BOOKS AND PUBLICATIONS

All interested medical physicists are encouraged to have their names added to a list of available reviewers. Please rank your interest among radiation therapy, x-ray, imaging, nuclear medicine imaging, ultrasound imaging, MR imaging, radiation injury, radiation protection, and others. Make your interest known to Dimitris Mihailidis, Ph.D., Books Review Editor (dimitris@charlestonradiation.com). Include your name and e-mail address in the body of the response.

Second Primary Cancers and Cardiovascular Disease after Radiation Therapy. NCRP Report No. 170. NCRP Publications, Bethesda, MD, 2011. $160.00. ISBN: 978-0-9823843-9-8, 386, pp. (hardcover).

Description

This report is a comprehensive review of major epidemiologic studies that have evaluated the risk of developing second primary cancers (SPCs) and cardiovascular disease (CVD) in patients whose treatments included radiation therapy. The report primarily focuses on large retrospective outcome studies of cancer survivors who received mainly historical photon therapies, i.e., radioepidemiology studies. Many readers will appreciate the fact that this report also considers the potential implications of these retrospective data from historical radiation therapy on contemporary radiation therapy.

Purpose

According to the authors, the purpose of this National Council on Radiation Protection Report 170 is to comprehensively address the issue of SPCs and CVD in patients who received radiation therapy for primary cancers; specifically, the authors say they aimed to (1) review the worldwide epidemiological literature on the occurrence of SPCs and CVD, (2) describe the fundamental radiobiological principles that may underlie the occurrence of SPCs and CVD, and (3) consider the potential benefit of using modern radiation therapy modalities in reducing the risk of SPCs and CVD. In my opinion, the authors not only met these objectives, but did so in a way that allowed them to report the relevant data in a logical, progressive, and concise manner. Moreover, this report includes a wealth of information about the design of epidemiological studies; in particular, nested case-control studies which have yielded very useful information regarding dose response models for late effects.

Owing to advances in cancer therapy, earlier detection and improved supportive care, the number of cancer survivors in the United States has increased every year since 1971 (tripling in just over 40 yrs). There are now more than 12 million cancer survivors in the United States, accounting for approximately 3.5% of the population. Moreover, it is estimated that approximately half of these survivors received radiation therapy as part of their cancer treatment. Both SPCs and CVD are physically and emotionally devastating and are among the most frequently reported late effects among survivors. Given these facts, the objectives of this report are both important and timely, for a wide range of readers.

Audience

Regarding the potential reach of the information, the authors again succeed. Their stated audience includes oncologists, clinicians, epidemiologists, patients, medical physicists, health physicists, dosimetrists, pediatricians, cardiologists, other healthcare professionals, and government personnel involved with radiation and cancer treatment issues. Overall, the report has sufficient technical information to be of interest to those working in radiation therapy, e.g., radiation oncologists, medical physicists, and dosimetrists, and is also sufficiently thorough to be of interest to those working in related fields, such as cardiologists, pediatricians, epidemiologists, and health physicists. In addition, this report provides an excellent overview of diverse topics in a manner that will be easily understandable and of general interest to a broad audience of readers, e.g., patients and other healthcare professionals. For example, the report nicely describes the evolution of modern radiation therapy and how its improved conformality reduces dose to organs near the target, but may increase stray radiation to organs farther away. I believe the concise summaries of the radioepidemiological studies of SPCs and CVD are extremely valuable, but the section of this report that I found of greatest interest is the section on epidemiological study design, which provides welcome and sorely needed insight on how to interpret the results of such studies.

The chairman and vice chairman of this report, Lois B. Travis and John D. Boice, are among the foremost experts in the field of radioepidemiology. Both have been principal investigators on numerous cohort and nested case-control studies of late effects from cancer therapy and specifically those related to radiation therapy. Their contribution to this field is unparalleled, making them uniquely qualified to lead this report. Likewise, the other committee members represent leading experts in the fields of epidemiology, radiobiology, medical physics, nuclear engineering, radiology, and radiation oncology. With their combined expertise, they were able to meet the report's objective of addressing the issue of radiation therapy-related SPCs and CVD in a comprehensive manner. However, in my opinion, the report could have been strengthened by expanding the authorship to include a medical physicist who has done retrospective dose reconstructions for studies which have yielded dose-response models.

Content/Features

Overall, the layout of the report is very good, and the content covers the topics relevant to understanding the results of radioepidemiological studies. The report also nicely summarizes the results of the most important studies

of radiation therapy-related SPCs and CVD. The tables throughout the book are exceptional and serve as short but informative summaries of the major points in each chapter.

Section I of the report is an executive summary. The summary is well written and clearly communicates the objectives of the report as well as the recommendations of its authors and of the NCRP. Sections II and III provide the reader with essential background information including definitions of terms used in radiobiology and a description of the historical relevance of these studies, as well as an overview of the basic principles of radiobiology and radiation physics. Section IV, which describes methods and study designs that have been used in various radioepidemiological late-effects studies, is a truly insightful addition to the report because a good understanding of the results from large outcome studies requires clear comprehension of the studies' designs. More importantly, this topic is not well known to most of the intended target audience; this section fills this gap in knowledge and provides just enough detail without being overly technical. Section V describes the evolution of modern radiation therapy. This section is a nice overview of recent technological innovations and clearly describes why organ doses from modern radiation therapy can be vastly different from those in historical radiation therapy.

Section VI is titled "Radiation therapy dosimetry relevant to second cancers and cardiovascular effects," but I found the title of this section somewhat misleading, and there seems to be a disconnect between Sec. VI and the rest of the report. The report primarily focuses on results of radioepidemiological studies. Moreover, the report emphasizes that studies that have generated dose-response models are the most informative because "*once risk is expressed as a function of dose, it is possible to evaluate the risk associated with any specified dose*." The report further suggests that such models can be used to predict the late effects of contemporary radiation therapy. However, Sec. VI is largely an overview of the literature on out-of-field dose, i.e., stray dose. This topic is clearly important and needed to be included in the report, but in my opinion, the information should have been more clearly distinguished from discussions of how dosimetry actually was performed in previous radioepidemiological studies and whether those methodologies can be adapted for use with modern technologies. For example, in Sec. VI the authors spend considerable effort discussing stray neutron dose and numerous measurement and computational studies that have found higher neutron doses for intensity-modulated radiation therapy than for conventional radiation therapy. However, no mention is made about the lack of radioepidemiological studies that have included stray neutron dose in their dose reconstruction methods. This example highlights my opinion that a serious shortcoming of this report is the lack of distinction between what types of measurements and calculations can be preformed verses those that have actually been used in (and are practically suitable for) radioepidemiologial studies with thousands of patients.

The remainder of the report is focused on the late effects of SPCs and CVD. Section VII discusses the genetic underpinnings of SPCs. The authors are to be commended for presenting this very technical information so that it is clear even to those with little expertise in this area. There is also a very informative table in this section that summarizes the literature regarding syndromes that predispose patients to radiogenic cancer. This section concludes with a comment that summarizes the importance of research in this area and is worth quoting here: "An understanding of susceptibility to radiation-induced cancers could lead to therapeutic benefit such that patients at high risk could be identified and offered alternative therapies where possible or post-therapy surveillance."

Section VIII considers SPCs in populations of patients whose primary cancer therapy included radiation therapy. This section considers individuals who received treatment as adults and as children separately and is further subdivided according to the site or type of primary cancer. This section is a well written, easily accessible, and comprehensive review of the literature. Of particular interest is a table that summarizes the relative risk and excess absolute risk of developing any SPC for selected primary cancers treated with and without radiation. The data themselves are extremely useful, of course, but this table also represents an excellent example of the logical progression that guides the narrative. The risk measures are defined and their limitations and advantages discussed in Sec. IV; thus, by Sec. VIII, the reader has all the background information needed to interpret the outcome data.

Section IX focuses on SPCs for which dose-response models have been reported and so will be of particular interest for those interested in predicting risk when using contemporary radiation therapy techniques. This section is very well written, easy to follow, and again provides a comprehensive review of the existing literature. As in Secs. I–VIII, the tables presented here are of exceptional value and provide comprehensive summaries of reported data. Specifically, there is a table for each SPC having a reported dose-response model, and each table contains valuable information regarding the study design from which the model was drawn, such as a description of the patient and control groups, mean dose to the organ where the SPC occurred, main results, and more. Again, these data are more easily interpreted in this section because of the background information presented in Sec. IV. However, the disconnect between Sec. VI and the rest of the report becomes more obvious when reading Sec. IX, which states "to be included in this section, organ doses for individual subjects must have been estimated based on radiation therapy records as described in Sec. VI and outlined by Stovall *et al.* (2006).[1]" As previously noted, Sec. VI does not clearly distinguish between all methods for determining stray organ doses and those that have actually been used in radioepidemiological studies. Nevertheless, Sec. IX is timely and, to my knowledge, the most cohesive summary of existing dose-response models for SPCs.

Section X focuses on CVD in patients who were treated with radiation. The authors of this section clearly met their objective of providing a comprehensive overview of the literature in this area. In addition, they have described the pathophysiology of various types of radiation-induced damage as well as the damage's clinical manifestations. Because there are so many different types of CVD (each of which may be associated with damage to different parts of the heart and cardiac structures), CVD is perhaps more difficult to describe than SPCs. Furthermore, there is considerably less information on CVD than on SPCs, especially with regard to dose-response models. Given these limitations, the authors conclude by noting the need for prospective clinical trials based on three-dimensional dosimetric data and careful long-term follow-up for patients who have received potentially cardiotoxic chemotherapy and radiation therapy.

Assessment/Comparison

There are several excellent reports in the literature that have summarized some portions of the topics discussed in NCRP Report 170. For example, the National Cancer Institute (NCI) published a comprehensive summary of studies of new malignancies in participants of the surveillance epidemiology and end results (SEER) program between the years of 1973 and 2000.[2] While the NCI report considered SPCs from many different cancer treatments, this NCRP report only considers those related to radiation therapy, but it summarizes SPCs for a much broader spectrum of patient populations. Similar to this NCRP report, the Biological Effects of Ionizing Radiation Report VII (BEIR VII) also published dose-response models for radiation-related SPCs.[3] While the BEIR VII dose-response models are extremely valuable and have been used to predict risk of SPCs from treatment with contemporary radiation therapy techniques by several authors,[4–8] those models were largely based on late effects from low doses of radiation in survivors of the atomic bomb. In contrast, the dose response models summarized in NCRP Report 170 are specific to patients treated with radiation therapy and are based on carefully designed retrospective outcome studies that included detailed patient specific dose reconstructions. Moreover, the doses for individual organs on which the models were based span a wide range of doses from very high doses, i.e., organs inside the treatment field to very low doses, i.e., organs far from the treatment field. This report is unique in that it focuses entirely on radiation-therapy related late effects. In my opinion, this report is the most useful single reference on the topic of radiation therapy-related CVD and SPCs as it both summarizes the results of radioepidemiological studies and provides the background information needed to interpret the results.

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[3]National Research Council (U.S.). Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation., *Health Risks from Exposure to Low Levels of Ionizing Radiation : BEIR VII Phase 2* (National Academies, Washington, DC, 2006).
[4]B. S. Athar and H. Paganetti, "Comparison of second cancer risk due to out-of-field doses from 6-MV IMRT and proton therapy based on 6 pediatric patient treatment plans," Radiother. Oncol. **98**, 87–92 (2011).
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[7]S. F. Kry *et al.*, "Monte Carlo study shows no significant difference in second cancer risk between 6-and 18-MV intensity-modulated radiation therapy," Radiother. Oncol. **91**, 132–137 (2009).
[8]W. D. Newhauser and M. Durante, "Assessing the risk of second malignancies after modern radiotherapy," Nat. Rev. Cancer **11**, 438–448 (2011).

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