Follow-up Longitudinal Study of Bone Mineral Density in Adult Survivors of Solid Pediatric Cancers
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Introduction
Specific subgroups of children who survive treatment for childhood malignancies have been shown to develop relative osteopenia following treatment and are felt to be at risk for developing osteoporosis later in life due to their inability to reach peak bone mass during childhood. In earlier work, our group has shown in a cross-sectional study that approximately 50% of pediatric solid cancer survivors have at least regional low bone mineral density (BMD).1 Prior to this work, solid tumor survivors were not known to be among the groups at higher risk for development of low bone density. Subsequent studies have shown pediatric osteosarcoma survivors in particular to be at increased risk for low bone density.

The purpose of the current report was to determine whether with longitudinal follow-up these survivors of solid pediatric malignancies would show increasing BMD, as would be expected to occur in untreated subjects. We hypothesized that their chemotherapy will have rendered them unable to continue to increase their BMD, leaving them at an even greater risk for the subsequent complications of osteoporosis.

Methods
All research subjects were obtained from the institutional long-term survivor Kids Now Off Therapy (KNOT) clinic. Excluded were subjects treated for acute lymphoblastic leukemia or those with cranial irradiation, total body radiation, or non-autologous bone marrow transplant (all groups already known to be at high risk).Bone mineral density measurements were made on a single GE Lunar DPX-IQ dual energy x-ray absorptiometer (DEXA) located in the Institute for Human Performance. All 41 patients met the inclusion criteria for the original and subsequent studies and provided their informed consent. Subjects were classified as osteopenic or osteoporotic based on their Z-scores, as defined by the WHO classification. A Z-score of less than or equal to -1.0 but greater than -2.0 was considered “osteopenia” while a score of less than or equal to -2.0 was considered “osteoporosis.” Bone-specific alkaline phosphatase (BAP) and N-telopeptides (NTx) were used as serum markers of bone metabolism. Results were analyzed using paired, two-tailed t-tests via SPSS with significance at p<0.05.

In Part I of the study, the updated original data set was reviewed. Since the collection of data for the original longitudinal study consisting of 38 subjects, data for three additional patients was added to the data set, yielding a new contingent of 41 subjects (23 male, 18 female). The most common diagnoses were lymphoma (18), sarcoma (9), Wilm’s tumor (5), and neuroblastoma (4). Median age was 22 years (range, 12 to 32).

Time from diagnosis of underlying cancer averaged 12.2 years (range, 5.5 to 20.0).

In Part II of this study, patients from Part I were recruited for follow-up DXA analysis a minimum of five years later. Ten (5 male, 5 female) of the 41 patients in Part I have returned for follow-up visits. Median age was 27.5 years (range 23-31). Diagnoses included lymphoma (4), Wilm’s tumor (2), sarcoma (1), yolk sac carcinoma (1), Hodgkin’s Disease (1), and Triton tumor (1). Time from diagnosis of underlying cancer averaged 16.7 years (range, 11.1 to 22.7).

Results
Using The World Health Organization’s classification criteria for osteopenia and osteoporosis for any one or more areas including total body, lumbar spine (L2-L4), total hip, femoral neck, ultra distal radius, or 33% radius, 3 of the 10 subjects (30%) exhibited osteopenia. None had osteoporosis at any site.

However, total body BMD decreased in 50% of patients. Lumbar spine BMD decreased in 60% of patients. Right femoral neck BMD decreased in 100% of patients, left femoral neck BMD decreased in 75% of patients, left total hip BMD decreased in 77.8% of patients, and right femur BMD decreased in 75% of patients. Right ultra distal radius BMD decreased in 50% of patients, right 33% radius decreased in 50% of patients, left ultra distal radius BMD decreased in 25% of patients, and left 33% radius BMD decreased in 12.5% of patients. Overall, 100% of patients showed a decrease in BMD at some site.

Furthermore, statistically significant decreases in bone mineral density over the 5-year interval were observed in the femoral neck (right p=0.003; left p=.01) as well as the ultra distal (p=0.042) and 33% (p=0.006) radius. Changes in total body, spine, and total hip were insignificant.

The prevalence of osteopenia changed over time in mixed directions. Comparing the 10 patients to their original BMD classification, 1 (10%) more patient had osteopenia in the total hip region, 1 (10%) more had osteopenia in the femoral neck, and 1 (10%) more had osteopenia in the left 33% radius while 2 (20%) fewer patients had osteopenia in the spine, 2 (20%) less in the ultra distal radius, and 3 (30%) less in the right 33% radius region.

Discussion
The data support the hypothesis that young adult survivors of pediatric solid tumors do not follow normal bone mass progression. Specific areas, including the femoral neck and ultra distal and 33% radius, show the significant decreases in BMD over time at an age when BMD should be increasing. Moreover, decreases in BMD in numerous sites, including total body, spine, total hip, femoral neck, ultra distal radius and 33% radius, suggest altered normal maturation of bone density in this patient population. Subjects ranging in age from 23-31 should still be increasing their BMD.2 Instead, more than half of the patients are decreasing their BMD in the lumbar spine, total hip, and femoral neck sites.

In the original data set, 13 of the 38 (34%) subjects had total body and/or lower extremity osteopenia or osteoporosis; 6 subjects (16%) had upper extremity osteopenia or osteoporosis.4 While BMD decreased over time in the spine, fewer patients fit the criteria for osteopenia. Conversely, more patients were categorized as having osteopenia in the total hip and femoral neck, which parallels our finding of a generalized numerical decrease in BMD in the femoral neck.

In a similar cross-sectional study as ours but restricted to osteosarcoma survivors, longer follow-up revealed a higher prevalence of decreased BMD, suggesting that these patients fail to increase their BMD as normal young adults do.5 Despite the limitations of this small patient population, based on these results, young adult survivors of pediatric solid tumors do not exhibit normal bone mass progression over time and warrant close follow-up and consideration for early treatment.

References

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