COMMENTARY

Second Malignant Neoplasms and Cardiovascular Disease Following Radiotherapy

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Manuscript received May 24, 2011; revised November 21, 2011; accepted November 30, 2011.

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Second malignant neoplasms (SMNs) and cardiovascular disease (CVD) are among the most serious and life-threatening late adverse effects experienced by the growing number of cancer survivors worldwide and are due in part to radiotherapy. The National Council on Radiation Protection and Measurements (NCRP) convened an expert scientific committee to critically and comprehensively review associations between radiotherapy and SMNs and CVD, taking into account radiobiology; genomics; treatment (ie, radiotherapy with or without chemotherapy and other therapies); type of radiation; and quantitative considerations (ie, dose–response relationships). Major conclusions of the NCRP include: 1) the relevance of older technologies for current risk assessment when organ-specific absorbed dose and the appropriate relative biological effectiveness are taken into account and 2) the identification of critical research needs with regard to newer radiation modalities, dose–response relationships, and genetic susceptibility. Recommendation for research priorities and infrastructural requirements include 1) long-term large-scale follow-up of extant cancer survivors and prospectively treated patients to characterize risks of SMNs and CVD in terms of radiation dose and type; 2) biological sample collection to integrate epidemiological studies with molecular and genetic evaluations; 3) investigation of interactions between radiotherapy and other potential confounding factors, such as age, sex, race, tobacco and alcohol use, dietary intake, energy balance, and other cofactors, as well as genetic susceptibility; 4) focusing on adolescent and young adult cancer survivors, given the sparse research in this population; and 5) construction of comprehensive risk prediction models for SMNs and CVD to permit the development of follow-up guidelines and prevention and intervention strategies.

J Natl Cancer Inst 2012;104:357–370

Advances in cancer therapy, early detection, and supportive care have contributed to steady gains in the 5-year relative survival rate for all cancers combined, which reached 66.0% for patients diagnosed during 1999–2006 (1). Commensurately, the number of cancer survivors in the United States has tripled since 1971 and is growing by 2% each year. As of 2007, there were approximately 12 million men and women in the United States—approximately 3.5% of the US population—with a history of cancer (1). For many patients, these gains in survival have come at the price of serious treatment-associated late adverse effects.

Radiation remains a cornerstone of successful cancer treatment, with 50% of all patients estimated to receive radiotherapy (2). Second malignant neoplasms (SMNs) and cardiovascular disease (CVD) are two of the most frequent and important life-threatening adverse events associated with radiotherapy. Multiple primary cancers now account for approximately one in six of all incident cancers reported to the US Surveillance, Epidemiology, and End Results Program cancer registry (1). For patients with Hodgkin lymphoma (3), testicular cancer (4,5), and certain childhood cancers (6), SMNs have emerged as an important cause of death (7). Radiotherapy-associated CVD refers to a wide spectrum of disorders and is an important cause of morbidity and mortality, most notably after thoracic

radiotherapy for Hodgkin lymphoma and tangential radiotherapy for breast cancer (8,9).

With the increased awareness of the adverse consequences of cancer therapy, it has become critically important to identify measures to mitigate and ameliorate these late adverse effects and to provide cancer survivors with counseling, surveillance, and supportive care. In addition, it is essential to review and balance the risks and benefits of new treatment options as they become available. Providing a research infrastructure for transdisciplinary studies of cancer survivors is also important (10). The Childhood Cancer Survivorship Study (CCSS) is a critical resource for outcome and intervention research in survivors of pediatric and adolescent cancer (11); however, a comparable research base is lacking for survivors of young adult-onset (12,13) and other cancers. The expanding use of radiotherapy and development of new radiation modalities to treat cancer, coupled with improvements in long-term patient survival, underscores the importance of continuing to provide long-term risk estimates as well as additional research into the molecular underpinnings of treatment-related SMNs and CVD. Moreover, optimal screening and intervention efforts for these late adverse events must be identified (5).

To review and address the expanding burden of late adverse effects after treatment with radiation, the National Council on

Radiation Protection and Measurements (NCRP) convened a scientific committee (ie, NCRP 1-17) of experts in radiation biology, radiation oncology, radiation physics, molecular genetics, medical oncology, pediatric oncology, cardiology, biostatistics, and epidemiology to comprehensively review radiotherapy-associated SMNs and CVD and recommend future research. This commentary provides a synthesis of the 425-page NCRP Report titled *Second Primary Cancers and Cardiovascular Disease After Radiotherapy* (14).

Radiobiology

The traditional paradigm for the genesis of radiation-induced adverse effects, such as cell killing and carcinogenesis, is that biological responses result from the deposition of energy in or near cellular DNA (15). Radiation then interacts with DNA, either directly via ionization or indirectly via water-derived free radicals, resulting in genetic and/or epigenetic changes that are passed on to cellular progeny and that can contribute to malignant transformation. However, based on both in vitro and in vivo studies, there is increasing realization that low doses of radiation (eg, <0.5 Gy) may also contribute to radiation-induced adverse effects such as carcinogenesis and CVD (16). Differences in cellular responses to “low” vs “high” doses of radiation have also been reported for a number of different biological endpoints, including DNA damage signaling, cell cycle checkpoint activation, DNA repair, gene and protein expression, apoptosis, and cell transformation (17). However, evidence is emerging that radiation-induced carcinogenesis may be a modifiable process (18). For example, some agents appear to be capable of either reducing or increasing the incidence of radiation-induced cancer in animal models (19–21). Given this prospect, more research is needed to identify clinical interventions to reduce late adverse effects of radiotherapy.

Genetic Foundations of Late Effects of Radiotherapy

Data from animal models and human studies demonstrate that the genotype of the host influences the risk of radiation-associated late effects. For example, patients who inherit rare pathogenic mutations in genes associated with human cancer susceptibility syndromes are predisposed to radiogenic cancers, including *TP53* mutations in Li–Fraumeni syndrome (22–24), *NF1* mutations in neurofibromatosis (25,26), *PTCH1* mutations in Gorlin syndrome (27), *WT1* mutations in Wilms tumor (28–30), and *RB1* mutations in retinoblastoma (31,32). The increased susceptibility of mice heterozygous for the murine homologs of *PTCH1* (33,34), *TP53* (35), and *NF1* (36) to radiogenic cancers suggests the importance of these loci in human radiogenic cancers. The well-characterized roles of *BRCA1*, *BRCA2*, and *ATM* in mediating cellular response to ionizing radiation have prompted speculation that germline mutations associated with hereditary cancer may also predispose the mutation carriers to radiogenic cancer, particularly in the contexts of contralateral breast cancer (37,38) and radiotherapy for Hodgkin lymphoma (39,40). However, whether pathogenic mutations in these loci confer increased susceptibility to radiogenic cancer remains controversial. Several studies found no

association (39–41), whereas others provided limited evidence suggesting that specific *ATM* (37) and *BRCA1* (38) alleles may be associated with increased risk of breast cancer, particularly in *BRCA1* mutation carriers exposed to radiotherapy before age 40 years (38,42,43).

Many human cancer susceptibility genes that encode proteins that mediate cellular responses to ionizing radiation have a high frequency of genetic variants. For example, polymorphisms in *TP53* and *ATM*, with corresponding amino acid changes in the respective proteins, can affect the cellular response to ionizing radiation (44–47), making them candidate risk modifiers for radiogenic cancer and other late adverse effects of radiotherapy in a polygenic disease. Targeted gene- and/or pathway-based studies investigating adverse events after low- (48–55) and high-dose (56–67) radiation exposure have identified numerous other variants, loci, and pathways that warrant further investigation; others are readily testable based on known gene–exposure interactions identified by in vitro and ex vivo studies (68). Genome-wide association studies (69–71) might identify new gene–exposure interactions; however, this approach will require large well-controlled studies with sufficient statistical power to account for various phenotypic and exposure-related risk factors. Indeed, a genome-wide approach led to the discovery of an allelic variant in *PRDM1* (also known as *BLIMP1*), a gene that predisposes Hodgkin lymphoma survivors to radiogenic cancer (71). As parallel approaches, whole-genome (72) or exon-based sequencing technologies could prove equally informative. The ongoing development of radiogenomics consortia (73) with annotated biospecimens is anticipated to provide additional data with regard to genetic variants that may increase the risk for radiogenic cancer.

The low frequencies of overtly pathogenic alleles, such as *TP53* and *ATM*, suggest that they make a relatively small contribution at the population level. In addition, the heterogeneous patient responses to the acute and chronic effects of radiotherapy imply that these toxicities have complex genetic etiologies, rather than representing a monogenic trait. Furthermore, the fact that a single susceptibility locus with high-penetrance allelic variants for radiogenic cancer has not yet, to our knowledge, been identified further underscores the hypothesis that susceptibility to radiogenic cancer constitutes a polygenic trait, where cumulative risk is determined by co-inheritance of multiple low- and/or intermediate-penetrance “risk” alleles at several different loci, including, for example, *PRDM1* (71). Understanding how multiple variants interact with each other and with radiation and phenotypic risk modifiers should be considered when developing risk prediction models to inform intervention strategies. Indeed, the inclusion of genetic data has substantially improved the accuracy of risk prediction models for SMNs or recurrence after head and neck cancer (74). Risk models that integrate genotypic, phenotypic, and treatment data and other variables should also be developed for Hodgkin lymphoma (75,76) and other malignancies (5) where SMNs, CVD, and other late effects are important causes of morbidity and mortality.

An understanding of genetic and molecular factors that predispose individuals to the development of radiotherapy-induced cancers will also provide a foundation for the study of other late effects of radiation that have, in part, a known genetic basis, including CVD (77,78). Although some genetic risk factors will undoubtedly

be effect specific, the observation that some human diseases have overlapping transcriptional signatures in pathways such as lipid metabolism and carcinogenesis suggests that some pathways might apply to seemingly unrelated radiation-induced late effects, including cancer and CVD (79). Other pathways directly responsible for mediating cellular response to ionizing radiation are also likely to involve nonspecific risk factors. For example, radiation-induced reactive oxygen species can initiate an inflammatory response that leads to genomic instability and fibrosis, which have been implicated in the etiologies of cancer and CVD, respectively. In addition, Wethal et al. (80) showed that long-term survivors of testicular cancer with elevated serum levels of C-reactive protein, which is produced in response to inflammatory stimuli, had a two- to three-fold increased risk of developing either SMN (HR = 2.21; $P < .05$) or CVD (HR = 2.79; $P < .05$).

Radiotherapy Modalities, Technologies, and Dosimetry

Technical innovations have changed the practice of radiotherapy (81). Modern anatomical imaging technologies provide three-dimensional anatomical models of the patient that are often complemented with functional imaging studies such as positron emission tomography or magnetic resonance spectroscopy. Advanced imaging results in a more accurate determination of the tumor volumes and spatial relationships with the surrounding tissue and organs. Three-dimensional treatment planning systems, which take full advantage of these imaging advances, have facilitated the implementation of three-dimensional conformal radiation therapy as a standard of practice (81).

The development of medical linear accelerators equipped with computer-controlled multileaf collimator systems along with advanced computer-based treatment planning systems allow precise shaping of radiation dose distributions for each patient. Intensity-modulated radiation therapy (IMRT) can achieve even greater dose conformity through a computer-aided optimization process that creates a fluence of photons per radiation beam that is customized to the patient (82). The use of conformal radiation therapy has further evolved from IMRT to image-guided IMRT, also called image-guided radiation therapy. For very small tumor volumes adjacent to sensitive critical structures, cobalt-60 and linear accelerator-based stereotactic radiosurgery have been increasingly used in recent years, and new image-guided stereotactic body radiation therapy systems have been developed (83–86).

These advances have renewed interest in the use of protons for external beam radiotherapy (87). This technology allows conformal therapy to take advantage of the improved depth dose characteristics of the proton beam, which peak at the end of the range of the charged particle (87). In proton therapy, there are two techniques for beam production: passive scattering and beam scanning (87), with the latter method resulting in a lower amount of secondary neutrons.

The use of real-time imaging techniques to ensure the accuracy of new treatment modalities is increasing (88). Although the radiation dose from a single imaging technique is small compared with a therapeutic dose, repeated and daily image-guidance procedures can lead to cumulative exposures to normal tissues and possibly

a slight increase in the risk of SMN (89). The transition from two-dimensional radiation therapy to three-dimensional conformal radiation therapy and/or IMRT has also resulted in changes in dose distribution compared with techniques used in prior SMN studies (90).

Advances in radiotherapy have also resulted in increased doses to normal tissue but an overall reduction in the volume of normal structures receiving high doses. However, especially with IMRT, a considerably larger volume of normal tissue within the irradiated field receives low doses. Because these doses outside the target field are much smaller than the tumor doses, they are generally not recorded in radiotherapy documentation nor are additional doses due to image-guided radiation therapy reported in medical records. This unwanted radiation leakage and scatter dose can be decreased through several designs, as reviewed elsewhere (91). It will be important for clinical trial quality assurance centers that monitor radiotherapy protocols to capture radiation doses to multiple organs outside radiation fields for those patients enrolled in advanced technology clinical trials to enable eventual correlation with late effects (91).

SMNs Following Radiotherapy for Adult-Onset Cancer

A sizable amount of SMN data has accrued for several adult-onset cancers in which radiotherapy has played pivotal roles, including Hodgkin lymphoma, non-Hodgkin lymphoma, and cancers of cervix, testis, breast, and prostate (14). The methods for estimating risk of SMNs from epidemiological data are described in Supplementary Material 1 (available online).

Hodgkin lymphoma survivors have elevated relative risks (RRs) for most SMNs (except bladder and prostate cancers), particularly breast and lung (90). Radiotherapy at a young age, especially before the age of 35 years, is associated with increased breast cancer risk (92–95), whereas treatment-related premature menopause is associated with decreased risk (92,93,95,96). Both radiotherapy and alkylating chemotherapy have been associated with increased risks of lung cancer (97,98). The risk of SMNs for pediatric Hodgkin lymphoma survivors appears to persist following low therapeutic doses of radiation and chemotherapy (99). Several case-control studies, some with detailed organ-specific dose reconstructions (92,93,97,100,101), have reported statistically significant trends of increasing risks of breast (92,93,100,102), lung (97,103), and stomach (101) cancers with increasing radiation dose among several populations of survivors of adult-onset cancer.

Survivors of non-Hodgkin lymphoma are at increased risk for SMNs (104–115), and some of the increased risks are associated with radiotherapy. Radiotherapy for non-Hodgkin lymphoma has been linked to increased risks of acute leukemia (111,116), bladder cancer (104,105,110), kidney cancer (110), and mesothelioma (90,107,117). The use of total body irradiation as part of transplantation approaches is associated with increased risks of acute leukemia and myelodysplastic syndrome (86,118–120) and solid tumors (86,121,122), including breast cancer (121).

Among testicular cancer survivors, past treatment with large-field radiotherapy is statistically significantly associated with the risk of leukemia; past treatment with infradiaphragmatic radiation

is associated with a threefold increased non-statistically significant risk of leukemia (123). Statistically significant increased risks of cancers of the lung, thyroid, esophagus, stomach, pancreas, colon, rectum, kidney, bladder, and connective tissue have also been observed among long-term survivors of testicular cancer (124). These SMNs typically represent nontarget sites that were included in radiation fields (124). Concerns about radiation-related SMNs have prompted the adoption of observation-alone strategies following stage I seminoma (125).

Cancers associated with breast cancer radiotherapy include those of the contralateral breast (100,126–129), lung (126,130–132), and esophagus (133), as well as sarcoma (134). The risk of contralateral breast cancer after radiotherapy for breast cancer appears to be limited to women who are younger than age 40–45 years at receipt of radiotherapy (100,128,129) and is dose related (100). Risks for cancers of the lung and esophagus are higher after postmastectomy radiotherapy than after post lumpectomy radiotherapy (130,132,133), likely reflecting the differing volumes of normal tissue in the treatment fields. Although the risk of sarcoma after breast cancer radiotherapy is increased compared with the risk of sarcoma in the general population, radiation-induced sarcoma remains a rare event (absolute risk <0.5% at 15 years after radiotherapy) (134).

Kleinerman et al. (135) reported that radiotherapy for cervical cancer was associated with statistically significantly increased risks of cancers of bladder, kidneys, rectum, corpus uteri, and ovaries; these findings were confirmed in subsequent surveys (136–138). In the most recent update (139), the risks for several solid pelvic tumors remained statistically significantly elevated for more than 40 years after radiotherapy.

Some (140–143), but not all (144–146), studies have reported increased risks of colorectal cancer, bladder cancer, soft tissue sarcoma, and lung cancer among men treated with radiation for prostate cancer. The absolute risk of developing any SMN appeared modest (1 in 290 patients) (142), and some excess SMNs were detected incidentally during colonoscopies or cystoscopies.

SMNs Following Radiotherapy for Childhood Cancer

The risk of SMNs among childhood cancer survivors is associated with radiotherapy, chemotherapy, and genetic predisposition. In a recent CCSS update (6), the cumulative incidence of all subsequent neoplasms at 30 years after diagnosis was 20.5% (95% confidence interval [CI] = 19.1% to 21.8%) among 5-year survivors of childhood cancer treated from 1970 through 1986 and was higher for patients who received radiation therapy than for those who did not (~25% vs 10%); radiation therapy exposure was associated with a statistically significantly increased risk of a subsequent neoplasm (RR = 2.7, 95% CI = 2.2 to 3.3). Overall, cumulative incidence of SMNs at 30 years of follow-up was 7.9%, and, again, was higher among patients who received radiotherapy than among those who did not receive radiotherapy (~10% vs 5%). Radiotherapy was associated with increased risks of secondary central nervous system tumors, bone and soft tissue sarcomas, thyroid cancer, and non-melanoma skin cancer. A more recent CCSS report showed that,

overall, patients who developed a second neoplasm had a cumulative incidence of developing yet another primary cancer by 20 years after the SMN of 46.9%; the cumulative incidence of an additional primary cancer after an SMN was 41.3% among patients who received radiotherapy for the first cancer compared with 25.7% for those not treated with radiation; however, treatment for the SMN was not considered in these estimates (147). A study of 5-year survivors of childhood solid tumors in Great Britain and France showed an association between integral radiation dose and risk of death from SMNs, with secondary carcinoma as the leading cause of death, followed by sarcoma and then hematological malignancies (148). Survivors of hereditary retinoblastoma have the highest risk of SMNs, with a cumulative incidence at 50 years after diagnosis of 36% (95% CI = 31% to 41%) compared with 5.7% (95% CI = 2.4% to 11%) for survivors of nonhereditary retinoblastoma (32).

Among survivors of nonfamilial or hereditary malignancies, survivors of Hodgkin lymphoma appear to have the highest overall risk for SMNs. In a recent CCSS report of 2742 Hodgkin lymphoma survivors, of whom 94% received radiation (149), the 30-year cumulative incidence of any SMN was 10.9% (95% CI = 8.3% to 13.4%) in males and 26.1% (95% CI = 22.4% to 29.8%) in females; the difference in cumulative incidence was due to invasive breast cancer (cumulative incidence = 18.3%; 95% CI = 16.0% to 20.6%). The highest absolute excess risks (excess cancers per 10000 person-years of follow-up) were observed for the following solid cancers: bone = 22.3 (95% CI = 10.0 to 49.6), thyroid = 17.6 (95% CI = 13.0 to 24.0), and breast = 17.0 (95% CI = 14.0 to 21.7). The median time from Hodgkin lymphoma diagnosis to diagnosis of invasive breast cancer was 21.0 years (range = 6.7–33.5 years), with no apparent plateau.

The lower risk of SMN in survivors of childhood leukemia compared with survivors of childhood solid tumors is due to the less frequent use of radiotherapy in the former group (6,148,150–155). The most frequent second neoplasms following radiotherapy for acute lymphoblastic leukemia are brain tumors, acute myeloid leukemia, and carcinomas of skin, thyroid, and parotid gland (150–154). The majority of late-onset radiation-associated second neoplasms in survivors of acute lymphoblastic leukemia are low-grade (ie, meningiomas and basal cell carcinomas) (154,156).

The risk of a radiation-associated brain tumor in survivors of childhood cancer is positively associated with young age at time of radiation (<6 years), higher radiation dose (>30 Gy), and concomitant treatment with antimetabolites (especially in patients with thiopurine methyltransferase deficiency) or growth hormone (157–160). In the Berlin–Frankfurt–Münster trials, which involved multimodal intensive therapy that includes chemotherapy and radiation (151,161), the 15-year cumulative risk of SMNs was 1.7% (95% CI = 0.1% to 3.4%) among patients treated with 12-Gy cranial irradiation, which was lower, albeit not statistically significantly, compared with a 15-year cumulative risk of 3.2% (95% CI = 1.1% to 5.3%) for those receiving at least 18 Gy. The markedly reduced use of prophylactic cranial irradiation in contemporary clinical trials for pediatric leukemia is anticipated to reduce the occurrence of SMNs. Indeed, the 10-year cumulative risk of SMNs ranged from only 0.1% (SE = 0.1%) to 3.3% (SE = 1.2%) in patients treated for leukemia in the 1990s (162)

and was particularly low (ie, 0.1% and 0.3%) in the two studies that did not use cranial irradiation (163,164).

SMNs With Radiation Dose–Response Relationships

Table 1 summarizes epidemiological studies of SMNs following radiotherapy that included the estimated dose of radiation to the organ of interest. Most of these studies had a nested case–control design, and the relative risk parameter served as the primary risk measure.

Radiotherapy is associated with secondary leukemia (138,167, 168), and several studies have reported an attenuation of the risk of secondary leukemia at very high radiation doses. For example, in an international study of nearly 150 000 women treated for cervical cancer, the risk of leukemia increased with increasing dose to active bone marrow up to approximately 4 Gy (RR ~2.5) and then declined to approximately 1.5 at a dose of 17 Gy (138). In these studies (138,167), secondary chronic lymphocytic leukemia was not associated with radiotherapy (138,167).

Case–control studies of female breast cancer following treatment for Hodgkin lymphoma before age 30 years (92) and in childhood cancer survivors (165) provide evidence of a radiation dose–response relationship. In both studies, the risk of breast cancer increased with increasing radiation dose to the breast, reaching an odds ratio of 8 or more at doses of 40 Gy or more with no evidence of a downturn in the risk of breast cancer at the highest doses (Figure 1, A). A radiation dose to the ovary exceeding 5 Gy reduced the slope of the radiation dose–response relationship for breast cancer in women given chest radiotherapy, and alkylating agents also reduced the risk of breast cancer in Hodgkin lymphoma survivors. Several studies (92,93,95,96) have shown that this latter effect is due to treatment-related premature menopause. Dose–response relationships have been identified at lower doses (mainly doses <5 Gy) for contralateral breast cancer but only among patients diagnosed with a first breast cancer before the age of 45 years (100,128,129).

An international study of lung cancer in survivors of Hodgkin lymphoma demonstrated a statistically significant radiation dose–response relationship (97,169). This radiation dose–response was well described by a linear relationship with a modeled risk of sevenfold at 40 Gy; thus, lung cancer risk increased with increasing radiation dose (ie, a downturn in risk at the highest doses was not apparent). This finding implies that the lower radiation doses administered to treat Hodgkin lymphoma today will likely be associated with lower risks of lung cancer. Elevated risk was apparent 5–9 years after radiation treatment and persisted for at least 20 years. The combined effect of radiation dose and therapy with alkylating agents was additive, whereas the combined effect of radiation and smoking was more than additive ($P < .001$) and consistent with a multiplicative relationship.

There are few data on the relationship between radiation dose incidentally received by active bone marrow in the course of cancer treatment and subsequent leukemia risk. Kaldor et al. (170) found that among 11 Hodgkin lymphoma survivors who developed leukemia, the risk of leukemia in those who had received more than

20 Gy to the bone marrow was seven times larger than in those who had received smaller doses.

Information regarding radiation dose–response relationships and subsequent tumors of the central nervous system is sparse. Neglia et al. (157) found statistically significant radiation dose–response relationships for both gliomas and meningiomas in childhood cancer survivors, and the relative risks at a given dose were higher for meningiomas than for gliomas (Figure 1, B). In a case–control study of childhood cancer survivors (166), the risk of thyroid cancer increased with increasing dose to approximately 29 Gy (RR ~10) and then decreased for doses of 30 Gy or higher (Figure 1, C).

Increased risks of bone cancer and soft tissue sarcomas have been reported in many patient populations that received therapeutic doses exceeding 10 Gy (31,137,171). Especially, high relative risks of these SMNs have been observed among childhood cancer survivors, and a genetic interaction has been demonstrated in retinoblastoma survivors (31). A large international case–control study of cervical cancer that provided dose–response curves for 16 SMNs in addition to leukemia found statistically significant dose–response relationships at very high doses (≥ 30 Gy) for cancers of the rectum and bladder and all female genital cancers (137).

CVD in Patients Who Received Radiation Therapy

Radiation, chemotherapy, and biological agents, independently and in combination, increase the risk of CVD in cancer survivors. For survivors of some cancers, radiotherapy-related CVD is the leading noncancer cause of mortality (93,170,172–175). Radiation-related CVD includes pericardial disease, coronary artery disease, valvular dysfunction, conduction abnormalities, and cerebrovascular disease. However, the risk of pericarditis is rare with modern techniques of irradiation and dose fractionation. When at least 60% of the heart is irradiated at doses of 40 Gy or less, the risk for mild pericarditis is less than 5%, and severe pericarditis is rare (176).

Coronary artery disease results from injury and replacement of damaged cells by myofibroblasts and the deposition of platelets, followed by a cascade of events that result in atherosclerosis (102). Myocardial infarction is one of the most common types of CVD in long-term Hodgkin lymphoma survivors. High-dose (ie, >30–35 Gy) mediastinal radiation, particularly in younger Hodgkin lymphoma patients, increases the risk of coronary artery disease (177,178). The resulting high rate of complications and/or death most frequently occurs in Hodgkin lymphoma patients who have diastolic dysfunction (179). Among 2232 consecutive Hodgkin lymphoma patients treated from 1960 through 1991, irradiated children and adolescents had a markedly increased risk of death due to heart disease (RR = 28–37), and all of these deaths were in patients who received doses of 42–45 Gy (180). When this analysis was extended to include all Hodgkin lymphoma patients, the overall relative risk of death from acute myocardial infarction was 3.2 (180). The increased risks of death from myocardial infarction were statistically significant within 5 years after radiotherapy, the average time from completion of radiotherapy to myocardial infarction was 10.3

Table 1. Selected case-control studies of second cancers following radiotherapy with estimates of radiation dose to the organ of interest for individual patients*

Second cancer type or site (reference)	Underlying cohort	No. of case subjects with secondary cancer/ No. of matched control subjects	Age at first cancer diagnosis, y	Calendar years of first cancer diagnosis	Interval between first and second cancer diagnosis, y	Mean dose to the organ of interest, Gy (range)	Dose-response relationship†
Leukemia‡ (138)	~150 000 1-y survivors of invasive cervical cancer in North America and Europe	Total: 141/545; RT: 133/489	Mean = 52	1920–1978§	62% 1–9; 38% ≥10	7.2 (<0.2 to >15)	RR increased up to 4 Gy then decreased. Modeled RR at 1 Gy = 1.7
Breast (92)	5-y female survivors of Hodgkin lymphoma in North America and Europe (3817 1-y survivors)	Total: 105/266; RT: 104/253	<30; Mean = 22	1965–1994	Mean = 18	Case subjects: 25.1 ; Controls subjects: 21.1 (<0.1 to 61)	ERR/Gy = 0.15 (95% CI = 0.04 to 0.73)¶
Breast (165)	6647 5-y female survivors of childhood cancer in the United States	Total: 120/464; RT: 107/328	<21; Median = 16	1970–1986	Median = 19	Control subjects: 13.4 (<0.25 to >40)	ERR/Gy = 0.27 (95% CI = 0.10 to 0.67)#
Lung (97)	19046 1-y survivors of Hodgkin lymphoma in North America and Europe	Total: 222/666; RT: 179/356	Mean = 49	1965–1994	Mean = 11	Case subjects: 27.2**; Control subjects: 21.8 (<1 to >60)	ERR/Gy = 0.15 (95% CI = 0.06 to 0.39)
Thyroid (166)	14 054 5-y survivors of childhood cancer in the United States	Total: 69/265; RT: 62/197	<21; 40% <10	1970–1986	Median = 16	Case subjects: 24; Control subjects: 13 (0.01 to 62)	RR increased to up 29 Gy then decreased. ERR/Gy at radiation doses <15 Gy = 1.3 (95% CI = 0.4 to 4.1)
Central nervous system (157)	14 361 5-y survivors of childhood cancer in the United States	Total: 116/464; RT: 107/309	<21; 77% <10	1970–1986	Median = 14 (gliomas, median = 9; meningiomas, median = 17)	Case subjects: >29 (<0.5 to >49); Control subjects: 9.3 (<0.5 to >49)	Gliomas: ERR/Gy = 0.33 (95% CI = 0.07 to 1.71); Meningiomas: ERR/Gy = 1.06 (95% CI = 0.21 to 8.14)
Sixteen sites or types (137)	~150 000 1-y survivors of invasive cervical cancer in North America and Europe	Total: 4188/6880; RT: 3912/6336	Mean = 52	1918–1978§	Varied by cancer site	Varied by cancer site††	Statistically significant dose-response relationship for rectum, bladder, and all female genital sites combined; non-statistically significant dose-response relationships existed for several other sites

* The selected studies are the analytic investigations included in the National Council on Radiation Protection and Measurements report (14) that included estimates of radiation dose to the organ in which the second cancer developed. AA = alkylating agents; ERR = excess relative risk; CI = confidence interval; RR = relative risk; RT = radiotherapy.

† ERR/Gy estimates based on a linear model.

‡ Results are for the combined group of acute leukemia and chronic myelogenous leukemia.

§ Most patients were treated in the period 1940–1970.

|| Radiation dose was estimated to the area of the breast in which cancer developed and a comparable area in matched control subjects.

¶ Estimates are shown for patients who were not treated with AA and who did not receive doses ≥5 Gy to the ovaries. Both of these exposures were associated with a reduced risk of breast cancer.

Estimates are shown for patients who did not receive doses ≥5 Gy to the ovaries, an exposure that was associated with a reduced risk of breast cancer.

** Radiation dose was estimated to the area of the lung in which cancer developed and a comparable area in matched control subjects.

†† The 16 cancer sites (mean doses in Gy) are colon (24), rectum (30–60), stomach (2), bladder (30–60), all genital cancer (32–165), uterus (165), vagina (66), ovary (32), bone (22), connective tissue (7), non-Hodgkin lymphoma (8), multiple myeloma (7), pancreas (2), kidney (2), and thyroid (0.1).

Figure 1. Selected cancer risks by radiation dose. **A)** Breast cancer risk according to radiation dose to the breast. From Inskip et al. (165). Reprinted with permission. Copyright 2008 American Society of Clinical Oncology. All rights reserved. **B)** Relative risk of subsequent glioma and meningioma within the Childhood Cancer Survivor Study cohort by radiation dose (**open boxes**, mean observed relative risk for meningioma; **closed boxes**, mean observed relative risk for glioma; **solid line**,

fitted line for meningioma risk; **hatched line**, fitted line for glioma risk). $P < .001$ (likelihood ratio test, two-sided). From Neglia et al. (157). Reprinted with permission from Oxford University Press. **C)** Thyroid cancer risk by radiation dose in case subjects and control subjects after adjustment for first cancer. From Sigurdson et al. (166). Reprinted from *Lancet* 2005;365:2014–2023, with permission from Elsevier. **Error bars** represent 95% confidence intervals. ORs = odds ratios.

years, and the risk of death from myocardial infarction remained elevated throughout the follow-up period (>20 years).

Many studies of breast cancer survivors have reported a statistically significant increase in coronary artery disease and/or nonfatal myocardial infarction associated with left-sided radiotherapy compared with right-sided radiotherapy or no radiotherapy (181–187). Breast cancer patients treated with internal mammary node radiotherapy may also be at increased risk for coronary artery disease (129, 182,188).

Radiotherapy is associated with an increased risk of valvular dysfunction (189,190). Hull et al. (191) reported that valvular dysfunction developed in 25 of 415 Hodgkin lymphoma survivors at a median of 22 years after radiotherapy. In a large Dutch study of breast cancer survivors (184), the hazard ratio of valvular dysfunction for internal mammary node radiotherapy vs no radiotherapy was 3.17 (95% CI = 1.90 to 5.29). The 2009 CCSS survey (9) showed that the cumulative incidence of self-reported

valvular disease increased with increasing cardiac radiation dose.

Radiation may cause fibrosis of cardiac conduction pathways, which can lead to life-threatening arrhythmias or other conduction defects. Serious post-radiation abnormalities include atrioventricular nodal bradycardia, all levels of heart block including complete heart block, and sick sinus syndrome (192). The frequency of one type of cardiac conduction damage (ie, QTc > 0.44 seconds) in 134 childhood cancer survivors was 12.5% after chest radiotherapy alone and 18.9% after radiotherapy and anthracyclines (192). Persistent fixed-rate tachycardia and loss of circadian variability in the heart rate have also been documented following chest radiotherapy that resulted in cardiac exposure. In one study (193), 74.5% of long-term survivors of Hodgkin lymphoma treated with chest radiotherapy had a cardiac conduction defect or arrhythmia, 31% had sustained tachycardia, and 57% had a monotonous heart rate. Autonomic nervous system dysfunction

Figure 2. Cumulative incidence of cardiac disorders among childhood cancer survivors by average cardiac radiation dose. From Mulrooney et al. (9), with permission from BMJ Publishing Group Ltd. cGy = centigray.

could lead to the decreased perception of angina observed by some patients.

Myocardial infarction due to radiotherapy can also lead to congestive heart failure. When myocardial dysfunction develops after standard-dose mediastinal irradiation, it is typically mild or sub-clinical (194) and involves diastolic and systolic left ventricular dysfunction (195). Restrictive cardiomyopathy is more common in cancer survivors treated with radiotherapy who have not received

an anthracycline (196). Subtle left ventricular dysfunction has been detected by echocardiography and radionuclide angiography in Hodgkin lymphoma patients evaluated a few years after mediastinal irradiation (197). Two retrospective studies (184,188) of congestive heart failure among irradiated breast cancer patients yielded conflicting results. A multi-institutional study with a median follow-up of 18 years found an increased risk of congestive heart failure with radiotherapy compared with no radiotherapy

Box 1. Conclusions and research recommendations of the NCRP 1-17 Report (14): Second Primary Cancers and Cardiovascular Disease after Radiotherapy*

Conclusions

1. Second primary cancers and cardiovascular disease after radiotherapy (RT) experienced by an ever-growing number of cancer survivors, with the most data accrued for second malignant neoplasms (SMNs).
2. Quantitative estimates of radiation-induced SMNs are: a) derived from studies incorporating comprehensive dose reconstructions; and b) although based on past regimens, are applicable to risk assessment following current RT in terms of organ-specific doses and dose-response relationships.
3. Newer RT modalities and treatment techniques, which include intensity-modulated radiotherapy (IMRT) and protons, result in different organ dose distributions.
4. Computational models are useful for SMN risk assessment and comparisons with older RT modalities; similar models to evaluate CVD should be developed.
5. Low-dose cardiac exposures have not been convincingly linked to CVD, but associations between CVD and whole-body doses of <1 Gy among atomic bomb survivors are of potential clinical importance because many RT-treated patients receive low-dose cardiac doses from scatter and collimator leakage.
6. Few reports describe survival after SMN or CVD.
7. For individual and epidemiological risk assessment, the effective dose (a construct for radiation protection purposes) should not be used. Instead, the organ-specific absorbed dose coupled with the appropriate relative biological effectiveness for endpoint of interest and radiation type (eg, electrons, protons, neutrons) should be used for risk assessment.

Research Recommendations

1. Overarching recommendations
 - a. Long-term large-scale follow-up of extant cancer survivors to characterize the risks of SMNs and CVD and to evaluate role of comorbidities and effect modifiers.
 - b. Follow-up of prospective cohorts of cancer patients to evaluate life-long risks of SMNs, CVD, and other late effects, including
 - Populations treated with newer RT modalities (including IMRT, tomotherapy, stereotactic RT, Cyberknife, gamma knife, and protons).
 - Cancer sites for which reductions in field size and radiation dose have been implemented (eg, Hodgkin lymphoma, testis cancer), and cancer populations not treated with radiation (eg, testis cancer patients treated with surgery) to define natural history and baseline risks.
 - Collect biological samples for evaluation of genetic factors in survival and development of SMNs and CVD.
2. Specific recommendations:
 - a. Given the differing dose-response relationships for various SMNs, analytic studies should continue to address the relationship between dose and risk, with similar efforts undertaken for CVD.
 - b. Compare the risks of SMNs and CVD after different RT modalities.
 - c. Address interactions between RT and other risk factors for SMNs and CVD.
 - d. Particular attention should be given to adolescent and young adult cancer survivors, given the scarcity of data (200).
 - e. Molecular and genetic underpinnings:
 - Investigate genetic contributions of RT-associated SMNs and CVD.
 - Intensively study patients who develop two or more primary cancers likely associated with RT.
 - f. Risk prediction models
 - Develop comprehensive risk prediction models for SMN and CVD to stratify patients into risk groups to customize follow-up strategies and develop evidence-based interventions.

* Before publication, NCRP reports undergo comprehensive review by an outside panel of experts, who provide substantive and critical comments that are then addressed by the report's co-authors. The revised report is then reviewed by all members of the NCRP (<http://www.ncrponline.org/Members/Council.html>) before final revision, publication and endorsement by the NCRP.

(184), whereas another investigation (188) found no increased incidence of congestive heart failure associated with radiotherapy laterality or internal mammary node radiotherapy.

Few analytic data describe the relationship between radiation dose to the heart and adverse outcomes. The 2009 CCSS survey (9) is thus noteworthy for the detailed dose–response evaluations conducted following radiotherapy and anthracycline treatments and the risks (albeit self-reported) of congestive heart failure, myocardial infarction, pericardial disease, and valvular abnormalities (Figure 2). Compared with siblings, childhood cancer survivors were statistically significantly more likely to report congestive heart failure (HR = 5.9, 95% CI = 3.4 to 9.6), myocardial infarction (HR = 5.0, 95% CI = 2.3 to 10.4), pericardial disease (HR = 6.3, 95% CI = 3.3 to 11.9), and valvular abnormalities (HR = 4.8, 95% CI = 3.0 to 7.6). Cardiac radiation exposure of at least 15 Gy increased the risk of congestive heart failure, myocardial infarction, pericardial disease, and valvular abnormalities by two- to sixfold compared with nonirradiated survivors. There was no evidence for increased risks of any of these conditions following exposure to less than 5 Gy, and the slight elevations in these risks were not statistically significant at exposures between 5 and 15 Gy. The hazard ratios for the four cardiac conditions ranged from 3.6 to 5.5 for cardiac doses greater than 35 Gy. The cumulative incidence of adverse cardiac outcomes in childhood cancer survivors continued to increase up to 30 years after diagnosis and ranged from approximately 2% to slightly more than 4% overall, but to much higher levels for those who received the highest cardiac radiation doses (Figure 2) and the highest cumulative dose of anthracyclines. Recent data from the German–Austrian DAL-HD (German Association for Childhood Leukemia Research and Treatment and Hodgkin’s disease) studies show a dose–response relationship for cardiac diseases in children treated for Hodgkin lymphoma with combined anthracycline-based chemotherapy (cumulative doxorubicin dose was uniformly 160 mg/m²) and radiation (198). The 25-year cumulative incidence of cardiac disease was 3% with no radiotherapy, 5% after 20 Gy, 6% after 25 Gy, 10% after 30 Gy, and 21% after 36 Gy (198).

Patients treated for head and neck cancer with radiation doses of 40–70 Gy, and particularly with doses greater than 60 Gy, have an elevated risk for stroke and occlusive carotid artery disease (199–201). In one study (201), the median time from radiotherapy to stroke diagnosis was 10.9 years (range = 1.3–21 years). Another study (199) reported 66 cerebrovascular events among 2567 head and neck cancer patients who were treated with 30–66 Gy radiotherapy compared with only 12 events among 4119 nonirradiated patients (odds ratio = 9.0; $P < .001$).

In a 2009 study of 2201 5-year survivors of Hodgkin lymphoma (201), 96 patients developed cerebrovascular disease (55 had a stroke, 31 had a transient ischemic attack, and 10 had both) at a median age of 52 years. The standardized incidence ratio was 2.2 for stroke and 3.1 for transient ischemic attack. Radiation to the neck and mediastinum was an independent risk factor for ischemic cerebrovascular disease (HR = 2.5, 95% CI = 1.1 to 5.6 compared with no radiotherapy).

The incidence of stroke in the CCSS cohort was almost 10-fold higher than in the sibling comparison group (202). Leukemia survivors were six times more likely to suffer a stroke compared

with the siblings, and brain tumor survivors were 29 times more likely. Of the brain tumor cohort, 69 (4.9%) of 1411 patients who had a history of radiotherapy reported a stroke, and the cumulative incidence of stroke at 25 years after radiation therapy was 6.9% (95% CI = 4.5% to 9.3%). Cancer survivors who were exposed to cranial radiotherapy at a dose of 30 Gy or higher had an increased risk for stroke, with the highest risk among those treated with a dose of 50 Gy or higher (202). Adult survivors of childhood Hodgkin lymphoma who were treated with thoracic radiotherapy (median dose = 40 Gy), which included mediastinal and neck radiotherapy, had a 5.6-fold increased risk of stroke compared with the siblings.

Conclusions and Research Recommendations

The conclusions and recommendations of the NCRP (14) are summarized in Box 1 and reproduced in their entirety in the Supplementary Material 2 (available online). The reader is referred to the NCRP report (14) for in-depth discussion of each of the conclusions and recommendations. In summary, although modern therapies prolong the lives of cancer patients, this success carries an increased risk of late adverse health effects, including SMNs and CVD. Awareness, evaluation, counseling, and amelioration strategies are recommended (14).

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Funding

Supported in part by grant CA21765 from the National Institutes of Health, the American Lebanese Syrian Associated Charities (C.-H.P), and the University of Rochester Medical Center (L.B.T.).

Notes

We wish to thank Ms Laura Atwell (NCRP) and Dr Charles Church (National Center for Physical Acoustics, University of Mississippi) for their support of NCRP Scientific Committee 1-17, as well as Dr Tom Tenforde (President, NCRP) and Dr David Schauer (Executive Director, NCRP). We are also indebted to Ms Laura Brumbaugh (URMC) for expert editorial assistance. The NCRP Committee was responsible for preparing the comprehensive report (upon which this commentary is based) with NCRP's financial support from the National Cancer Institute under Grant Number R24 CA074206. The funding agency had no role in design, analysis, or interpretation of the reviewed data; in the decision to submit the commentary for publication; or the writing of the commentary. The content of this commentary is the sole responsibility of the co-authors and does not necessarily reflect the views of the funding agency (NCI). The NCRP Scientific Committee 1-17 report will be available Spring 2012 at www.ncrponline.org.

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