



Mini Review Article

The effects of radiation therapy in musculoskeletal system of children

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Abstract

This review summarizes the literature investigating the radiotherapy related early and late musculoskeletal abnormalities in children, concerning non-malignant conditions and secondary malignancies. We searched the PubMed for English written articles and 10 relevant articles were found published between 1992 and 2015. We found that the late musculoskeletal effects were the more frequent among the survivors of childhood cancer, that they occurred more in children who have been irradiated for cranial or abdominal tumors and they were age and dose related. Further research with larger clinical trials examining the radiation dose, especially in younger children, should be done, to refine radiation dose protocols and also annual screening for high risk survivors should be recommended.

Keywords: Childhood cancer, Radiation therapy, Musculoskeletal, Early and late effects

Introduction

The last 40 years, due to advanced therapeutic strategic, there has been significant improvement in the survival rates of childhood cancer, now exceeding 80% 5-year survival rates and radiation therapy is established, either as the main treatment or as an adjuvant therapy to reduce the risk of recurrence after surgery¹. However, the side-effects of radiation therapy are very frequent and approximately the two thirds of the survivors suffer from musculoskeletal complications, half of them suffering from life-threatening conditions, sometimes decades following radiation therapy². Despite the high 5-year survival rates and the advanced treatment options, approximately 16 % of the deaths during the first 5 years from the diagnosis are caused by treatment complications³. Unfortunately today, there are no systematic studies examining the complications of the therapy, especially the rare ones, and also there are no standardized guidelines for long-term follow-up of these patients.

In this study, the effects of radiation therapy in the musculoskeletal system will be analyzed and interventions to prevent or delay these chronic health conditions will be suggested. The studies selected to review, were retrieved from PubMed database. We searched the PubMed using the terms "childhood cancer", "musculoskeletal effects", "radiation therapy", "radiotherapy complications". We selected 10 articles with relevant abstracts.

Effects of radiation therapy in musculoskeletal system

Radiation therapy uses high energy radiation beam to damage the DNA of cancerous cells. There is also injury to adjacent healthy tissues. The injury is less when more advanced methods are used, such as intensity-modulated or stereotactic external beam radiation therapy³.

We searched the PubMed for English written articles and 10 relevant articles were found published between 1992 and 2015. The pathophysiology correlating radiation to muscular abnormalities is not well understood. However, it is suggested that radiation disrupts the mitosis and the function of the cells, causing problems at the neuromuscular junction. Furthermore, the post-radiation inflammation can influence the growth of the muscle fibers⁴.

The effects of the radiotherapy can be acute-subacute or late, continuing or appearing many years later. These

The author has no conflict of interest.

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Edited by: George Lyritis

Accepted 14 June 2017

complications are usually local, unless whole body radiation is performed⁴. According to Ducassu et al who viewed the late effects of radiation therapy in neuroblastoma, the musculoskeletal abnormalities were the commonest, appearing to 31% of the patients, with median time 6 years following the therapy. The important finding of that study was that these late effects happened only in doses higher than 31 Gy⁵. Also, the study of Gawade reveals that younger age, high radiation dose (>20 Gy) and asymmetric radiation increase the risk of muscular complications. So, according to this study, late muscular effects are more frequent in survivors of neuroblastoma and Wilms tumor because of the early age of diagnosis and also these effects are common among survivors of sarcomas due to the high dose (>30 Gy) required for the treatment. Also, the female sex was found to be of increased risk to develop muscular hypoplasia⁴.

Early effects

1. Osteonecrosis is a common side-effect of radiation therapy, especially with concurrent use of steroids and is usually an early effect, more common in children older than 10 years old and in long bones of the lower limbs, although sometimes it happens later. Unfortunately, osteonecrosis is asymptomatic in early stages and the role of imaging is important in early diagnosis. Due to the low sensitivity of conventional radiology, MRI is advised to depict the early changes of the disease, but whole-body MRI should be used for the diagnosis of widespread osteonecrosis in children with ALL³. Osteonecrosis is very common in children diagnosed with acute lymphocytic leukemia (ALL) and is symptomatic only in 1-9% of patients with ALL. The therapeutic procedures are questioned due to the long-term implications for the children whose skeleton is growing. On the other hand, osteonecrosis occurs rarely in solid tumors⁶.
2. Fatty replacement of bone marrow is seen early in the first weeks of the radiation therapy and must be early diagnosed and recovered with hematopoietic growth factors to avoid infections³. According to Chavhan et al, the bone marrow recovery is radiation dose-dependent³.
3. Myositis is an early complication and it occurs when combined with chemotherapy, most likely when the interval between chemotherapy and radiotherapy is short³.

Late effects

According to Medaws et al, who studied 400 cases, the late complications involving the musculoskeletal system, were the most frequent in patients who received radiotherapy⁷. There is no clear correlation between the radiation and the muscular pathology; however there is evidence that the vascular and parenchymal damage may disturbance muscle nutrition, causing muscle atrophy and fibrosis⁴.

It was found that the effects in musculoskeletal system were most common in younger children and also in high radiation doses (≥ 20 Gy). As a result, the effects are more

common in survivors of Wilms tumor and neuroblastoma due to the early age of the patients and also in the survivors of sarcomas due to the high dose required (>30 Gy)⁴. However, Medaws et al study didn't find any significant difference in the development of secondary malignancies, including soft tissue sarcomas, in children under or over 2 years old⁷.

1. Avascular necrosis of the femoral head is associated more with steroids, but it has also been described as a late effect of radiation therapy in high doses (30-40 Gy)⁸.
2. Radiation osteitis is a rather early effect of related-dose radiotherapy, developing 2-3 years after therapy and although differential diagnosis with other abnormalities is difficult (e.g. sarcoma, osteomyelitis), biopsy should be avoided if possible, to avoid possible infections. Radiation osteitis is an atrophic change of the bone and not a necrosis, but the risk of developing pathologic fractures is increased, approximately affecting 20% of the patients⁸.
3. Osteoporosis or osteopenia is usually found in patients treated for ALL, when methotrexate and/or corticosteroids are also given⁶, but there is evidence that bone density increases with time in these patients. Also, approximately one third of patients with brain tumors were also diagnosed with low bone mineral density due to several reasons, the most significant being the cranial irradiation⁹. Kotecha et al reported these patients that were irradiated in skull for acute lymphocytic leukemia are of great risk to develop low bone mineral density that develop osteoporosis and predisposes to osteonecrosis and they treated these patients with biphosphonates¹⁰. The low levels of calcium and vitamin D as well the lack of physical activity can contribute to low BMD and increase the risk of fractures⁶. Fortunately, it was found that the severity of low bone mineral density decreases with time after treatment in patients with ALL⁹.
4. Misalignment of the spine, such as scoliosis, lordosis and kyphosis can occur post radiation and there is higher risk in children who received craniospinal or abdominal irradiation⁶. The spine misalignment is usually a late complication, is frequent and Gawade et al reports that in his review the prevalence of scoliosis and kyphosis was high, ranged from 10-80% and 2-48% respectively⁴. The age under 6 years old, the high doses and the large irradiated fields are factors that influence the severity of these deformities^{4,6}. Also it was found that scoliosis was more common in asymmetric radiation fields, and the survivors of Wilms tumor suffered more than patients with Hodgkin lymphoma where the field was symmetric⁴. Scoliosis is a result either of asymmetric vertebral growth or from radiation related changes in adjacent soft tissues and it is found to develop 5 years or more after radiation⁸. Also, kyphosis and scoliosis of the thoracic spine were associated with restrictive lung disease^{4,6}. Furthermore, in significant kyphosis or other chest wall abnormalities, further than the deterioration in breathing, lower extremities' weakness can occur due to pressure of

the spinal nerve roots. The vertebral deformities have a significant impact in children's psychology as they limit physical activities related to leisure⁶.

5. Limb – length discrepancy is commonest in survivors of lower extremities Ewing sarcoma, but there is also increased prevalence in patients suffering from Wilms tumor, especially when the pelvis is included in the irradiation field. Again, the younger age (<10 years old) is found to be a predisposing factor for the deformity⁶.
6. Several craniofacial deformities are commonest in retinoblastoma and rhabdomyosarcoma patients and less common in other head and neck tumors. The craniofacial bones are sensitive in even very low radiation doses (400 rads) and deformities are present more often in younger patients⁶. Craniofacial deformities are also noted in patients younger than 5 years old treated for ALL with high radiation doses (> 24 Gy)⁴. Furthermore, the radiation for sarcomas near the jaw was related to mandibular muscle abnormalities and temporomandibular joint dysfunction⁶.
7. Muscle weakness involving hypoplasia, atrophy and fibrosis are common late findings in survivors of childhood cancer, because of the high sensitivity of growing skeletal muscles in radiation. Although these complications are frequent and they are also significant for physical functioning and quality of life, they have not been studied in detail⁴. Reduced muscle strength has been correlated with high morbidity and mortality among the survivors. Atrophy and fibrosis are related with the radiation dose and the location of the abnormalities is depended of the irradiation site. In asymmetric radiation fields, the deformities may be significant⁶. Several studies reveal that after the decrease of the radiation dose in treatment of Wilms tumors (before 1980 treated with 18-40 Gy and after with 10,8 Gy) the muscular atrophy is now uncommon in these group of patients⁴.
8. Growth retardation can be a result of either direct post cranial irradiation or indirect after spinal irradiation resulting in abnormal vertebral growth⁴. Growth retardation was demonstrated in 30-35% of children who survived for brain tumors, with higher risk of severe retardation in children below 8 years. Early treatment with growth hormone can solve the problem, except in cases where the spine is also irradiated².
9. Spinal growth retardation is noticed when the spine is irradiated, again presenting more often in younger children and in high radiation dose, causing significant deformities since the growth of upper and lower extremities is normal⁴.
10. Skeletal hypoplasia is caused by radiation during osteogenesis and is more common in flat bones⁴. The radiation alters the normal chondrogenesis and reabsorbs the calcified cartilage and bone, causing disturbance in the growing ends of bones⁸. The higher radiation dose (>25 Gy) is a negative predictive factor⁸.
11. Orbital hypoplasia can be present in retinoblastoma survivors and is also correlated with younger age⁴.
12. Slipped femoral capital epiphysis (SFCE) is a late disorder

happening 1-8 years after treatment and it occurs in patients with local irradiation for pelvic malignancies or sarcomas. Some of the cases reported were non-dependent on the radiation dose⁸.

13. Osteochondroma was found to be a late complication (up to 12 % of survivors) related to irradiation, rarely transforming to chondrosarcoma^{4,8}. Osteochondromas may appear in any irradiated site and are found to be more common in patients who received whole body radiation therapy before bone marrow transplantation⁸.
14. Osteosarcoma is a late effect of radiotherapy and it is dependent of the radiation dose and on the concurrent use of alkylating agents. The incidence was higher in survivors of Hodgkin's lymphoma and retinoblastoma, however the osteosarcoma in these patients was not clearly associated with prior radiation therapy, especially in hereditary retinoblastoma where there is predispose for development of osteosarcoma^{2,9}.

Conclusion

The studies that we have reviewed in this article conclude that the musculoskeletal effects, especially the late ones, are the more frequent among the survivors of childhood cancer that have been irradiated. The frequency of these abnormalities was found to be dependent to radiation dose, the younger age of the patients and the asymmetrical radiotherapy fields. However, the published studies are random and there is need for larger clinical trials to be done to examine the effects of the radiation dose⁵. According to these trials, new therapeutic approaches with lower doses in younger children should be scheduled⁴. An example of better understanding of the factors contributing to skeletal deformities is the model that Krasin et al suggested to predict flat bone growth based in radiation dose, time after treatment, patient age and initial bone volume¹.

There is also need to further investigate which patients are of high risk to develop musculoskeletal abnormalities, especially the ones that interfere with physical function and quality of life and also the life threatening ones⁴. Landier et al suggest that long-term guidelines should be formed and recommend annual screening to exclude secondary malignancies².

Intervention strategies applying to high-risk survivors of childhood cancer should be educational and behavioral. Survivors have to be educated about the risks of developing health problems related to prior radiation and also about the appropriate follow-up. They also should be taught how to develop healthier behaviors and lifestyle². Wilson et al, also emphasize that good lifestyle behaviors are essential to prevent or delay the onset of musculoskeletal complications⁶. A probable barrier for the proposed interventions and the recommended long-term follow-up is the increased costs for the health care systems. Further research should also be done to examine the costs and benefits of these interventions².

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