.

**Table 3** lists the HRs of RT-related HZ stratified by age, cancer type, comorbidities, cancer-related surgery and CT compared to the non-RT cohort. The risk increased in several subgroups, including patients without hepatitis B (aHR=1.54, 95% CI=1.03–2.23, p=0.034), without hepatitis C (aHR=1.54, 95% CI=1.04–2.32, p=0.020), without systemic lupus erythematosus (aHR=1.57, 95% CI=1.06–2.36, p=0.022), without rheumatoid arthritis (aHR=1.56; 95% CI=1.03–2.37, p=0.035), without COPD (aHR=1.89, 95% CI=1.21–2.97, p=0.005), and without gynecological surgery (aHR=1.54, 95% CI=1.02–2.44, p=0.037). In addition, there was an increased risk in patients aged <50 years (aHR=2.47, 95% CI=1.03–6.16, p=0.032) but not in those older than 50 years. Regarding different cancer types, the RT effect on HZ was evident in cervical cancer (aHR=1.63, 95% CI=1.06–2.66, p=0.043) and ovarian cancer (aHR=16.57, 95% CI=1.24–220.33, p=0.032), but not in endometrial cancer (aHR=0.62, 95% CI=0.24–1.62, p=0.331) and others (aHR=4.79, 95% CI=0.38–60.25, p=0.224).

As more patients in the RT cohort were exposed to CT than the non-RT cohorts, patients were further stratified according to the treatment modalities to clarify the effect of the individual treatment. As depicted in **Fig. 2**, patients with RT and CT experienced the highest cumulative incidence of HZ (log-rank test, p<0.001). The 5-year actuarial incidence of HZ for patients with neither RT nor CT, RT alone, CT alone, and combined modalities was 5.4%, 6.9%, 3.7%, and 9.9%, respectively. Using the cancer cohort without RT or CT as a reference, only patients receiving combined modalities had an increased HZ risk (aHR=2.21, 95% CI=1.51–3.20, p<0.001), whereas there was no statistical difference between patients with RT alone or CT alone and the reference (**Supplementary Tables 3** and **4**). Moreover, when


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**Table 2.** Hazard ratios and 95% CIs of herpes zoster development among all gynecological cancer patients

| Variables | Herpes zoster (n=143) | | | Crude HR (95% CI) | p-value | Adjusted HR* (95% CI) | p-value |
|---|---|---|---|---|---|---|---|
| | Event | PY | IR | | | | |
| Radiotherapy | | | | | | | |
| No | 63 | 6,156 | 10.23 | 1 (reference) | | 1 (reference) | |
| Yes | 80 | 3,892 | 20.55 | 1.90 (1.36–2.64)† | <0.001 | 1.68 (1.16–2.36)‡ | 0.009 |
| Adjuvant | 15 | 678 | 22.12 | 1.94 (1.10–3.43)§ | 0.02 | 1.87 (0.89–3.93) | 0.091 |
| Primary | 65 | 3,213 | 20.23 | 1.89 (1.33–2.67)† | <0.001 | 1.52 (1.03–2.33)§ | 0.033 |
| Age (yr) | | | | | | | |
| <50 | 33 | 3,361 | 9.82 | 1 (reference) | | 1 (reference) | |
| 50–65 | 60 | 3,774 | 15.90 | 1.56 (1.02–2.39)§ | 0.03 | 1.56 (1.01–2.41)§ | 0.045 |
| >65 | 50 | 2,912 | 17.17 | 1.66 (1.07–2.58)§ | 0.02 | 1.75 (1.08–2.84)§ | 0.023 |
| Comorbidity | | | | | | | |
| Hypertension | | | | | | | |
| No | 84 | 6,385 | 13.16 | 1 (reference) | | 1 (reference) | |
| Yes | 59 | 3,662 | 16.11 | 1.18 (0.85–1.65) | 0.32 | 1.07 (0.74–1.55) | 0.699 |
| Diabetes mellitus | | | | | | | |
| No | 116 | 8,236 | 14.08 | 1 (reference) | | 1 (reference) | |
| Yes | 27 | 1,811 | 14.91 | 1.02 (0.67–1.56) | 0.91 | 0.96 (0.62–1.50) | 0.857 |
| Hepatitis B | | | | | | | |
| No | 140 | 9,824 | 14.25 | 1 (reference) | | 1 (reference) | |
| Yes | 3 | 223 | 13.45 | 0.90 (0.29–2.83) | 0.86 | 0.98 (0.31–3.10) | 0.974 |
| Hepatitis C | | | | | | | |
| No | 141 | 9,945 | 14.18 | 1 (reference) | | 1 (reference) | |
| Yes | 2 | 103 | 19.42 | 1.28 (0.32–5.16) | 0.73 | 1.23 (0.30–5.01) | 0.777 |
| Systemic lupus erythematosus | | | | | | | |
| No | 143 | 10,023 | 14.27 | 1 (reference) | | 1 (reference) | |
| Yes | 0 | 24 | 0.00 | - | | - | |
| Rheumatoid arthritis | | | | | | | |
| No | 139 | 9,742 | 14.27 | 1 (reference) | | 1 (reference) | |
| Yes | 4 | 305 | 13.11 | 0.91 (0.33–2.47) | 0.86 | 0.92 (0.34–2.52) | 0.879 |
| COPD | | | | | | | |
| No | 113 | 7,735 | 14.61 | 1 (reference) | | 1 (reference) | |
| Yes | 30 | 2,312 | 12.98 | 0.87 (0.58–1.31) | 0.87 | 0.78 (0.51–1.19) | 0.257 |
| Gynecological surgery | | | | | | | |
| No | 113 | 7,886 | 14.33 | 1 (reference) | | 1 (reference) | |
| Yes | 30 | 2,162 | 13.88 | 0.93 (0.62–1.40) | 0.74 | 0.99 (0.66–1.50) | 0.985 |
| Chemotherapy drugs | | | | | | | |
| No | 81 | 7,137 | 11.35 | 1 (reference) | | 1 (reference) | |
| Yes | 62 | 2,911 | 21.30 | 1.77 (1.27–2.48)† | <0.001 | 1.41 (0.94–2.10) | 0.094 |

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IR, incidence rate, per 1,000 person-years; PY, person-years.
*Adjusted for age, hypertension, diabetes mellitus, hepatitis B, hepatitis C, systemic lupus erythematosus, rheumatoid arthritis, COPD, gynecological surgery, chemotherapy drugs, and cancer type; †p<0.001; ‡p<0.01; §p<0.05.

compared to non-cancer individuals, only the patients receiving combine modalities were more vulnerable to HZ infection with an odds ratio (OR) of 2.24 (**Supplementary Table 5**).

To minimize the potential bias associated with imbalanced cancer deaths between groups, the survival of the four treatment groups was analyzed. The 5-year survival for patients with neither RT nor CT, RT alone, CT alone, and combined modalities was 97%, 81%, 88%, 73%, respectively (**Supplementary Table 6** and **Supplementary Fig. 2**). Although the recipients of combined modalities had inferior survival, their HZ events still surpassed those of the other treatment groups.

**Table 4** presents the individual incidence of RT-related HZ according to follow-up time. Generally, the HZ incidence was higher in the RT cohort, especially within one year after RT, with an aHR of 3.11 within 6 months (95% CI=1.22–7.91, p=0.018) and 3.81 between 6 and 12 months (95% CI=1.41–10.30, p=0.008). Thereafter, a statistical difference was not reached after one year.


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**Table 3.** Hazard ratios and 95% confidence intervals of herpes zoster development with and without radiotherapy stratified by age, comorbidities, surgery and chemotherapy

| Variables | Radiotherapy | | | | | | Crude HR (95% CI) | p-value | Adjusted HR* (95% CI) | p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | No | | | Yes | | | | | | |
| | Event | PY | IR | Event | PY | IR | | | | |
| All | 63 | 6,156 | 10.23 | 80 | 3,892 | 20.55 | 1.90 (1.36–2.64)† | <0.001 | 1.68 (1.16–2.36)‡ | 0.007 |
| Age (yr) | | | | | | | | | | |
| <50 | 10 | 2,126 | 4.70 | 23 | 1,235 | 18.62 | 3.30 (1.56–6.98)‡ | 0.002 | 2.47 (1.03–6.16)§ | 0.032 |
| 50–65 | 31 | 2,304 | 13.45 | 29 | 1,469 | 19.74 | 1.37 (0.83–2.29) | 0.20 | 1.24 (0.64–2.41) | 0.520 |
| >65 | 22 | 1,725 | 12.75 | 29 | 1,187 | 24.43 | 1.84 (1.05–3.22)§ | 0.03 | 1.66 (0.87–3.21) | 0.124 |
| Cancer type | | | | | | | | | | |
| Cervical cancer | 47 | 4,540 | 10.35 | 62 | 2,894 | 21.42 | 1.96 (1.34–2.87)† | <0.001 | 1.63 (1.06–2.66)§ | 0.043 |
| Endometrial cancer | 13 | 912 | 14.25 | 9 | 689 | 13.06 | 0.89 (0.38–2.10) | 0.80 | 0.62 (0.24–1.62) | 0.331 |
| Ovarian cancer | 1 | 359 | 2.79 | 6 | 145 | 41.38 | 12.59 (1.49–106.42)§ | 0.02 | 16.57 (1.24–220.33)§ | 0.032 |
| Others | 1 | 343 | 2.92 | 3 | 162 | 18.52 | 2.16 (0.36–13.07) | 0.40 | 4.79 (0.38–60.25) | 0.224 |
| Comorbidity | | | | | | | | | | |
| Hypertension | | | | | | | | | | |
| No | 35 | 3,998 | 8.75 | 49 | 2,387 | 20.53 | 2.17 (1.40–3.36)† | <0.001 | 1.61 (1.02–2.83) | 0.092 |
| Yes | 28 | 2,157 | 12.98 | 31 | 1,505 | 20.60 | 1.55 (0.93–2.60) | 0.09 | 1.55 (0.87–2.79) | 0.137 |
| Diabetes mellitus | | | | | | | | | | |
| No | 52 | 5,069 | 10.26 | 64 | 3,166 | 20.21 | 1.85 (1.28–2.67)‡ | 0.001 | 1.47 (0.83–2.33) | 0.100 |
| Yes | 11 | 1,086 | 10.13 | 16 | 725 | 22.07 | 2.18 (1.01–4.72)§ | 0.04 | 2.32 (0.96–5.94) | 0.061 |
| Hepatitis B | | | | | | | | | | |
| No | 63 | 6,015 | 10.47 | 77 | 3,809 | 20.22 | 1.84 (1.31–2.56)† | <0.001 | 1.54 (1.03–2.23)§ | 0.034 |
| Yes | 0 | 140 | 0.00 | 3 | 82 | 36.59 | - | | - | |
| Hepatitis C | | | | | | | | | | |
| No | 63 | 6,088 | 10.35 | 78 | 3,856 | 20.23 | 1.85 (1.33–2.58)† | <0.001 | 1.54 (1.04–2.32)§ | 0.020 |
| Yes | 0 | 67 | 0.00 | 2 | 35 | 57.14 | - | | - | |
| Systemic lupus erythematosus | | | | | | | | | | |
| No | 63 | 6,149 | 10.25 | 80 | 3,874 | 20.65 | 1.91 (1.37–2.66)† | <0.001 | 1.57 (1.06–2.36)§ | 0.022 |
| Yes | 0 | 6 | 0.00 | 0 | 18 | 0.00 | - | | - | |
| Rheumatoid arthritis | | | | | | | | | | |
| No | 62 | 5,986 | 10.36 | 77 | 135 | 570.37 | 1.87 (1.34–2.62)† | <0.001 | 1.56 (1.03–2.37)§ | 0.035 |
| Yes | 1 | 169 | 5.92 | 3 | 135 | 22.22 | 3.58 (0.37–34.62) | 0.27 | - | |
| COPD | | | | | | | | | | |
| No | 50 | 4,806 | 10.40 | 63 | 2,929 | 21.51 | 1.93 (1.33–2.81)† | <0.001 | 1.89 (1.21–2.97)‡ | 0.005 |
| Yes | 13 | 1,349 | 9.64 | 17 | 962 | 17.67 | 1.81 (0.88–3.73) | 0.11 | 1.17 (0.26–2.14) | 0.715 |
| Gynecological surgery | | | | | | | | | | |
| No | 52 | 4,786 | 10.87 | 61 | 3,099 | 19.68 | 1.93 (1.33–2.81)† | <0.001 | 1.54 (1.02–2.44)§ | 0.037 |
| Yes | 11 | 1,369 | 8.04 | 19 | 793 | 23.96 | 1.91 (1.10–3.30)§ | 0.02 | 1.59 (0.74–3.92) | 0.215 |
| Chemotherapy drugs | | | | | | | | | | |
| No | 57 | 5,563 | 10.25 | 24 | 1,573 | 15.26 | 1.38 (0.84–2.27) | 0.20 | 1.40 (0.86–2.28) | 0.173 |
| Yes | 6 | 592 | 10.14 | 56 | 2,318 | 24.16 | 1.94 (1.12–3.39)§ | 0.02 | 2.20 (0.90–5.42) | 0.086 |

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IR, incidence rate, per 1000 person-years; PY, person-years.
*Adjusted for age, hypertension, diabetes mellitus, hepatitis B, hepatitis C, systemic lupus erythematosus, rheumatoid arthritis, COPD, gynecological surgery, chemotherapy drugs, and cancer type; †p<0.001; ‡p<0.01; §p<0.05.

**Table 4.** The individual incidence of radiotherapy-related herpes zoster development according to different follow-up period

| Follow-up time | Radiotherapy | | | | | | Crude HR (95% CI) | p-value | Adjusted HR* (95% CI) | p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | No | | | Yes | | | | | | |
| | Event | PY | IR | Event | PY | IR | | | | |
| All | 63 | 6,156 | 10.23 | 80 | 3,892 | 20.55 | 1.90 (1.36–2.64)† | <0.001 | 1.68 (1.16–2.36)‡ | 0.007 |
| <6 mo | 6 | 478 | 12.55 | 17 | 446 | 38.12 | 3.08 (1.21–7.79)‡ | 0.01 | 3.11 (1.22–7.91)§ | 0.018 |
| 6–12 mo | 5 | 479 | 10.44 | 18 | 448 | 40.18 | 3.78 (1.40–10.19)‡ | 0.008 | 3.81 (1.41–10.30)‡ | 0.008 |
| 1–2 yr | 8 | 893 | 8.96 | 12 | 597 | 20.10 | 2.21 (0.91–5.43) | 0.08 | 2.39 (0.97–5.92) | 0.058 |
| >2 yr | 44 | 4,313 | 10.20 | 33 | 2,474 | 13.34 | 1.30 (0.83–2.05) | 0.25 | 1.20 (0.76–1.89) | 0.427 |

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IR, incidence rate, per 1000 person-years; PY, person-years.
*Adjusted for age, hypertension, diabetes mellitus, hepatitis B, hepatitis C, systemic lupus erythematosus, rheumatoid arthritis, COPD, gynecological surgery, chemotherapy drugs, and cancer type; †p<0.001; ‡p<0.01; §p<0.05.


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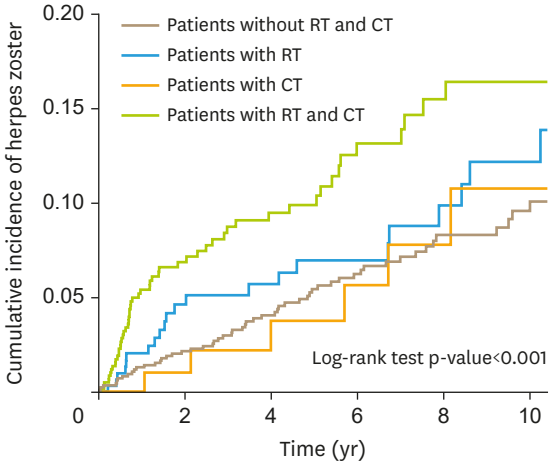


**Fig. 2.** Kaplan Meier curves of cumulative incidence of herpes zoster in patients divided into four groups: with both CT and RT, with CT only, with RT only, and with neither.
CT, chemotherapy; RT, radiotherapy.

## DISCUSSION

This is the first national population-based study for HZ risk in patients with gynecological cancers. In general, the HZ risk increased in these cancer patients compared to age-adjusted women without cancer. In the cancer population, RT combined with CT had the highest cumulative incidence with a 5-year actuarial incidence of 9.9%. Of note, a rapid surge of the infection was observed within the first year. Given that RT or CT plays an important role in treating gynecological cancers currently, our findings indicated that early surveillance for HZ infection is important especially in recipients of the combined modalities. Moreover, it is worth noting that the HZ incidence in these cancer populations was relatively higher in the elderly. Therefore, health care professionals should be aware of potential toxicities.

Many immunocompromised conditions such as HIV infection [12], diabetes mellitus [13], organ transplantation [14,15], old age, or cancer-related therapy [16] were indicated as predisposing factors of HZ development. When investigating the impact of specific cancer treatments on HZ risk, malignancy itself or other cancer treatments were major potential confounders [5-7,16]. Our result indicated that RT plays a role in HZ development. Both cohorts were matched by age and cancer type, and the effect of surgery and CT was adjusted. Habel et al. reported that the age- and sex-standardized rates of HZ were 4.8 times higher in patients with hematologic malignancies and 1.9 times higher in those with solid tumors compared with non-cancer US population [5]. Another study reported that patients with hematological and solid cancers had higher relative risks of HZ than the normal population (aHR 3.74 and 1.30, respectively) [6]. In a population-based study, the association between 21 common malignancies and subsequent HZ risk was estimated [7], with malignancy positively associated with the occurrence of HZ (adjusted OR=1.29), particularly for hematological cancer (adjusted OR=2.46, 2.33–2.60). In their study, an increase in the odds of HZ risk only presented in patients with ovarian cancer, but did not present in cancer of cervix or uterus. Our study disclosed that the HZ risk was 1.38-fold higher in the gynecological patients compared to the normal control, and the aHR increased to 1.89 in those receiving RT.


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Among other treatment-related factors, previous studies have suggested that patients receiving CT had an increased HZ risk [5,6,17-19]. However, limited investigators adjusted the risk with cancer itself, or the receipt of other cancer treatments. Kim et al. analyzed 1,768 patients with solid tumors receiving CT and reported that 5.1% of the patients had HZ infection following treatment [17]. To date, the synergistic effect of CT and RT on the HZ risk was not well studied. Our population-based study first disclosed that RT combined with CT had the highest cumulative incidence of HZ in women with gynecological cancers. Compared to the non-cancer control, the risk of HZ was 1.41 times higher in the patients with RT alone, further increasing to 2.24 times higher in those who received combined modalities. Although the statistical difference existed only in the combined modality group when compared to non-cancer control, the contribution of RT on the HZ development could not be overlooked in this nationwide population-based analysis. Qian et al. [6] conducted an HZ risk analysis in several solid cancer patients, showing that compared to the non-cancer population, the aHR was 1.84 for those receiving CT alone, 1.81 for combined modalities, 1.38 for RT alone, and 1.1 for neither CT nor RT. Only the patients without the two modalities experienced the same risk of HZ as the non-cancer control. The role of RT was further evaluated by subdividing CT patients according to the receipt of RT, and the HZ turned out to be similar. Thus, the authors concluded that the increased risk appears to be largely associated with the receipt of CT in patients with solid cancers [6].

A recent study disclosed that cancer patients receiving RT were associated with an increased risk of HZ, which occurred commonly within the RT field [9]. However, in their study, patients with gynecological cancers made up only a small proportion of the cancer population (6% in the RT group and 4.2% in the non-RT group). The incidence per 1,000 person-years for RT and non-RT was 22.2 vs. 0, respectively and there was no statistical significance. Previous studies of HZ risk in Hodgkin's disease revealed that aggressive treatment, such as extended-field RT, was responsible for a higher incidence [20,21], with two-fold greater risk in patients undergoing extended-field RT than those with limited-field RT (23.8% vs. 11.1%) [20]. However, some researchers have contended this claim [8,10]. A retrospective study from Surveillance, Epidemiology, and End Results showed 6.3% of 944,777 solid cancer patients had HZ infection with an adjusted incidence ratio of 1.2 compared with the non-cancer population, suggesting that age, gender, race, and immunocompromised conditions were the risk factors [8]. In contrast, RT solid cancer recipients had a lower risk than non-RT cancer patients (incidence ratio 0.94, $p<0.001$) [8]. To understand the effect of RT, we divided the RT cohort into adjuvant and primary groups. With adjustment for all the confounding factors including CT and cancer type, the HZ incidences were higher in both groups than in the non-RT cohort. Particularly, the effect of RT on HZ was more pronounced in the primary group (aHR=1.52, 95% CI=1.03–2.33, p=0.033) than in the adjuvant group (aHR=1.87, 95% CI=0.89–3.93, p=0.091).

In women with gynecological cancers, RT combined CT had the highest cumulative incidence of HZ infection when compared to cancer patients without RT or CT, or non-cancer control. However, when using patients with RT alone as a reference, there was no statistical difference in those with combined modalities (aHR=1.51, 95% CI=0.93–2.45, p=0.093). Based on these findings, although RT combined CT could augment the HZ risk, RT alone might contribute toward the activation of HZ as proposed by Ramirez-Fort et al. [22]. Accordingly, a serologic assay for human herpes virus is recommended before RT to determine whether antiviral therapy should be administered during and after treatment. Also, the test can differentiate between RT-related necrosis and herpetic infection [22].


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With regard to different gynecological cancer types, our analysis revealed that RT effect on HZ seemed to be more evident in cervical cancer and ovarian cancer. In these two cancers, little variations existed in the primary and adjuvant treatment. As to endometrial cancer, there is no standardized agreement in adjuvant therapy. Further subgroup analysis was carried out to evaluate the effect of CT and RT, which could be helpful in adjuvant treatment determination. In our cohort, 344 endometrial cancer patients were enrolled and the result was listed in **Supplementary Table 7**. The HZ risk did not significantly elevate in patients with RT and CT, RT alone, or CT alone compared to those without CT and RT. Although the highest incidence rate of HZ was observed in the CT alone group, the statistical significance did not exist. Certainly, these results should be interpreted carefully and future studies are warranted to clarify this issue.

This study has several limitations. First, several potential confounders such as body mass index, family history, smoking, alcoholic consumption, or cancer stage were not included since this information was not available in the NHIRD. Second, the association between the anatomical location of the HZ and irradiated field was unknown through the NHIRD. Cancer stage would be a potential confounder because advanced disease itself affects the immunity of cancer patients. As a result, the compromised immunity might be associated with the HZ development. Besides, cancer stage might be imbalanced between these cohorts. It is possible that patients in the RT cohort had more advanced disease than those in the non-RT group. Generally, both RT and CT are usually administrated as adjuvant therapy for locally advanced disease or palliative treatment for recurrent or metastatic disease. Detailed treatment-related information, personal risk factors, and cancer stage should be considered in future studies aiming to investigate the factors associated with HZ among cancer patients.

The strengths of our study were adequate control for cancer type, potential comorbidities, and treatment-related factors, and analysis of treatment intent of RT and the HZ risk over time. Accordingly, surveillance of the risk for gynecological patients receiving combined modalities should be intensified.

This nationwide population study disclosed that gynecological cancer patients receiving RT combined with CT had the highest cumulative incidence of HZ with a 5-year actuarial incidence of 9.9%. In cancer populations, age >50 years was an independent risk factor. After initiating RT, the HZ risk rose rapidly in the first year and became steady thereafter. Health care professionals should be aware of the potential risks of HZ development.

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

The risk of herpes zoster among general population and gynecological cancer patients

**Click here to view**

### Supplementary Table 2

Cumulative incidence of herpes zoster associated with radiotherapy by follow-up time

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### Supplementary Table 3
The risk of herpes zoster associated with combination of RT and CT

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### Supplementary Table 4
Cumulative incidence of herpes zoster associated with combination of RT and CT by follow-up time

Click here to view

### Supplementary Table 5
The risk of herpes zoster associated with combination of RT and CT compared with general population

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### Supplementary Table 6
Survival analysis among gynecological cancer patients with combination of RT and CT

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### Supplementary Table 7
The risk of herpes zoster associated with combination of RT and CT among endometrial cancer

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### Supplementary Fig. 1
Flow chart for case and control selection.

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### Supplementary Fig. 2
Kaplan Meier curves of survival in patients divided into four groups: with both CT and RT, with CT only, with RT only, and with neither.

Click here to view

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