1. Executive Summary

1.1 General

Advances in cancer therapy, early detection of cancer, and supportive care have contributed to steady gains in the 5 y relative survival rate for all cancers considered together, reaching 66.1 % between 1999 to 2006. These successes are associated with a tripling of the number of cancer survivors in the United States since 1971, and the numbers are growing by 2 % each year. As of 2007, there were ~12 million men and women in the United States with a history of cancer, representing 3.5 % of the population. Radiation remains a cornerstone of successful cancer treatment, with 50 % of all patients estimated to have received radiation therapy (RT)[1] for the management of their cancer. For many patients, the gains in survival have come at the cost of radiation-induced late effects.

Second primary cancer (SPC) and cardiovascular disease (CVD) are two of the most frequent and important life-threatening events associated with RT. Multiple primary cancers now account for approximately one in six of all incident cancers reported each year to the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) Program. This Report provides a comprehensive and current assessment of the risk of SPC and CVD following RT among the growing number of cancer survivors worldwide. The Report focuses on the complex epidemiologic and dosimetry issues surrounding past, conventional, and the modern RT modalities and techniques, including intensity-modulated radiation therapy (IMRT) and proton-beam therapy.

Major epidemiologic studies are reviewed that have provided estimates of the risk of SPC and CVD following RT in children, adolescents and adults. Special attention is given to those cancer sites for which dose-response relationships between radiation dose and

[1]The use of high-energy radiation from x rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam RT), or it may come from radioactive material placed in the body near cancer cells (internal RT). Systemic RT uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body (also called radiotherapy and irradiation).

SPC or CVD have been provided. There is a wealth of knowledge on the risk of SPC following RT indicating clear increases. For example, radiation-specific increases in the risk of second cancers have been reported for breast, lung, thyroid, brain, bone, soft tissue, and leukemia. Quantitative estimates of risk for CVD are just now emerging and are an important area of future research. Past and current approaches to estimate doses to organs outside the primary treatment fields from various radiation modalities are summarized in this Report.

Radiobiologic principles provide a foundation for understanding the underlying mechanisms of radiation cell damage important in the development of either SPC or CVD. The study of well-known genetic syndromes that predispose to the development of multiple primary cancers, such as heritable retinoblastoma and other familial cancer syndromes, has provided valuable insights into the interaction between high-dose radiation and underlying genetic susceptibilities in causing SPCs. The conventional methods of RT delivery in the past included orthovoltage machines, ^{60}Co teletherapy units, and brachytherapy with radium. Modern RT modalities and technical innovations, however, have significantly changed the practice of RT over the last two decades. Three-dimensional treatment-planning systems take full advantage of the modern imaging advances, such as x-ray computed tomography (CT) and magnetic resonance imaging (MRI), so that three-dimensional conformal radiation therapy (3D-CRT) is becoming firmly established as the standard of practice in the United States. IMRT can achieve even greater dose conformality, particularly for those volumes having complex or concave shapes. There has been a concern that the increased time the machines have to be on to attain this superb dose distribution to tumor, also increases the whole-body dose relative to that from conventional RT. There is renewed and expanding interest in the use of protons for external-beam RT. Patients treated with protons and high-energy x rays are also exposed to low-level secondary neutrons.

Sections 2 through 10 of this Report are organized by the following topics:

- general introduction (Sections 2 through 4) that cover definitions, historical perspective in the study of iatrogenic SPC and CVD, current issues, radiobiological and epidemiological principals;
- modern RT modalities and technical innovations that over the last two decades have significantly changed the practice of RT (Section 5);

- approaches to estimate doses to organs outside the primary treatment fields from various radiation modalities (Section 6);
- clinical and epidemiologic studies on multiple primary cancers, underlying genetic principles and familial cancer syndromes (Section 7);
- quantitative estimates of the risks of SPCs following RT for both adult-onset cancers and childhood/adolescent cancers and dose-response relationships (Sections 8 and 9); and
- risk of CVD following thoracic RT (Section 10).

This material is intended to provide background information for the reader, including the oncologist, clinician, epidemiologist, patient, medical physicist, health physicist, dosimetrist, pediatrician, cardiologist, health-care professional, and government personnel involved with radiation and cancer treatment issues. The Report ends with a summary of recommended research initiatives that could be undertaken to advance knowledge on SPC and CVD risk following RT in the treatment of cancer (Section 11).

1.2 Recommendations

The expanding use of RT and development of modern radiation modalities to treat cancer, coupled with improvements in long-term patient survival, underscores the importance of future research into the molecular and genetic underpinnings of SPC and CVD, in addition to optimal screening and interventional efforts.

The National Council on Radiation Protection and Measurements (NCRP) research recommendations in this Report are listed in Table 1.1 in summary form for ready reference. The recommendations, however, should not be read in isolation, and the subsections in which each statement is discussed more fully should be consulted for a more complete explanation. The Report's conclusions and recommendations are fully itemized in Section 11.

Because of the expanding use of RT and modern modalities and technologies to treat cancer patients, coupled with long-term favorable survival, constant vigilance is needed to monitor and evaluate the possible risks of SPC and CVD associated with these new and innovative treatments, through epidemiologic, laboratory and clinical studies. While the number of patients undergoing RT is just under 1 % of the number having diagnostic procedures, the absorbed dose to the target volume (*i.e.*, the treatment dose) is on the order of 5,000 to 50,000 times as large as the organ doses resulting from the diagnostic procedures (NCRP, 2009). The population is aging, lifespans are increasing, and RT continues to be an important

TABLE 1.1—*NCRP Report No. 170 recommendations with a brief summary.*

Research Recommendations[a]
• Long-term and large-scale follow-up of extant cancer survivors *should* be instituted to characterize the risk of second primary cancer (SPC) and cardiovascular disease (CVD) and to evaluate the role of comorbidities and effect modifiers, such as age, gender and race/ethnicity.
• Integrated measures *should* be developed to evaluate the life-long burden of all medical morbidities, including SPC and CVD, according to prior cancer treatment.
• Epidemiologic studies *should* be integrated with molecular and genetic approaches to ascertain the potential risk of emerging treatment modalities, and to understand the evolution of late effects, especially among the aging population of cancer survivors.
• Prospective cohorts of cancer patients *should* be established to evaluate the life-long risk of SPC, CVD, and other late effects. These include but are not limited to: - populations treated with modern treatment modalities (including IMRT, tomotherapy, stereotactic radiation therapy (SRT), Cyberknife®, Gamma Knife®, and proton-beam therapy); - populations treated for certain primary cancer sites for which reductions in field size and radiation dose have been implemented (*e.g.*, Hodgkin's lymphoma); and - populations of cancer survivors not treated with radiation (*e.g.*, testis cancer patients treated with surgery) in order to understand the natural history of these cancers and establish baseline risks of SPC and CVD for comparison with patients treated with RT.
• For late-effects studies of modern treatments, it *should* be established whether increased risks for site-specific SPC are indeed reduced or just delayed, and any effect on histologic type of SPC.
• For late-effects studies of patients treated with radiation, biological samples *should* be collected to enhance future evaluation of genetic factors in patient survival and development of SPC and CVD following treatments.
• Analytic epidemiological studies *should* continue to address the relation between radiation dose and SPC risk, and the role of modifying factors, taking into account histologic type (*e.g.*, meningiomas compared with gliomas). Similar efforts *should* be undertaken for the major categories of CVD.
• Particular attention *should* be given to evaluating dose-response relationships among survivors of adolescent and young adult cancer (18 to 39 y of age), given the dearth of data in this area and the particular needs of this understudied population.

- A better understanding *should* be developed of the possible genetic underpinnings of radiation-induced SPC and CVD. These include the use of both candidate and genome-wide approaches to investigate genetics, epigenetics, mitochondrial DNA, microRNA, and proteomics to understand the underlying basis for late effects.
- Standardized approaches *should* be developed for biospecimen collection to support genetic and molecular studies.
- Patients who develop two or more primary cancers likely associated with RT *should* be intensely studied, since they may have unique genetic profiles.
- Study sizes *should* be adequately powered to characterize interactions between RT and other risk factors as additive, multiplicative or other. Several putative interactions justify further study, as follows:
  - *SPC*: The possible interaction *should* be addressed between RT and other variables (chemotherapy, age at exposure, attained age, gender, race, lifestyle factors such as tobacco and alcohol use), energy balance, and genetic modifiers of treatment in the development of site-specific SPCs.
  - *CVD*: The possible interaction *should* be addressed between RT, anthracyclines, and other therapeutic interventions in the development of heart disease, as well as the concomitant influence of other known modifiable cardiac risk factors such as cigarette smoking, hypertension, diabetes, and hyperlipidemia.
- The risk of SPC and CVD *should* be compared after different RT modalities, including conventional RT, IMRT, tomotherapy, SRT, and proton-bean therapy.
- Comprehensive risk-prediction models *should* be developed for SPC and CVD that incorporate genetic modifiers of late sequelae, as well as treatment variables and well-established disease risk factors.
- Risk-prediction models *should* also be appropriate to stratify patients into risk groups in order to customize follow-up strategies and develop evidence-based interventions.

[a]*Should* (in italics) in this table indicates an advisory recommendation for which consensus-based data suggest that implementation may help better understand and lead to measures that help reduce the risk of radiation-induced SPC and CVD.

component of cancer treatment. The number of long-term cancer survivors will continue to increase. Despite the clinical benefit afforded by the modern treatment strategies, it is recognized that adverse late effects are possible consequences of these therapeutic advancements. Late effects, such as iatrogenic SPCs and heart disease, will continue to increase, based on absolute numbers alone, although conceivably at a lower level than those associated with past therapies and methods. Clinical and public-health awareness of these adverse consequences is now prominent, and the development of means to mitigate and ameliorate and to provide counseling, surveillance and supportive care is essential both now and in the future.