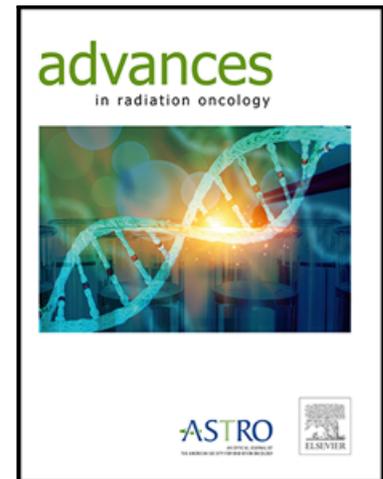# Journal Pre-proof

Impact of testicular boost in children with leukemia receiving total body irradiation and stem cell transplantation: a single-institution experience

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Short Running Title: Testicular boost in addition to TBI prior to HSCT

Impact of testicular boost in children with leukemia receiving total body irradiation and stem cell transplantation: a single-institution experience

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Short Running Title: Role of testicular boost in addition to TBI prior to HSCT

Abbreviations:

TBI	Total body irradiation
HSCT	Hematopoietic stem cell transplant
BMT	Bone marrow transplant
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
OS	Overall survival
RFS	Relapse free survival

Abstract:

Purpose: Children with leukemia who receive fractionated total body irradiation (fTBI) to 12-13.2 Gy as part of conditioning for hematopoietic stem cell transplantation (HSCT) are frequently treated with an additional 4 Gy testicular boost to reduce the risk of testicular relapse. While institutional practices vary, limited data exists regarding whether the 4 Gy testicular boost reduces the risk of relapse, and whether it causes toxicity beyond that imparted by TBI. This study compared the survival and endocrine outcomes among the patients who were treated with and without a testicular boost as part of fTBI from 1990 – 2019 at our center.

Methods and Materials: We retrospectively reviewed charts of male children with leukemia treated with fTBI as part of a conditioning regimen for SCT from 1990 – 2019. Reported outcomes included progression free survival (PFS), testicular relapse rate, and overall survival (OS). Gonadal dysfunction and fertility were assessed by comparing the rate of abnormally low testosterone or high luteinizing hormone (LH) or follicular stimulating hormone (FSH), number of offspring, fertility service use, and abnormal sperm count in subsequent follow-up period between the testicular boost and non-boost subset.

Results: 93 males (63 acute lymphoblastic leukemia, 30 acute myeloid leukemia) with median age of 9 years (range 1 – 22) and follow up of 3.3 years were included. In addition to 12 – 13.2Gy fTBI, 51 males (54%) received a testicular boost to 4 Gy. There was 1 testicular relapse in the boost subset and none in the non-boost subset. 5-year PFS for the boost and non-boost subset was 74% and 66% respectively (p=0.31). On multivariable analysis, boost was not associated with improved RFS or OS. More patients in the boost subset (35 of 51, 69%) had abnormal serum gonadal blood work compared to the non-boost subset (18 of 42, 43%) (p=0.03).

Conclusion: Omission of testicular boost may be associated with comparable oncologic but improved gonadal endocrine outcomes and should be further studied.

Abbreviations:

TBI	Total body irradiation
HSCT	Hematopoietic stem cell transplant
BMT	Bone marrow transplant
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
OS	Overall survival
PFS	Progression free survival

Introduction:

Leukemias are the most common type of pediatric cancer in North America, accounting for approximately 30% of all pediatric malignancies.[1] Total body irradiation (TBI) is an important part of conditioning for many children undergoing allogenic hematopoietic stem cell transplant (HSCT) for leukemia, with disease-free and overall survival benefits as compared to chemotherapy-alone conditioning regimens.[2-4] A benefit of incorporating TBI into myeloablative conditioning regimens includes the ability to target cells in potential sanctuary sites, including the testes in male children. Historically, testicular relapse has been associated with poor survival outcomes.[5,6] Previous small studies have reported high rates of testicular relapse with traditional doses (12 – 13.2 Gy) of TBI and suggested the incorporation of a 4-6 Gy testicular radiation boost in addition to TBI to decrease the risk of testicular recurrence.[7-9] Although institutional practices regarding testicular boosts vary, it is generally acknowledged in the literature that a significant number of institutions currently employ a testicular boost in TBI conditioning for leukemia, particularly in the pediatric population.[10] At our institution where we treat a large volume of pediatric patients with TBI, testicular boosts were routinely added to TBI for all males with acute lymphoblastic leukemia (ALL) and for males with acute myelogenous leukemia (AML) with additional high-risk features until 2018 with the goal of minimizing testicular relapse, while recognizing that limited data exists in this setting.

While the additional dose of radiation given as testicular boost therapy is relatively low, it may still be associated with an increased risk of gonadal dysfunction.[11] As overall survival (OS) rates improve, the sequelae of long-term survivorship are increasingly important to consider. Hypogonadism in male leukemia survivors has been associated with lower quality of life, worse mental health, sexual dysfunction, osteoporosis, and metabolic syndrome.[12,13]

Moreover, recent series have reported the rarity and decreasing incidence of testicular relapse with the use of modern systemic therapy regimens that typically include high dose methotrexate (HDMTX).[14-22] As a result, incorporation of a testicular radiation boost in addition to TBI has not been universally adopted, with many institutions using it, and some institutions reserving it only for persistent or recurrent leukemic disease in the testes after completion of induction systemic therapy.[14-17]

Thus, the current role of testicular radiation boost as part of TBI in children with leukemia remains unclear, with a lack of clarity and paucity of data regarding the effects of testicular boost on disease control and toxicity outcomes available to guide practice[1]. This single-institution study reports our 30-year experience in a cohort of children both with and without testicular boost, which we believe is the largest series to date investigating this question around which practice patterns vary significantly between institutions.

Materials and Methods:

Study Design and Patient Selection

The study received ethics approval from the Institutional Review Board (XXXX). This retrospective cohort study includes males 1 – 22 years who received fractionated TBI (fTBI) prior to HSCT transplant for acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) at our institution from 1990 to 2019. We excluded patients who died in the peri-transplant period, defined as death within +/- 30 days from the day of transplant, and those who had testicular leukemia prior to the transplantation procedure. Regarding patient selection for

testicular boost at our institution, patients with ALL routinely received testicular boost as part of therapy until institutional standard change in 2018, from which point no ALL patient without upfront testicular involvement received boost. Patients with AML did not receive testicular boost unless they had therapy-associated high risk secondary AML. The primary outcome was progression-free survival (PFS), defined as time from transplant to any first relapse or progression, among the testicular boost and non-boost subsets. Secondary outcomes were OS, rates of testicular relapse, gonadal function, and fertility between the subsets.

Investigation and Management

All patients were assessed at the XXXX Pediatric Hematology/Oncology clinic and evaluated for stem cell transplantation. Initial investigations included detailed physician exam including testicular examination, routine blood work, peripheral blood smear, bone marrow biopsy, CSF analysis, and disease-directed imaging as part of the work up and staging. Patients were admitted for the duration of the peri-transplant period and had regular interval follow-up for surveillance. Follow-up gonadotropic and fertility evaluations were not standardized, but some of them included serum luteinizing hormone (LH), follicular stimulating hormone (FSH), total testosterone, referral to fertility clinics, and sperm count.

All patients had a consultation with a radiation oncologist and underwent simulation for TBI, which included chest X-ray, chest CT, and body measurements for fabrication of lung blocks and compensator designs. TBI was delivered with anterior posterior (AP)/posterior anterior (PA) approach with extended surface to source distance (SSD).

For testicular boost, 4Gy in 2 fractions with electrons was prescribed to cover the bilateral testes with the 90% isodose line and delivered on the 2nd and 3rd day of fractionated TBI. In general, 9 – 16 MeV electrons were used depending on the thickness of the testes. Bolus was used on an as needed basis to ensure adequate coverage.

Outcomes and Data Analysis

PFS and OS were determined for both groups by Kaplan-Meier analysis and stratified by AML and ALL. OS and PFS were defined from the time of stem cell transplant to the time of the event, which was death and any first relapse confirmed by biopsy respectively. Multivariable Cox regression analysis was used to assess any clinically important factors associated with PFS or OS. To assess the date of stem cell transplant as a factor in survival outcomes, patients were categorized as having received the transplant either prior to or after year 2010 (range 1990 to 2019). A patient was considered to have gonadal dysfunction if he had higher luteinizing hormone (LH), follicular stimulating hormone (FSH), or lower total testosterone than normal range at any point during the surveillance period. The normal range of LH, FSH, and testosterone were stratified by age and Tanner stage (tables in appendix).[23] Reproductive outcomes including the frequency of fertility service use, number of offspring, and abnormal sperm count (normal range in appendix) were tabulated and analyzed. Chi square or Mann-Whitney analysis was used to assess the differences in demographic and treatment characteristics between the boost and non-boost subset. Chi-squared test was used to compare the subsets for gonadal and reproductive outcomes.

Results:

Demographic, Disease, and Treatment Characteristics

We identified 93 males for the study, 63 with ALL and 30 with AML. Median age at treatment was 9 years (range 1 – 22) and the median follow up was 3.3 years (range 1 – 27 years). In addition to fTBI to 12-13.2 Gy, 51 males received a testicular boost dose of 4 Gy (49/63 [78%] with ALL, 2/30 [7%] with AML), while 42 patients did not receive a testicular boost (14 with ALL, 28 with AML). There were proportionally more patients in the non-boost subset who were treated for AML, and the median follow up was shorter for the non-boost subset. Otherwise, there were no significant differences in demographic or treatment characteristics between the subsets (Table 1).

Oncologic Outcomes

The 5-year PFS for the cohort was 71%. 5-year PFS for ALL patients was 74% and AML patients was 65% (p=0.287). The 5-year PFS for the boost and non-boost subset was 74% and 66% respectively (p=0.309) (Figure 1A). 5-year OS for the entire cohort was 71%. The 5-year OS for the boost and non-boost subset was 78% and 60% (p=0.054) respectively (Figure 1B). There were 23 deaths in total, and 11 were due to progression or recurrence of the disease. There were 6 potential treatment-related deaths, including 3 due to acute graft-versus-host disease (GVHD) and 3 due to chronic GVHD. After stratification by disease, 5-year PFS for ALL boost and non-boost subset was 75% and 60% (p=0.508), while the 5-year PFS for AML boost and non-boost subset was 50% and 67% respectively (p=0.781). 5-year OS for ALL boost and non-

boost subset was 80% and 70% (p=0.536), while 5-year OS for AML boost and non-boost subset was 50% and 58% (p=0.996). Testicular RT boost was not associated with PFS or OS in multivariable Cox regression analysis (MVA) (Table 2, 3). Patients who were older had worse OS in MVA.

Testicular Relapse

There was 1 testicular relapse in this series, a patient who had undergone a testicular boost as part of his TBI conditioning. He was diagnosed with ALL Central Nervous System (CNS) 1 disease (white blood cell count less than 5 and no blasts in cerebrospinal fluid [CSF]) at age 4 years and was treated with XXXX (XXXX), achieving first Complete Remission (CR). However, he developed bone marrow relapse 1 year later, requiring re-induction therapy followed by HSCT. The conditioning regimen included VP16, cyclophosphamide, and fTBI to12 Gy in 6 fractions delivered BID and 4 Gy boost to the testicles. Subsequently, he achieved second CR but then experienced an isolated right sided testicular relapse 2 years later, which was treated with right orchidectomy, and prophylactic left testicular RT with 24Gy/12 fractions. Since then, he has been followed > 10 years without evidence of disease.

Gonadal and Reproductive Outcomes

There were significantly more patients among the boost subset (35 of 51, 69%) compared to the non-boost subset (18 of 42, 43%) who had an abnormality in serum gonadal blood work

detected at follow up periods (p=0.027). Breakdown of the LH, FSH, and total testosterone abnormalities are listed in Table 4. Binomial multivariate regression model demonstrated that the risk of having any abnormal gonadal laboratory value was associated with testicular boost alone (HR 7.1 95% confidence interval [CI] 1.3 - 38, p=0.021) but not with age, race, diagnosis, cyclophosphamide-containing regimen, or treatment year. To measure fertility outcomes, we assessed the number of offspring, fertility utilization service rate, and the rate of abnormal sperm count. No patient has had an offspring. Four (7.7%) of the boost subset and 6 (14%) of the non-boost subset utilized fertility services. Six patients in the boost subset and 9 patients in the non-boost subset had sperm studies: 50% (3/6) from the boost and 56% (5/9) from the non-boost subset had abnormal sperm studies. There was no difference between the boost and non-boost subsets in fertility.

Discussion:

Many institutions adopted low-dose testicular boost as part of the TBI regimen for leukemia after the series by Shank et al. in the 1980s-1990s demonstrated significant reduction in testicular relapse rates using testicular boost in males with leukemia.[7] However, more recent data suggest that testicular relapse rate has decreased while overall survival has improved significantly with modern therapies, and there is a growing interest in reducing late effects associated with treatment. As a result, there is lack of consensus regarding the need for routine testicular boost for male children who undergo TBI for leukemias. Our study demonstrates that testicular relapses are rare regardless of the testicular boost status with current therapies, and that testicular boost may be associated with worse gonadal function in long-term leukemia survivors.

Historically, the risk of testicular relapses among pediatric patients with leukemia ranged from 10 – 15%.[7,24] However, more recent studies suggest that testicular relapse rates are 0.5 – 3% (and consistent with the 1% observed in our study) coinciding with the introduction of HDMTX.[20-22] HDMTX, typically dose >500mg/m^2, is effective in penetrating the blood-brain and blood-testes barrier, exerting cytocidal effect in the interstitial tissue of the testes.[19] This has translated to decreased use of radiotherapy, even in the setting of testicular relapse. Our institution has been incorporating HDMTX since the 1990s, which is likely contributing to the low testicular relapse rates even among the non-boost subsets.[17,19]

Even among patients treated with testicular boost, relapses in the testes have been observed. Li et al. also described an isolated testicular relapse in a boy with Ph+ ALL who received 4 Gy testicular boost in addition to 12 Gy TBI as part of the conditioning regimen. The patient was notable in that he had a very high-risk disease for relapse due to early bone marrow relapse after initial induction requiring re-induction, and he did not receive MTX as part of the treatment. Our patient achieved CR1 with initial treatment including HDMTX but had early bone marrow relapse, suggestive of aggressive disease. He underwent subsequent stem cell transplant with TBI and testicular boost as part of his conditioning regimen but still developed late testicular relapse. After receiving orchiectomy and high-dose testicular RT, he remains alive after 10 years of follow-up. Thus, in some patients with high risk of relapse, a testicular boost of 4 Gy may not be sufficient, and better stratification of testicular relapse risk and selective use of testicular boost at a potentially higher dose may be a preferred approach over routine use of a low dose testicular RT boost.

Although the risk of overt or isolated testicular relapse may be low, there is a theoretical concern that occult malignant cells in the testes may migrate to other sites and cause relapse (so-

called "sanctuary site" phenomenon), particularly in the bone marrow.[25,26] However, studies have

not demonstrated improved bone marrow PFS or OS with testicular boost.[27,28] Similarly,

testicular boost did not improve the 5-year PFS and OS in our study. As expected, older age was

associated with poor overall survival.[29] Furthermore, recent studies incorporating modern

systemic agents and second stem cell transplant have demonstrated much improved outcomes for

patients with testicular relapse compared to the historical cohort.[17,19] Reflecting the success of

systemic therapy in controlling leukemia in the testes, most recent protocols for patients with

testicular relapse consist of initial systemic therapy alone, reserving radiation therapy only for

rare refractory disease conditions.[15,17] Given this judicial use of testicular radiation even in the

presence of detectable disease in the organ, radiation as a boost intended for prevention of

testicular relapses must be carefully considered in the context of potential morbidities.

The survival rates of pediatric leukemia patients have been increasing over the past

decades likely due to the improvement in systemic therapy, supportive care, and access to

medical treatments.[30,31] With improved survival rates however, there is growing awareness of the

wide range of late side effects that may be associated with the treatments.[32] With 12 – 13.2 Gy of

TBI, there is a high likelihood of infertility but variable risk of hypergonadotropic

hypogonadism, which can increase with additional dose to the testes. Studies have demonstrated

that there may be dose-dependent trend toward decreased testosterone and increase in LH after

14 – 16 Gy of radiation to the testicle.[33,34] Although systemic therapy and stem cell transplant

could impact fertility, profound and persistent primary hypogonadism after leukemia is often

associated with high doses of RT to the testes. Low testosterone in turn is associated with

numerous morbidities, including delayed puberty, osteoporosis, and metabolic syndrome.[12,13] In

our study, we found that no patient produced a biologically related offspring (although it is

unclear how many attempted and failed), and there was no difference in the rate of abnormal sperm count and utilization of fertility services between the boost and non-boost subsets as expected. There was no significant difference between the boost and non-boost subset in LH, FSH, or testosterone. However, a composite analysis of any abnormal gonadal laboratory value stratified by age and Tanner stage demonstrated that the boost subset may have a higher risk of hypogonadism compared to the non-boost subset. These findings were independent of cyclophosphamide use, consistent with the potential dose-dependent hypogonadism demonstrated by other studies.[33,34] Although some recovery of Leydig cells could be expected transiently, most patients who demonstrate initial abnormal gonadal endocrine levels after the treatments could suffer late and irreversible subtler Leydig cell damage ultimately.[35,36] While a definitive conclusion cannot be made about the long term impact of testicular boost to the gonadal function from the current data, the finding highlight the need to further investigate the benefits and harms of routine low-dose testicular RT boost.

There are several strengths and limitations to this study. This is the first analysis to compare the low-dose RT testes boost and non-boost subsets in the context of modern systemic regimen including HDMTX in terms of both fertility and reproductive endocrinopathy outcomes as well as oncologic outcomes. However, our study is a retrospective analysis consisting of a heterogeneous population with potential bias in treatment selection, limiting generalizability of the results. Serum endocrine lab values and testicular sizes were not measured prospectively at regular intervals for all patients. Composite abnormal gonadal bloodwork abnormality was used due to the small sample size and inconsistent measurements of gonadal blood work, and such an outcome may or may not have clinical validity. The follow up for this cohort is short, and there is

discrepancy in median follow up between boost and non-boost subset, and interpretation of the

PFS, OS, and gonadal bloodwork data should be made cautiously. Additional treatment and

disease information such as donor type and match, use of reduced intensity, timing of transplant

rate of minimal residual disease or complete response prior to TBI were missing in this study,

and such parameters should be included in future studies to further contextualize and stratify the

PFS and OS. Moreover, our sample size may not have been powered to detect subtle differences

in relapse or survival that could potentially exist between the boost and non-boost subsets.

Larger power would be also required to analyze the differences in semen quality and fertility

between the two subsets. Multi-institutional collaboration with longer follow up would be useful

to further examine the potential oncologic or subsequent gonadotrophic dysfunction between the

boost and non-boost subset.

Conclusion:

In our study there was no difference in oncologic outcomes including testicular relapse

rate, PFS or OS between the patients who received low-dose RT testicular boost and those who

did not receive the boost. We did not observe differences in the rate of abnormal sperm studies,

number of offspring, or reproductive services utilization between the two subsets. However,

receipt of a testicular boost was associated with abnormal laboratory values associated with

hypogonadism. Given the context of low testicular relapse rates seen in recent data as well as

concerns for late toxicity, our data further demonstrate oncologic equipoise between boost and

no boost regimens and therefore suggest that omission of boost may prove to be a preferable

treatment strategy. We acknowledge the potential biases inherent to retrospective studies and the

possibility for confounding as treatment paradigms changed over the decades of our study. However, the data reported here are potentially provocative and hypothesis-generating and warrant further investigation in larger multi-institutional reviews or prospective trials. These studies have the potential to further characterize the benefits and risks of routine use of a testicular boost in pediatric leukemia patients undergoing TBI as a component of conditioning for stem cell transplantation.

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Figure 1. K-M Survival Curve for Testicular Boost (+) and Non-Boost Status (-) A) K-M for Overall Survival (OS) B) K-M for Relapse-Free Survival (PFS)

Figure 1. K-M Survival Curve for Testicular Boost (+) and Non-Boost Status (-) A) Progression-Free Survival (PFS) B) Overall Survival (OS)
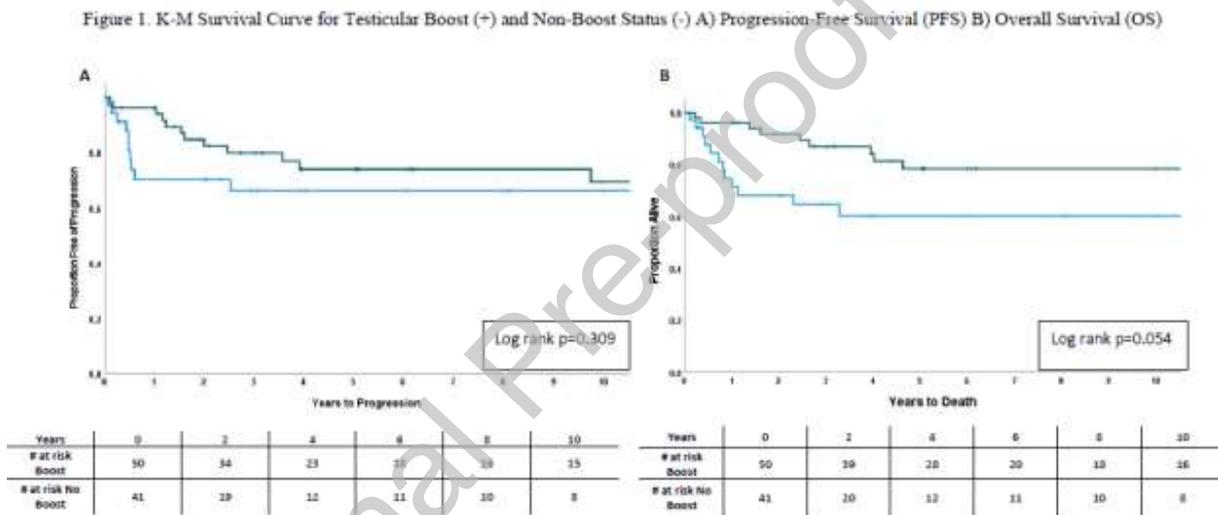
Table 1. Demographic and treatment characteristic differences between the testicular radiation boost and non-boost subsets

	Boost subset (N=51)	Non-boost subset (N=42)	P-value
Median age (interquartile range [IQR])	8 (5 – 12)	11 (5 – 14)	0.81
Median Follow up in years (IQR)	5.1 (2.7 – 15.3)	1.1 (0.21 – 8.1)	<0.001
Ethnicity	N (%)	N (%)	
Non-hispanic White Hispanic White Non-White	21 (42%) 20 (39%) 10 (20%)	14 (33%) 21 (50%) 7 (17%)	0.56
Type of conditioning	N (%)	N (%)	

regimen			
Cyclophosphamide-containing regimen	20 (40%)	17 (40%)	0.38
Non-cyclophsphamide containing regimen	31 (60%)	25 (60%)	
Disease type	N (%)	N (%)	
AML	2 (4%)	13 (31%)	<0.001
ALL	49 (96%)	29 (69%)	
Year of Bone Marrow Transplant	N (%)	N (%)	
Prior to year 2010	18 (35%)	14 (33%)	0.90
After year 2010	33 (65%)	28 (66%)	

Table 2. Cox-regression univariable analysis (UVA) and multivariable analysis (MVA) of the factors associated with progression free survival (PFS)

	UVA			MVA		
	Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value
Age (Years)	1.06	0.98 1.14	0.14	1.02	0.94 1.11	0.66
Ethnicity						
Non-Hispanic White	Reference	NA	NA	Reference	NA	NA
Hispanic White	5.74	1.88 17.54	0.002	4.61	0.54 39.09	0.15
Non-White	2.02	0.45 9.06	0.36	1.79	0.17 18.7	0.16
Conditioning regimen						
Cyclophosphamide-containing regimen	Reference	NA	NA	Reference	NA	NA
Non-cyclophosphamide containing regimen	2.08	0.38 11.5	0.40	1.45	0.54 3.89	0.46
Disease type						
ALL	Reference	NA	NA	Reference	NA	NA
AML	1.58	0.68 3.70	0.29	1.98	0.34 11.52	0.45
Year of Bone Marrow Transplantation						

Prior to year 2010	Reference	NA	NA	Reference	NA	NA	
After year 2010	4.01	1.17 13.8	0.03	1.36	0.13 14.85	0.80	
Boost							
No	Reference	NA	NA	Reference	NA	NA	
Yes	0.65	0.28 1.5	0.31	0.98	0.17 5.55	0.98	

Table 3. Cox-regression univariable analysis (UVA) and multivariable analysis (MVA) of the factors associated with overall survival (OS)

	UVA			MVA		
	Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value
Age (Years)	1.12	1.04 1.20	0.003	1.10	1.01 1.19	0.02
Ethnicity						
Non-Hispanic White	Reference	NA	NA	Reference	NA	NA
Hispanic White	2.17	0.63 7.50	0.22	2.54	0.54 12.0	0.24
Non-White	2.72	0.51 14.4	0.24	1.72	0.30 9.80	0.54
Conditioning regimen						
Cyclophosphamide-containing regimen	Reference	NA	NA	Reference	NA	NA
Non-cyclophosphamide containing regimen	0.77	0.34 1.75	0.53	0.68	0.27 1.73	0.42
Disease type						
ALL	Reference	NA	NA	Reference	NA	NA
AML	2.38	1.04 5.44	0.04	2.35	0.50 11.6	0.31
Year of Bone Marrow Transplant						
Prior to year 2010	Reference	NA	NA	Reference	NA	NA
After year 2010	5.0	1.43 17.4	0.01	2.00	0.37 16.8	0.35

Boost						
No	Reference	NA	NA	Reference	NA	NA
Yes	0.46	0.20 1.04	0.06	0.84	0.17 4.06	0.83

Table 4. Abnormality in luteinizing hormone (LH), follicular stimulating hormone (FSH), and total testosterone at any point between testicular radiation boost and non-boost subsets

	Boost subset (N=51)	Non-boost subset (N=42)	P-value*
LH	N (%)	N (%)	
Normal	15 (29%)	12 (29%)	0.06
Abnormal	20 (39%)	5 (12%)	
Missing	16 (31%)	25 (60%)	
FSH	N (%)	N (%)	
Normal	6 (12%)	4 (9.5%)	0.58
Abnormal	29 (57%)	13 (31%)	
Missing	16 (31%)	25 (60%)	
Testosterone	N (%)	N (%)	
Normal	27 (53%)	20 (48%)	0.14
Abnormal	13 (25%)	5 (12%)	
Missing	11 (22%)	17 (40%)	
Any abnormality[‡]	N (%)	N (%)	
Normal	7 (14%)	12 (29%)	0.03
Abnormal	35 (68%)	18 (43%)	
Missing	9 (18%)	12 (29%)	

*Patients with missing values removed for Chi square analysis

 Any abnormality of LH, FSH, or testosterone at any point during the follow up counted as an event