Childhood cancer survivors (CCS) are at High Risk of Reduced Bone Mass during Bone Mass Accrual

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BACKGROUND and AIM

Childhood cancer survivors (CCS) are at risk for low bone mineral density (BMD).
Aim of our study was to evaluate the prevalence of low BMD and it's determinants in a single-center cohort of CCS.

SUBJECTS and METHODS

CCS subjects n= 187 (84F, 103M), 13,2±2.0 yrs of age
- Diagnosis:
  - Liquid Tumor (LT) n=48 (ALL n=34)
  - Solid Tumor (ST) n=88; (NB/GNB n=24; Wilms n=16; NHL n=12; HL n=12; RMS n=10, Ewing n=6)
  - Brain Tumor (BT) n=51; (Embrional n=20; Germinal n=9, Sellar region n=6, Astrocytic n=6)
- Age at cancer diagnosis: 4,8±3,4 yrs
- Endocrine defects: n=9 LT, n=16 ST and n=50 BT (all pts were on substitutive hormone therapy)
- Radiotherapy:
  - CRT n=48/51BT (mean total dose 5397,5±1426,1 cGy)
  - TBI n=8/34 ALL (mean dose 1140.0 ± 102.0 cGy)
  - Other RT for LT n=6 (mean 2403.3 ± 770.0 cGy)
  - Other RT for solid tumor n=36 (mean total dose 3327.5±1483.7 cGy)

Study design: monocentric cross-sectional observational study

Methods:
- Anthropometric evaluation for Height (Z-score), Body Mass Index (BMI, Z-score), Tanner pubertal evaluation
- Vitamin D and PTH evaluation
- DXA scan (Lunar Prodigy, GE) for:
  - total body-TB and spine-L1-L4 BMD (gr/cm^2, Z-score), BMC (gr)
  - TB fat mass (FM, Kg) and free fat mass (FFM, Kg)
  - BMC/height^2 and FFM/height^2 were calculated

RESULTS

Table 1. Age, time since off therapy and anthropometric characteristics of CCS

	Liquid M ± SD (range) n=48	Solid M ± SD (range) n=88	Brain Tumor M ± SD (range) n=51
Age at DXA (yrs)	12.9 ± 1.8* (10.2 – 16.4)	13.1 ± 2.1 (9.3 – 17.0)	13.7 ± 1.7 (10.2 – 16.0)
Off therapy (yrs)	6.0 ± 2.9 (2.0 – 13.0)	7.6 ± 3.4** (1.0 – 15.5)	6.2 ± 3.2 (0.7 – 12.1)
Ht (Z-score)	-0.2 ± 1.5 (-4.0 – 3.1)	0.2 ± 1.4§ (-3.7 – 3.1)	-0.6 ± 1.3 (-3.5 – 2.5)
BMI (Z-score)	1.3 ± 1.5 (-2.0 – 4.1)	1.4 ± 1.3 (-2.0 – 4.1)	1.6 ± 1.5 (-3.3 – 4.9)
Tanner PP, P, M n(%)#	7;32;9 (14,6; 66,6;18,8)	13;57;18 (14,8; 64,8; 20,4)	7;31;13 (13,7; 60,8; 25,5)

*P-value <0.05 (LT vs BT); ** P-value <0.05 (ST vs BT); § P-value <0.001 (ST vs BT)

#PP-prepubertal=G1/B1; P-pubertal=G or B 2-4, M-mature =G5/B5

Figure 1. Height and BMI Z-scores based on type of cancer in Females and Males

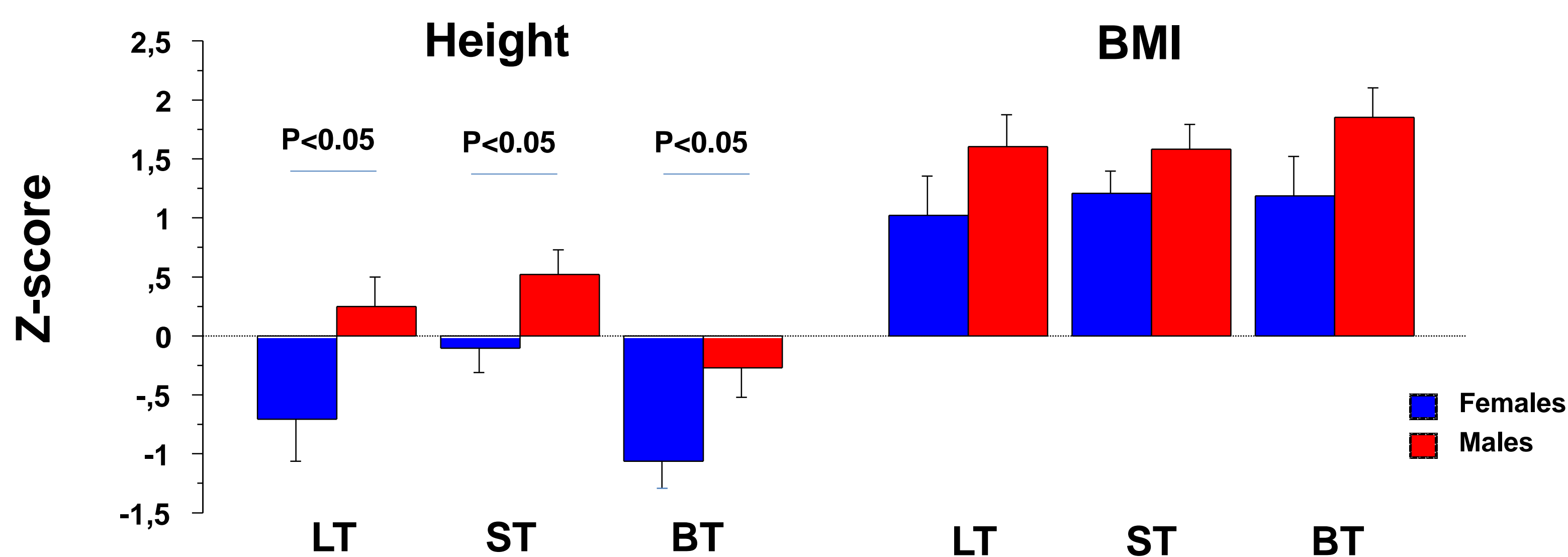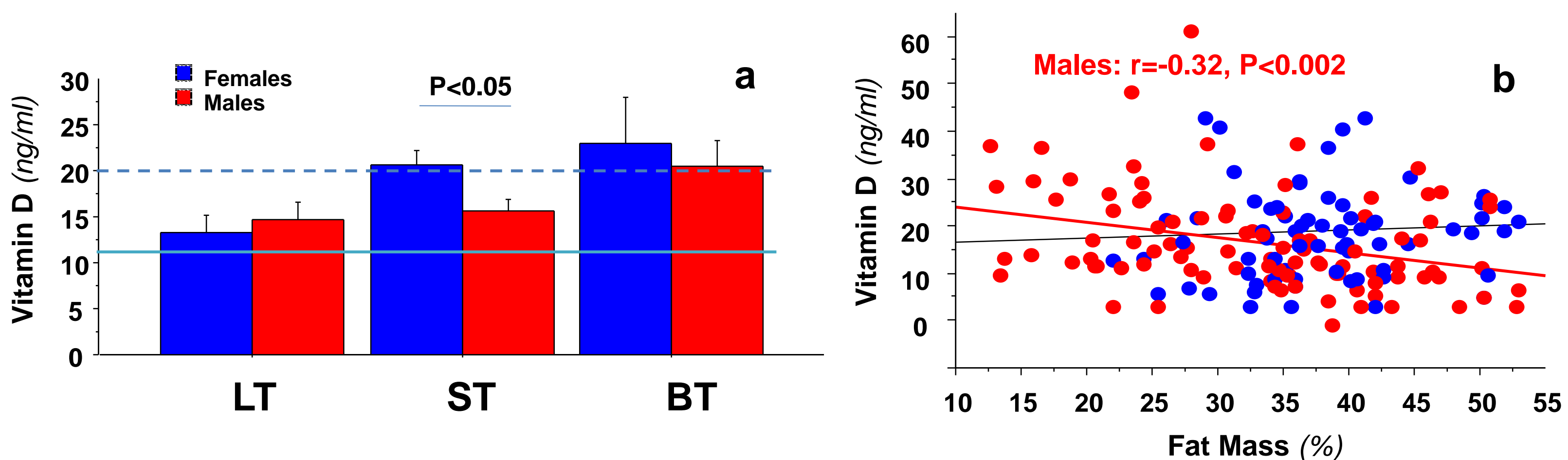- PTH was not different between type of cancer nor between Females and Males

Figure 2. a) Vitamin D (25OHD) levels based on type of cancer in Females and Males; b) Pearson's correlation between vitamin D and Fat mass in Females and Males

Males: r=-0.32, P<0.002

Table 2. Bone mass at the Total body and Lumbar Spine and Body composition of CCS based on type of cancer

	Liquid M ± SD n=48	Solid M ± SD n=88	Brain Tumor M ± SD n=51
L1-L4 BMD (gr/cm^2)	0.919 ± 0.176	0.964 ± 0.219*	0.883 ± 0.154
L1-L4 BMC (gr)	39.0 ± 14.3	42.4 ± 16.5*	37.1 ± 11,8
L1-L4 area (cm^2)	41.3 ± 7.9	43.0 ± 8.9	41.3 ± 7.3
TB BMD (gr/cm^2)	0.861 ± 0133	0.880 ± 0.144*	0.830 ± 0.138
TB BMC (gr)	1406.8 ± 442.6	1503.1 ± 474.6	1429.1 ± 393.5
Fat mass (%)	35.4 ± 8.3	34.5 ± 9.5	37.2 ± 9.9
Fat mass (kg)	15.7 ± 7.2	16.8 ± 7.4	19.0 ± 9.1**
Free Fat mass (kg)	28.2 ± 9.5	30.9 ± 8.6	30.8 ± 8.8

*P-value <0.05 (ST vs BT); ** P-value <0.05 (LT vs BT)

Figure 3. TB and L1-L4 BMD Z-scores based on type of cancer in Females and Males

L1-L4   Total Body less head   P<0.05

L1-L4 BMD Z-score   4.8%   14.0%
TB BMD Z-score   7.0%   15,6%

<2 and <1 SDS: low normal range for age and sex
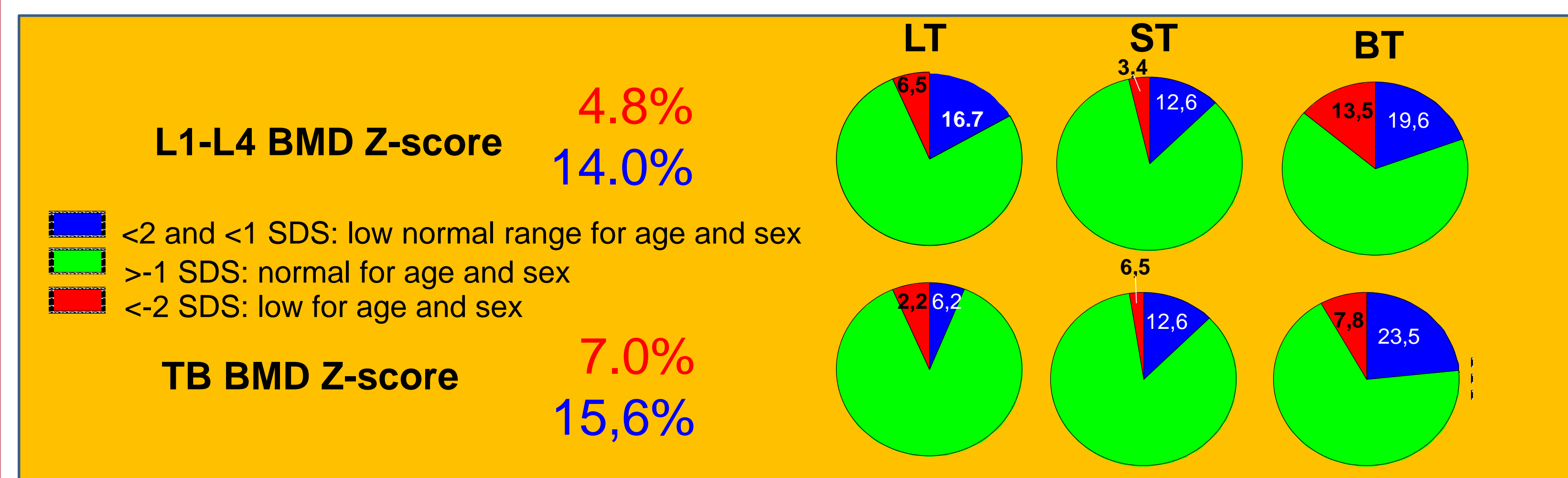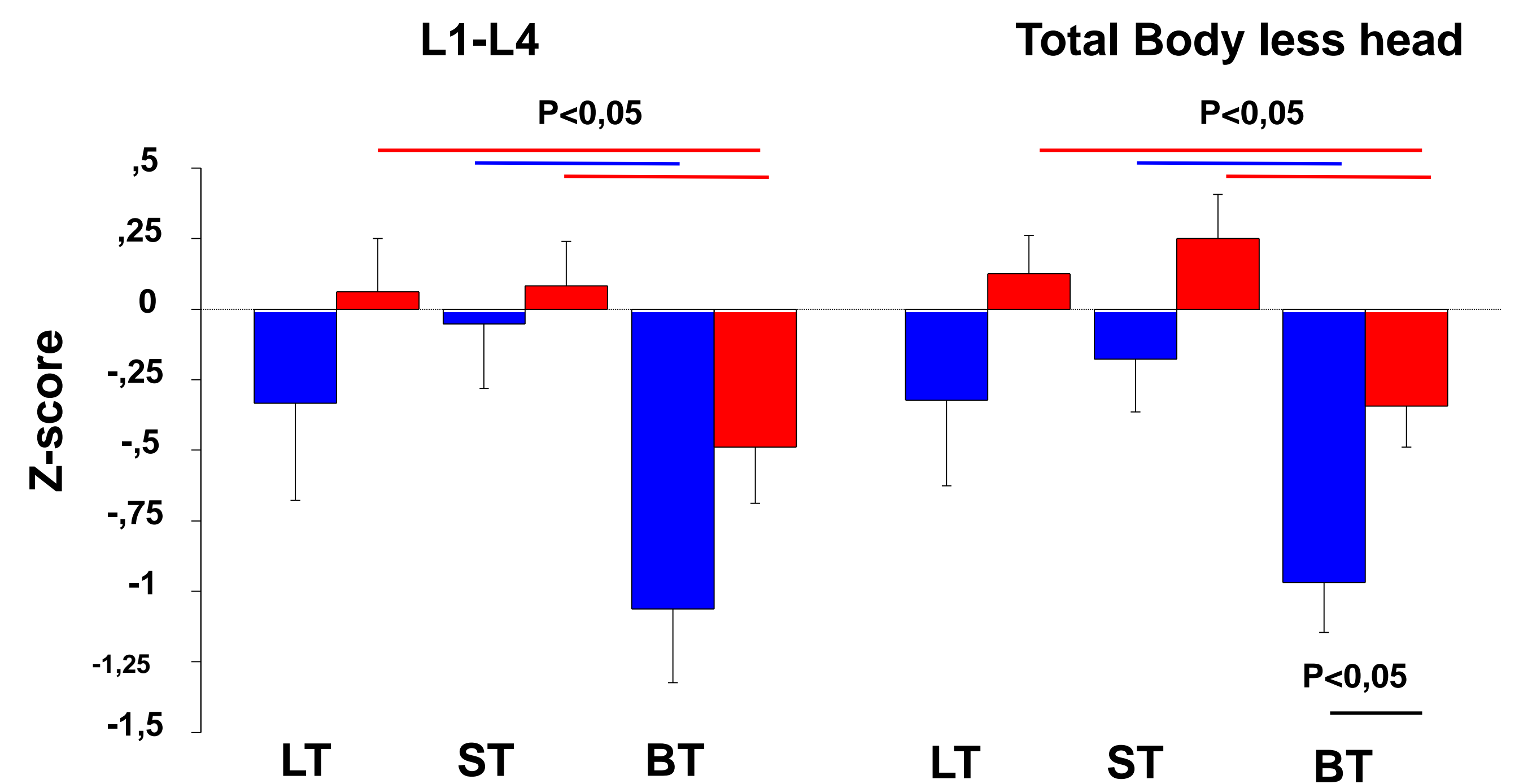>-1 SDS: normal for age and sex
<-2 SDS: low for age and sex

Table 3. Pearson's correlations between TB BMD and anthropometric and body composition parameters, CRT and hormone defects based on type of cancer

	Liquid Tumor	Solid Tumor	Brain Tumor
Height Z-score	0.61*	0.54*	0.38**
BMI Z-score	0.59*	0.50*	0.47**
Free Fat Mass	0.57*	0.52*	0.52*
Fat Mass	0.46**	0.30**	0.14
RT (dose)	0.37	-0.19	-0.30**
Hormone defects (n)	-0.35**	-0.28**	-0.10

*P<0.0001; **P<0.05

Milder but similar relations were found for L1-L4 BMD Z-score; age was inversely related in LT and BT;

Tanner stage was not correlated to bone parameters

Multiple regression analyses:

- L1-L4 BMD Z-score was independently and inversely predicted by age at evaluation and hormone defects and directly by FFM and FM after correction for Tanner stage and height SDS (R^2 0,33, P<0,0001)

- TB BMD Z-score was predicted by all the previous parameters, except for Tanner stage (R^2 0,50, P<0,0001)

CONCLUSIONS

- Up to 14% of Brain Tumor and 6,5% of Liquid Tumor CCS present a low bone mass at the age of 13 yrs, 7 yrs since off-therapy, during pubertal development
- Trabecular bone at the spine is more compromised than cortical bone
- Females display both a reduced height after standardization and a reduced BMD compared to males
  - *Delay in subclinical hypogonadism diagnosis and treatment?*
- Vitamin D was in the normal range in Brain Tumor CCS and higher in females
- Younger age, hormone defects and RT are negative predictors of low BMD