



# The Link between Increased Body Mass Index and Radiotherapy of Childhood Leukemia: The Need to Manage Obesity in Pediatric Leukemia Patients

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## Keywords

Radiotherapy; Body mass index; Obesity; Childhood leukemia; Acute lymphoblastic leukemia

## Short Communication

Although radiotherapy is one of the most important modalities used to cure cancer, radiation exposure can damage the human body. There is great debate regarding the health risks of radiation on metabolism, but strong epidemiological evidence argues that radiotherapy of childhood leukemia may be linked with an increase of body mass index. This short report seeks to summarize these epidemiological data and the apparent alteration of certain obesity-related genes in radiotherapy-treated childhood leukemia patients. Although radiation is considered to be unfavorable for the preservation of metabolic homeostasis, we further propose that pediatric leukemia patients need interventions to control metabolic dysfunction and prevent subsequent obesity.

### Radiotherapy increases the body mass index of patients with childhood leukemia

The use of radiation has increased tremendously in modern years, and many humans have been exposed to medical radiation. Radiotherapy (RT) has become an essential part of the treatment of childhood cancer; it improves survival for some of the most common malignancies, including lymphoid leukemia, which accounts for 76% of all leukemia cases in children [1,2]. Cranial Radiotherapy (CRT) is part of an effective multimodality therapy that has been used to treat and prevent the spread of childhood Acute Lymphoblastic Leukemia (ALL) [3]. Allogeneic stem-cell transplantation, which is the treatment of choice for some leukemia patients, requires Total Body Irradiation (TBI) as a conditioning therapy that suppresses the recipient's immunity to allow sustained engraftment, prevent rejection, and eradicate tumor cells [4]. Abdominal radiation is another important tool used in the treatment of many childhood cancers, including neuroblastoma, soft tissue sarcomas, and Wilms tumor [5]. Unfortunately, however, almost 75% of survivors of childhood ALL have chronic health conditions that negatively impact their morbidity and mortality [6]. RT has been associated with increased risks for late mortality, the development of cancer, the acquisition of pulmonary, cardiac, and thyroid dysfunctions, and an increased overall risk for chronic health conditions [3]. Overweight and obesity are frequently seen following RT for childhood ALL, and strong epidemiological evidence links RT of childhood ALL with increased body mass index (BMI) [6-12] (Table 1). BMI is a statistical measure of human weight scaled according to height; both BMI and its alteration appear to be comprehensive indicators of health status. However, although it is generally accepted that obesity is one of the most common late effects seen among childhood ALL survivors, the radiobiological mechanisms of radiation-induced obesity in RT-treated childhood leukemia patients are not well understood.

### Genetic contributors to obesity in survivors of RT-treated childhood leukemia

Generally, Ionizing Radiation (IR) stimulates both pro- and anti-proliferative signaling pathways to create an imbalance in cell fate decision. IR can regulate numerous genes and factors involved in DNA damage and repair, cell-cycle progression, cell death, and various intracellular radiation-dependent responses [13]. IR induces the abundant production of Reactive Oxygen Species (ROS), and increased cellular levels of ROS cause oxidative damage to DNA, providing a mechanistic basis for the ability of radiation to cause DNA damage and affect cell division [14]. RT-related obesity appears to be related more to metabolic dysfunction and over-activation of nutrient-sensing mechanisms than to radiation-induced oxidative stress or DNA-damage responses. However, some investigations have found that the main energy-sensing signaling pathways could be linked to

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**Table 1:** Summary of studies on radiotherapy related to increase of BMI in acute lymphoblastic leukemia patients.

Characteristic	BMI(kg/m <sup>2</sup> )						Ref
	Males			Females			
	N	Mean	SD	N	Mean	SD	
Chemo only	204	25.1	5.2	217	23.7	5.3	Oeffinger et al. [6]
Chemo+CRT (10-19Gy)	269	25.1	4.9	234	24.0	5.0	
Chemo+CRT(20 ≥Gy)	422	26.1	5.2	419	26.1	5.9	
Non-CRT	7	21.4	2	9	23.6	2	Baillargeon et al.[20]
CRT (18-24Gy)	10	26.2	2	9	23.4	2	
Non-CRT	37	26.2	4.5	38	27.2	7.2	Janiszewski et al. [9]
CRT (18-24Gy)	15	27.8	7.4	24	31.6	8.6	
Chemo only	147	27.3	5.1	186	25.6	5.7	Garmey et al.[8]
Chemo+CRT (10-19Gy)	211	28.1	5.7	195	27.9	6.7	
Chemo+CRT(20 ≥Gy)	347	28.1	5.8	359	29.3	7.3	

**Abbreviations:** BMI: Body Mass Index; Chemo: Chemotherapy; CRT: Cranial Radiation Therapy; N: Number; SD: standard deviation

radiation-induced DNA damage signaling [15]. Therefore, we need to better understand these metabolic alterations and generate additional data confirming that IR can induce the metabolic abnormalities. Several genetic association studies have evaluated potential genetic risk factors for obesity among adult survivors of childhood ALL. Ross et al. [16] reported that female survivors (N = 600) with BMI  $\geq 25$  mg/m<sup>2</sup> (i.e., overweight) or obesity were twice as likely as those with BMI  $< 25$  mg/m<sup>2</sup> to be homozygous for the Arg allele at residue 223 of the leptin receptor gene (LEPR; Gln223Arg, rs1137101) [16]. This finding is consistent with other reports suggesting that leptin levels are increased in female survivors of childhood ALL, and that soluble leptin receptor levels are negatively correlated with body mass [17]. Leptin, which is among the best known hormones for obesity, exerts pleiotropic effects on multiple organs and is important for the central and peripheral signaling that maintains energy homeostasis [18]. Therefore, the absence of leptin activity in childhood ALL patients with genetic variations of leptin receptor genes may lead to morbid obesity. Another group of investigators evaluated associations between obesity and Single Nucleotide Polymorphisms (SNPs) of the Fat Mass and Obesity-associated (FTO) gene, which was the gene to be reproducibly associated with human body mass [19]. Among ALL survivors treated with CRT, they found lower rates of obesity in those homozygous for the T allele at rs9939609 compared to those with at least one copy of the A allele [20]. Early study of FTO gene expression indicated that it was highly expressed in the brain and hypothalamus [21]. This is interesting because the hypothalamus is a major site responsible for controlling the energy balance, and genes responsible for obesity are known to function in the hypothalamus. While the exact function of the FTO gene is not yet known, it has been associated with the regulations of energy homeostasis, body size, and body fat accumulation. Wilson et al. [22] conducted a genetic study among 1996 adult survivors of childhood cancer (42% were ALL survivors) and found potential genetic predictors of obesity on chromosomes 13 (FAM155A), 2 (SOX11), 4 (GLRA3), and 5 (CDH18 and BASP1) among those exposed to CRT. FAM155A is expressed in the hypothalamus and pituitary; GLRA3 encodes a receptor protein involved in glycine neurotransmitter signaling; and CDH18 and SOX11 influence neuronal function. Thus, these findings may support the hypothesis that CRT-induced brain damage influences obesity. Although association does not mean causation, these

findings suggest that we should undertake large genome-wide linkage studies and candidate gene connection studies in RT-treated patients of childhood ALL, in the hopes of helping them cope with overweight and obesity.

### Perspective: Supposing interventions for controlling obesity in children

Treatment advances have improved the 5-year survival rates for children diagnosed with lymphoid leukemia to over 90% [1]. To our knowledge, there have been relatively few reports concerning overweight both during and after RT of childhood ALL patients. The early onset of obesity and its persistence into adulthood is arguably one of the most significant chronic health situations in childhood leukemia survivors, who are also at increased risk for progressive cardiovascular and metabolic co-morbidities. Understanding the etiology of obesity in radiation-exposed childhood leukemia survivors is an important public health concern given the recent epidemic rise in obesity rates in the pediatric population worldwide. To track the extent to which elevated BMI persists after the completion of RT, it will be essential for future studies to develop or assess specific blood biomarkers related with increased BMI, such as leptin, glucose, insulin, cholesterol, etc. In addition to facilitating the development of new treatments, learning about how these biomarkers are associated with RT-related weight gain may help us critically improve the existing clinical interventions. If we hope to prevent obesity and metabolic syndrome in survivors, we will need evidence-based intervention strategies that are tailored to the specific demands of children who are undergoing or have recently completed RT. Although the existing guidelines on lifestyle changes aimed at controlling obesity in the general population (e.g., aspects of diet and exercise) can be valuable for ameliorating obesity and metabolic syndrome in survivors, further research should evaluate survivor-specific interventions for monitoring metabolic status and providing targeted education on nutrition and physical activity. Data from long-term studies in large survivor cohorts should be used to inform the most appropriate strategies for medical management in this distinctive pool of childhood and adolescent patients, and to develop adjuvant interventions to treat obesity. Patients who receive RT should be followed up throughout their lives to track and address the development of RT-associated metabolic syndrome. Radiobiologists might study the mechanisms of radiation-induced metabolic dysfunction and search for serum biomarkers that may be used to estimate the obesity risk of RT-treated childhood ALL patients. Clinicians should be aware of the late effects in this susceptible population; they should screen for dyslipidemia and hypertension and generate risk factor profiles for obesity, diabetes, and cardiovascular issues, in order to promote better healthcare for childhood cancer survivors. Finally, governments around the world should continue to promote health-promotion programs to cope with obesity issues among pediatric leukemia patients.

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