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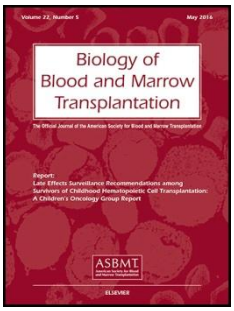

Title: Evolution of Body Composition Following Autologous and Allogeneic Hematopoietic Cell Transplantation: Incidence of Sarcopenia and Association with Clinical Outcomes

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Title Page

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Running Title:	Longitudinal change in body composition following HCT
Article Type:	Regular article

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Highlights

- The authors use CT images to longitudinally assess change in body composition in recipients of HCT.
- Increases in fat mass were observed following both allo-HCT and auto-HCT.
- Significant loss in lean body mass and increased sarcopenia were identified in allo-HCT recipients.

Abstract

Sarcopenia, the loss of muscle mass, has been identified as a potential risk factor for adverse outcomes in hematopoietic cell transplantation (HCT) recipients. However, much remains unknown about change in body composition following HCT. We retrospectively evaluated computed tomography (CT) imaging from 315 lymphoma patients undergoing HCT at our institution between 2000 and 2014. Cross-sectional area of lean muscle, subcutaneous adipose tissue and visceral adipose tissue were measured on CT at the level of the third lumbar vertebral body prior to HCT, 1-year post-HCT, and 2.5 years post-HCT. The incidence of sarcopenia prior to HCT was 47% in the auto-HCT cohort (n=218) and 55% in the allo-HCT cohort (n=97). Older age (OR=1.04, 95%CI 1.01-1.04, p<0.001) and male gender (OR=4.59, 95%CI 1.42-4.93, p<0.001) were associated with sarcopenia prior to HCT. Increasing body mass index (OR=0.78, 95%CI 0.73-0.84, p<0.001) was protective against sarcopenia prior to HCT. A significant decline in total lean body mass (β=1.96, 95%CI 0.79-3.13, p=0.001) and increased sarcopenia incidence (OR=1.72, 95%CI 1.13-2.62, p=0.012) was observed over time for patients in the allo-HCT cohort when compared to the trend in the auto-

HCT cohort. Both auto-HCT and allo-HCT recipients experienced an increase in total body fat mass over time (β=3.75, 95%CI 2.77-4.73, p<0.001). In multivariate analysis of patients undergoing allo-HCT, the presence of sarcopenia on baseline imaging prior to HCT was associated with a lower risk of acute GVHD (OR 0.30, 95%CI 0.09-0.98, p=0.047). In conclusion, we found that total body fat mass increases after both auto-HCT and allo-HCT. Following allo-HCT, total lean body mass significantly decreases corresponding to increased incidence of sarcopenia. Future studies are needed to further characterize changes in body composition in HCT recipients and investigate its impact on HCT outcomes.

Keywords: hematopoietic cell transplantation; late effect; sarcopenia; muscle; adipose tissue; body composition

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Introduction

Recent exploration into the influence of body composition on patient outcomes in oncology has demonstrated that the loss of muscle mass is associated with poor prognosis in patients with solid tumors.[1-3] In the context of hematopoietic cell transplantation (HCT), the development of sarcopenia, the loss of muscle mass, may contribute to adverse outcomes in HCT survivors.[4] Higher mortality rates in HCT survivors compared to the general population have been associated with the development of metabolic syndrome and cardiovascular events.[5] Although studies on the incidence of sarcopenia in HCT recipients are limited, it has been reported in up to 65% of survivors.[6] Given the relationship between body composition and cardiovascular outcomes,[7] the 2016 National Institutes of Health Blood and Marrow Transplant Late Effects Consensus Conference identified studies focusing on sarcopenia as a research priority.[8] Much remains unknown about body composition in patients undergoing autologous (auto-HCT) and allogeneic (allo-HCT) transplant, including its incidence, risk factors, longitudinal changes over time, as well as its impact on post-HCT outcomes.

While body composition in HCT recipients has been previously assessed by dual-energy X-ray absorptiometry (DEXA), computed tomography (CT) imaging offers the advantage of increased accuracy and reproducibility.[9, 10] CT has been established to assess body composition in patients with solid tumors[11-13] as well as hematologic malignancies,[14] but studies addressing the use of CT to assess body composition in

HCT survivors are just starting to emerge.[15] As many patients with lymphoma frequently undergo CT imaging as part of routine care during their treatment course, imaging data are readily available. The purpose of this study was to describe the evolution of body composition following auto-HCT and allo-HCT in patients with lymphoma, and to investigate the association of body composition measurements with outcomes.

Patients and Methods

This study was approved by the institutional review board at the Dana-Farber Harvard Cancer Center. All patients ≥18 year of age with lymphoma who received HCT between 2000 and 2014 at the Massachusetts General Hospital Cancer Center were identified through institutional databases. All lymphoma subtypes were included. Clinical data was extracted from the medical record. To be eligible for the study, patients were required to have CT images at the level of the third lumbar vertebral body level (L3) within 6 months prior to HCT available in the institutional radiology database. If multiple examinations were available, images obtained closest to HCT date were selected for analysis. Patients with suboptimal CT images prior to HCT due to artifact were excluded. Patients receiving more than one auto- or allo-HCT, and those undergoing HCT for indications other than lymphoma were excluded from the study. Eligible patients were divided into two cohorts based on HCT history. The auto-HCT cohort included patients who received high-dose chemotherapy and auto-HCT, but never received allo-HCT. Patients in the allo-HCT cohort received allo-HCT and may have previously received an auto-HCT. There were no restrictions based on conditioning regimen, donor source, graft source, or GVHD prophylactic regimen.

Image analysis

CT images were assessed at 3 time points: baseline (up to 6 months prior to HCT), 1 year post-HCT (±3 months), and 2.5 years post-HCT (±6 months). Measurements of cross-sectional area (in cm2) of lean muscle, subcutaneous fat (SAT), and visceral fat (VAT) were performed on an axial CT image at the level of the L3 vertebral body.[16, 17] Semi-automated threshold-based segmentation was used (OsiriX; Pixmeo, Bernex, Switzerland). Lean muscle was identified with attenuation thresholds set at -29 and +150 Hounsfield units (HU), and fat was identified with attenuation thresholds set at -190 and -30 HU. Serial CT images from a sample patient are shown in **Figure 1**. Skeletal muscle cross-sectional area was normalized for stature and reported as skeletal muscle index in cm^2/m^2. Sarcopenia was defined as an L3 skeletal muscle index of <55 cm^2/m^2 for men and <39 cm^2/m^2 for women, as proposed by international consensus for cancer cachexia.[18] Total lean body mass was estimated as previously described: total lean body mass (kg) = 0.3 x [skeletal muscle at L3 (cm^2)] + 6.06 ($r=0.94$; $p<0.001$, SEE=0.72 kg).[19] Total body fat mass was estimated as previously described: total body fat mass (kg) = 0.042 x [fat tissue at L3 (cm^2)] + 11.2 ($r=0.88$; $p<0.001$, SEE=0.80 kg).[19]

To assess inter- and intra-analyst agreement, 13% of the images were randomly selected and re-analyzed independently 3 months later by a second analyst and by the primary analyst in order to assess intraclass correlation coefficients (ICCs). Excellent inter-analyst agreement (ICCs of 0.988 and 0.991 for muscle area and muscle HU,

0.997 and 0.974 for VAT area and VAT HU, and 0.993 and 0.978 for SAT area and SAT HU) and intra-analyst agreement (ICCs of 0.993 and 0.966 for muscle area and muscle HU, 0.990 and 0.999 for VAT area and VAT HU, and 0.999 and 0.999 for SAT area and SAT HU) was achieved.

Statistical analysis

Descriptive statistics, including means or medians for continuous variables depending on the normality of the data, and proportions for categorical variables were calculated. For all analyses, two-sided p-values <0.05 were considered to be statistically significant. All calculations were made using STATA (version 9; Stata Corp, College Station, Texas, USA).

We computed linear mixed models to characterize trajectories of changes in continuous body composition measurements (sarcopenia, total lean body mass, total body fat mass, SAT, and VAT). Analyses estimated baseline values and rate of change separately for each outcome. Each model was constructed in two steps. Step 1 included a baseline model to estimate intercept and slope random effects for the outcome of interest. In step 2, we added HCT type as a fixed effect variable predicting both outcome of interest and slope of change over time (HCT type X time interaction). To examine longitudinal changes in rates of sarcopenia over time (binary outcome), non-linear mixed effects models with binomial distribution were used.

We constructed multivariable models to identify potential predictors of baseline body composition measurements. Separate models were computed to identify predictors of the various body composition measurements (sarcopenia, total lean body mass, total body fat mass, SAT, or VAT). Predictors that were included in the model were age, gender, race, body mass index (BMI), type of HCT, prior lines of chemotherapy, and the receipt of radiation prior to transplant.

In an exploratory analysis, we used multivariate logistic regression models to assess the associations between baseline sarcopenia, total lean body mass, and total fat mass with acute and chronic GVHD. Separate models were built for each body composition measurement. All models controlled for age, gender, donor source, the use of total body irradiation in HCT conditioning, and GVHD prophylaxis. Acute GVHD was graded according to the Glucksberg criteria.[20] Chronic GVHD was graded according to NIH consensus criteria.[21] We also utilized Cox proportional hazards regression models to explore the association between baseline sarcopenia, total lean body mass, and total fat mass with overall survival in auto-HCT and allo-HCT recipients. Overall survival was defined as the time from date of HCT to date of death, with survivors censored at the time of last contact. For overall survival in auto-HCT recipients, the Cox regression model adjusted for age, gender, diagnosis, and disease status at the time of HCT. For overall survival in allo-HCT recipients, the Cox regression model adjusted for age, gender, diagnosis, disease risk index[22], donor source, and GVHD prophylactic regimen.

Results

Patient and disease characteristics

In total, 569 adult patients with lymphoma who underwent HCT between 2000 and 2014 were identified. Of these, 254 were excluded according to the eligibility criteria listed in Methods (**Figure 2**), leaving 315 patients eligible for evaluation. There were 218 patients in the auto-HCT cohort and 97 patients in the allo-HCT cohort. Patient characteristics are shown in **Table 1**. The median time from pre-HCT imaging to HCT was 1 month (range, 0-5). In the auto-HCT cohort, the number CT images evaluable at 1-year post-HCT was 154 and at 2.5-years post-HCT was 120. In the allo-HCT cohort, the number CT images evaluable at 1-year post-HCT was 61 and at 2.5-years post-HCT was 54.

Incidence of sarcopenia and change of muscle

The incidence of sarcopenia prior to HCT was 47% in the auto-HCT cohort and 55% in the allo-HCT cohort. In multivariate analysis, older age (OR=1.04, 95%CI 1.01-1.04, p<0.001) and male gender (OR=4.59, 95%CI 1.42-4.93, p<0.001) were associated with sarcopenia prior to HCT. Increasing BMI (OR=0.78, 95%CI 0.73-0.84, p<0.001) was protective against sarcopenia prior to HCT. A significant increase in sarcopenia was observed over time for patients in the allo-HCT cohort when compared to the trend in the auto-HCT cohort (OR=1.72, 95%CI 1.08-1.13, p=0.012). For patients in the allo-HCT cohort, the incidence of sarcopenia was 64% at 1 year post-HCT and 75% at 2.5 years post-HCT (**Figure 3**). The incidence of sarcopenia in the auto-HCT cohort remained stable (1 year post-HCT 45%, 2.5 year post-HCT 42%). Similarly, there was a significant decline in total lean body mass over time for recipients of allo-HCT as

compared to patients in the auto-HCT cohort (β=-1.95, 95%CI -0.79 to -3.12, p<0.001) (**Figure 4A**).

Change of adipose tissue

In multivariate analysis of factors associated with baseline adipose tissue measurements, older age (β=2.10, 95%CI 1.55-2.65, p<0.001), male gender (β=79.15, 95%CI 64.17-94.13, p<0.001), increasing BMI (β=11.93, 95%CI 10.56-13.31, p<0.001), and lines of prior therapy (β=7.33, 95%CI 1.35-13.31, p=0.016) were predictive of higher VAT prior to HCT. Non-white or Caucasian race was associated with lower VAT measurements prior to HCT (β=-26.19, 95%CI -50.37 to -2.00, p=0.034). Increasing BMI (β=17.14, 95%CI 15.75-18.52, p<0.001) was predictive of higher SAT prior to HCT. Older age (β=-0.55, 95%CI -1.10 to 0.001, p=0.050) and male gender (β=-41.07, 95%CI -56.11 to -26.04, p<0.001) were associated with lower SAT prior to HCT. A significant increase in total body fat mass was observed overtime for patients in both the auto-HCT and allo-HCT cohorts (β=3.75, 95%CI 2.77-4.73, p<0.01) (**Figure 4B**). There was no significant difference in change in SAT (β=6.28, 95%CI -4.60 to 17.16, p=0.26) or VAT (β=2.22, 95%CI -1.54 to 5.99, p=0.25) indices over time among auto-HCT and allo-HCT patients.

Associations of baseline body composition with clinical outcomes

An exploratory analysis was performed to evaluate for associations between body composition measurements and important clinical outcomes following autologous and allogenic-HCT (**Table 2**). Sarcopenia prior to HCT was protective against acute GVHD

(OR=0.30, 95%CI 0.09-0.98, p=0.047). Associations between other baseline body composition measurements and acute GVHD were not significant. There was no significant association between baseline body composition measurements and chronic GVHD or overall survival among allogenic HCT recipients. Higher baseline total lean body mass was associated with lower risk of mortality (OR=0.95, 95%CI 0.91-0.99, P = 0.016) in the autologous HCT cohort. Baseline sarcopenia and total body fat mass were not associated with mortality in autologous HCT recipients.

Discussion

This is one of the first studies to use CT imaging to characterize body composition in patients following HCT. Furthermore, we are the first to use this imaging method to assess longitudinal change in body composition in survivors after auto- and allo-HCT. We report a high incidence of sarcopenia prior to HCT, in both auto-HCT and allo-HCT cohorts. We observed a significant loss of total lean body mass and increased rate of sarcopenia incidence in patients who underwent allo-HCT. Additionally, we discovered a significant increase in total body fat mass for patients in both the auto-HCT and allo-HCT cohorts.

These trends in body composition following HCT are unique and differ from what has been observed in lymphoma patients following upfront chemotherapy. In a retrospective analysis of 342 patients with diffuse large B-cell lymphoma following initial treatment with CHOP-based chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) that compared CT measurements prior to therapy and at 24 months after

treatment, muscle area decreased during treatment, but returned to baseline 24 months after treatment. Both SAT and VAT increased by 21% by 24 months after treatment.[14] In our analysis of patients undergoing HCT, we observed a similar trend in adipose tissue, with total fat mass increasing over time in both auto-HCT and allo-HCT cohorts. While lean body mass was stable in patients in the auto-HCT cohort, a significant decrease was observed in patients receiving allo-HCT. It remains unclear how body composition is impacted by HCT as compared to previous therapy or other clinical factors. There may be a compound effect of previous auto-HCT in the allo-HCT cohort, but we believe that the trends observed in the allo-HCT cohort are likely driven by chronic GVHD and its treatments (immunosuppressive therapy and steroid exposure). It is also important to study how these changes, such as increased total body fat mass, may impact long-term health outcomes for HCT survivors.

We are also the first to report an association between the presence of sarcopenia prior to transplant and important clinical outcomes. Specifically, the association between sarcopenia and a lower risk for acute GVHD is novel. The reason for this association is unclear and its clinical significance is undetermined. However, we note this in the context of studies that have investigated the impact of obesity-related inflammation on the risk for GVHD.[23] While large retrospective studies evaluating obesity by body mass index (BMI) have not demonstrated a clear association between obesity and GVHD, these studies have not evaluated body composition.[24-26] We did not observe an association between total body fat mass and GVHD, but we believe that future

investigations on obesity in this setting may benefit from more detailed characterization of body composition using CT or magnetic resonance imaging.

Our findings are consistent with previous studies that evaluated body composition in HCT survivors with DEXA imaging and noted loss of muscle mass and increase in adipose tissue.[6, 27, 28] A retrospective analysis of body composition measurements by DEXA in 82 allo-HCT recipients showed that patients were significantly more likely to have low lean body mass index (LBMI) following HCT as compared to healthy volunteers. Only 38% of patients were able to regain their pre-transplant muscle level, and low LBMI was significantly associated with steroid treatment, chronic GVHD, and decreased performance status. Body fat increased above baseline measurements by 2-6 years post-HCT.[29] Similarly, in a cross-sectional study using DEXA, 54 pediatric survivors of allo-HCT were shown to have significantly lower lean body mass and greater fat mass compared to healthy reference participants.[30]

There are a number of limitations to our study, outside of the relatively small number of patients and retrospective nature. First, our data set is subject to selection bias. A significant number of patients were excluded from our study because pre-HCT CT images were not available at our institution. However, this reflects the large number of patients that are referred for HCT from community practices and thus, we believe that our study results are applicable to lymphoma patients undergoing HCT. However, as patients were not censored at the time of relapse, patients with relapsed disease may be overrepresented in post-HCT imaging and imaging findings may be influenced by

subsequent therapies. Second, additional information that was not available in this data set would be of interest for this analysis, including CT images from the time of diagnosis, HCT-specific comorbidity index and evaluation of muscle strength and function. Third, we believe it would be important to evaluate body composition at time points later than 2.5 years post-HCT, which would require a larger number of patients with longer follow up. Fourth, we limited this study to patients with lymphoma given the routine use of CT imaging in disease evaluation, but an expanded study should include evaluation of other disease types. Finally, a comprehensive intake of cardiovascular and endocrine factors that can contribute to obesity and change in body composition would be also help characterize the impact of patient specific factors.

Future studies are needed to better characterize the clinical factors which impact changes in body composition and to further investigate the association between these changes and HCT-related outcomes. With the increasing number of HCT survivors, we must better understand physiologic changes in HCT recipients so that we can design interventions to reduce risk factors for adverse outcomes in survivors.

References

1. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31: 1539-1547.
2. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA, et al. Loss of Muscle Mass During Chemotherapy Is Predictive for Poor Survival of Patients With Metastatic Colorectal Cancer. J Clin Oncol. 2016;34: 1339-1344.
3. Tamandl D, Paireder M, Asari R, Baltzer PA, Schoppmann SF, Ba-Ssalamah A. Markers of sarcopenia quantified by computed tomography predict adverse long-term outcome in patients with resected oesophageal or gastro-oesophageal junction cancer. Eur Radiol. 2016;26: 1359-1367.
4. DeFilipp Z, Duarte RF, Snowden JA, et al. Metabolic Syndrome and Cardiovascular Disease after Hematopoietic Cell Transplantation: Screening and Preventive Practice Recommendations from the CIBMTR and EBMT. Biol Blood Marrow Transplant. 2016;22: 1493-1503.
5. Baker KS, Chow E, Steinberger J. Metabolic syndrome and cardiovascular risk in survivors after hematopoietic cell transplantation. Bone Marrow Transplant. 2012;47: 619-625.
6. Greenfield DM, Boland E, Ezaydi Y, Ross RJ, Ahmedzai SH, Snowden JA. Endocrine, metabolic, nutritional and body composition abnormalities are common in advanced intensively-treated (transplanted) multiple myeloma. Bone Marrow Transplant. 2014;49: 907-912.
7. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Sarcopenic obesity and risk of cardiovascular disease and mortality: a population-based cohort study of older men. J Am Geriatr Soc. 2014;62: 253-260.
8. Armenian SH, Chemaitilly W, Chen M, et al. National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: Consensus Recommendations for Cardiovascular Disease and Associated Risk Factors. Biol Blood Marrow Transplant. 2016.
9. Silver HJ, Welch EB, Avison MJ, Niswender KD. Imaging body composition in obesity and weight loss: challenges and opportunities. Diabetes Metab Syndr Obes. 2010;3: 337-347.
10. Yip C, Dinkel C, Mahajan A, Siddique M, Cook GJ, Goh V. Imaging body composition in cancer patients: visceral obesity, sarcopenia and sarcopenic obesity may impact on clinical outcome. Insights Imaging. 2015;6: 489-497.
11. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res. 2009;15: 6973-6979.
12. Gibson DJ, Burden ST, Strauss BJ, Todd C, Lal S. The role of computed tomography in evaluating body composition and the influence of reduced muscle mass on clinical outcome in abdominal malignancy: a systematic review. Eur J Clin Nutr. 2015;69: 1079-1086.
13. Nipp RD, Fuchs G, El-Jawahri A, et al. Sarcopenia Is Associated with Quality of Life and Depression in Patients with Advanced Cancer. Oncologist. 2017.

14. Xiao DY, Luo S, O'Brian K, et al. Longitudinal Body Composition Changes in Diffuse Large B-cell Lymphoma Survivors: A Retrospective Cohort Study of United States Veterans. J Natl Cancer Inst. 2016;108.
15. Chughtai K, Song Y, Zhang P, et al. Analytic morphomics: a novel CT imaging approach to quantify adipose tissue and muscle composition in allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2016;51: 446-450.
16. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. Journal of applied physiology. 1998;85: 115-122.
17. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. Journal of applied physiology. 2004;97: 2333-2338.
18. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12: 489-495.
19. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Applied Physiology, Nutrition, and Metabolism. 2008;33: 997-1006.
20. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation. 1974;18: 295-304.
21. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11: 945-956.
22. Armand P, Gibson CJ, Cutler C, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. Blood. 2012;120: 905-913.
23. Wu D, Dawson NA, Levings MK. Obesity-Associated Adipose Tissue Inflammation and Transplantation. Am J Transplant. 2016;16: 743-750.
24. Fuji S, Kim SW, Yoshimura K, et al. Possible association between obesity and posttransplantation complications including infectious diseases and acute graft-versus-host disease. Biol Blood Marrow Transplant. 2009;15: 73-82.
25. Fuji S, Takano K, Mori T, et al. Impact of pretransplant body mass index on the clinical outcome after allogeneic hematopoietic SCT. Bone Marrow Transplant. 2014;49: 1505-1512.
26. Nikolousis E, Nagra S, Paneesha S, et al. Allogeneic transplant outcomes are not affected by body mass index (BMI) in patients with haematological malignancies. Ann Hematol. 2010;89: 1141-1145.
27. Frisk P, Rossner SM, Norgren S, Arvidson J, Gustafsson J. Glucose metabolism and body composition in young adults treated with TBI during childhood. Bone Marrow Transplant. 2011;46: 1303-1308.
28. Slater ME, Steinberger J, Ross JA, et al. Physical Activity, Fitness, and Cardiometabolic Risk Factors in Adult Survivors of Childhood Cancer with a History of Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2015;21: 1278-1283.

29. Kyle UG, Chalandon Y, Miralbell R, et al. Longitudinal follow-up of body composition in hematopoietic stem cell transplant patients. Bone Marrow Transplant. 2005;35: 1171-1177.
30. Mostoufi-Moab S, Ginsberg JP, Bunin N, et al. Body composition abnormalities in long-term survivors of pediatric hematopoietic stem cell transplantation. J Pediatr. 2012;160: 122-128.

Figure Legend

Figure 1.

Serial axial computed tomography images at the level of the third lumbar veterbral body from a sample patient demonstrate identification of muscle, visceral adipose tissue, and subcutaneous adipose tissue prior to and at 1 and 2.5 years following hematopoietic cell transplantation.

HCT: hematopoietic cell transplantation; *SAT*: subcutaneous adipose tissue; *VAT*: visceral adipose tissue;

Figure 2.

Study flow diagram

Figure 3.

Incidence of sarcopenia in patients with lymphoma before and following autologous hematopoietic cell transplantation (auto-HCT) and allogeneic hematopoietic cell transplantation (allo-HCT).

Figure 4.

Change in A) total lean body mass and B) total body fat mass in patients with lymphoma following hematopoietic cell transplantation.

SE: standard error;

Table 1. Patient and disease characteristics

	Auto-HCT	Allo-HCT
Number of patients, n	218	97
Median age at transplant, range	56 (19-77)	53 (18-69)
Gender, n (%)		
Female	90 (41)	37 (38)
Male	128 (59)	60 (62)
Race		
White or Caucasian	195 (89)	81 (84)
Black or African American	4 (2)	5 (5)
Asian	4 (2)	5 (5)
Hispanic or Latino or Other	15 (7)	6 (6)
Body mass index		
Underweight (<18.5)	7 (3)	2 (2)
Normal (18.5-24.9)	54 (25)	33 (34)
Overweight (25-29.9)	88 (40)	35 (36)
Obese (>30)	59 (27)	16 (16)
Not available	10 (5)	11(11)
Lymphoma subtype, n (%)		
NHL, B-cell	159 (73)	65 (67)
NHL, T-cell	45 (21)	19 (20)
Hodgkin	14 (6)	13 (13)
Lines of treatment prior to HCT, n (%)		
1	54 (25)	7 (7)
2-3	144 (66)	33 (34)
≥4	20 (9)	57 (59)
Radiation therapy prior to HCT, n (%)		
Yes	58 (27)	27 (28)
No	160 (73)	70 (72)
Previous auto-HCT, n (%)		
Yes	n/a	56 (58)
No	n/a	41 (42)

Abbreviations:

Allo-HCT: allogeneic hematopoietic cell transplantation; *Auto-HCT*: autologous hematopoietic cell transplantation; *NHL*: non-Hodgkin lymphoma; *HCT*: hematopoietic cell transplantation;

Table 2. Association between baseline body composition and clinical outcomes after autologous and allogeneic HCT.

Grade III-IV acute GVHD	**OR**	**95%CI**	**p-value**
Sarcopenia	0.29	0.10-0.83	***0.02***
Total lean body mass	1.03	0.98-1.07	0.27
Total body fat mass	0.92	0.80-1.06	0.25
Moderate-severe chronic GVHD	**OR**	**95%CI**	**p-value**
Sarcopenia	2.11	0.91-4.91	0.08
Total lean body mass	0.99	0.95-1.02	0.46
Total body fat mass	0.96	0.87-1.08	0.54
Mortality	**OR**	**95%CI**	**p-value**
Sarcopenia	1.63	1.02-2.61	***0.04***
Total lean body mass	1.00	0.97-1.02	0.67
Total body fat mass	0.97	0.92-1.02	0.29

Abbreviations:

GVHD: graft-versus-host disease; HCT: hematopoietic cell transplantation; OS: overall survival

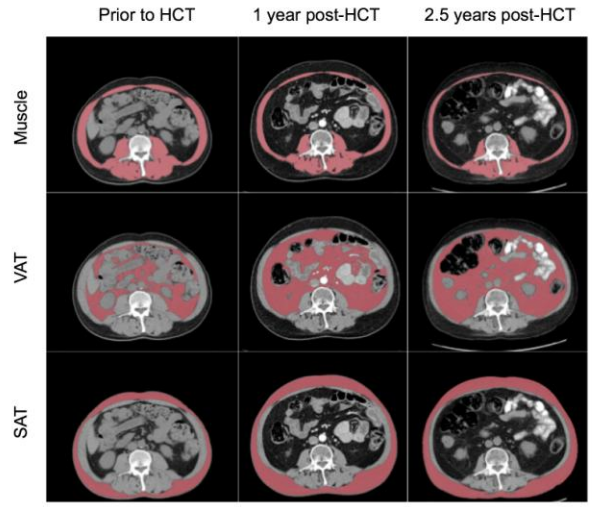

Figure 1.tiff

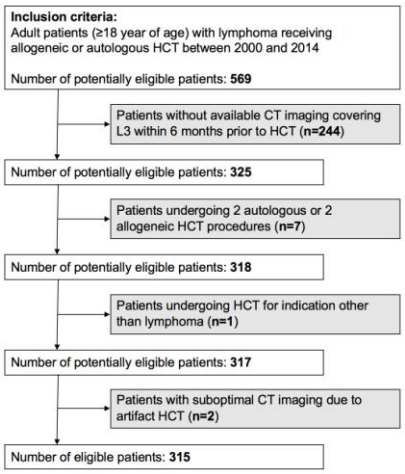

Figure 2.tiff

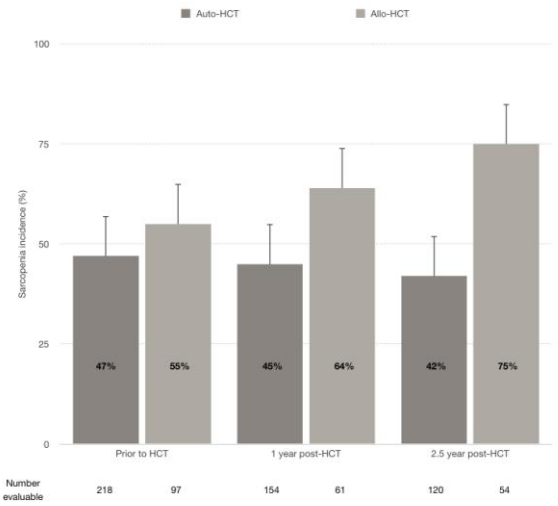

Figure 3.tiff

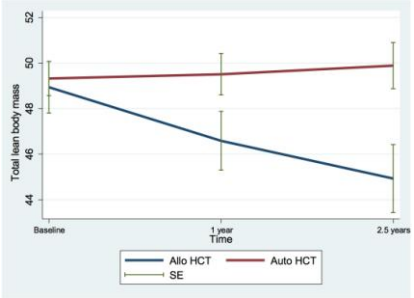

Figure 4A.tiff

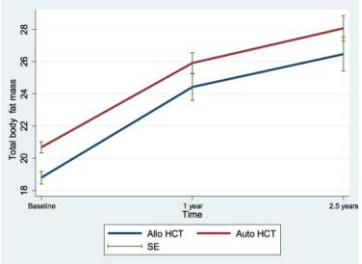

Figure 4B.tiff