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Diabetes risk after radiation – not out of the woods

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A retrospective cohort study has shown that pancreatic radiation is a risk factor for diabetes in survivors of paediatric cancer. This validates and refines prior epidemiological observations of diabetes after radiation to the abdomen and total-body irradiation, and will result in modification of surveillance recommendations in national survivor guidelines.

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Survival of paediatric cancer has improved significantly in the past four decades, to the extent that currently 80% of patients will become five-year survivors, and it is estimated that there are now more than 320,000 survivors of paediatric cancer in the USA.^{1,2} In light of these statistics, in 2006, the Institute of Medicine called for the expansion of traditional practice

in oncology and the development of programmes that included survivorship as a phase of cancer care.³ The Institute of Medicine emphasised the importance that every survivor be regularly assessed for potential late effects of treatment, and that interventions be put in place to avoid or ameliorate the late effects of cancer therapy.⁴ Cooperative groups such as the Children's Oncology Group

(COG) in North America, the Scottish Intercollegiate Guidelines Network (SIGN) and the UK Children's Cancer Study Group (UKCCSG) have scoured the literature to develop evidence-based long-term follow-up guidelines that can be used to assist in the early detection of late effects associated with cancer therapy.⁵ Concern for cancer-related origins of chronic disease prompted De Vathaire et al.⁶ to assess the risk of diabetes among young adult survivors of paediatric cancer. They showed that pancreatic radiation is a risk factor for diabetes in survivors of paediatric cancer.

Through the efforts of the above-mentioned cooperative groups and other groups that focused on long-term follow-up, it has been found that most cancer survivors have been living with chronic health conditions.

Diabetes is a serious health condition, with patients having a two-fold to four-fold higher risk of cardiovascular death, which accounts for about 70% of premature death among patients with type 2 diabetes.⁷ Oeffinger et al.⁸

reported that the 30-year cumulative incidence for a chronic health condition in cancer survivors was 73%, with 42% of survivors living with a severe disabling or life-threatening condition, or a condition that had resulted in death.⁸ It is now standard practice to begin guideline-based surveillance for late effects in all patients who had paediatric cancer once they are two years beyond the completion of cancer therapy. Some late effects begin soon after the cancer therapeutic agent exposure (neuropathy), some worsen as the survivor ages (cardiac disease) and some late effects do not emerge until the survivor is a young or middle-aged adult (second malignancies and infertility). This variable pattern of emergence of health conditions in survivors of paediatric cancer supports the need for lifelong follow-up and ongoing research to continue to identify the late effects of cancer treatment. In addition, the late development of new conditions or progressive worsening of established late effects supports that there is not a window of follow up after which a survivor is 'out of the woods'.

The concern for cancer-treatment-related diabetes in this population was first reported in 1995 by Teinturier and coauthors, with the observation of a non-autoimmune insulinopenic form of diabetes 20 years after radiation.⁹ Further assessment of 121 patients who had received abdominal radiation revealed that 6.6% of them had diabetes. These eight patients were said to have pancreatic diabetes, which was not considered as classic type 1 diabetes or non-insulin-dependent diabetes mellitus. In this Letter to the Editor, Teinturier questions the role of abdominal radiation, specifically left-sided radiation, in the development of diabetes in survivors.⁹ In a report

from the Childhood Cancer Survivor Study, survivors' self-report of treatment for diabetes was found to be 1.8 times more likely in 8599 survivors compared with 2936 siblings after adjustment for BMI, age, sex, race and ethnicity, household income and insurance. Survivors of neuroblastoma were seven times more likely and survivors of Wilms tumour and Hodgkin lymphoma twice as likely to develop diabetes after treatment if they received abdominal radiation.¹⁰

De Vathaire et al.⁶ have taken this observation and further refined the investigation of risk for diabetes after radiation by verifying the self-report of diabetes in young adult survivors of paediatric cancer, and then calculating the radiation dose to the pancreas through dosimetry. Self-report questionnaires were sent to survivors treated for solid tumours or lymphoma (excluding leukaemia) from eight centres in France and the UK.⁶ Of

the 3468 survivors, questionnaires were sent to 2923 and returned by 86% of survivors, yielding 95 self-reports of diabetes. Diabetes was confirmed in 65 patients through communication with the

healthcare providers for these survivors. Of the confirmed cases, 18% were treated with insulin only, 54% with oral medications, 17% with both insulin and oral medications and 11% had no treatment. Diabetes was associated with radiation to the tail of the pancreas – at the site where the islets of Langerhans are most concentrated – with a relative risk (RR) of diabetes of 11.5 (95%CI 3.9–34.0) in patients who received 10 Gy of radiation to the tail of the pancreas. The effect was dose dependent, with a plateau of risk at 20–29 Gy. Children who were younger than two years at the time of radiation were at higher risk, with a RR

Key point

Radiation to the tail of the pancreas increases risk of the development of diabetes in survivors of paediatric cancer and thus is a risk factor prompting the Children's Oncology Group to recommend routine screening of at-risk patients using fasting glucose or haemoglobin A1c.

of 2.1 (95%CI 1.4–4.3) at 1 Gy compared with 1.4 (95%CI 1.1–2.2) for older patients. These findings were unchanged when adjusting for BMI, and no associations were found with chemotherapeutic exposures or radiation to the head or body of the pancreas.

The limitations of this study are the retrospective approach and the dependence on self-report of medical conditions in survivors. The true prevalence of diabetes is difficult to determine without a standardised methodology of screening and a prospective approach to surveillance. With a prospective approach, the time frame for emergence of disease can be better characterised, as well as having the advantage of improved biochemical classification of the impaired glucodynamics. Although associations with chemotherapy were not found, ascertainment of exposure to glucocorticoids was an acknowledged gap in this study, which did not routinely collect steroid exposure data.

The data reported by de Vathaire et al.⁶ confirm and further define the risk of abdominal radiation in the development of diabetes as a late effect of cancer treatment. This study has led to modifications of the COG Long-Term Follow-Up Guidelines for Survivors of Pediatric Adolescent and Young Adult Cancers. At the 2012 Fall COG meeting, a new section will be proposed for the COG guidelines recommending prospective

“This study has led to modifications of the COG Long-Term Follow-Up Guidelines for Survivors”

surveillance for diabetes in all patients treated with abdominal radiation.*

Patients who are at risk will be screened with history and physical exam and will be monitored with fasting glucose or haemoglobin A1c prospectively for new development of diabetes. This story of recognition of a new late effect of cancer treatment, confirmation of additional cases in an at-risk population and investigation into potential causal pathways emphasises the need for ongoing research in the field of survivorship. Next steps will include further investigation in the mechanistic role of radiation in beta-cell dysfunction or other possible mediators of impaired glucose metabolism. This understanding could lead to modification in treatment or interventional strategies aimed at minimising risk.

*Update: Since this article was first published, the Children's Oncology Group has added Diabetes mellitus as a potential late effect after radiation to the abdomen and after total body irradiation. Specific recommendations for surveillance are being created and will be implemented with changes to the COG Long Term Follow Up Guidelines for Survivors of Paediatric Adolescent and Young Adult Cancers in 2013.

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