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ORIGINAL RESEARCH

Association Between Radiotherapy and Death From Cardiovascular Disease Among Patients With Cancer: A Large Population-Based Cohort Study

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BACKGROUND: This study aimed to investigate the association between radiotherapy for cancer and cardiovascular disease (CVD) deaths and evaluate the relative risk for CVD deaths in the general population and among patients with cancer treated with radiotherapy.

METHODS AND RESULTS: The statistics of cancers from 16 sites were extracted from the Surveillance, Epidemiology, and End Results database and evaluated. Multivariable Cox proportional hazards regression analysis was used to analyze the association between radiotherapy and cardiovascular-specific survival. The standardized mortality ratio for CVD deaths was estimated by comparing the observed deaths of patients with cancer treated with radiotherapy to the expected deaths of the general population. Of the 2 214 944 patients identified from the database, 292 102 (13.19%) died from CVD. Multivariable Cox proportional hazards regression analyses demonstrated that radiotherapy was an independent risk factor for cardiovascular-specific survival among patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers. The long-term cardiovascular-specific survival of patients with cancer who underwent radiotherapy was significantly lower than that of patients who did not undergo radiotherapy. The incidence of CVD deaths among patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers who underwent radiotherapy was higher than that among the general population. Standardized mortality ratio significantly decreased with increasing age at cancer diagnosis, gradually decreased within 10 years of diagnosis and increased after 10 years of diagnosis.

CONCLUSIONS: Radiotherapy is associated with worse cardiovascular-specific survival in patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers. Long-term surveillance of cardiovascular conditions should be performed after radiotherapy.

Key Words: cardiovascular disease ■ neoplasms ■ radiotherapy ■ standardized mortality ratio

Cardiovascular disease (CVD) and cancer, which are the leading causes of mortality worldwide, have a complex relationship.[1–3] Previous studies have shown that smoking, alcohol abuse, obesity, and poor lifestyle habits are common modifiable risk factors for CVD and cancer, increasing a considerable overlap between both diseases.[4–6] The incidence of CVD in patients with cancer, especially lung cancer, is almost twice that of the general population, which provides evidence of a higher rate of cardiovascular mortality in patients with cancer.[7] As the age and life expectancy of a population improve, CVD deaths

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CLINICAL PERSPECTIVE

What Is New?

- Radiotherapy increases the incidence of cardiovascular disease deaths among patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers.
- Our results showed a higher incidence of cardiovascular disease deaths among patients with these aforementioned cancers who underwent radiotherapy than among the general population.

What Are the Clinical Implications?

- The findings of this study highlight the importance of cardiovascular care and provide the reference for the prevention of cardiovascular disease deaths in patients with cancer undergoing radiotherapy.

Nonstandard Abbreviations and Acronyms

CVSS	cardiovascular-specific survival
SMR	standardized mortality ratio

among patients with cancer steadily increase.[8,9] CVD, rather than the cancer itself, has even become the leading cause of death among patients with endometrial cancer, indicating that patients with cancer may require heightened surveillance to prevent CVD deaths.[5]

Cancer-related treatment, such as chemotherapy with anthracycline antibiotics and/or radiotherapy, may be responsible for the increased incidence of CVD deaths among patients with cancer, especially if the heart is in the radiation field.[9,10] The available evidence indicates that irradiation of the heart and major blood vessels could promote CVD deaths in patients with breast cancer many years later. Furthermore, it has been reported that radiotherapy is associated with an increased absolute risk of breast cancer of 125.5 cases of CVD deaths per 100 000 person-years.[11,12] Hence, ignoring the negative effects of cancer-related treatment may increase the incidence of CVD deaths.

Considering the findings of previous studies, we performed a comprehensive analysis to investigate the association between radiotherapy and CVD deaths in patients with cancer. In addition, we compared the incidence of CVD deaths among patients with cancer who underwent radiotherapy with the incidence of CVD deaths in the general population.

METHODS

Data Source

All data are available at the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/) using the SEER*Stat 8.3.9 software (https://seer.cancer.gov/seerstat/). The demographic characteristics, treatment, and survival data of patients with cancer were extracted from the SEER database, which covers approximately 28% of the population of the United States.[13] Cause of death was categorized using the *International Classification of Diseases, Eighth Revision* (*ICD-8*; 1968–1978), *Ninth Revision* (*ICD-9*; 1979–1998), and *Tenth Revision* (*ICD-10*; 1999+) codes. CVD was coded with heart disease, hypertension, cerebrovascular disease, atherosclerosis, aortic aneurysm/dissection, and other diseases of arteries, arterioles, or capillaries.

Standardized mortality ratios (SMRs) were introduced to estimate the relative risk for CVD deaths among patients with cancer compared with the general population of the United States (standard population of the United States in 2000), adjusted for race, sex, and age at the same time.

Study Population

The inclusion criteria for this study were as follows: (1) first primary solid malignant tumors; (2) diagnosis between January 1, 1975 and December 31, 2014; and (3) patients with cancer who have more than 100 000 person-years of survival time. Patients with less than 2 months of survival time were excluded to maintain consistency with the minimum period following cancer diagnosis in which SMR can be estimated (starts at 2 months).

We identified 16 cancer sites from the database. The sites included the brain, breast, cervix uteri, colon and rectum, corpus uteri, kidney and renal pelvis, larynx, lung and bronchus, melanoma of the skin, ovary, prostate, soft tissue including heart, stomach, testis, thyroid, and urinary bladder.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this study, informed consent was not required.

Statistical Analysis

The distributions of baseline characteristics of the patients with cancer were compared using the chi-square test. The multivariable Cox proportional hazards regression analyses were performed to estimate the hazard ratios (HRs) and 95% CIs for the association between radiotherapy and cardiovascular-specific

survival (CVSS), adjusted for race, sex, age at diagnosis, and year at diagnosis. The Kaplan–Meier method was used to analyze CVSS in patients with cancer who underwent radiotherapy and in those who did not undergo radiotherapy. Adjusted *P* values were estimated using the multivariable Cox proportional hazards regression analyses to reduce confounding effects. SMRs and 95% CIs for CVD were calculated using the SEER*Stat 8.3.9 software.

RESULTS

Patient Characteristics

A total of 2 214 944 patients with cancer were identified from the SEER database. Of these, 292 102 (13.19%) died of CVD (Table 1). A total of 718 979 patients were included in the radiotherapy group, whereas 1 495 965 patients were in the no-radiotherapy group. Of the patients in the radiotherapy group, 67 003 (9.32%) died of CVD, whereas 225 099 (15.05%) patients in the no-radiotherapy group died of CVD. The percentage of patients who died from CVD increased with increasing age at diagnosis in both the groups. In the radiotherapy group, patients with cancer of the larynx had the highest percentage of those who died from CVD (20%), followed by those with corpus uteri (19.19%), prostate (17.88%), urinary bladder (14.49%), and cervix uteri (10.2%) cancers. In the no-radiotherapy group, those with cancer of the urinary bladder had the highest percentage of those who died from CVD (23.29%), followed by those with cancer of the larynx (21.54%), prostate (19.42%), colon and rectum (18.51%), and breast (17%).

Multivariable Cox Proportional Hazards Regression Analysis

In the multivariable Cox proportional hazards regression analyses, radiotherapy was considered an independent risk factor for CVSS among patients with lung and bronchus (HR, 1.09; 95% CI, 1.06–1.13; adjusted $P<0.001$), cervix uteri (HR, 1.47; 95% CI, 1.36–1.59; adjusted $P<0.001$), corpus uteri (HR, 1.13; 95% CI, 1.09–1.17; adjusted $P<0.001$), and urinary bladder (HR, 1.13; 95% CI, 1.07–1.20; adjusted $P<0.001$) cancers (Figure 1 and Tables S1 through S16). Potential confounders were adjusted for race, sex, and age at the same time.

Cardiovascular-Specific Survival of 4 Cancers

The long-term CVSS of 4 cancers was estimated using the Kaplan-Meier method (Figure 2). Among patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers, those who underwent radiotherapy had significantly lower 40-year CVSS than those who did not undergo radiotherapy (lung and bronchus: 21.9% versus 33.3%, adjusted $P<0.001$; cervix uteri: 52.0% versus 80.6%, adjusted $P<0.001$; corpus uteri: 29.1% versus 38.1%, adjusted $P<0.001$; and urinary bladder: 26.0% versus 33.4%, adjusted $P<0.001$).

Standardized Mortality Ratios

When the incidence of CVD deaths among patients with cancer treated using radiotherapy was compared with that of the general population, the overall SMR indicated a 13% increase in CVD deaths among all patients with cancer (SMR, 1.13 [1.13–1.14]) (Table 2). The incidence of CVD deaths among patients with lung and bronchus (SMR, 2.83 [2.61–3.07]), cervix uteri (SMR, 1.67 [1.59–1.74]), corpus uteri (SMR, 1.13 [1.10–1.16]), and urinary bladder (SMR, 1.51 [1.43–1.59]) cancers who underwent radiotherapy was higher than that in the general population.

Cardiovascular Deaths According to Age at Diagnosis

Different age groups showed higher-than-expected incidences of CVD deaths. In addition, SMRs decreased with increasing age at cancer diagnosis among patients with lung and bronchus (≤39 years old: SMR, 25.00 [13.31–42.75]; 40–59 years old: SMR, 5.95 [5.57–6.35]; 60–79 years old: SMR, 3.09 [3.00–3.18]; ≥80 years old: SMR, 1.33 [1.27–1.40]), cervix uteri (≤39 years old: SMR, 4.81 [2.07–9.47]; 40–59 years old: SMR, 3.06 [2.62–3.56]; 60–79 years old: SMR, 2.11 [1.97–2.26]; ≥80 years old: SMR, 2.29 (1.21–1.38]), corpus uteri (≤39 years old: SMR, 6.46 [0.78–23.32]; 40–59 years old: SMR, 2.32 [2.02–2.81]; 60–79 years old: SMR, 1.33 [1.28–1.39]; ≥80 years old: SMR, 1.03 [1.00–1.06]), and urinary bladder cancers (≤39 years old: SMR, 17.08 [0.43–95.14]; 40–59 years old: SMR, 3.92 [2.85–5.26]; 60–79 years old: SMR, 1.86 [1.70–2.02]; ≥80 years old: SMR, 1.29 [1.19–1.38]) (Figure 3A).

Cardiovascular Deaths According to Year of Diagnosis

The historical trends of CVD deaths among patients who underwent radiotherapy for lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers are shown in Figure 3B. Patients with these cancers showed higher incidences of CVD deaths than the general population in different eras. In addition, SMRs decreased with advancing time among patients with lung and bronchus (1985–1994: SMR, 2.73 [2.36–2.63]; 1995–2004: SMR, 2.61 [2.50–2.72]; 2005–2014: 2.26 [2.16–2.37]) and cervix uteri cancers (1995–2004: SMR, 1.76 [1.62–1.91]; 2005–2014: 1.60 [1.46–1.75]).

Table 1. Baseline Characteristics of Patients With Cancer According to Treatment Modality

Characteristic	Radiotherapy		No radiotherapy	
	Overall	CVD deaths (%)	Overall	CVD deaths (%)
All patients	718 979	67 003 (9.32)	1 495 965	225 099 (15.05)
Race				
White	588 034	56 366 (9.59)	1 257 323	196 386 (15.62)
Black	75 714	7033 (9.29)	132 008	18 620 (14.11)
Other*	53 073	3560 (6.71)	94 842	9761 (10.29)
Unknown	2158	44 (2.04)	11 792	332 (2.82)
Sex				
Female	370 142	28 133 (7.60)	739 775	102 783 (13.89)
Male	348 837	38 870 (11.14)	756 190	122 316 (16.18)
Age at diagnosis, y				
≤39	50 821	657 (1.29)	107 112	1203 (1.12)
40–59	236 548	8848 (3.74)	413 743	21 988 (5.31)
60–79	382 428	47 847 (12.51)	739 609	132 545 (17.92)
≥80	49 182	9651 (19.62)	235 501	69 363 (29.45)
Year at diagnosis				
1975–1984	114 016	16 254 (14.26)	275 164	70 444 (25.60)
1985–1994	154 289	22 753 (14.75)	355 418	78 972 (22.22)
1995–2004	206 684	20 647 (9.99)	396 093	54 163 (13.67)
2005–2014	243 990	7349 (3.01)	469 290	21 520 (4.59)
Tumor stage				
Localized/regional	461 179	44 930 (9.74)	1 058 923	163 236 (15.42)
Distant	108 887	3126 (2.87)	202 686	8222 (4.06)
Unknown	148 913	18 947 (12.72)	234 356	53 641 (22.89)
Surgery				
Yes	393 442	35 390 (8.99)	1 161 459	185 616 (15.98)
No	309 865	30 166 (9.74)	315 656	37 157 (11.77)
Unknown	15 672	1447 (9.23)	18 850	2326 (12.34)
Chemotherapy				
Yes	243 154	8267 (3.40)	259 245	11 508 (4.44)
No	475 825	58 736 (12.34)	1 236 720	213 591 (17.27)
Primary cancer site				
Larynx	17 618	3523 (20.00)	5822	1254 (21.54)
Corpus uteri	32 172	6174 (19.19)	64 445	10 055 (15.60)
Prostate	145 996	26 102 (17.88)	305 388	59 293 (19.42)
Urinary bladder	9145	1325 (14.49)	101 089	23 539 (23.29)
Cervix uteri	18 297	1866 (10.20)	16 652	1080 (6.49)
Colon and rectum	38 803	3352 (8.64)	266 007	49 232 (18.51)
Ovary	2295	181 (7.89)	47 471	2554 (5.38)
Breast	185 898	14 193 (7.63)	246 309	41 874 (17.00)
Soft tissue including heart	7889	530 (6.72)	11 135	988 (8.87)
Stomach	10 825	485 (4.48)	40 168	3545 (8.83)
Lung and bronchus	172 697	7400 (4.28)	167 036	13 195 (7.90)
Testis	7864	302 (3.84)	14 804	277 (1.87)
Kidney and renal pelvis	6726	209 (3.11)	61 548	7295 (11.85)
Melanoma of the skin	2441	70 (2.87)	101 601	8837 (8.70)
Thyroid	28 916	688 (2.38)	33 390	1717 (5.14)
Brain	31 397	603 (1.92)	13 100	364 (2.78)

CVD indicates cardiovascular disease.
*Other refers to American Indian/Alaskan Native, Asian/Pacific Islander.
P values were calculated using χ^2 test and all *P* values <0.001.

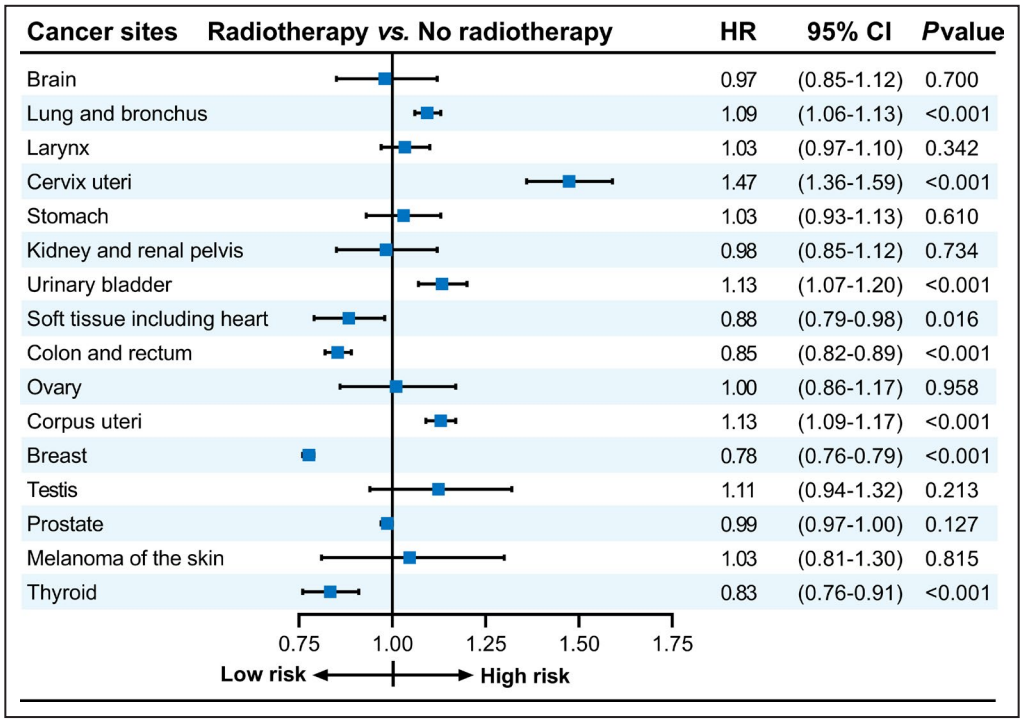

Figure 1. Hazard ratios for cardiovascular-specific survival in patients with cancer in the radiotherapy vs no radiotherapy group.
Multivariable Cox proportional hazards regression analyses were used to calculate hazard ratios and 95% CIs for cardiovascular-specific survival in patients with cancer in the radiotherapy vs no radiotherapy group, adjusted for race, sex, age at diagnosis, and year of diagnosis. HR indicates hazard ratio.

However, SMR gradually increased with advancing time among patients with urinary bladder cancer (1975–1984: SMR, 1.37 [1.21–1.53]; 1985–1994: SMR, 1.40 [1.27–1.55]; 1995–2004: SMR, 1.60 [1.44–1.78]; 2005–2014: SMR, 1.74 [1.54–1.95]).

Cardiovascular Deaths According to Time After Diagnosis

We estimated the relative risk of CVD deaths according to time after diagnosis and compared the results of patients with cancer who underwent radiotherapy with those of the general population. The results showed that patients with cancer who underwent radiotherapy had a higher incidence of CVD deaths than the general population from the time of diagnosis onward (Figure 3C). SMRs gradually decreased within 10 years of diagnosis and increased after 10 years of diagnosis among patients with lung and bronchus (2–11 months: SMR, 2.63 [2.54–2.73]; 12–59 months: SMR, 2.39 [2.31–2.48]; 60–119 months: SMR, 2.38 [2.23–2.54]; 120+ months: SMR, 2.97 [2.74–3.22]), cervix uteri (2–11 months: SMR, 1.99 [1.71–2.31]; 12–59 months: SMR, 1.87 [21.71–2.04]; 60–119 months: SMR, 1.49 [1.34–1.66]; 120+ months: SMR, 1.59 [1.48–1.70]), corpus uteri (2–11 months: SMR, 1.29 [1.15–1.45]; 12–59 months: SMR, 1.10 [1.03–1.16]; 60–119 months: SMR, 1.06 [1.00–1.13]; 120+ months: SMR, 1.39 [1.24–1.56]), and urinary bladder cancer (2–11 months: SMR, 1.88 [1.67–2.10]; 12–59 months: SMR, 1.50 [1.37–1.64]; 60–119 months: SMR, 1.33 [1.17–1.51]; 120+ months: SMR, 1.39 [1.24–1.56]).

DISCUSSION

In this large population-based cohort study, we evaluated the association between radiotherapy and CVD deaths among patients with cancer treated with radiotherapy. The results showed that radiotherapy was a significant independent risk factor for CVSS among patients with 4 cancers: lung and bronchus, urinary bladder, cervix uteri, and corpus uteri cancers. In addition, radiotherapy was associated with worse CVSS in patients with these cancers. Furthermore, a comparison of the relative risk of CVD deaths between patients with cancer and the general population showed a higher incidence of CVD deaths among patients with these 4 cancers who underwent radiotherapy than among the general population. We also found that the SMR for CVD among patients with these cancers significantly decreased with increasing age at cancer diagnosis, gradually decreased within 10 years of diagnosis, and increased after 10 years of diagnosis.

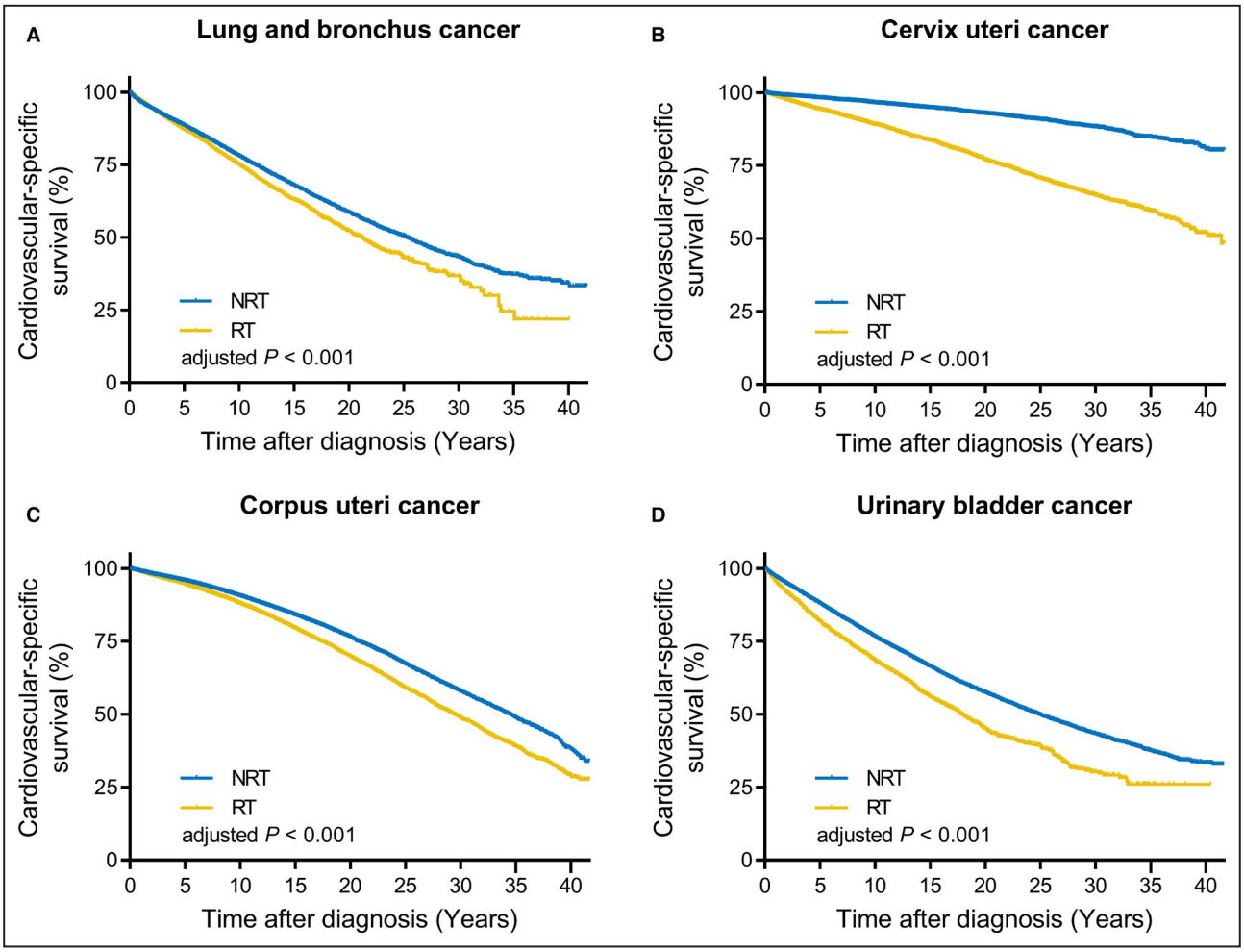

Figure 2. Cardiovascular-specific survival in patients with lung and bronchus (A), cervix uteri (B), corpus uteri (C), and urinary bladder cancers (D) in the radiotherapy vs no radiotherapy group.
P values were calculated using the multivariable Cox proportional hazards regression analyses, adjusted for race, sex, age at diagnosis, and year of diagnosis. NRT indicates no radiotherapy; and RT, radiotherapy.

These epidemiological characteristics provided a reference for the implementation of strategies for the prevention of CVD deaths in patients with cancer after radiotherapy.

To our knowledge, this is the most comprehensive population-based study of the association between radiotherapy and CVD deaths in patients with cancer of 16 different sites. Previous studies have reported elevated incidences of CVD deaths among patients with solid tumors after radiotherapy.[14–18] However, some previous studies have also reported that the incidence of CVD deaths among patients with cancer is not elevated.[19–21] Hence, a unified conclusion on the relationship between radiotherapy and CVD deaths in patients with solid tumors has not yet been reached. In addition, knowledge of the tumors that increase the incidence of CVD deaths after radiotherapy is particularly important. In a previous population-based study, CVD deaths in patients with 10 common malignant tumors were evaluated and the results indicated that radiotherapy is an independent risk factor for CVSS in lung cancer,[14] a finding that is in line with our results. However, a recent study showed that the incidence of CVD deaths among patients with non-small cell lung cancer who underwent chemotherapy and/or radiotherapy decreased.[22] The conflicting result could be explained by the advent of chemotherapy, which may affect the survival outcome. Another explanation may be the tumor heterogeneity between non-small cell lung cancer and other types of lung cancer. We also found that radiotherapy could promote the likelihood of CVD deaths among patients with urinary bladder, cervix uteri, and corpus uteri cancers, a finding that could not be obtained from the aforementioned study. This difference might be caused by the fact that only patients with more than 5 years of survival were included in the aforementioned study, whereas patients with almost all types of cancer were included in the present study. The Kaplan–Meier

Table 2. Standardized Mortality Ratios of Patients With Different Cancers According to Treatment Modality

Primary cancer site	Total	Radiotherapy	No radiotherapy
	SMR (95% CI)	SMR (95% CI)	SMR (95% CI)
Brain	2.60* (2.44–2.77)	2.83* (2.61–3.07)	2.29* (2.06–2.54)
Lung and bronchus	2.04* (2.02–2.07)	2.52* (2.46–2.58)	1.85* (1.82–1.88)
Larynx	1.81* (1.76–1.86)	1.83* (1.77–1.89)	1.76* (1.67–1.86)
Cervix uteri	1.53* (1.47–1.58)	1.67* (1.59–1.74)	1.33* (1.25–1.41)
Stomach	1.43* (1.39–1.48)	1.79* (1.63–1.96)	1.39* (1.35–1.44)
Kidney and renal pelvis	1.40* (1.37–1.43)	1.73* (1.50–1.98)	1.39* (1.36–1.43)
Urinary bladder	1.29* (1.27–1.31)	1.51* (1.43–1.59)	1.28* (1.26–1.30)
Soft tissue including heart	1.21* (1.15–1.27)	1.12* (1.02–1.21)	1.26* (1.19–1.35)
Colon and rectum	1.15* (1.14–1.16)	1.14* (1.10–1.18)	1.15* (1.14–1.16)
Ovary	1.08* (1.04–1.12)	1.19* (1.02–1.38)	1.08* (1.03–1.12)
Corpus uteri	1.08* (1.06–1.10)	1.13* (1.10–1.16)	1.05* (1.03–1.07)
Breast	1.06* (1.05–1.07)	0.92* (0.91–0.94)	1.11* (1.10–1.12)
Testis	1.01 (0.93–1.09)	1.00 (0.89–1.12)	1.02 (0.90–1.14)
Prostate	0.99 (0.99–1.00)	0.92* (0.91–0.93)	1.03* (1.02–1.04)
Melanoma of the skin	0.98* (0.96–1.00)	1.06 (0.83–1.34)	0.98 (0.96–1.00)
Thyroid	0.87* (0.84–0.91)	0.78* (0.73–0.84)	0.92* (0.87–0.96)
Overall	1.13* (1.13–1.14)	1.09* (1.08–1.10)	1.14* (1.14–1.15)

SEER indicates Surveillance, Epidemiology, and End Results; and SMR, standardized mortality ratio.
SMRs and 95% CIs were calculated using SEER*Stat 8.3.9, adjusted for age, race, and sex at the same time.
**P* values <0.05.

analysis demonstrated worse CVSS after radiotherapy in patients with lung and bronchus, urinary bladder, cervix uteri, and corpus uteri cancers. This is the first study to demonstrate an association between radiotherapy and CVD deaths among patients with urinary bladder, cervix uteri, and corpus uteri cancers. Some existing evidence alludes to the robustness of our findings. A previous retrospective study demonstrated that patients with uterine cancer who underwent radiotherapy are more likely to die from intercurrent illness, including cardiac arrhythmia, congestive heart failure, cardiac arrest, and other complications, 10 years later than from cancer.[23] Okajima et al.[24] discovered that 13% of patients with urinary cancer died within 10 years after radiotherapy and that except for cancer, CVD was the leading cause of death among them. These previous studies suggest that CVD deaths are associated with cancer-related radiotherapy. In addition, reports in recently published literature[25] indicate that short- and long-term radiotherapy elevates the incidence of adverse cardiovascular events in patients with multiple types of cancer, especially breast, lung, and esophagus cancer, which often require mediastinal radiotherapy. Although these studies only focused on the incidence of CVD in patients with cancer, they provided a theoretical basis for our results.

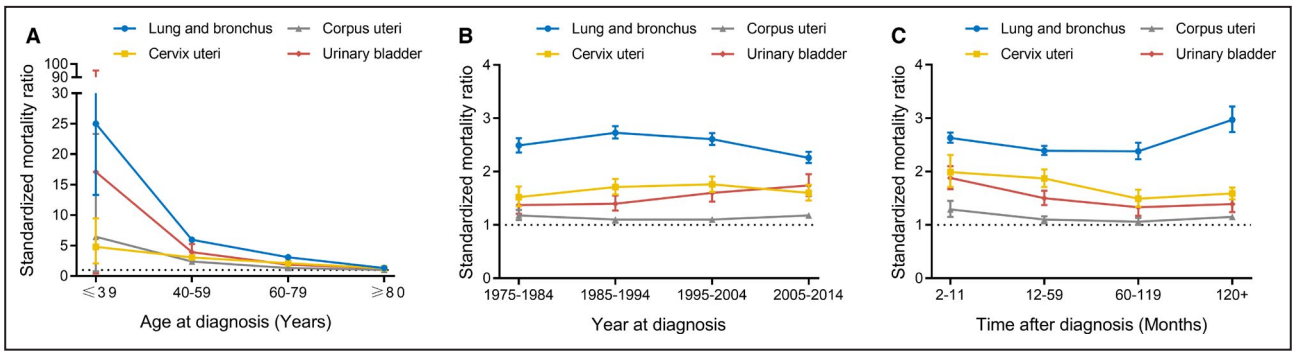

Figure 3. Standardized mortality ratios for cardiovascular disease among patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers after radiotherapy according to age at diagnosis (A), year at diagnosis (B), and time after diagnosis (C).
Standardized mortality ratios represent the relative risk of cardiovascular disease deaths in patients with cancer compared with the general population, adjusted for age, race, and sex at the same time.

In this study, we also observed a lower incidence of CVD deaths in patients who underwent radiotherapy for breast, thyroid, and colorectal cancer than among the general population. It is generally agreed that radiotherapy is associated with a high incidence of CVD deaths in patients with cancer. However, the latest randomized trials showed no increase in CVD deaths among patients with breast and colorectal cancer who underwent radiotherapy.[26,27] In addition, Killander emphasized that serious late side effects of radiation are limited and that with the current therapeutic strategies, the risk for cardiac events due to exposure of the breasts to radiation is likely to be decreased.[26,28,29] Significantly, breast, thyroid, and colorectal cancers have good oncological prognoses and long survival times, which may increase the incidence of CVD deaths. However, radiotherapy may be used to treat patients with more advanced cancers with poor oncological prognoses. Therefore, patients with cancer who undergo radiotherapy are more likely to die from tumors than from CVD. In addition, elderly patients may reject recommendations for radiotherapy because of concomitant CVD, which might increase the risk of CVD deaths. Previous studies have reported that CVD deaths often occur 15 years after cancer diagnosis. In the present study, patients were diagnosed between 1975 and 2014, and more than a quarter of them were followed up for less than 15 years, which may have affected the incidence of CVD deaths.[28,30] However, Greenlee et al. reported that patients with breast cancer are at an increased risk for cardiovascular-related diseases. Furthermore, Guan et al. reported that the tumor itself, not just the cardiotoxicity of radiotherapy, might increase the incidence of CVD deaths in patients who did not undergo radiotherapy.[20,31] Given these findings, the limitations of the present study led to the misconception that radiotherapy reduced CVD deaths in patients with breast, thyroid, and colorectal cancers.

Radiotherapy is an effective treatment for tumors that can kill tumor cells and shrink tumors through high doses of ionizing radiation. Although this local treatment may control tumor progression and improve survival time, it also leads to several adverse events, especially CVD.[32,33] The potential mechanisms behind this are not fully clear, however, the results of some studies suggest that pathogenesis of radiotherapy-induced CVD is related to inflammatory activation, production of reactive oxygen species, and oxidative stress. This may be because radiotherapy could directly cause cell death and premature endothelial senescence and could impair endothelium-dependent vasodilation. In addition, the promotion of coagulation and thrombosis could influence the incidence of CVD. Radiotherapy-induced CVD is also affected by the dose of cardiac radiation.[32,34] Therefore, radiotherapy-induced CVD is a complex and modifiable pathophysiological process.

Radiologists have been trying to find the most effective treatment method that limits the risk of developing CVD. Radiation techniques are constantly being updated with newer methods, such as intensity-modulated radiotherapy, image-guided radiotherapy, and proton therapy. In addition, advances in radiation techniques have reduced accidental cardiac radiation.[35–37] In the present study, the risk of CVD deaths decreased significantly with increasing years of diagnosis in the radiotherapy and no-radiotherapy cohorts, especially in the last decade. However, radiation-induced CVD most often occurs several years after radiation therapy, and late cardiovascular toxicity still causes CVD deaths.[35,38] Therefore, a short follow-up duration may be one of the reasons for the reduced risk of CVD deaths in recent years. Thus, this conclusion should be interpreted with caution.

We used SMR to compare the relative risk for CVD between patients with cancer and the general population. The results demonstrated that patients with 4 different types of cancer who underwent radiotherapy had higher incidences of CVD deaths than the general population. The underlying CVD was a critical factor; however, the cardiotoxicity associated with treatment should not be overlooked. Epidemiological studies have shown that risk factors for cancer and CVD have significant overlaps, which suggests that patients with cancer may be more susceptible to CVD.[2] These are some possible explanations for the higher incidence of CVD deaths among patients with cancer than in the general population.

We found that patients with the 4 aforementioned cancers who underwent radiotherapy had a higher incidence of CVD deaths than the general population. Tukenova reported a similar conclusion, which is that cardiovascular SMRs for cancer survivors increase after radiotherapy.[19] On the other hand, Boekel et al. emphasized that the SMR of CVD for patients with breast cancer who underwent surgery plus radiotherapy or surgery alone did not vary.[21] However, the author also explained that the impact of radiotherapy on CVD deaths may be underestimated because of short follow-up durations and low doses of radiation.[21]

As mentioned previously, the results of the present study showed that patients with cancer who underwent radiotherapy had a higher incidence of CVD deaths than the general population. Similar trends were observed in subgroups stratified according to age at diagnosis, year of diagnosis, and follow-up duration. These results suggest that attention should be paid to the risk of CVD deaths in patients with cancer undergoing radiotherapy. Efforts should be made to prevent cardiotoxicity and maximize outcomes, while ensuring that the therapeutic effect of the treatment is not compromised.[33]

Although strong evidence supports the credibility of our results, this study has some limitations. First,

we could not access detailed information on the indications for radiotherapy (or exceptions of user-patient or provider preferences/refusals/access to care), individual-level patient data on comorbidities (or underlying CVD), or prognostic information on individual tumors (which may affect the CVD deaths studied). Thus, these factors were not adjusted in the analysis. Second, the general population represents individuals not exposed to radiation. However, as we did not exclude patients with a history of cancer from this population or adjust for potential CVD risk factors, this is inevitably a comparison biased in favor of the cancer population. Therefore, future prospective randomized trials are necessary to verify the reliability and accuracy of the findings of this study. Third, the wide period is a notable limitation of the study, as indications and modalities for radiotherapy continued to improve during this period. Moreover, advances in radiation techniques might influence CVD mortality. However, CVD deaths were few and mostly occurred several years after radiotherapy; hence, we had to expand the period and sample size to enhance the credibility of this study.

CONCLUSIONS

In summary, this study demonstrated that radiotherapy increases the incidence of CVD deaths among patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers. The findings of this study highlight the importance of cardiovascular care in patients with cancer undergoing radiotherapy.

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Disclosures

None.

Supplemental Material

Table S1–S16

REFERENCES

1. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, Casey DC, Charlson FJ, Chen AZ, Coates MM, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1459–1544. doi: 10.1016/S0140-6736(16)31012-1
2. Bray F, Laversanne M, Weiderpass E, Soerjomataram I. The ever-increasing importance of cancer as a leading cause of premature death worldwide. *Cancer*. 2021;127:3029–3030. doi: 10.1002/cncr.33587
3. Whelton SP, Berning P, Blumenthal RS, Marshall CH, Martin SS, Mortensen MB, Blaha MJ, Dzaye O. Multidisciplinary prevention and management strategies for colorectal cancer and cardiovascular disease. *Eur J Intern Med*. 2021;87. doi: 10.1016/j.ejim.2021.02.003
4. Vincent L, Leedy D, Masri SC, Cheng RK. Cardiovascular disease and cancer: is there increasing overlap? *Curr Oncol Rep*. 2019;21:47. doi: 10.1007/s11912-019-0796-0
5. Ward KK, Shah NR, Saenz CC, McHale MT, Alvarez EA, Plaxe SC. Cardiovascular disease is the leading cause of death among endometrial cancer patients. *Gynecol Oncol*. 2012;126:176–179. doi: 10.1016/j.ygyno.2012.04.013
6. Leerink JM, de Baat EC, Feijen EAM, Bellersen L, van Dalen EC, Grotenhuis HB, Kapusta L, Kok WEM, Loonen J, van der Pal HJH, et al. Cardiac disease in childhood cancer survivors: risk prediction, prevention, and surveillance: state-of-the-art review. *JACC CardioOncol*. 2020;2:363–378. doi: 10.1016/j.jaccao.2020.08.006
7. Navi BB, Reiner AS, Kamel H, Iadecola C, Okin PM, Elkind MSV, Panageas KS, DeAngelis LM. Risk of arterial thromboembolism in patients with cancer. *J Am Coll Cardiol*. 2017;70:926–938. doi: 10.1016/j.jacc.2017.06.047
8. Kolodziejczyk C, Jakobsen M, Sall Jensen M, Poulsen PB, Khan H, Kümler T, Andersson M. Mortality from cardiovascular disease in women with breast cancer - a nationwide registry study. *Acta Oncol*. 2021;60:1257–1263. doi: 10.1080/0284186X.2021.1959054
9. Ell P, Martin JM, Cehic DA, Ngo DTM, Sverdlov AL. Cardiotoxicity of radiation therapy: mechanisms, management, and mitigation. *Curr Treat Options Oncol*. 2021;22:70. doi: 10.1007/s11864-021-00868-7
10. Brown AJ, Jessup W. Oxysterols and atherosclerosis. *Atherosclerosis*. 1999;142:1–28. doi: 10.1016/S0021-9150(98)00196-8
11. Darby S, McGale P, Peto R, Granath F, Hall P, Ekbom A. Mortality from cardiovascular disease more than 10 years after radiotherapy for breast cancer: Nationwide cohort study of 90 000 Swedish women. *BMJ*. 2003;326:256–257. doi: 10.1136/bmj.326.7383.256
12. Cheng YJ, Nie XY, Ji CC, Lin XX, Liu LJ, Chen XM, Yao H, Wu SH. Long-term cardiovascular risk after radiotherapy in women with breast cancer. *J Am Heart Assoc*. 2017;6. doi: 10.1161/JAHA.117.005633
13. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the seer-medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care*. 2002;40(suppl):IV-3–IV-18. doi: 10.1097/00005650-200208001-00002
14. Abdel-Rahman O. Risk of cardiac death among cancer survivors in the United States: a seer database analysis. *Expert Rev Anticancer Ther*. 2017;17:873–878. doi: 10.1080/14737140.2017.1344099
15. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, Cutter D, Gagliardi G, Gigante B, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368:987–998. doi: 10.1056/NEJMoa1209825
16. Park HS, Harder EM, Mancini BR, Decker RH. Central versus peripheral tumor location: influence on survival, local control, and toxicity following stereotactic body radiotherapy for primary non-small-cell lung cancer. *J Thorac Oncol*. 2015;10:832–837. doi: 10.1097/JTO.0000000000000484
17. Lin SH, Zhang N, Godby J, Wang J, Marsh GD, Liao Z, Komaki R, Ho L, Hofstetter WL, Swisher SG, et al. Radiation modality use and cardiopulmonary mortality risk in elderly patients with esophageal cancer. *Cancer*. 2016;122:917–928. doi: 10.1002/cncr.29857
18. Henson KE, McGale P, Darby SC, Parkin M, Wang Y, Taylor CW. Cardiac mortality after radiotherapy, chemotherapy and endocrine therapy for breast cancer: cohort study of 2 million women from 57 cancer registries in 22 countries. *Int J Cancer*. 2020;147:1437–1449. doi: 10.1002/ijc.32908
19. Tukenova M, Guibout C, Oberlin O, Doyon F, Mousannif A, Haddy N, Guérin S, Pacquement H, Aouba A, Hawkins M, et al. Role of

cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *J Clin Oncol*. 2010;28:1308–1315. doi: 10.1200/JCO.2008.20.2267
20. Guan T, Zhang H, Yang J, Lin W, Wang K, Su M, Peng W, Li Y, Lai Y, Liu C. Increased risk of cardiovascular death in breast cancer patients without chemotherapy or (and) radiotherapy: a large population-based study. *Front Oncol*. 2020;10:619622. doi: 10.3389/fonc.2020.619622
21. Boekel NB, Schaapveld M, Gietema JA, Rutgers EJ, Versteegh MI, Visser O, Aleman BM, van Leeuwen FE. Cardiovascular morbidity and mortality after treatment for ductal carcinoma in situ of the breast. *J Natl Cancer Inst*. 2014;106. doi: 10.1093/jnci/dju156
22. Sun J-Y, Zhang Z-Y, Qu Q, Wang N, Zhang Y-M, Miao L-F, Wang JI, Wu L-D, Liu Y, Zhang C-Y, et al. Cardiovascular disease-specific mortality in 270,618 patients with non-small cell lung cancer. *Int J Cardiol*. 2021;330:186–193. doi: 10.1016/j.ijcard.2021.02.025
23. Kupelian PA, Eifel PJ, Tornos C, Burke TW, Delclos L, Oswald MJ. Treatment of endometrial carcinoma with radiation therapy alone. *Int J Radiat Oncol Biol Phys*. 1993;27:817–824. doi: 10.1016/0360-3016(93)90454-4
24. Okajima K, Ishikawa K, Matsuura T, Tatebe H, Fujiwara K, Hiroi K, Hasegawa H, Nishimura Y. Multiple primary malignancies in patients with prostate cancer: increased risk of secondary malignancies after radiotherapy. *Int J Clin Oncol*. 2013;18:1078–1084. doi: 10.1007/s10147-012-0496-3
25. Nielsen KM, Offersen BV, Nielsen HM, Vaage-Nilsen M, Yusuf SW. Short and long term radiation induced cardiovascular disease in patients with cancer. *Clin Cardiol*. 2017;40:255–261. doi: 10.1002/clc.22634
26. Killander F, Wieslander E, Karlsson P, Holmberg E, Lundstedt D, Holmberg L, Werner L, Koul S, Haghanegi M, Kjellen E, et al. No increased cardiac mortality or morbidity of radiation therapy in breast cancer patients after breast-conserving surgery: 20-year follow-up of the randomized SweBCGRT Trial. *Int J Radiat Oncol Biol Phys*. 2020;107:701–709. doi: 10.1016/j.ijrobp.2020.04.003
27. Obi N, Eulenburg C, Seibold P, Eilber U, Thöne K, Behrens S, Chang-Claude J, Flesch-Janys D. Associations between adjuvant radiotherapy and different causes of death in a German breast cancer cohort. *Breast*. 2018;38:75–80. doi: 10.1016/j.breast.2017.12.006
28. Bonsignore A, Warburton D. Radiation therapy and cardiovascular disease risk in breast cancer. *Curr Cardiovasc Risk Rep*. 2013;7:514–519. doi: 10.1007/s12170-013-0347-4
29. Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B. The stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. *Cancer*. 2001;92:896–902. doi: 10.1002/1097-0142(20010815)92:4<896:AID-CNCR1398>3.0.CO;2-R
30. Gagliardi G, Lax I, Rutqvist LE. Partial irradiation of the heart. *Semin Radiat Oncol*. 2001;11:224–233. doi: 10.1053/srao.2001.23483
31. Greenlee H, Iribarren C, Neugebauer R, Rana JS, Nguyen-Huynh M, Cheng R, Shi Z, Izano M, Laurent C, Lee VS, et al. Risk of cardiovascular disease in women with and without a history of breast cancer: the pathways heart study. *J Clin Oncol*. 2020;38:12016. doi: 10.1200/JCO.2020.38.15_suppl.12016
32. Atkins KM, Rawal B, Chaunzwa TL, Lamba N, Bitterman DS, Williams CL, Kozono DE, Baldini EH, Chen AB, Nguyen PL, et al. Cardiac radiation dose, cardiac disease, and mortality in patients with lung cancer. *J Am Coll Cardiol*. 2019;73:2976–2987. doi: 10.1016/j.jacc.2019.03.500
33. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, Lyon AR, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC committee for practice guidelines: the task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;2016:2768–2801. doi: 10.1093/eurheartj/ehw211
34. Sallam M, Benotmane MA, Baatout S, Guns PJ, Aerts A. Radiation-induced cardiovascular disease: an overlooked role for DNA methylation? *Epigenetics*. 2022;17:59–80. doi: 10.1080/15592294.2021.1873628
35. Bergom C, Bradley JA, Ng AK, Samson P, Robinson C, Lopez-Mattei J, Mitchell JD. Past, present, and future of radiation-induced cardiotoxicity: refinements in targeting, surveillance, and risk stratification. *JACC CardioOncol*. 2021;3:343–359. doi: 10.1016/j.jaccao.2021.06.007
36. Hong JC, Rahimy E, Gross CP, Shafman T, Hu X, Yu JB, Ross R, Finkelstein SE, Dosoretz A, Park HS, et al. Radiation dose and cardiac risk in breast cancer treatment: an analysis of modern radiation therapy including community settings. *Pract Radiat Oncol*. 2018;8:e79–e86. doi: 10.1016/j.prro.2017.07.005
37. D'Agostino GR, Diletto B, Mantini G, Nardone L, Mattiucci GC, Catucci F, Canna R, Martino A, Azario L, Valentini V. Reducing heart dose during left breast cancer radiotherapy: comparison among 3 radiation techniques. *Tumori J*. 2016;102:184–189. doi: 10.5301/tj.5000414
38. Mitchell JD, Cehic DA, Morgia M, Bergom C, Toohey J, Guerrero PA, Ferencik M, Kikuchi R, Carver JR, Zaha VG, et al. Cardiovascular manifestations from therapeutic radiation: a multidisciplinary expert consensus statement from the international cardio-oncology society. *JACC CardioOncol*. 2021;3:360–380. doi: 10.1016/j.jaccao.2021.06.003

SUPPLEMENTAL MATERIAL

Table S1. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with prostate cancer.

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	1.29	1.26-1.31	<0.001
Other	0.87	0.84-0.9	<0.001
Unknown	0.32	0.27-0.37	<0.001
Sex			
Female	Reference	/	/
Male	NA	NA	NA
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	2.89	1.20-6.96	0.018
60-79	13.44	5.59-32.31	<0.001
≥80	54.47	22.67-130.91	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.67	0.66-0.68	<0.001
1995-2004	0.42	0.42-0.43	<0.001
2005-2014	0.25	0.24-0.25	<0.001
Radiotherapy			
No	Reference	/	/
Yes	0.99	0.97-1.00	0.127

HR, hazard ratio; CI, confidence interval.

Table S2. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with soft tissue including heart

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	1.59	1.34-1.88	<0.001
Other	0.88	0.71-1.10	0.259
Unknown	0.51	0.19-1.35	0.173
Sex			
Female	Reference	/	/
Male	1.43	1.29-1.58	<0.001
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	9.35	6.90-12.68	<0.001
60-79	63.05	47.00-84.59	<0.001
≥80	288.89	212.39-392.93	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.79	0.69-0.90	<0.001
1995-2004	0.58	0.50-0.67	<0.001
2005-2014	0.44	0.37-0.52	<0.001
Radiotherapy			
No	Reference	/	/
Yes	0.88	0.79-0.98	0.016

HR, hazard ratio; CI, confidence interval.

Table S3. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with urinary bladder cancer

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	1.27	1.19-1.36	<0.001
Other	0.76	0.71-0.82	<0.001
Unknown	0.21	0.14-0.32	<0.001
Sex			
Female	Reference	/	/
Male	1.36	1.33-1.40	<0.001
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	8.43	6.58-10.79	<0.001
60-79	37.06	29.00-47.35	<0.001
≥80	131.51	102.8-168.23	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.80	0.77-0.82	<0.001
1995-2004	0.60	0.58-0.62	<0.001
2005-2014	0.41	0.40-0.43	<0.001
Radiotherapy			
No	Reference	/	/
Yes	1.13	1.07-1.20	<0.001

HR, hazard ratio; CI, confidence interval.

Table S4. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with ovary cancer

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	1.79	1.56-2.05	<0.001
Other	0.89	0.75-1.07	0.217
Unknown	0.50	0.19-1.33	0.164
Sex			
Female	Reference	/	/
Male	NA	NA	NA
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	9.09	6.88-12.01	<0.001
60-79	52.03	39.48-68.57	<0.001
≥80	238.63	178.78-318.51	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.67	0.62-0.74	<0.001
1995-2004	0.47	0.42-0.52	<0.001
2005-2014	0.33	0.29-0.39	<0.001
Radiotherapy			
No	Reference	/	/
Yes	1.00	0.86-1.17	0.958

HR, hazard ratio; CI, confidence interval.

Table S5. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with thyroid cancer

Variables	HR	95% CI	*P*
Race			
White	Reference		
Black	1.86	1.61-2.15	<0.001
Other	0.94	0.82-1.07	0.33
Unknown	0.16	0.04-0.65	0.01
Sex			
Female	Reference	/	/
Male	1.63	1.50-1.78	<0.001
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	7.07	5.97-8.38	<0.001
60-79	59.68	50.39-70.68	<0.001
≥80	316.01	258.66-386.08	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.72	0.64-0.80	<0.001
1995-2004	0.50	0.44-0.57	<0.001
2005-2014	0.31	0.27-0.36	<0.001
Radiotherapy			
No	Reference	/	/
Yes	0.83	0.76-0.91	<0.001

HR, hazard ratio; CI, confidence interval.

Table S6. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with melanoma of the skin

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	1.44	1.12-1.85	0.004
Other	0.89	0.69-1.15	0.38
Unknown	0.27	0.20-0.37	<0.001
Sex			
Female	Reference	/	/
Male	1.54	1.48-1.61	<0.001
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	8.94	7.58-10.55	<0.001
60-79	74.97	63.74-88.19	<0.001
≥80	427.57	361.82-505.25	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.77	0.73-0.82	<0.001
1995-2004	0.56	0.53-0.60	<0.001
2005-2014	0.36	0.33-0.39	<0.001
Radiotherapy			
No	Reference	/	/
Yes	1.03	0.81-1.30	0.815

HR, hazard ratio; CI, confidence interval.

Table S7. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with stomach cancer

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	1.42	1.29-1.55	<0.001
Other	0.73	0.67-0.80	<0.001
Unknown	0.61	0.29-1.29	0.197
Sex			
Female	Reference	/	/
Male	1.28	1.2-1.36	<0.001
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	5.94	3.49-10.13	<0.001
60-79	23.53	13.88-39.89	<0.001
≥80	72.90	42.9-123.89	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.81	0.75-0.88	<0.001
1995-2004	0.67	0.62-0.73	<0.001
2005-2014	0.43	0.39-0.48	<0.001
Radiotherapy			
No	Reference	/	/
Yes	1.03	0.93-1.13	0.61

HR, hazard ratio; CI, confidence interval.

Table S8. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with testis cancer

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	2.06	1.28-3.30	0.003
Other	0.87	0.54-1.41	0.574
Unknown	/	/	/
Sex			
Female	Reference	/	/
Male	NA	NA	NA
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	4.97	4.11-6.01	<0.001
60-79	40.25	31.45-51.52	<0.001
≥80	144.09	82.04-253.07	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.46	0.38-0.56	<0.001
1995-2004	0.27	0.21-0.35	<0.001
2005-2014	0.21	0.14-0.32	<0.001
Radiotherapy			
No	Reference	/	/
Yes	1.11	0.94-1.32	0.213

HR, hazard ratio; CI, confidence interval.

Table S9. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with lung and bronchus cancer

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	1.47	1.41-1.53	<0.001
Other	0.81	0.76-0.86	<0.001
Unknown	0.33	0.18-0.61	<0.001
Sex			
Female	Reference	/	/
Male	1.48	1.44-1.52	<0.001
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	5.37	4.28-6.74	<0.001
60-79	14.20	11.32-17.8	<0.001
≥80	35.50	28.25-44.61	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.88	0.84-0.91	<0.001
1995-2004	0.67	0.65-0.70	<0.001
2005-2014	0.47	0.45-0.49	<0.001
Radiotherapy			
No	Reference	/	/
Yes	1.09	1.06-1.13	<0.001

HR, hazard ratio; CI, confidence interval.

Table S10. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with corpus uteri cancer

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	1.64	1.53-1.76	<0.001
Other	0.86	0.8-0.94	0.001
Unknown	0.36	0.22-0.58	<0.001
Sex			
Female	Reference	/	/
Male	NA	NA	NA
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	3.14	2.61-3.77	<0.001
60-79	13.72	11.44-16.46	<0.001
≥80	73.88	61.35-88.97	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.89	0.86-0.93	<0.001
1995-2004	0.68	0.65-0.71	<0.001
2005-2014	0.45	0.42-0.48	<0.001
Radiotherapy			
No	Reference	/	/
Yes	1.13	1.09-1.17	<0.001

HR, hazard ratio; CI, confidence interval.

Table S11. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with kidney and renal pelvis cancer

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	1.59	1.47-1.71	<0.001
Other	0.88	0.79-0.98	0.018
Unknown	0.23	0.11-0.49	<0.001
Sex			
Female	Reference	/	/
Male	1.29	1.23-1.35	<0.001
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	7.65	6.11-9.59	<0.001
60-79	31.77	25.42-39.71	<0.001
≥80	110.55	87.93-138.99	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.83	0.78-0.88	<0.001
1995-2004	0.59	0.55-0.63	<0.001
2005-2014	0.40	0.37-0.43	<0.001
Radiotherapy			
No	Reference	/	/
Yes	0.98	0.85-1.12	0.734

HR, hazard ratio; CI, confidence interval.

Table S12. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with larynx cancer

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	1.37	1.25-1.49	<0.001
Other	0.76	0.64-0.90	0.002
Unknown	0.27	0.10-0.73	0.010
Sex			
Female	Reference	/	/
Male	1.12	1.04-1.21	0.004
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	4.95	3.24-7.55	<0.001
60-79	13.44	8.82-20.47	<0.001
≥80	36.06	23.46-55.43	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.87	0.81-0.93	<0.001
1995-2004	0.71	0.66-0.77	<0.001
2005-2014	0.50	0.45-0.56	<0.001
Radiotherapy			
No	Reference	/	/
Yes	1.03	0.97-1.1	0.342

HR, hazard ratio; CI, confidence interval.

Table S13. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with colon and rectum cancer

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	1.26	1.22-1.30	<0.001
Other	0.76	0.73-0.79	<0.001
Unknown	0.33	0.25-0.43	<0.001
Sex			
Female	Reference	/	/
Male	1.32	1.3-1.35	<0.001
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	6.04	4.95-7.37	<0.001
60-79	31.15	25.58-37.93	<0.001
≥80	116.66	95.75-142.13	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.81	0.79-0.83	<0.001
1995-2004	0.63	0.62-0.65	<0.001
2005-2014	0.44	0.43-0.46	<0.001
Radiotherapy			
No	Reference	/	/
Yes	0.85	0.82-0.89	<0.001

HR, hazard ratio; CI, confidence interval.

Table S14. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with breast cancer

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	1.42	1.37-1.46	<0.001
Other	0.75	0.72-0.79	<0.001
Unknown	0.45	0.34-0.6	<0.001
Sex			
Female	Reference	/	/
Male	1.57	1.44-1.72	<0.001
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	4.04	3.63-4.50	<0.001
60-79	31.35	28.2-34.85	<0.001
≥80	154.74	139.03-172.22	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.76	0.74-0.77	<0.001
1995-2004	0.58	0.57-0.59	<0.001
2005-2014	0.39	0.38-0.41	<0.001
Radiotherapy			
No	Reference	/	/
Yes	0.78	0.76-0.79	<0.001

HR, hazard ratio; CI, confidence interval.

Table S15. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with cervix uteri cancer

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	1.60	1.46-1.75	<0.001
Other	0.74	0.64-0.85	<0.001
Unknown	0.81	0.42-1.57	0.54
Sex			
Female	Reference	/	/
Male	NA	NA	NA
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	6.39	5.44-7.52	<0.001
60-79	35.39	30.04-41.69	<0.001
≥80	139.66	115.84-168.37	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.81	0.74-0.88	<0.001
1995-2004	0.64	0.57-0.71	<0.001
2005-2014	0.41	0.34-0.49	<0.001
Radiotherapy			
No	Reference	/	/
Yes	1.47	1.36-1.59	<0.001

HR, hazard ratio; CI, confidence interval.

Table S16. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with brain cancer

Variables	HR	95% CI	*P*
Race			
White	Reference	/	/
Black	2.23	1.80-2.75	<0.001
Other	1.00	0.74-1.36	0.976
Unknown	1.00	0.25-4.00	0.996
Sex			
Female	Reference	/	/
Male	1.18	1.04-1.34	0.011
Age at diagnosis (Years)			
≤39	Reference	/	/
40-59	9.32	7.57-11.48	<0.001
60-79	43.81	35.07-54.73	<0.001
≥80	154.09	115.01-206.46	<0.001
Year at diagnosis			
1975-1984	Reference	/	/
1985-1994	0.68	0.58-0.80	<0.001
1995-2004	0.45	0.38-0.55	<0.001
2005-2014	0.33	0.27-0.41	<0.001
Radiotherapy			
No	Reference	/	/
Yes	0.97	0.85-1.12	0.70

HR, hazard ratio; CI, confidence interval.