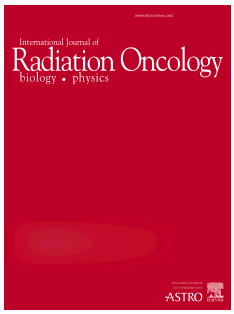

Radiation Related Toxicities Using Organ Sparing Total Marrow Irradiation Transplant Conditioning Regimens

Ashwin Shinde, MD, Dongyun Yang, PhD, Paul Frankel, PhD, An Liu, PhD, Chunhui Han, PhD, Bianca Del Vecchio, MS, Timothy Schultheiss, PhD, Jonathan Cheng, MD PhD, Richard Li, MD, Daniel Kim, MD, Eric H. Radany, MD PhD, Susanta Hui, PhD, George Somlo, MD, Joseph Rosenthal, MD, Anthony Stein, MD, Stephen Forman, MD, Jeffrey Y.C. Wong, MD

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Radiation Related Toxicities Using Organ Sparing Total Marrow Irradiation Transplant Conditioning Regimens

Ashwin Shinde MD[1], Dongyun Yang PhD[2], Paul Frankel PhD[2], An Liu PhD[1], Chunhui Han PhD[1], Bianca Del Vecchio MS[2], Timothy Schultheiss PhD[1], Jonathan Cheng MD PhD[1], Richard Li, MD[1]; Daniel Kim, MD[1]; Eric H. Radany, MD PhD[1], Susanta Hui PhD[1], George Somlo MD[3], Joseph Rosenthal, MD[4], Anthony Stein, MD[5], Stephen Forman MD[5] and Jeffrey Y.C. Wong MD[1]

[1]Department of Radiation Oncology, [2] Department of Information Sciences, [3]Department of Medical Oncology, [4]Department of Pediatrics, and [5]Department of Hematology and Hematopoietic Transplantation; City of Hope National Medical Center, Duarte, CA, USA

Dongyun Yang, PhD and Paul Frankel, PhD performed the statistical analyses.

Corresponding author: Jeffrey Y.C. Wong MD, Department of Radiation Oncology, City of Hope National Cancer Center, 1500 E. Duarte Road, Duarte, CA 91010, USA. Tel: 626-218-2247 Fax: 626-218-5334 Email: jwong@coh.org

Running title: Late toxicities after total marrow irradiation

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Radiation Related Toxicities Using Organ Sparing Total Marrow Irradiation Transplant Conditioning Regimens

Running title: Late toxicities after total marrow irradiation

Summary: Intermediate and long term pulmonary, renal, thyroid, and cataract toxicities are reported in 142 patients after total marrow irradiation (TMI). Mean lung dose of 8 Gy or less is associated with a significant decrease in pulmonary toxicity. IMRT delivery of TMI reduces organ doses and toxicities compared to conventional TBI. Further evaluation of IMRT to deliver TMI, TMLI and organ sparing conformal TBI is warranted.

Abstract

Purpose: Toxicities after organ sparing myeloablative total marrow irradiation (TMI) conditioning regimens have not been well characterized. The purpose of this study is to report pulmonary, renal, thyroid, and cataract toxicities from a prospective trial monitoring patients up to 8 years after TMI.

Methods: A total of 142 patients with primarily multiple myeloma or acute leukemia undergoing hematopoietic cell transplantation (HCT) were evaluated. Follow-up included pulmonary function tests, serum creatinine, GFR, thyroid panel, and ophthalmologic exams performed at 100 days, 6 months, and annually. Median TMI dose was 14 Gy (10-19 Gy) delivered at 1.5-2.0 Gy twice a day at a dose-rate of 200 cGy/minute.

Results: Median age was 52 years (range 9-70). Median follow-up (range) for all patients was 2 years (0-8) and for patients alive at the time of last follow-up (n=50) 5.5 years (0-8). Mean organ doses in Gy were lung 7.0, kidneys 7.1, thyroid 6.7 and lens 2.8. The crude incidence of radiation pneumonitis (RP) was 1/142 (0.7%). The cumulative incidence (CI) of infection and RP (I/RP) was 22.7% at 2 years post TMI. Mean lung dose (MLD) $\leq$ 8 Gy predicted for significantly lower rates of I/RP (2-year CI 20.8% vs 31.8%, p=0.012). No radiation induced renal toxicity was noted. Hypothyroidism (HT) occurred in 6.0% and cataract formation (CF) in 7.0% of patients.

Conclusion: TMI delivered with IMRT results in lower organ doses and was associated with fewer toxicities compared to historical cohorts treated with conventional TBI. Keeping the mean lung dose to 8 Gy or less was associated with lower pulmonary complications. Further evaluation in clinical trials of IMRT to deliver TMI, TMLI and organ sparing conformal TBI is warranted.

Introduction

Total body irradiation (TBI) is frequently used as part of the conditioning regimen to prepare patients with hematologic malignancies for hematopoietic cell transplant (HCT). However, multiple organs are dose-limiting with TBI, such as lung and kidney [1-3]. There have also been concerns of hypothyroidism and cataract formation [4-6]. Some reports have demonstrated a dose-response to oncologic outcomes in TBI patients, but with potential risk of increased toxicity [1,7-10]. The primary concern has been significant pulmonary toxicity, with TBI-based regimens showing approximately a 33% incidence of grade 3+ pulmonary toxicity [11]. Higher dose rate has also been associated with greater pulmonary toxicity [12]. Although lung blocking has reduced the risks of pneumonitis and lethal pulmonary toxicity, recent studies have demonstrated that mean lung doses below 8 Gy are needed to further reduce lung toxicity risks and improve overall survival [13].

The side effects associated with TBI potentially limit its role in patients undergoing HCT. Patients older than age 60 or with co-morbidities are not able to undergo TBI. Dose escalation of conventional TBI in an attempt to improve outcomes has also proven challenging. Two randomized phase II single institution trials in CML and AML have compared cyclophosphamide (Cy) combined with 12 Gy at 2 Gy/day or 15.75 Gy at 2.25 Gy/day [14,15]. Each trial demonstrated a decrease in relapse rate but no gain in overall survival due to an increase in treatment related mortality at the higher TBI dose. These factors may in part explain the decline in the use of TBI in HCT conditioning regimens [16]. More targeted forms of TBI are needed to reduce associated toxicities, to offer radiation containing conditioning regimens to a broader spectrum of patients, to allow for the evaluation of dose escalation to improve outcomes and to potentially redefine and expand the role of radiotherapy in HCT.

Image guided intensity modulated radiation therapy (IG-IMRT) to large regions of the body now allow for more targeted forms of TBI, are often referred to as total marrow irradiation (TMI) or total marrow and lymphoid irradiation (TMLI) and represent a spectrum of targeted TBI dose distributions. TMI is now being performed at multiple centers and can be delivered using a helical tomographic or volumetric arc based IMRT approach [17-20]. Clinical trials are currently evaluating TMLI dose escalation in patients with advanced refractory acute leukemia [21], TMLI added to reduced intensity conditioning (RIC) regimens [22,23], and TMI/TMLI as an alternative to TBI [24-26].

TMI and TMLI using Tomotherapy (Accuray, Inc. Sunnyvale, CA) to deliver organ sparing IMRT to large regions of the body was initially developed at this institution in patients undergoing HCT and is currently being evaluated in patients with advanced refractory disease who are not candidates for standard HCT conditioning regimens. Our group has demonstrated the feasibility and safety of dose escalating TMI or TMLI for multiple myeloma and refractory leukemia, respectively [21-23,27,28]. The purpose of this study is to report the incidence and predictors of intermediate and late toxicity outcomes in a pooled prospective cohort of patients undergoing TMI/TMLI at this institution.

Materials and Methods

Patient Selection

Patients diagnosed with multiple myeloma, lymphoma or acute leukemia/MDS received TMI or TMLI on one of 3 separate prospective trials in preparation for autologous or allogeneic HCT (Table 1 and Figure 1). The term TMI was used if bone was the target structure. The term TMLI was used if the target structure included bone, major lymph node chains and spleen. Liver

and brain were included as target organs in one of the two TMLI trials. These patients were consented and entered on a separate Institutional Review Board (IRB) approved prospective long-term follow up study to determine incidence of pulmonary, renal, thyroid and cataract toxicities up to 8 years after HCT. In addition to standard follow-up care, markers of organ dysfunction, including pulmonary function studies, serum creatinine, GFR, urine analyses, thyroid panel, and ophthalmologic exams were performed at 100 days, 6 months, 12 months and annually.

Toxicity Evaluation)

Pulmonary toxicity, renal toxicity, hypothyroidism (HT), and cataract formation (CF) were documented at each follow-up time point by the hematology transplant team and graded using NCI CTCAE version 3. Radiation pneumonitis (RP) was defined as $\geq$ Grade 3 pneumonitis not attributable to infection, graft versus host disease (GVHD), or disease progression. Work up of pulmonary toxicity was evaluated through standard institutional post-HCT protocols including bronchoscopy for identification of potential infection. Radiation induced nephropathy was defined as $\geq$ Grade 3 acute or chronic nephropathy not attributable to infection, GVHD, or disease progression. Hypothyroidism was defined as new onset elevation of thyroid stimulating hormone (TSH) requiring initiation of thyroid supplement medication. Cataract formation was defined as development of cataracts post TMI or TMLI of any grade.

Radiation Treatment

Patients were planned and treated using a Tomotherapy system, using a 1.5-2.0 Gy twice-daily fractionated schedule, given over 4 to 5 consecutive days to a total dose between 10 and 19

Gy. Patients were treated at a dose-rate of 200 cGy/minute. Methods for immobilization, simulation, treatment planning and delivery of TMI at this institution have previously been published [17,29,30] . Briefly, patients were simulated in the head-first supine position using whole body Vac-Lok (CIVCO Radiotherapy, Orange City, Iowa) and S-frame shoulder and head (Klarity Medical, Newark, Ohio) immobilization. An additional simulation scan was performed in the feet first supine position in the same Vac-Lok to allow for delineation and planning of distal lower extremities. Target and avoidance structures were contoured on an Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA). Avoidance structures included lungs, heart, kidneys, liver, esophagus, oral cavity, parotid glands, thyroid gland, eyes, lens, optic chiasm and nerves, brain, stomach, small and large intestine, breasts, rectum, testes, ovary and bladder. Target structures were defined by the clinical trial (see table 1 and figure 1). DICOM-RT images were transferred to the Tomotherapy treatment planning system. Plans were designed such that a minimum of 85% of the target received the prescribed dose. For the body treatment plan, jaw size of 5cm, pitch of 0.287 and modulation factor of 2.5 were used for most patients. Legs and feet were planned in Tomo-Direct mode or standard AP-PA opposed fields.

Dosimetric parameters from the generated plans were extracted from the Tomotherapy planning system to evaluate for correlation with clinical toxicity. The volume of total lung, bilateral kidneys, bilateral lenses, and thyroid receiving a dose of radiation, from 2.5 Gy to 20 Gy, in 2.5 Gy increments, was extracted as both a percentage volume of the organ (relative volume) and an absolute volume of cubic centimeters (cc). Mean and median organ doses were also collected.

Statistical Analysis

Radiation-related toxicities including pulmonary toxicity, renal toxicity, hypothyroidism (HT), and cataract formation (CF) after HCT were evaluated using cumulative incidence to account for competing events such as death from disease relapse/progression, or other causes. Associations between dosimetric parameters of interests and radiation-related toxicities were evaluated using random survival forests for competing risks (RSF) with 1000 trees generated. RSF analysis identifies importance of variables to outcomes and determines an error rate: a threshold of importance of 0.01 was chosen to select variables worth additional evaluation, with a required error rate of less than 50% (equal to the flip of a coin). RSF was used because it is a non-parametric method and effective for selecting which variables associated with outcomes from high-dimensional data [31] by taking interactions and nonlinearity into account. Variable importance for each variable and prediction error rate were calculated from RSF. Two random variables (a continuous variable with mean of 0 and standard deviation of 1, and another variable uniformly distributed from 0 to 1) were included in all RFS to assess whether a dosimetric variable was better to predict toxicity than random variables. A modified weighted log-rank statistic derived from Gray's test was used as a splitting rule for RSF. Gray test and Fine and Gray regression model was used for the associations between baseline factors and pre-specified lung radiation dose ($\leq$ 8 Gy versus > 8 Gy) and radiation-related toxicities in the univariate and multivariable analyses, respectively. All analyses were performed using SAS/STAT 14.1 of SAS Version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.5.2 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) package 'random Forest SRC'. Tests were 2-sided and significant at 0.05 level.

Results

Baseline Characteristics

A total of 142 patients made up the study population. Thirty-six patients with multiple myeloma received TMI prior to autologous HCT and 106 with advanced hematopoietic malignancies, mostly acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL), received TMLI prior to allogeneic HCT (Table 1). The vast majority (92%) of patients were enrolled between 2006 and 2013. Baseline demographics are shown in Table 2. Median follow-up (range) for all 142 patients was 2 years (0-8) and for patients alive at the time of last follow-up (n=50) 5.5 years (0-8). Complete dosimetric parameters were available for 137 out of 142 (96.5%) patients. For the remaining 5 patients, the archived treatment plans were corrupted and not available for analysis. For all analyzable patients mean doses to lung, kidney, thyroid and lens were 7.0 Gy, 7.1 Gy, 6.7 Gy and 2.8 Gy respectively. Values obtained for each organ analyzed are presented in Table 3.

Incidence and Predictors of Toxicity

Incidence of RP was low in this cohort, with only 1 out of 142 (0.7%) patients developing RP. This patient with MM received 18 Gy TMI on trial 1. The patient developed significant respiratory distress requiring up to 6 liters of supplemental oxygen per nasal cannula and required re-admission 40 days after date of transplant. The patient had a bronchoscopy confirming no infection as a cause of symptoms. This patient received a mean total lung dose of 8.1 Gy. Symptoms and radiologic changes resolved after steroid administration.

Some groups have reported on pulmonary toxicity after TBI combining RP and pulmonary infections in the analysis [11,12,32,33]. There were an additional 45 patients who developed pulmonary symptoms attributed to infection. The 2-year cumulative incidence of

infection or RP (I/RP) was 22.7%, increasing to 32.3% by 6 years post-treatment (Figure 2A). MLD > 8 Gy was associated with a higher rate of I/RP, with 2-year cumulative incidence of 31.8% vs. 20.8%, and 6-year cumulative incidence of I/RP was 53.9% vs. 28.2% (p=0.012, Figure 2B). No other dosimetric parameters or baseline characteristics (Table 2) were identified as predictors of I/RP toxicity based on the RSF method. The error rate was 56% and the variable importance was smaller than 0.01 for all dosimetric measures.

No radiation related renal toxicity was observed. Thirty-nine patients had evidence of renal impairment attributed to non-radiation related reasons, such as progressive disease or sepsis. Incidence of hypothyroidism (HT) was low as well, with a total of 8 out of 134 (6.0%) patients without pre-treatment HT developing new onset HT after treatment with TMI or TMLI. The 2 and 6 year cumulative incidence of HT was 1.6% and 5.2%, respectively (Figure 3A). Female gender was a significant predictor of developing HT; no males developed HT. Two and 6-year incidence of HT in females was 3.2% and 11.0%, respectively (Gray test p=0.004, supplemental figure 1A). No dosimetric parameters were identified as predictive of development of HT based on RSF. The error rate was 60% and the variable importance was less than 0.01 for all dosimetric measures among female subjects.

Incidence of CF was low in this study population, with a total of 10 out of 142 (7.0%) patients experiencing post-treatment CF. The 2 and 6 year cumulative incidence of CF was 0.8% and 5.5%, respectively (Figure 3B). Patients undergoing autologous transplant were more likely to have CF than patients undergoing allogeneic transplant. At 2-years post-treatment, no allogeneic patients had CF, while 2.9% of autologous patients had CF; at 6-years; rates of CF were 3.4% and 11.8% for allogeneic and autologous patients, respectively (Gray test p=0.013, supplemental figure 1B). No dosimetric parameters were identified as predictive of CF based on

RSF. The error rate was 64% and the variable importance was less than 0.02 for all dosimetric measures.

Discussion

To our knowledge this is the first study reporting intermediate and long term radiation related organ toxicities in a large group of patients receiving myeloablative TMI or TMLI prior to HCT. The rates of toxicity observed in our patient population were low and compare favorably to those reported after conventional TBI. The rates of hypothyroidism and cataract formation were 6.0% and 7.0%, respectively. Nephropathy attributed to radiation was not observed. These toxicity rates are lower than those reported in patients undergoing TBI. Renal toxicity can range between 0% and 46.7% [1,34]. Rates of hypothyroidism requiring medication replacement range from 10.5% to 12.0% [5,35,36] and cataract formation has been reported to be as high as 89-100% [1,37]. These toxicities have been shown to correlate with total dose and dose per fraction [9]. TMI and TMLI in this study used fraction sizes similar to that used to deliver standard TBI. Therefore, the low rates of toxicity observed in this study are likely due to organ sparing and reduction in organ dose using IMRT compared to conventional opposed fields used to deliver TBI [38]. With conventional TBI these organs would usually receive the full total body dose.

Radiation pneumonitis (RP) is a clinically important complication of TBI in patients undergoing HCT. Experimental and clinical data have confirmed that fractionated TBI is less toxic to the lung than single-dose TBI [39-41]. Fractionated doses above 15 Gy [32] are associated with a higher incidences of RP. Using a multivariate logistic regression analysis of 1090 patients who received single fraction or daily fractionated TBI reported in 20 published studies, Sampath et al. demonstrated a correlation of RP with lung dose and dose per fraction [8].

The α/β ratio was low at 2.8 in this study and indicates that RP is significantly diminished with increasing fractionation. Because of the organ sparing and dose reduction in this study, patients benefitted from lower dose per fraction as well as lower total dose to critical organs.

Lung doses in this study were lower than that reported with conventional TBI and probably explain the observed incidence of radiation pneumonitis of 0.7% (1/142). This compares favorably to conventional TBI where RP rates are approximately 28 to 31% even with the use of lung shielding and fractionation [2,4,42]. When combined with pulmonary infection events the incidence of pulmonary toxicity was 32.3% (46/142) which compares favorably to that reported with TBI given the fact that over half of patients in this study (n=72) were treated to a prescribed dose of 14-19 Gy which is higher than with standard TBI.

Others have also reported that higher lung dose is associated with lethal pulmonary complications of all causes including pulmonary infections [33,43]. Recently, a retrospective analysis of 143 patients who received TBI to 12 or 13.2 Gy on a Children's Oncology Group (COG) clinical trial reported a mean lung dose of 9.0 Gy and found that a MLD of < 8 Gy was predictive of significantly improved overall survival [13]. In the present study mean lung doses were lower (7.0 Gy, range 4.9 - 9.0) for the entire study group and 6.4 Gy (range 5.2-7.4) for the patients receiving 12 Gy, and similarly identified that MLD $\leq$ 8 Gy was clinically important and associated with a reduction in the cumulative incidence of pulmonary toxicity, defined as a combination of infection and RP. Taken together the results of this study and the COG analysis suggest that regardless of the methods used to deliver myeloablative radiotherapy prior to HCT, the mean lung dose $\leq$ 8 Gy is a clinically important dose constraint to meet.

To our knowledge this is also the first study reporting long term toxicities in patients receiving myeloablative radiation therapy prior to HCT at dose rates higher than conventional

TBI. In this study the estimated dose-rate was 200 cGy/minute, which has raised concerns of an associated greater degree of toxicities. With conventional TBI dose-rates range from 5 to 30 cGy/minute. Within this range, some but not all studies have reported that the incidence of cataract formation [10,44], renal toxicity [9] and pulmonary toxicity [12,42,45,46] is greater at higher end of this range. The low incidence of toxicity in this study suggests that the higher dose rate did not measurably contribute to organ dysfunction. This is predicted from the pre-clinical and clinical literature. Dose-rate effects are clinically important primarily at very low dose-rates. Travis et al [47] evaluated one year survival and histologic changes in mice receiving TBI at dose-rates ranging from 1 to 25 cGy/minute. The dose-rate effects were greatest for dose-rates ranging from 1 to 5 cGy/minute. Consistent with this are the observations of Weiner et al [48] who reported on 932 patients in the IBMTR database treated from 1978 to 1983 and observed a decrease in incidence of pneumonitis with lower dose-rate but only in patients treated at less than 6 cGy/minute. Dose-rate effects in this study were likely further mitigated through fractionation and reduction in total dose to critical organs such as lung [8,49].

This study has a number of strengths, such as being a prospective evaluation of toxicity to allow for incidence calculation at various time points and the largest reported series of TMI patients to date. This study also provides organ dose data based on CT planning from a large number of patients which can be used in the future to guide planning of patients treated with TMI and TMLI (Table 3). There are also a number of limitations with this study. The poor prognosis of this patient population results in a median follow-up which is relatively short for the entire group and reduces the number of patients available for long term analysis. The results are from a single institution and long term toxicity results from other centers evaluating TMI are needed for comparison. There is also no TBI cohort for comparison. The inability to determine

other dosimetric predictors of toxicity may be driven by the low rates of clinical toxicity seen in regards to renal, thyroid and lens toxicity. It is unclear why all patients who developed HT were female. The higher incidence of CF in patients undergoing autologous transplant for multiple myeloma may be explained by the fact that this cohort was older, had longer follow up since they were treated on our first TMI trial, and routinely received steroids as part of the maintenance therapy.

The results of this study and the published TMI and TMLI experience to date support the continued evaluation of this approach in patients undergoing HCT. TMI and TMLI delivery is no longer limited to a Tomotherapy device and can therefore be performed at a larger number of transplant centers. Clinical trials are needed to continue to define toxicities and outcomes, to determine the most appropriate patient populations, target dose, organ dose constraints, and fractionation schedules, and ultimately to determine whether these approaches are preferred over current standard TBI and non-TBI conditioning regimens.

Although this study did not include a TBI cohort for comparison, the results of this study also support the need for clinical trials to evaluate using IMRT as a method to deliver TBI. A number of centers have already initiated trials using IMRT to deliver TBI [24-26,50]. The use of helical tomographic and volumetric arc-based IMRT devices to deliver TMI and TMLI has been shown to be better at reducing dose to lung and other critical normal organs compared to conventional TBI delivery methods [18,51,52]. Achieving a MLD $\leq$ 8 Gy in TBI patients using conventional non-conformal methods can be challenging even with the use of lung blocking, but can be more easily achieved using IMRT. At our center mean lung and kidney doses are approximately 5-7 Gy using IMRT to deliver TMLI to a prescribed dose of 12 Gy. Comparable lung sparing should be seen with TBI [22,23]. In clinical situations which require significant

reduction in lung and kidney doses, such as in patients with systemic sclerosis undergoing TBI prior to autologous HCT [53], mean lung and kidney doses as low as 25%-30% of the prescribed TBI dose have been achieved using IMRT at this center (data unpublished). Whether these dosimetric advantages translate into improved clinical outcomes compared to conventional TBI will require further evaluation through clinical trials.

Conclusion

The rates of pulmonary, thyroid, renal and lens toxicity due to radiation therapy in patients receiving TMI/TMLI were lower than historically reported for TBI. This is due to the greater ability to spare normal organs using an IMRT based delivery approach. The higher dose-rate with TMI/TMLI delivery does not appear to be associated with increased organ dysfunction. Keeping MLD $\leq$ 8 Gy is recommended to reduce a patient's risk of pulmonary I/RP. Continued evaluation of TMI and TMLI in well-designed clinical trials is warranted. IMRT should be also evaluated as method to deliver organ sparing conformal TBI in future trials.

Figure captions

Figure 1. Dose color washes for trials 1, 2 and 3 (from left to right)

Figure 2. A) Cumulative incidence of pulmonary infection and radiation pneumonitis (RP) and B) cumulative incidence of pulmonary infection and radiation pneumonitis (RP) for < 8 Gy or > 8 Gy mean lung dose.

Figure 3. Cumulative incidence of A) hypothyroidism and B) cataract formation.

References

1. Kal HB, Kempen-Harteveld ML. Induction of severe cataract and late renal dysfunction following total body irradiation: Dose-effect relationships. *Anticancer Res* 2009; **29:** 3305-3310.

2. Chen C, Abraham R, Tsang R *et al.* Radiation-associated pneumonitis following autologous stem cell transplantation: predictive factors, disease characteristics and treatment outcomes. *Bone Marrow Transplant* 2001; **27:** 177-182.

3. Moulder JE, Fish BL, Holcenberg JS *et al.* Hepatic function and drug pharmacokinetics after total body irradiation plus bone marrow transplant. *Int J Radiat Oncol Biol Phys* 1990; **19:** 1389-1396.

4. Bolling T, Kreuziger DC, Ernst I *et al.* Retrospective, monocentric analysis of late effects after total body irradiation (TBI) in adults. *Strahlenther Onkol* 2011; **187:** 311-315.

5. Berger C, Le-gallo B, Donadieu J *et al.* Late thyroid toxicity in 153 long-term survivors of allogeneic bone marrow transplantation for acute lymphoblastic leukaemia. *Bone Marrow Transplant* 2005; **35:** 991-995.

6. Fahnehjelm KT, Tornquist AL, Olsson M *et al.* Cataract after allogeneic hematopoietic stem cell transplantation in childhool. *Acta Paediatrica* 2016; **105:** 82-89.

7. Gopal R, Ha CS, Tucker SL *et al.* Comparison of two total body irradiation fractionation regimens with respect to acute and late pulmonary toxicity. *Cancer* 2001; **92:** 1949-1958.

8. Sampath S, Schultheiss TE, Wong J. Dose response and factors related to interstitial pneumonitis following bone marrow transplant. *Int J Radiat Oncol Biol Physics* 2005; **63:** 876-884.

9. Cheng JC, Schultheiss TE, Wong JYC. Impact of drug therapy, radiation dose, and dose rate on renal toxicity following bone marrow transplantation. *Int J Radiat Oncol Biol Phys* 2008; **71:** 1436-1443.

10. Hall MD, Schultheiss TE, Smith DD *et al.* Dose response for radiation cataractogeneisis: A meta-regression of hematopoietic stem cell transplantation regimens. *Int J Radiat Oncol Biol Phys* 2015; **91:** 22-29.

11. Kelsey CR, Horwitz ME, Chino JP *et al.* Severe pulmonary toxicity after myeloablative conditioning using total body irradiation: An assessment of risk factors. *Int J Radiat Oncol Biol Phys* 2011; **81:** 812-818.

12. Abugideiri M, Nanda RH, Butker C *et al.* Factors influencing pulmonary toxicity in children undergoing allogeneic hematopoietic stem cell transplantation in the setting of total body irradiation-based myeloablative conditioning. *Int J Radiat Oncol Biol Phys* 2016; **94:** 349-359.

13. Esiashvili, N., Lu, X, Ulin, K, Kessel, l. S., Kalapurakal, J. A., Merchant, T. E., Followill, D. S., Sathiaseelan, V, Schmitter, M. K., Devidas, M., Chen, Y-J, Wall, D. A., Brown, P. A., Hunger, S. P, Grupp, S. A., and Pulsipher, M. A. Higher reported lung dose received during total body irradiation for allogeneiv hematopoietic stem cell transplantation in children with acute lymphoblastic leukemia is associated wtih inferior survival: A report from the Children's Oncology Group. Int J Radiat Oncol Biol Phys . 2019.

14. Clift RA, Buckner CD, Appelbaum FR *et al.* Allogeneic marrow transplantation in patients with chronic myeloid leukemia in the chronic phase: A randomized trial of two irradiation regimens. *Blood* 1991; **77:** 1660-1665.

15. Clift RA, Buckner CD, Appelbaum FR *et al.* Long-term follow-up of a randomized trial of two irradiation regimens for patients receiving allogeneic marrow transplants during first remission of acute myeloid leukemia. *Blood* 1998; **92:** 1455-1456.

16. Mohty M, Malard F, Savani BN. High-dose total body irradiation and myeloablative conditioning before allogenic hematopoietic cell transplantation: Time to rethink? *Biol Blood Marrow Transplant* 2015; **21:** 620-624.

17. Schultheiss TE, Wong J, Liu A *et al.* Image-guided total marrow and total lymphatic irradiation using helical tomotherapy. *Int J Radiat Oncol Biol Phys* 2007; **67:** 1259-1267.

18. Aydogan B, Yeginer M, Kavak GO *et al.* Total marrow irradiation with rapidArc volumetric arc therapy. *Int J Radiat Oncol Biol Phys* 2011; **81:** 592-599.

19. Symons K, Morrison C, Parry J *et al.* Volumetric modulated arc therapy for total body irradiation: A feasibility study using Pinnacle^3 treatment planning system and Elekta Agility^{TM} linac. *J Appl Clin Med Phys* 2018; **19:** 103-110.

20. Wong JYC, Hui S, Dandapani SV *et al.* Biologic and Image Guided Systemic Radiotherapy. In: *Advances in Radiation Oncology.* Heildelberg: J. Y. C. Wong, T. E. Schultheiss, E. H. Radany, 2017: 155-189.

21. Stein A, Palmer J, Tsai N-C *et al.* Phase I trial of total marrow and lymphoid irradiation transplantation conditioning in patients with relapsed/refractory acute leukemia. *Biol Blood Marrow Transplant* 2017; **23:** 618-624.

22. Jensen LJ, Stiller T, Wong JYC *et al.* Total marrow lymphoid irradiation/Fludarabine/Melphalan conditioning for allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2018; **24:** 301-307.

23. Rosenthal J, Wong J, Stein A *et al.* Phase 1/2 trial of total marrow and lymph node irradiation to augment reduced-intensity transplantation for advanced hematologic malignancies. *Blood* 2011; **117:** 309-315.

24. Springer A, Hammer J, Winkler E *et al.* Total body irradiation with volumetric modulated arc therapy: Dosimetric data and first clinical experience. *Radiation Oncology* 2016; **11:** 1-9.

25. Gruen A, Ebell W, Wlodarczyk W *et al.* Total body irradiation (TBI) using helical tomotherapy in children and young adults undergoing stem cell transplantation. *Radiation Oncology* 2013; **8**.

26. Sarradin V, Simon L, Huynh A *et al.* Total body irradiation using Helical Tomotherapy: Treatment technique, dosimetric results and initial clinical experience. *Cancer/Radiotherapie* 2018; **22:** 17-24.

27. Somlo G, Spielberger R, Frankel P *et al.* Total Marrow Irradiation: A new ablative regimen as part of tandem autologous stem cell transplantation for patients with multiple myeloma. *Clin Cancer Res* 2011; **17:** 174-182.

28. Wong JY, Forman S, Somlo G *et al.* Dose escalation of total marrow irradiation with concurrent chemotherapy in patients with advanced acute leukemia undergoing allogeneic hematopoietic cell transplantation. *Int J Radiat Oncol Biol Phys* 2013; **85:** 148-156.

29. Wong JYC, Liu A, Schultheiss T *et al.* Targeted total marrow irradiation using three-dimensional image-guided tomographic intensity-modulated radiation therapy: An alternative to standard total body irradiation. *Biol Blood Marrow Transplant* 2006; **12:** 306-315.

30. Wong JYC, Hui S, Dandapani SV *et al.* Biologic and Image Guided Systemic Radiotherapy. In: *Advances in Radiation Oncology.* Heildelberg: J. Y. C. Wong, T. E. Schultheiss, E. H. Radany, 2017: 155-189.

31. Ishwaran H, Gerds TA, Kogalur UB *et al.* Random survival forests for competing risks. *Biostatistics* 2014; **15:** 757-773.

32. Lohr F, Wenz F, Schraube P *et al.* Lethal pulmonary toxicity after autologous bone marrow transplantation/peripheral blood stem cell transplantation for hematological malignancies. *Radiother Oncol* 1998; **48:** 45-51.

33. Volpe AD, Ferreri AJM, Annaloro C *et al.* Lethal pulmonary complications significantly correlate with individually assessed mean lung dose in patients with hematologic malignancies treated with total body irradiation. *Int J Radiation Oncology Biol Phys* 2002; **52:** 483-488.

34. Kersting S, Verdonck LF. Chronic kidney disease after nonmyeloablative stem cell transplantation in adults. *Biol Blood Marrow Transplant* 2008; **14:** 403-408.

35. Farhadfar N, Stan MN, Shah P *et al.* Thyroid dysfunction in adult hematopoietic cell transplant survivors: risks and outcomes. *Bone Marrow Transplant* 2018; **53:** 977-982.

36. Medinger M, Zeiter D, Heim D *et al.* Hypothyroidism following allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia. *Leukemia Research* 2017; **58:** 43-47.

37. van Kempen-Harteveld ML, Struikmans H, Kal HB *et al.* Cataract-free interval and severity of cataract after total body irradiation and bone marrow transplantation: influence of treatment parameters. *International Journal of Radiation Oncology, Biology, Physics* 2000; **48:** 807-815.

38. Wong JYC, Filippi AR, Dabaja BS *et al.* Total body irradiation: Guidelines from the International Lymphoma Radiation Oncology Group (ILROG). *Int J Radiat Oncol Biol Phys* 2018; **101:** 521-529.

39. Pino Y Torres JL, Bross DS, Lam WC *et al.* Risk factors in interstitial pneumonitis following allogenic bone marrow transplantation. *Int J Radiation Oncology Biol Phys* 1982; **8:** 1301-1307.

40. Cosset JM, Baume D, Pico JL *et al.* Single dose versus hyperfractionated total body irradiation before allogeneic bone marrow transplantation: a non-randomized comparative study of 54 patients at the Institut Gustave-Roussy.[see comment]. *Radiother Oncol* 1989; **15:** 151-160.

41. Shank B, O'Reilly RJ, Cunningham I *et al.* Total body irradiation for bone marrow transplantation: the Memorial Sloan-Kettering Cancer Center experience. *Radiother Oncol* 1990; **18 Suppl 1:** 68-81.

42. Carruthers S, Wallington M. Total body irradiation and pneumonitis risk: a review of outcomes. *British Journal of Cancer* 2004; **90:** 2080-2084.

43. Savani BN, Montero A, Wu C *et al.* Prediction and prevention of transplant related mortality from pulmonary causes after total-body irradiation and allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 2005; **11:** 223-230.

44. Ozsahin M, Pene F, Touboul E *et al.* Total-body irradiation before bone marrow transplantation: Results of two randomized instantaneous dose rates in 157 patients. *Cancer* 1992; **69:** 2853-2865.

45. Belkacemi Y, Pene F, Touboul E *et al.* Total-body irradiation before bone marrow transplantation for acute leukemia in first or second complete remission. *Strahlenther Onkol* 1998; **174:** 92-104.

46. Gao RW, Weisdorf D, DeFor TE *et al.* Influence of total body irradiation dose rate on idiopathic pneumonia syndrome in acute leukemia patients undergoing allogeneic hematopoietic cell transplantation. *Int J Radiat Oncol Biol Phys* 2019; **103:** 180-189.

47. Travis EL, Peters LJ, McNeil J *et al*. Effect of dose-rate on total body irradiation: Lethality and pathologic findings. *Radiotherapy and Oncology* 1985; **4:** 341-351.

48. Weiner R, Bortin M, Gale RP *et al.* Interstitial pneumonitis after bone marrow transplantation. *Ann Intern Med* 1986; **104:** 168-175.

49. Tarbell NJ, Amato DA, Down JD *et al.* Fractionation and dose rate effects in mice: a model for bone marrow transplantation in man. *Int J Radiat Oncol Biol Phys* 1987; **13:** 1065-1069.

50. Tas B, Durmur IF, Okumus A *et al.* Total-body irradiation usinglinac-based volumetric modulated arc therapy: Its clinical accuracy, feasibility, and reliability. *Radiotherapy and Oncology* 2018; **129:** 527-533.

51. Zhuang AH, Liu A, Schultheiss TE *et al.* Dosimetric study and verification of total body irradiation using helical tomotherapy and its comparison to extended SSD technique. *Medical Dosimetry* 2010; **35:** 243-249.

52. Patel P, Oh AL, Koshy M *et al.* A phase I trial of autologous stem cell transplantation conditioned with melphalan 200mg/m^2 and total marrow irradiation (TMI) in patients with relapsed/refractory multiple myeloma. *Leuk Lymphoma* 2018; **59:** 1666-1671.

53. Sullivan KM, Goldmuntz EA, Keyes-Elstein L *et al*. Myeloablative autologous stem-cell transplantation for severe sceroderma. *N Engl J Med* 2018; **378:** 35-47.

Table 1. TMI and TMLI Clinical Trials.

Trial No.	Type (No. of Patients)	Type of HCT	Disease Type	Targets	TMI Dose (Gy)	Chemotherapy
1	Phase I/II [14]	autologous (tandem)	stage I-III multiple myeloma responding or stable	bone	10 to 18	Melphalan (Mel) 200 mg/m^2 first autologous HCT TMI alone second autologous HCT
2	Pilot [18]	allogeneic	Primarily AML, ALL relapsed or refractory; > 50 yrs old or with co-morbidities; And ineligible for standard HCT	bone, nodes, spleen, ALL - testes, brain	12	Fludarabine 25 mg/m^2/d x 4 Mel 140 mg/m^2
3	Phase I [17]	allogeneic	AML, ALL relapsed or refractory with active disease not eligible for standard HCT	bone, nodes, testes, spleen, 12 Gy - liver, brain	12 to 20	Cyclophosphamide 100 mg/kg Etoposide 60 mg/kg

Table 2. Baseline characteristics of study population

Baseline Characteristics	**All Patients (n = 142) n (%)**
Age (Median [IQR])	52 (range 37-57)
Year of Diagnosis	
2005-2008	47 (33.1)
2009-2012	67 (47.2)
2013-2017	28 (19.7)
Gender	
Male	72 (50.7)
Female	70 (49.3)
Karnofsky Performance Status	
80-100	102 (71.8)
<80	11 (7.7)
Unknown	29 (20.4)
HCT comorbidity index	
0	76 (53.5)
1-2	27 (19)
3+	11 (7.7)
Unknown	28 (19.7)
Primary Diagnosis	
Multiple Myeloma	39 (27.5)
MDS/Leukemia	91 (64.1)
Lymphoma	12 (8.5)
Conditioning Regimen	
TMI/TMLI only (Trial 1)	36 (25.4)
+ Fludarabine/Melphalan (Trial 2)	59 (41.5)
+ VP-16/CTX (Trial 3)	47 (33.1)
HCT Type	
Autologous	36 (25.4)
Allogeneic Related Donor	51 (35.9)
Allogeneic Unrelated Donor	55 (38.7)
TMLI Dose	
10 Gy	3 (2.1)
12 Gy	64 (45.1)
13.5 Gy	3 (2.1)
14 Gy	2 (1.4)
15 Gy	17 (12.0)
16 Gy	30 (21.1)
17 Gy	7 (4.9)
18 Gy	10 (7.0)
19 Gy	6 (4.2)

Table 3. Average Dosimetric Parameters for Lung, Kidneys, Thyroid and Lens

	Mean Dose in Gy (Range)	**Median Dose (D50) in Gy (Range)**	**V5 (Range)**	**V10 (Range)**
Lungs	7.0 (4.9-9.0)	6.4 (4.4-8.6)	79.7% (22.0-100)	13.2% (0.01-37.7)
Thyroid	6.7 (2.5-11.8)	6.4 (2.3-11.8)	73.3% (0.04-100)	11.2% (0-93.8)
Lens	2.8 (1.3-6.9)	2.7 (1.2-7.1)	4.8% (0-74.1)	0.52% (0-39.2)
Kidneys	7.1 (3.3-11.4)	6.5 (3.0-10.7)	78.7% (7.5-100)	13.2% (0-78.1)

V5 and V10 = percent of the organ receiving 5 Gy and 10 Gy, respectively

Figure 1

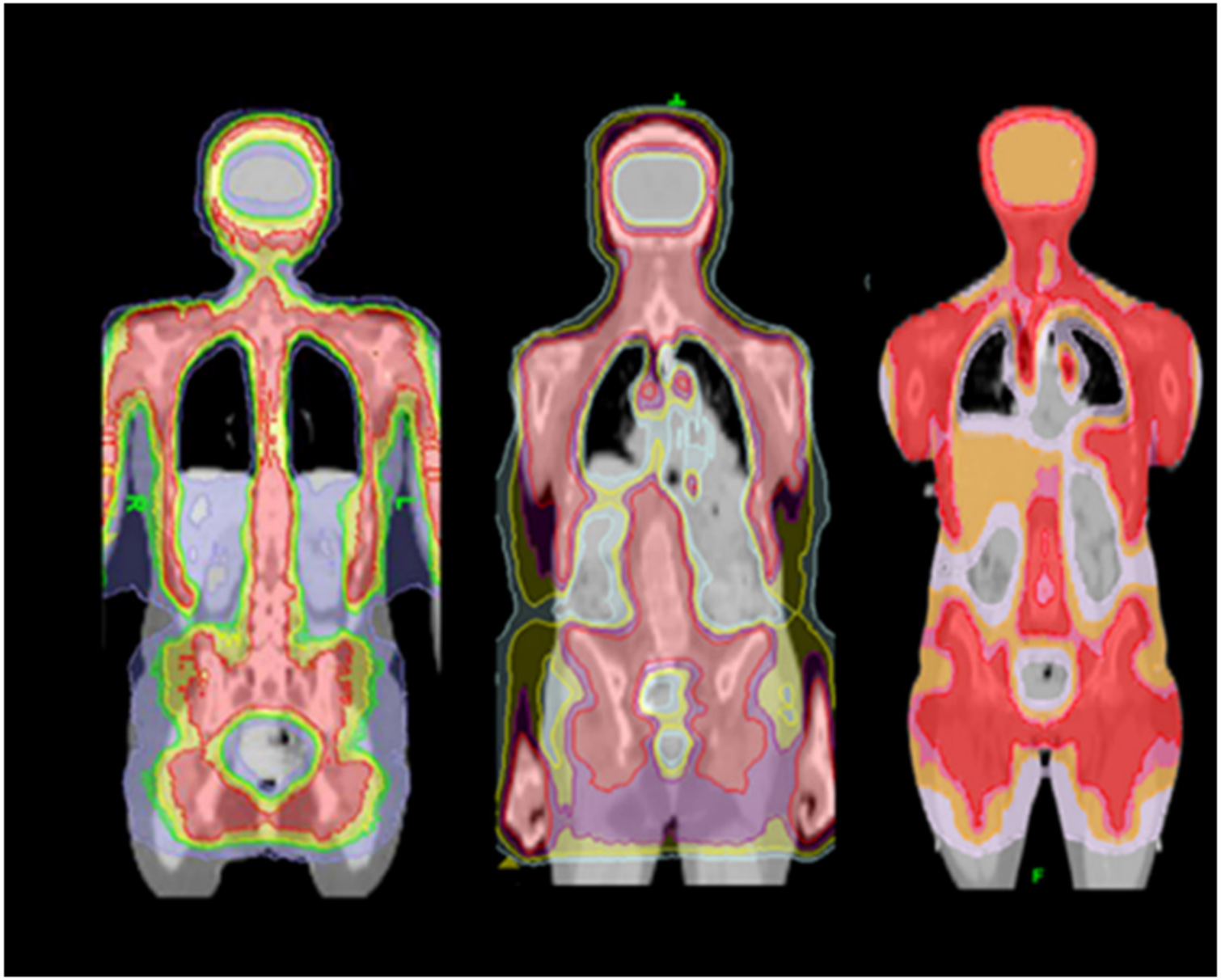
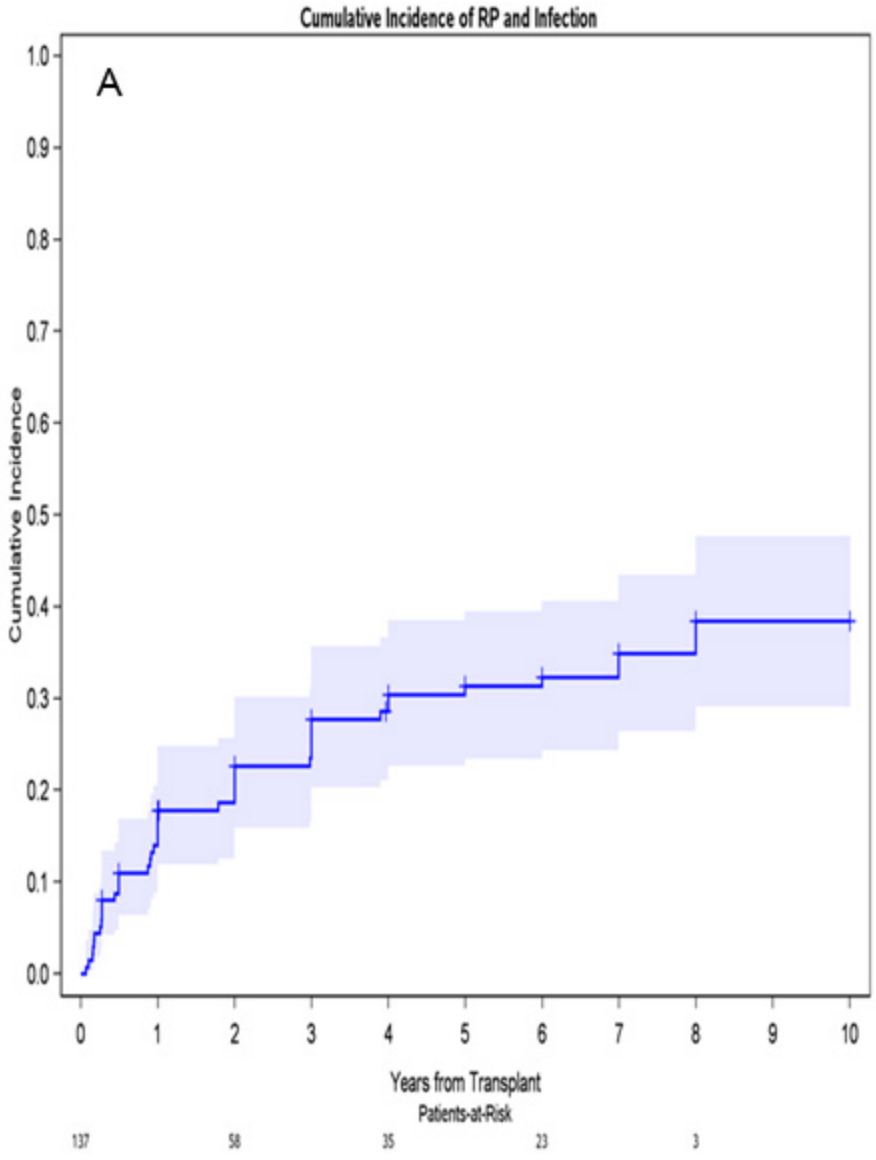


Figure 2


Cumulative Incidence of RP and Infection
A
Cumulative Incidence
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10
Years from Transplant
Patients-at-Risk
137 58 35 23 3

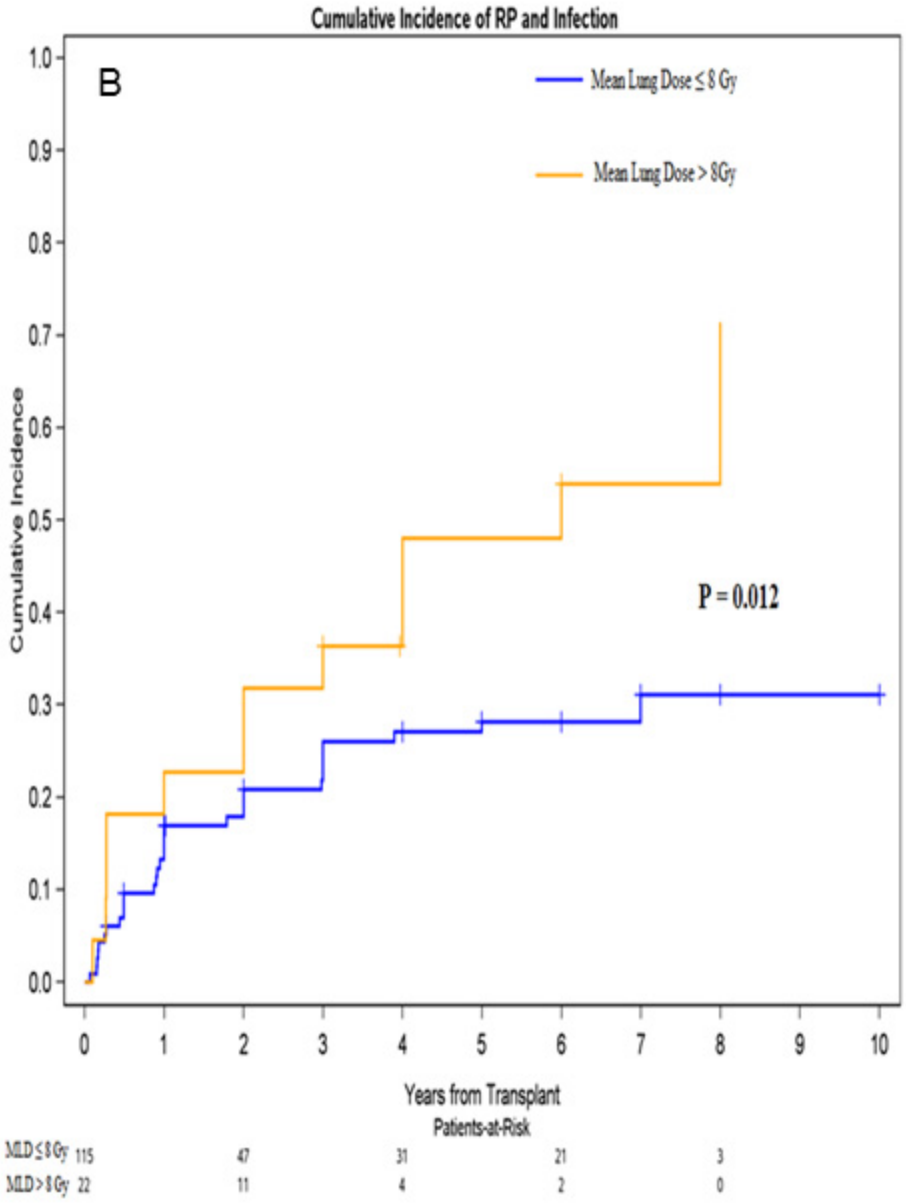
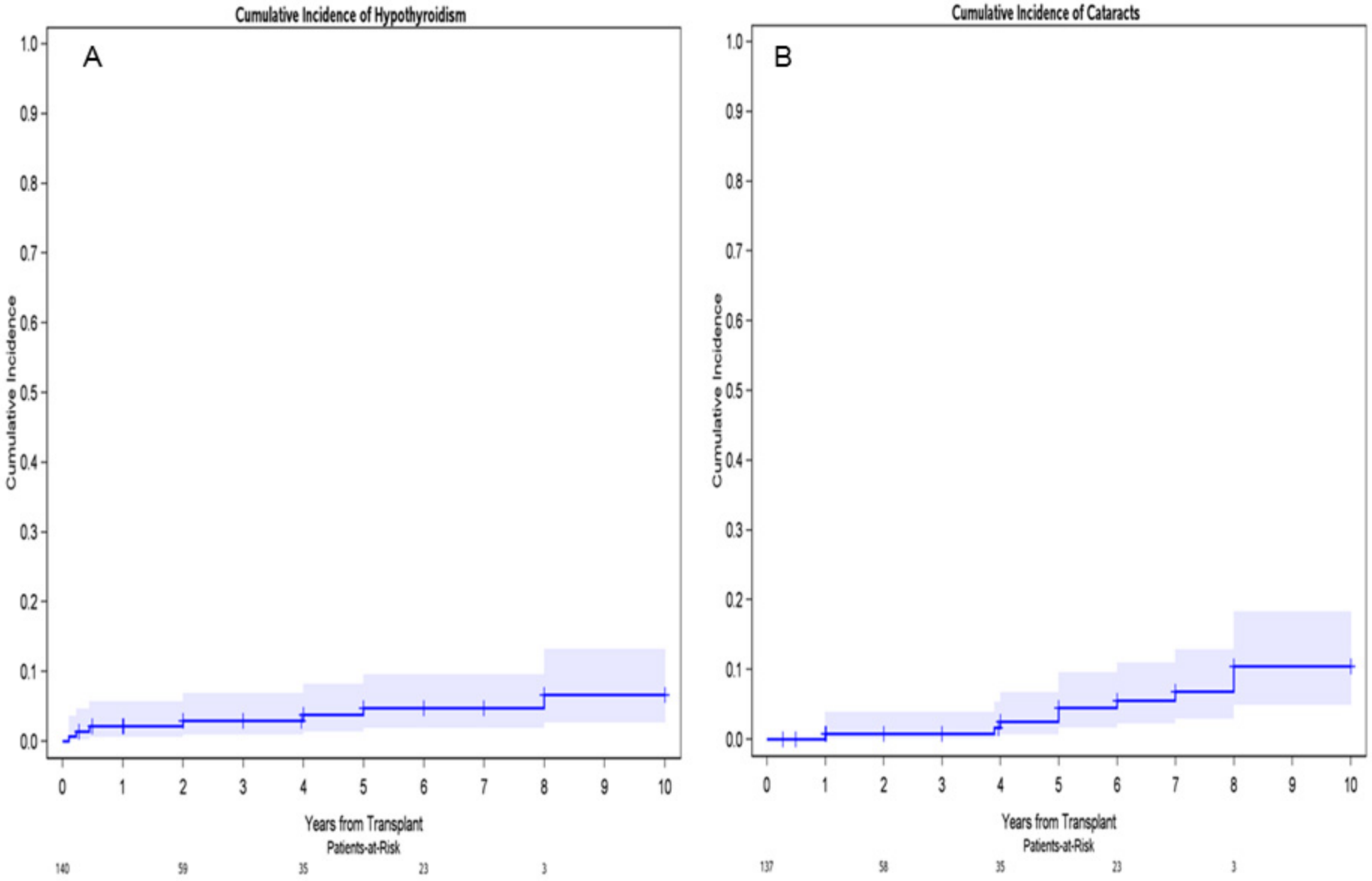

Cumulative Incidence of RP and Infection
B
Mean Lung Dose ≤ 8 Gy
Mean Lung Dose > 8Gy
P = 0.012
Cumulative Incidence
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10
Years from Transplant
Patients-at-Risk
MLD ≤ 8 Gy 115 47 31 21 3
MLD > 8 Gy 22 11 4 2 0

Figure 3


Cumulative Incidence of Hypothyroidism
A
Cumulative Incidence
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10
Years from Transplant
Patients-at-Risk
140 59 35 23 3
Cumulative Incidence of Cataracts
B
Cumulative Incidence
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10
Years from Transplant
Patients-at-Risk
137 58 35 23 3