Published in final edited form as:

Pediatr Blood Cancer. 2018 November ; 65(11): e27304. doi:10.1002/pbc.27304.

Insulin and glucose homeostasis in childhood cancer survivors treated with abdominal radiation: A pilot study

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Abstract

Background—Childhood cancer survivors exposed to abdominal radiation (abdRT) are at increased risk for both insulin-dependent and non-insulin-dependent diabetes. We sought to clarify the pathophysiology of diabetes after abdRT by performing dynamic studies of insulin and glucose and testing for type 1 diabetes-associated autoantibodies.

Procedure—Cross-sectional analysis of two-year childhood cancer survivors treated with abdRT at age 21 years who underwent oral glucose tolerance testing and assessment of diabetes-related autoantibodies from December 2014–September 2016. Prevalence of insulin/glucose derangements; indices of insulin sensitivity/secretion (homeostatic model assessment of insulin resistance [HOMA-IR]; whole body insulin sensitivity; insulinogenic index); autoantibody positivity; and treatment/demographic factors associated with adverse metabolic outcomes were assessed.

Results—Among 40 participants previously exposed to abdRT (57.5% male; median age at cancer diagnosis 3.3 years [range, 0.5–20.1]; median age at study 14.3 years [range, 8.3–49.8]; none with obesity), nine (22.5%) had glucose derangements (n=4 with impaired fasting glucose [>100 mg/dl]; n=4 with impaired glucose tolerance [2-hour glucose 140–199 mg/dl]; n=1 with previously unrecognized diabetes [2-hour glucose >200 mg/dl]). Three of the four individuals with impaired fasting glucose also had insulin resistance, as measured by HOMA-IR; an additional four subjects with normal glucose tolerance were insulin resistant. The subject with diabetes had normal HOMA-IR. No participant had absolute insulinopenia or >1 positive diabetes-related autoantibody.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

SUPPLEMENTAL MATERIALS

Legend: Five survivors previously treated with abdominal radiation were not eligible for this study due to a known diagnosis of diabetes. These patients' demographic and treatment exposures are outlined in Supplemental Table S1.

Conclusions—This study suggests that radiation-induced damage to the insulin-producing β -cells is an unlikely explanation for the early derangements in glucose metabolism observed after abdRT. Research into alternative pathways leading to diabetes after abdRT is needed.

Keywords

Late effects; pediatric oncology; diabetes; radiation; endocrinology

INTRODUCTION

Due to improved curative therapies for childhood cancer, five-year survival rates now exceed 80%. [1] Improved survival has led to increased recognition of survivors' risk of excess morbidity and premature mortality due to treatment-related late effects, [2] including diabetes mellitus. [3–7] Diabetes is a group of metabolic disorders resulting from defects in insulin secretion, insulin action, or both. Type 1 diabetes results from autoimmune destruction of the β cells of the pancreas and leads to insulinopenia, while type 2 diabetes is characterized by an initial period of insulin resistance and compensatory hyperinsulinemia, with subsequent progression over time to β cell failure. Chronic hyperglycemia, which characterizes the disease, results in long-term end-organ damage. By the year 2030, diabetes is estimated to affect 19 million individuals between the ages of 20 – 64 in the United States alone. [8] Children and young adults are increasingly affected and will face serious long-term complications of the disease as they age. [9,10] When compared to unaffected siblings, childhood cancer survivors have a 1.9-fold increased risk for diabetes [3,5]; risk is even greater among individuals previously exposed to abdominal radiation [3].

Recent observational data from large cohorts of cancer survivors have demonstrated that cancer survivors exposed to abdominal radiation have an increased risk of both insulin-dependent and non-insulin-dependent diabetes with a prolonged latency between radiation exposure and diabetes onset; radiation to the pancreatic tail, where insulin-producing cells are concentrated, has been implicated as the primary risk factor. [6,7] Beyond this, the pathophysiology underlying diabetes development after abdominal radiation remains unknown. One recent analysis of 2520 childhood solid tumor and lymphoma survivors suggested that diabetes risk plateaus at doses of 20–29 Gy to the pancreatic tail [6], while a subsequent study of Hodgkin lymphoma survivors demonstrated a linear radiation dose-response relationship without any such plateau [7]. Both of these studies, as well as the prior analysis from the Childhood Cancer Survivor Study [3], found that the association between diabetes risk and pancreatic radiation was independent of body mass index (BMI), thus leading investigators to surmise that treatment-related diabetes is secondary to β -cell dysfunction, and not obesity [11].

Due to the retrospective design of these large cohort studies, prospective testing of β -cell function or insulin action have not been performed. Furthermore, besides one study which reported negative islet cell antibodies in three Wilms tumor survivors with newly diagnosed diabetes [12], data are lacking on whether an autoimmune process might underlie the pathophysiology of diabetes after cancer therapy, as has been reported in type 1 diabetes in the general population [13]. The current study sought to fill this gap by assessing dynamic

studies of glucose and insulin homeostasis, and diabetes-related autoantibody status, in a single-institutional cohort of non-diabetic childhood cancer survivors exposed to abdominal radiation. To achieve this end, we performed oral glucose tolerance testing to determine the prevalence of glucose abnormalities, insulin resistance, insulin sensitivity, and insulin secretion in an at-risk cohort followed at our institution. We hypothesized that radiation-induced damage to the insulin-producing cells of the pancreas would result in insulinopenia, e.g. low insulin levels and impaired insulin secretion in the context of elevated glucose, prior to the onset of clinical diabetes.

METHODS

Study Population

Eligible participants were two-year survivors of childhood cancer treated with abdominal radiation at 21 years of age, and followed in our institution's Long-Term Follow-Up clinics. To allow for accurate pancreatic radiation dose reconstruction, subjects were only eligible if treated with abdominal radiation at our institution. Individuals with an established diagnosis of diabetes and/or prior treatment with insulin or oral glucose-lowering medications were excluded since oral glucose tolerance testing would be contraindicated in known diabetics and results would be uninterpretable in the context of use of anti-diabetes medication. Those previously exposed to total body irradiation or radiation impacting the hypothalamic-pituitary axis were also excluded, since these exposures are implicated in diabetes risk independent of abdominal radiation.[3]

Subject Recruitment

Eligible participants were identified via a query of our institutional database; an invitation to participate was mailed to 123 eligible patients (Figure 1). Prior to mailing introductory letters to eligible patients, we reviewed each person's medical record to verify that: (1) abdominal radiation has been administered at our center and (2) patients were non-diabetic at the time of last visit to our program. To our knowledge, none of the patients who were eligible for the study and did not participate had diabetes at the time of the study. However, a total of five patients with known diabetes were excluded (and were thus not asked to participate); these patients' demographic and treatment exposures are outlined in Supplemental Table S1.

The study was then discussed at patient visits and interest in participation was assessed; 22 patients actively refused participation, one initially consented but withdrew due to concerns about blood loss, and 40 individuals participated. Informed consent, as well as assent for participants 7–17 years of age, was obtained prior to enrollment. The protocol was approved by the Memorial Sloan Kettering Institutional Review Board/Privacy Board.

Study procedures and definitions

Anthropometrics—Body weight was measured with a digital scale to the nearest 0.1 kilogram and standing height was measured in duplicate with a single digital stadiometer. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters squared). Waist circumference was measured in a standing position at the level of the

superior iliac crest to the nearest 0.1 centimeter at the end of expiration. Waist-to-height (WHtR) ratio was calculated as waist circumference divided by height (both in centimeters) as a measure of abdominal adiposity.

Subjects were categorized as underweight (BMI <5% if age <20 years; BMI <18.5 if age ≥20); normal weight (BMI 5% to <85% if age <20 years; BMI 18.5 to <25 if age ≥20); overweight (BMI 85% to <95% if age <20 years; BMI 25 to <30 if age ≥20); or obese (BMI ≥95% if age <20 years; BMI ≥30 if age ≥20 years).[14] Abdominal adiposity was classified as WHtR >0.5.[15]

Laboratory testing—After a nine-hour overnight fast, all participants underwent an oral glucose tolerance test (OGTT). At the time of baseline venipuncture, specimens were collected for fasting insulin and glucose as well as autoantibodies typically associated with type 1 diabetes, including insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD-65), and islet antigen-2 (IA-2).[16] Subjects then ingested a calibrated oral glucose load (1.75 grams/kilogram; maximum 75 grams) after which glucose and insulin levels were drawn at 30, 60, 90, and 120 minutes post-consumption.

Glucose was analyzed using a hexokinase method (Abbott Architect, Chicago IL USA) and showed an inter-assay coefficient of variation (CV) of 1.98% at 80 mg/dL and 0.65% at 281 mg/dL. In accord with American Diabetes Association guidelines,[17] normal glucose tolerance was defined as: fasting glucose <100 mg/dL and two-hour glucose <140 mg/dL; impaired fasting glucose as a fasting glucose level 100–125 mg/dL; and impaired glucose tolerance as a two-hour glucose 140–199 mg/dL. A provisional diagnosis of diabetes was made with a fasting glucose ≥126 mg/dL or two-hour glucose ≥200 mg/dL.

Indices of insulin sensitivity and secretion—Insulin was analyzed on a sandwich immunoassay (Tosoh AIA analyzer, Tokyo, Japan) and showed an inter-assay CV of 3.4% at 10.8 µU/mL, 2.9% at 60 µU/mL and 2.3% at 149 µU/mL.

Basal insulin resistance was estimated from the homeostatic model for assessment of insulin resistance (HOMA-IR), which is defined as: $[\text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose } (\text{mg/dL})] / 22.5$. [18] HOMA-IR >3.16 was considered abnormal for those age 18 or younger,[19] while HOMA-IR >2.86 was abnormal for subjects over 18 years.[20] The composite whole body insulin sensitivity index (WBISI)[21,22] was used to estimate insulin sensitivity using the following formula: $\text{WBISI} = [10,000 / (\text{fasting glucose} \times \text{fasting insulin} \times \text{mean glucose} \times \text{mean insulin})]$, where mean glucose and mean insulin are the average glucose and insulin concentrations from all available time points in the OGTT. The WBISI has been shown to be highly correlated with the rate of whole-body glucose disposal during the hyperinsulinemic euglycemic clamp, and thus provides a reasonable index of insulin sensitivity.[21,23] While higher values on the WBISI indicate greater insulin sensitivity, less insulin resistance, and lower diabetes risk, clinically normal ranges for this index are lacking. Insulin secretion was estimated from the insulinogenic index, which is calculated as the ratio of the change in insulin and glucose responses from zero to 30 minutes. The insulinogenic index has been shown to correlate with the first-phase insulin secretory response to intravenous glucose. [23,24]

Pancreatic auto-antibodies—GAD-65 was analyzed with a radioimmunoassay that had an inter-assay CV of 7.5% at 1.0 nmol/L, 10.4% at 0.39 nmol/L and 9.8% at 0.2 nmol/L. IA-2 was measured with an immunofluorescence assay and IAA was measured with a radiobinding assay, both at a national reference laboratory.

Radiation dose reconstruction—Radiation doses to subsites of the pancreas (head, body and tail) were determined by review of radiotherapy treatment fields. Each patient had undergone CT scan simulation for design of radiotherapy fields, allowing the single treating and reviewing radiation oncologist (SLW) to estimate pancreatic doses.

Statistical considerations—Univariate associations between insulin sensitivity, resistance, and secretion; glucose status; and patient treatment characteristics were assessed using linear regression models. Due to skewness in the distribution of insulin sensitivity and resistance, both were modeled on the log scale. Differences in mean insulin levels over time were assessed using generalized estimating equations assuming a normal distribution with an identity link function and an independent working correlation. All analyses were completed in R version 3.3.2.

RESULTS

Description of the cohort

Baseline demographic characteristics of the cohort are summarized in Table 1. Twenty-eight of the 40 (70%) subjects enrolled in this study had a history of neuroblastoma (n=26 with stage 4 disease; n=1 with stage 3 disease; n=1 with stage 2B disease). Maximum abdominal radiation dose among all participants ranged from 10.8–36 Gy (median: 21 Gy); median dose to the pancreatic tail was 12.9 Gy (range: 0–36 Gy). None of the participants were obese; six were overweight and six were underweight. Seven patients had evidence of central adiposity (WtHR > 0.5).

When comparing baseline demographics of eligible survivors who did or did not participate in the study, there was no difference in sex among the two groups. However, study participants were more likely to be younger at the time of radiation (median age 3.8 versus 5.9 years, $p=0.002$) and younger at the time of study (median age 14.2 versus 21.8 years, $p<0.001$), when compared to non-participants

Glucose tolerance

Among 40 survivors, 9 (22.5%) had evidence of glucose derangements at a median of 11.0 years (range, 5.6–40.7) after abdominal radiation. All nine subjects had been exposed to an abdominal radiation dose of 21 Gy or more. Four subjects had impaired fasting glucose; four had impaired glucose tolerance; and one had a two-hour glucose level consistent with diabetes. Among these nine survivors, two had evidence of central adiposity (both with impaired fasting glucose). Two patients, both with normal glucose tolerance, had positive GAD-65 with negative IA-2 and IAA autoantibodies (Table 2).

Insulin dynamics

Table 2 outlines median basal, thirty-minute, and 2-hour insulin levels, as well as HOMA-IR, WBISI, and insulinogenic index in the cohort. Seven patients had insulin resistance as evidenced by elevated HOMA-IR (n=4 with normal glucose tolerance; 3 with abnormal glucose tolerance); two of these participants also had abdominal adiposity. None of the participants had absolute insulinopenia, or deficient secretion of insulin by the pancreas resulting in hyperglycemia. Abdominal radiation dose; pancreatic tail dose; age at radiation; and years since radiation were not associated with insulin resistance, as measured by HOMA-IR, whole body insulin sensitivity, as measured by WB ISI, or insulin secretion, as measured by the insulinogenic index, in this cohort (Table 3). There was no difference in mean insulin levels between those with normal or abnormal glucose tolerance ($p=0.45$) [Figure 2].

DISCUSSION

This is the first study, to our knowledge, to perform dynamic testing of insulin and glucose in conjunction with pancreatic auto-antibody status in a cohort of non-diabetic childhood cancer survivors exposed to abdominal radiation without total body irradiation. We sought to explore possible mechanisms underlying the development of treatment-related diabetes and found that derangements in glucose and insulin homeostasis are prevalent in childhood cancer survivors treated with abdominal radiation independent of obesity. Despite the established association between radiation dose to the pancreatic tail and diabetes risk, we found that autoimmunity and absolute insulinopenia, as would be expected after direct damage to the insulin-producing β -cells of the pancreas, did not appear to play a role in the pathophysiology of these derangements.

Prior large cohort studies have identified an association between abdominal radiation during childhood and subsequent risk of diabetes mellitus.[3,4,6,7] A report of 8,599 childhood cancer survivors enrolled in the Childhood Cancer Survivor Study (CCSS), and 2,936 randomly selected siblings, found that survivors treated with abdominal radiation were 3.4-times more likely than siblings to develop diabetes.[3] Patients with specific diagnoses such as neuroblastoma were even more likely to report being diabetic than siblings (odds ratio 6.9; 95% CI, 3.5–13.9). Interestingly, survivors of neuroblastoma who were not treated with abdominal radiation were no more likely than siblings to have diabetes, thus indicating a critical role for abdominal radiation rather than primary cancer diagnosis or other treatment exposures in the pathogenesis of diabetes in this population.

In this study, 70% (n=28) of enrolled patients were survivors of neuroblastoma treated with abdominal radiation; 26 of those 28 patients had stage 4 disease. Prior to the 1990s, survival rates for high-risk neuroblastoma were 15% [25]; intensification of therapy with aggressive multimodal treatment has resulted in improved event-free survival for high-risk neuroblastoma over the past two decades[26]. Beyond second malignancy risk [27,28], however, reports of long-term outcomes in these patients are often limited by relatively small numbers and/or short follow-up time[29–32]. One report of 51 high-risk neuroblastoma survivors found a high prevalence of endocrinopathies, including diabetes and prediabetes, but 80.4% (n=41) of participants had also received total body irradiation. Another study of

63 advanced stage neuroblastoma survivors (n=46 treated with abdominal radiation; n=6 treated with total body irradiation; median follow-up from diagnosis: 7 years) reported a range of endocrinopathies with no cases of reported diabetes[30], which may be related to the relatively short follow-up time. A more recent study found that adult male neuroblastoma survivors were less physically active than matched controls, which may further increase risk of metabolic complications in this cohort [33]. Abdominal radiation in neuroblastoma survivors and others has also been associated with components of the metabolic syndrome and body composition changes [34], which were not systematically assessed in this study. While other treatment-related comorbidities and lifestyle factors may certainly contribute to altered metabolic states, all enrolled patients in this study are followed closely in our long-term follow-up clinics with appropriate management of comorbid conditions, including hormone replacement therapy when indicated, and receive lengthy counseling on the importance of diet and regular physical activity at each long-term follow-up visit. Longer follow-up will be needed to better understand the risk of diabetes in stage 4 neuroblastoma survivors treated with abdominal radiation (without total body irradiation) as these patients mature into adulthood.

Radiation dosimetry has been used in other studies to clarify the mechanisms leading to diabetes after abdominal radiation. One study of 2,520 childhood cancer survivors treated in France and the UK demonstrated that survivors treated with 10 Gy to the tail of the pancreas, where the insulin-producing β -cells reside, were at 11.5-fold increased risk of diabetes; cases of diabetes were validated by subjects' physicians. Diabetes risk increased with increasing doses to the pancreatic tail through 20–29 Gy with subsequent plateau in risk.[6] While one would expect inadequate insulin secretion if damage to the β -cells were the primary insult, as in patients with type 1 diabetes, the authors found an increased risk of both insulin-dependent and non-insulin-dependent diabetes in this cohort. In both the French/UK and CCSS analyses, the association between diabetes and abdominal radiation was independent of BMI.[3,6] Prior studies, however, have indicated that BMI or waist circumference are not reliable measurements of adiposity in abdominally irradiated survivors and alternate measurements such as DEXA scanning to determine total body fat are needed [34]. Still, it is difficult to establish a single explanatory mechanism that might lead from modest doses of radiation to both type 1 and type 2 diabetes.

Interestingly, a more recent study of 2,264 Hodgkin lymphoma survivors (n=963 diagnosed prior to age 25) found a different dose-response relationship when exploring diabetes risk after infradiaphragmatic radiation. In this study, risk of diabetes was highest in individuals treated with 36 Gy to the para-aortic lymph nodes and spleen, a field which typically includes the tail of the pancreas, without a plateau in risk at higher radiation doses.[7] Obesity did not modify the risk of diabetes in this cohort.

Given these discrepancies across studies, and the difficulty in explaining how severe damage to the pancreatic islet cells could occur at relatively modest radiation doses, we sought to clarify the mechanism(s) responsible for the development of diabetes in this population. In this cohort of survivors previously exposed to abdominal radiation, we found a variety of defects in glucose tolerance without absolute insulinopenia or evidence of autoimmunity. In fact, there was no difference in mean insulin levels at different time points of the OGTT or

median insulinogenic index, which is a measure of insulin secretion, when comparing survivors with normal and abnormal glucose tolerance. Rather, decreased insulin sensitivity was an early and frequent finding, even in the absence of obesity, suggesting that this may be the initial insult following abdominal radiation. While descriptive and limited by the small sample size of this cohort, it is noteworthy that all subjects with glucose derangements had received radiation doses of at least 21 Gy to the abdomen. Since diabetes is an independent risk factor for all-cause and cardiovascular mortality, further work is urgently needed in both the preclinical and clinical arenas to better characterize the pathophysiology of diabetes after abdominal radiation in childhood cancer survivors who are already at high-risk for excess morbidity and premature mortality.

A number of limitations must be considered when interpreting the results of this study. First, this analysis is limited by its cross-sectional design and small sample size in a cohort that is relatively young with short follow-up time post-radiation, which may lead to an underestimate of the prevalence of glucose derangements given the long latency between radiation exposure and diabetes onset. Additionally, the oral glucose tolerance test only provides limited measures of insulin sensitivity and resistance; the gold standard approach for measuring these indices is the euglycemic-hyperinsulinemic clamp, which was felt to be too burdensome for this cohort of asymptomatic young individuals. Finally, the lack of a comparison group limits our ability to make accurate estimates of effect. Nonetheless, this study provides important clues into the pathophysiology of treatment-related diabetes in individuals exposed to abdominal radiation and includes a relatively large number of high-risk neuroblastoma survivors exposed to abdominal radiation without total body irradiation.

CONCLUSION

In contrast to existing data, this study suggests that radiation-induced damage to the insulin-producing β -cells is an unlikely explanation for the early derangements in glucose metabolism observed after abdominal radiation. Diabetes-related pancreatic autoantibodies also do not appear to mediate risk. Future studies of larger cohorts are needed to clarify the mechanism underlying treatment-related diabetes after abdominal radiation and inform the development of targeted, risk-reducing interventions among long-term survivors at risk for cardiometabolic disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by the MSK Cancer Center Support Grant/Core Grant (P30 CA008748), NIH/National Center for Advancing Translational Sciences [NCATS] grant KL2 TR000458 (DN Friedman), and the Chanel Endowment to Fund Survivorship Research at Memorial Sloan Kettering.

The authors wish to thank Joseph Olechnowicz for his editorial contributions.

Abbreviation Key

abdRT	Abdominal radiation
HOMA-IR	Homeostatic model assessment of insulin resistance
WHtR	Waist-to-height ratio
OGTT	Oral glucose tolerance test
IAA	Insulin autoantibody
GAD-65	Glutamic acid decarboxylase
IA-2	Islet antigen-2
CV	Coefficient of variation
95% CI	95% confidence interval
WBISI	Composite whole body insulin sensitivity index
CCSS	Childhood Cancer Survivor Study

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FIGURE 1. Contact and participation of eligible childhood cancer survivors treated with abdominal radiation

FIGURE 2.

Mean insulin levels during the oral glucose tolerance test, by categories of glucose tolerance

Note: Differences in mean insulin levels over time were assessed using a GEE model. Test for a difference in insulin levels over time, $p = 0.45$.

TABLE 1

Demographic and treatment characteristics of 40 survivors of childhood cancer treated with abdominal radiation, by glucose tolerance

	All patients (n=40)	Normal glucose tolerance (n=31)	Impaired glucose tolerance (n=8)	Diabetes mellitus (n=1)
Age at radiation, median (range)	3.8 (0.8–20.5)	3.6 (0.8–20.5)	5.1 (1.7–9.1)	3.9
Age at study, median (range)	14.3 (8.3–49.8)	14.2 (8.6–46.9)	14.5 (8.3–49.8)	27.0
Median follow-up since RT, years (range)	8.7 (3.5–40.7)	8.7 (3.5–26.4)	9.8 (5.6–40.7)	23.1
Sex, No. (%)				
Female	17 (42.5)	11 (35.5)	5 (62.5)	1
Male	23 (57.5)	20 (64.5)	3 (37.5)	0
Race, No. (%)				
White, non-Hispanic	30 (75.0)	21 (67.7)	8 (100)	1
Black, non-Hispanic	3 (7.5)	3 (9.7)	0 (0)	0
Hispanic	4 (10.0)	4 (12.9)	0 (0)	0
Other	3 (7.5)	3 (9.7)	0 (0)	0
Primary diagnosis, No. (%)				
Neuroblastoma	28 (70.0)	22 (71.0)	5 (62.5)	1
ERMS	5 (12.5)	3 (9.7)	2 (25.0)	0
Wilms	2 (5.0)	2 (6.5)	0 (0.0)	0
Rhabdoid tumor	2 (5.0)	2 (6.5)	0 (0.0)	0
Other	3 (7.5)	2 (6.5)	1 (12.5)	0
Weight status category, No. (%)				
Underweight	6 (15.0)	5 (16.1)	1 (12.5)	0
Normal/healthy weight	28 (70.0)	22 (71.0)	5 (62.5)	1
Overweight	6 (15.0)	4 (12.9)	2 (25.0)	0
Obese	0 (0.0)	0 (0.0)	0 (0.0)	0
Central adiposity, No. (%)				
WtHR > 0.5	7 (17.5)	5 (16.1)	2* (25.0)	0
Abdominal radiation (RT) field, No. (%)				
Abdomen/whole abdomen	30 (75.0)	22 (71.0)	8 (88.9)	1
Flank	4 (10.0)	4 (12.9)	0 (0.0)	0
Para-aortic	3 (7.5)	2 (6.5)	1 (11.1)	0
Other	3 (7.5)	3 (9.7)	0 (0.0)	0
Maximum RT dose to the abdomen (Gy), median (range)	21.0 (10.8–36.0)	21.0 (10.8–36.0)	22.5 (21.0–32.5)	21.0

Abbreviations: ERMS, embryonal rhabdomyosarcoma; Other diagnoses include: Hodgkin lymphoma and malignant teratoma of the ovary; Other abdominal RT fields include: pancreatic tail, retroperitoneum, adrenal bed;

* Both patients with abdominal adiposity had impaired fasting glucose and elevated HOMA-IR

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TABLE 2

Measures of insulin sensitivity or resistance in 40 survivors of childhood cancer treated with abdominal radiation, by glucose tolerance

Variable	Normal glucose tolerance (n=31)	Impaired glucose tolerance (n=8)	Diabetes mellitus(n=1)
Fasting insulin level (μU/mL), median (range)	5.8 (0.5–28.7)	7.2 (2.8–36.7)	2.3
Thirty-minute insulin level (μU/mL), median (range)	56.6 (0.6–330.3)	72.7 (1.5–279.1)	44.8
Two-hour insulin level (μU/mL), median (range)	22.8 (2.6–212.5)	52.8 (4.5–90.6)	77.7
HOMA-IR, median (range)	1.3 (0.1–6.6)	1.6 (0.5–9.3)	0.4
Abnormal HOMA-IR, No. (%)	4 (12.9)	3 (37.5)	0
WBISI, median (range)	7.7 (1.3–53.5)	5.0 (1.3–14.7)	7.7
Insulinogenic index, median (range)	1.0 (-0.8–4.0)	1.0 (-0.1–3.1)	0.3
Autoantibodies			
GAD65	2	0	0
Islet antigen-2	0	0	0
Insulin autoantibody	0	0	0

Abbreviations: HOMA-IR, homeostatic model assessment; WBISI, whole body insulin sensitivity index; GAD65, glutamic acid decarboxylase; RT, radiation therapy

Association between treatment-related exposures and measures of insulin sensitivity, resistance, and secretion in 40 survivors of childhood cancer treated with abdominal radiation

TABLE 3

Variable of interest	Insulin sensitivity, as measured by log(WBISI)		Insulin resistance, as measured by log(HOMA-IR)		Insulin secretion, as measured by the insulinogenic index	
	95% CI	p	95% CI	p	95% CI	p
Abdominal radiation dose	0.99 (0.94, 1.04)	0.57	1.01 (0.96, 1.07)	0.69	0.03 (-0.04, 0.10)	0.43
Pancreatic radiation tail dose	1.01 (0.99, 1.04)	0.40	0.98 (0.95, 1.00)	0.07	-0.005 (-0.04, 0.03)	0.73
Age at radiation > 3.8 years (median)	0.82 (0.48, 1.40)	0.46	1.32 (0.75, 2.35)	0.33	0.07 (-0.61, 0.75)	0.84
Years post-radiation > 8.7 years (median)	0.98 (0.57, 1.68)	0.95	1.02 (0.57, 1.82)	0.95	0.02 (-0.66, 0.69)	0.96

Note: Due to skewness in the WBISI and HOMA-IR values, log(WBISI) and log(HOMA-IR) were used as the outcome of interest. Estimates and 95% confidence intervals are given on the original scale. The model results for WBISI and HOMA-IR represent the multiplicative increase/decrease in the outcome due to a one unit change in the patient treatment characteristic of interest.

Abbreviations: WBISI, whole body insulin sensitivity index; HOMA-IR, homeostatic model of insulin resistance; 95% CI, 95% confidence interval; p, p-value