Supplementary Material 2. Conclusions and research recommendations of the NCRP 1-17 Report (14): Second malignant neoplasms (SMNs) and cardiovascular disease (CVD) following radiotherapy*

Conclusions:

1. SMN and CVD are the most serious and frequent late effects experienced by the ever growing number of cancer survivors. Curative interventions have prolonged life and late effects now present a substantial public health burden.
2. New and sophisticated radiotherapy modalities and treatment techniques are in widespread use and include intensity-modulated radiotherapy (IMRT) and proton beam therapy. The ever changing landscape of modern radiation oncology requires a continuing evaluation of possible excesses of SMN and CVD.
3. Direct examination of late effects associated with new radiation modalities and techniques is hampered by the long latency periods involved. Past studies of older radiation delivery methods and doses are thus relied upon for assessment of future risks. Although not strictly applicable to patients treated today, these past studies estimated organ-specific radiation doses and developed dose-response relationships which are relevant for current risk assessment and counseling.
4. Past studies of late effects are directly applicable to millions of patients in many parts of the developing world, who are currently treated with older techniques and therapy units. Further, in the U.S. and many other countries, there are millions of cancer survivors treated decades ago with older therapeutic strategies, for whom associated risks of past therapies remain applicable. These patients should be offered counseling and possible prevention strategies. Thus,

comprehensive studies of current cancer survivors with quantitative assessments of radiotherapy doses and chemotherapy administrations should be encouraged.

5. CVD after radiotherapy has not been as extensively studied as SMN. Interactions with host, genetic, other therapies, or other disease risk factors have not been adequately addressed.

6. Radiotherapy is used less often today than in the past to treat some (e.g., Hodgkin lymphoma and childhood leukemia) but not all (e.g., breast) malignancies.

7. Newer radiotherapy techniques result in different distributions of doses to organs outside the primary treatment field than in the past. For example, while IMRT spares structures near the tumor from high tissue doses, the increased time needed for treatment increases radiation dose to all organs of the body. Comparative risks of late effects (SMN and CVD) between the new and older modalities should be continued.

8. Because patients receiving proton therapy and associated secondary neutron exposure have not been studied for late effects, computational models are used for risk assessments and risk comparisons of possible SMN. No similar evaluations for proton therapy, IMRT and other new modalities exist for CVD and should be encouraged.

9. The use of proton therapy results in low-level neutron exposure which provides unique concerns for patient and hospital personnel. Despite a wealth of experimental knowledge on cancer risk following neutron exposures, no such data exist in humans and opportunities to conduct such investigations should be pursued. Experimental data on neutron-induced CVD are more limited than for cancer.

10. Quantitative estimates of radiation-induced SMN derive from nested case–control studies incorporating comprehensive dose reconstructions of average dose to the entire organ or to specific locations within the organ where the SMN occurred. These data, incorporating age at

exposure and gender, are most relevant to risk assessment following current radiotherapy practices. Comparable data on CVD risk do not exist and remain an important area for future research.

11. Although low-dose cardiac exposures of less than about 2 Gy have not been convincingly linked to CVD, the association between CVD and whole-body doses of <1 Gy among atomic bomb survivors is of potential clinical importance. Many patients treated with radiation receive low-dose cardiac doses from scatter and collimator leakage and any increased risk would have important consequences. Epidemiologic studies of late CVD should include both high-dose (i.e., direct heart exposure) and low-dose (i.e., outside the direct radiation fields) cardiac exposures.

12. Radiation-induced cardiac disease is recognized as a serious late effect following thoracic radiotherapy. An increased awareness among practicing physicians should stress that chest radiation given to cancer survivors is an additional, and very important, cardiac risk factor along with hypercholesterolemia, hypertension, diabetes and cigarette smoking. High-quality research is needed on the best methods and possible benefits of screening for late cardiac effects. Surveillance and targeted intervention strategies should include evidence-based guidelines for long-term cardiac follow-up.

13. The interaction between genetic susceptibility and radiotherapy to cause SMN is uncertain, apart from some genetic syndromes such as hereditary retinoblastoma, where increased risks of radiogenic SMN have been reported.

14. Among patients treated for a malignancy within the context of a cancer syndrome, dose-response effects and the influence of co-factors need to be further defined.

15. Sophisticated epidemiologic and laboratory methods are needed to elucidate the complex processes (co-morbidities, genetic susceptibility, host and lifestyle factors) that may interact with radiation to cause SMN and CVD.

16. There is a continuing need to understand the radiobiology underlying the adverse effects of high-dose partial-body radiotherapy exposure, including nontargeted effects such as the bystander effect, which may contribute to SMN and CVD.

17. Registries of patients treated with radiation should be established to facilitate the computation of radiation doses to organs, including heart, to enable long-term follow-up and to quantify risks in the low-dose realm of current environmental and medical concern.

18. Few data exist which describe the survival of cancer patients after they develop a SMN (or CVD) compared with those who develop only one primary cancer (or serious CVD).

19. For individual and epidemiologic risk assessment, effective dose (a construct for radiation protection purposes) should not be used, but rather organ-specific absorbed dose coupled with the appropriate relative biological effectiveness for the endpoint of interest and the specific type of radiation involved (e.g., photons, electrons, protons, neutrons, alpha particles).

20. To facilitate future studies of SMN (or radiation-induced CVD), patient records should be retained for sufficient time for late effects to develop. The development of late effects has been found to occur up to 50 years or more following radiotherapy, which is much longer than the legal minimum time for record retention in many states.

Research Recommendations

1. <u>Overarching recommendations</u>:

a. Institute long-term and large-scale follow-up of extant cancer survivors to characterize the risk of SMN and cardiac disease and to evaluate the role of co-morbidities and effect modifiers, such as age, gender, and race/ethnicity.
    - Develop integrated measures to evaluate the life-long burden of all medical morbidities, including SMN and cardiac disease, according to prior cancer treatment.
    - Integrate epidemiologic studies 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.

b. Establish prospective cohorts of cancer patients to evaluate the life-long risk of SMN, cardiac disease, and other late effects. These include:
    - Populations treated with newer treatment modalities (including IMRT, tomotherapy, stereotactic RT, Cyberknife, gamma knife, and proton therapy)
    - First primary cancer sites for which reductions in field size and radiation dose have been implemented (e.g., Hodgkin lymphoma). For these newer treatments, establish whether increased risks for site-specific SMN are indeed reduced or just delayed, and any effect on histologic type of second cancer.
    - Include selected populations of cancer survivors not treated with radiation (e.g., testis cancer patients treated with surgery) to understand the natural history of these cancers and establish baseline risks of SMN and cardiac disease for comparison with patients treated with radiotherapy.
    - Include collection of biological samples to enhance future evaluation of genetic factors in patient survival and development of SMN and CVD following treatments.

2. Specific recommendations:

a. Dose-response considerations:

Given the differing dose-response relations observed for various second cancer sites, analytic studies should continue to address the relation between radiation dose and second cancer 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 cardiac disease.

b. Adolescent and young adult cancer survivors:

Particular attention should be given to survivors of adolescent and young adult cancer (age 18 to 39 y), given the dearth of data in this area and the particular needs of this understudied population (200).

c. Molecular and genetic underpinnings:

- Develop a better understanding of the possible genetic underpinnings of radiotherapy-associated SMN and cardiac disease. 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.
- Develop standardized approaches for biospecimen collection to support genetic and molecular studies.
- Intensively study patients who develop two or more primary cancers likely associated with radiotherapy, since they may have unique genetic profiles.

d. Interactions between radiotherapy and other risk factors:

The types of comprehensive studies proposed require large patient cohorts with well characterized treatment information together with extended follow-up and systematic

collection of data on long-term morbidities. Study sizes should be adequately powered to characterize interactions between radiotherapy and other risk factors as additive, multiplicative or other. Several putative interactions justify further study, as follows:

- SMN: Address the possible interaction between radiotherapy 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 second cancers.
- Cardiac: Address the possible interaction between radiotherapy, 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.

e. Comparison of carcinogenicity and risk of CVD after different radiotherapy modalities:

- Recommend studies to compare the risk of second cancers and CVD following conventional radiotherapy and new modalities such as IMRT, tomotherapy, stereotactic radiotherapy, and proton therapy.

f. Risk prediction models

- Develop comprehensive risk prediction models for SMN and cardiac disease that incorporate genetic modifiers of late sequelae, as well as treatment variables and well-established disease risk factors. For example, for cardiac disease, this would include variables in the Framingham model, such as age, tobacco use, blood pressure and serum lipid profile as well as evolving genetic markers for CVD in the general population.
- Use results of risk prediction models to stratify patients into risk groups to customize follow-up strategies and develop evidence-based interventions.

*Prior to 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) prior to final revisions, publication and endorsement by the NCRP.