Received: 23 March 2022 | Revised: 3 August 2022 | Accepted: 5 August 2022

DOI: 10.1002/cncr.34596

ORIGINAL ARTICLE

Body composition and mortality in men receiving prostate radiotherapy: A pooled analysis of NRG/RTOG 9406 and NRG/RTOG 0126

Andrew M. McDonald MD[1,2] | Lyudmila DeMora MS[3,4] | Eddy S. Yang MD, PhD[1] | John M. Hoyle MSBME[5] | Andrew Lenzie BChE[5] | Grant R. Williams MD[2] | Jeff M. Michalski MD[6] | Don Yee MD, FRCP(C)[7] | Jean-Paul Bahary MD[8] | Robert B. Den MD[9] | Mack Roach III MD[10] | Robert Dess MD[11] | Mark V. Mishra MD[12] | Richard K. Valicenti MD[13] | Harold Y. Lau MD[14] | Samuel R. Marcrom MD[1] | Luis Souhami MD[15] | Lucas C. Mendez MD[16] | Yuhchyau Chen MD[17] | Desiree E. Doncals MD[18] | Stephanie L. Pugh PhD[3,4] | Felix Y. Feng MD[19] | Howard M. Sandler MD[20]

[1]Department of Radiation Oncology, University of Alabama at Birmingham O'Neal Comprehensive Cancer Center, Birmingham, Alabama, USA

[2]Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, Birmingham, Alabama, USA

[3]Statistics and Data Management Department, NRG Oncology, Philadelphia, Pennsylvania, USA

[4]Statistical and Data Management Department, American College of Radiology, Philadelphia, Pennsylvania, USA

[5]School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

[6]Department of Radiation Oncology, Washington University School of Medicine, Saint Louis, Missouri, USA

[7]Radiation Oncology Department of Radiation Oncology, Edmonton Cross Cancer Institute, Edmonton, Alberta, Canada

[8]Department of Radio Oncology, CHUM - Centre Hospitalier de l'Universite de Montreal, Montreal, Quebec, Canada

[9]Radiation Oncology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA

[10]Department of Radiation Oncology, UCSF Medical Center-Mount Zion, San Francisco, California, USA

[11]Department of Radiation Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan, USA

[12]Department of Radiation Oncology, University of Maryland/Greenebaum Cancer Center, Baltimore, Maryland, USA

[13]Department of Radiation Oncology, University of California Davis, Sacramento, California, USA

[14]Department of Oncology, Tom Baker Cancer Centre, Calgary, Alberta, Canada

[15]The Research Institute, McGill University Health Centre (MUHC), Montreal, Quebec, Canada

[16]Department of Oncology, London Regional Cancer Program, London, Ontario, Canada

[17]Department of Radiation Oncology, University of Rochester, Rochester, New York, USA

[18]Department of Radiation Oncology, Summa Health System - Akron Campus, Akron, Ohio, USA

[19]Department of Radiation Oncology, UCSF Medical Center-Mission Bay, San Francisco, California, USA

[20]Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, California, USA

See editorial on pages 668–70, this issue.

The trials are registered at ClinicalTrials.gov (NCT00002602 and NCT00033631).

 © 2022 American Cancer Society.

Correspondence
Andrew M. McDonald, University of Alabama at Birmingham O'Neal Comprehensive Cancer Center, 1700 Sixth Ave S, Birmingham, AL 35233 USA.
Email: ammcdonald@uabmc.edu

Funding information
National Cancer Institute, Grant/Award Number: U10CA180868, U10CA180822, UG1CA189867, U24CA180803; Post-Finasteride Syndrome Foundation; Varian Medical Systems; American Society for Radiation Oncology

Abstract

Purpose: To validate the association between body composition and mortality in men treated with radiation for localized prostate cancer (PCa). Secondarily, to integrate body composition as a factor to classify patients by risk of all-cause mortality.

Materials and Methods: Participants of NRG/Radiation Therapy Oncology Group (RTOG) 9406 and NRG/RTOG 0126 with archived computed tomography were included. Muscle mass and muscle density were estimated by measuring the area and attenuation of the psoas muscles on a single slice at L4–L5. Bone density was estimated by measuring the attenuation of the vertebral body at mid-L5. Survival analyses, including Cox proportional hazards models, assessed the relationship between body composition and mortality. Recursive partitioning analysis (RPA) was used to create a classification tree to classify participants by risk of death.

Results: Data from 2066 men were included in this study. In the final multivariable model, psoas area, comorbidity score, baseline prostate serum antigen, and age were significantly associated with survival. The RPA yielded a classification tree with four prognostic groups determined by age, comorbidity, and psoas area. Notably, the classification among older (≥70 years) men into prognostic groups was determined by psoas area.

Conclusions: This study strongly supports that body composition is related to mortality in men with localized PCa. The inclusion of psoas area in the RPA classification tree suggests that body composition provides additive information to age and comorbidity status for mortality prediction, particularly among older men. More research is needed to determine the clinical impact of body composition on prognostic models in men with PCa.

KEYWORDS
anthropometry, body composition, clinical trials, mortality, muscle mass, prostate cancer

INTRODUCTION

Modern treatment for localized prostate cancer (PCa) is highly effective, and current 10-year PCa-specific mortality rates are less than 10% even when high-risk features are present.[1–6] Overall survival (OS) among men with localized PCa is instead driven by competing causes of death, which has important ramifications for both patient care and clinical trial design.[7–10] Tools to predict the risk of mortality from competing risks have an important role for research and clinical care, but ongoing refinement of risk prediction models is needed to improve their accuracy.

Body composition is a biomarker of overall health that may provide additional prognostic information to improve current risk prediction models for mortality among men with PCa. Prior research investigating the relationship between body mass index (BMI) and mortality has been mixed, particularly when accounting for medical comorbidities.[11–13] More focused measurements of body composition such as fat mass, muscle mass, and bone density can be used as an alternative to BMI and conventional anthropometry. Although a variety of methods can be used to assess body composition, cross-sectional imaging is increasingly used because of the advantage of being able to assess adipose, muscle, and bone simultaneously using imaging already obtained as part of routine care. A prior study reported that body composition measurement using radiotherapy computed tomography (CT) simulation scans was feasible and provided additional information to improve non-PCa mortality risk prediction, but the study was limited to a single institution and has not been validated.[14] The primary purpose of the present study was to further investigate whether measurement of body composition provides additional information to improve mortality risk assessment for men with PCa who participated in NRG/Radiation Therapy Oncology Group (RTOG) clinical trials.

Body composition measurement using cross-sectional imaging also enables post hoc measurements using archived clinical trial data

to explore if body composition modulates the effects of treatment variables on outcomes. One area of ongoing debate is whether androgen deprivation therapy (ADT) increases mortality risk for some men.[15–19] Because ADT is known to have significant detrimental effects on male body composition, we also sought to explore whether men who have an unfavorable body composition phenotype experience worse survival outcomes when receiving ADT.[20,21]

METHODS AND MATERIALS

Inclusion criteria and regulatory approval

This study included all participants of NRG/RTOG 9406 and NRG/RTOG 0126 who had archived CT scans that extended cranially to include the L4–L5 interface and were without significant artifact. The full details of these two clinical trials have been previously published.[5,22] NRG/RTOG 9406 enrolled men who had T1–T3 PCa and were assigned to one of five radiation dose levels; neoadjuvant ADT for up to 6 months was allowed. NRG/RTOG 0126 enrolled men with intermediate-risk PCa and were assigned to one of two radiation dose levels; no ADT was allowed. The present study was approved by the University of Alabama at Birmingham institutional review board.

Body composition measurement

CT analysis was performed using MIM software (MIM Software Inc, Cleveland, Ohio, USA). Estimates of muscle mass, muscle density, bone density, and subcutaneous adipose density were calculated. The cross-sectional areas of all skeletal muscle at the L4–L5 interface, as well as the area of the paired psoas muscles, were used as surrogates for total body muscle mass. The cross-sectional area of skeletal muscle at the L4–L5 interface has previously been shown to have very high concordance with total body lean mass, and psoas area has also strongly been associated with survival outcomes in a number of populations.[23,24] Total skeletal muscle and the paired psoas muscles were separately segmented on a single slice, postprocessed to include only those voxels with a Hounsfield unit (HU) between −29 and 150 to exclude fatty infiltration, and area (cm^2) recorded (Figure S1). The CT attenuation of the paired psoas muscles was calculated on the single slice at the L4–L5 interface as a marker of myosteatosis.[25]

The CT attenuation of the trabecular bone of the L5 vertebral body was used a surrogate for bone mineral density and has previously been shown to have high concordance with bone mineral density assessed by dual x-ray absorptiometry.[26] The trabecular bone of the vertebral body was segmented at the slice bisecting mid-L5, with care taken to avoid any abnormalities such as bone islands or vascular channels, and the mean HU of the resulting region of interest was recorded.

Subcutaneous adipose tissue density is a measure of fat quality that has previously been found to be associated with all-cause mortality in two large population registry studies.[27] In our study, we measured subcutaneous adipose tissue density on a single slice at the L4–L5 interface. The adipose tissue outside of the abdominal cavity was segmented and postprocessed to include only those voxels with an HU between −195 and −45, and the mean HU of the resulting region of interest was recorded.

End points and statistical methods

Body composition measurements were analyzed as continuous and categorical variables. Unadjusted psoas and skeletal muscle areas were used for analysis because patient height was not available. Psoas area was categorized into tertiles (<25.2 cm^2, 25.2 to <29.9 cm^2, and ≥29.9 cm^2), as was psoas density (<35.6 HU, 35.6 to <46.9 HU, ≥46.9 HU). L5 vertebral radiodensity was categorized into three intervals (<105 HU, 105 to <150 HU, ≥150 HU), which have been previously used.[26,28] Adipose radiodensity was categorized into four intervals (<−104 HU, −104 to <−99.5 HU, −99.5 to <−95 HU, ≥−95 HU).[29] Comorbidity information was abstracted from trial registration forms and comorbidity score was obtained by assigning 1 point for the presence of each of 14 problems listed (Tables S1 and S2).

Between-group differences were tested using the Kruskal–Wallis test for continuous variables and χ^2 test for categorical variables. OS was measured from randomization to the date of death or censored at the last known follow-up for alive patients. OS was estimated using the Kaplan–Meier method; between-group differences were tested using the log-rank test. PCa-specific mortality (PCSM) was measured from the date of randomization to the date of death from PCa or study treatment (determined by the institution). Patients who died without an event for PCSM were treated as a competing risk and alive patients were censored. Time to PCSM was estimated using cumulative incidence with between group differences tested using Gray's test. Freedom from biochemical failure (FFBF) was assessed from randomization to the date of biochemical failure using the RTOG-Phoenix definition.[30] Cox proportional hazards models for OS, and cause-specific Cox proportional hazards models for time to PCSM and biochemical failure, were used to obtain unadjusted and adjusted hazard ratios (HRs) and 95% CIs. Correlations between the body composition variables, to avoid collinearity in the models, was assessed using Pearson correlation coefficients and variance inflation factor. Adjusted models also assessed the impact of variables of interest while adjusting for other possible confounders, such as age, comorbidity status, and induction ADT. A final multivariable model included body composition variables that were significant in adjusted models, after assessing for collinearity. Recursive partitioning analysis (RPA), using the R package rpart, was used to create a classification tree based on risk of death.[31] All variables from the final multivariable model were included in the RPA to build the

TABLE 1 Demographic and disease characteristics

	RTOG 0126 70.2 Gy (n = 605)	RTOG 0126 79.2 Gy (n = 597)	RTOG 9406 (n = 864)	Total (n = 2066)	p[a]
Age					.001
Median	71	71	69	70	
Min–max	33–86	49–87	41–85	33–87	
Q1–Q3	64–74	65–74	64–73	64–74	
Race[b]	White vs. Black/African American vs. other				<.001
American Indian or Alaskan Native	2 (0.3%)	4 (0.7%)	2 (0.2%)	8 (0.4%)	
Asian	6 (1.0%)	7 (1.2%)	0 (0.0%)	13 (0.6%)	
Black or African American	69 (11.4%)	78 (13.1%)	142 (16.4%)	289 (14.0%)	
Native Hawaiian or Other Pacific Islander	0 (0.0%)	1 (0.2%)	10 (1.2%)	11 (0.5%)	
White	515 (85.1%)	492 (82.4%)	642 (74.3%)	1649 (79.8%)	
More than one race	2 (0.3%)	1 (0.2%)	0 (0.0%)	3 (0.1%)	
Other	0 (0.0%)	0 (0.0%)	10 (1.2%)	10 (0.5%)	
Unknown	11 (1.8%)	14 (2.3%)	58 (6.7%)	83 (4.0%)	
Ethnicity	Not Hispanic or Latino vs. Hispanic or Latino/other				.054
Hispanic or Latino	19 (3.1%)	19 (3.2%)	57 (6.6%)	95 (4.6%)	
Not Hispanic or Latino	545 (90.1%)	543 (91.0%)	807 (93.4%)	1895 (91.7%)	
Unknown	41 (6.8%)	35 (5.9%)	0 (0.0%)	76 (3.7%)	
Comorbidity score[c]	(n = 602)	(n = 596)	(n = 864)	(n = 2062)	<.001
0	293 (48.7%)	275 (46.1%)	525 (60.8%)	1093 (53.0%)	
1–2	274 (45.5%)	291 (48.8%)	337 (39.0%)	902 (43.7%)	
3–5	35 (5.8%)	30 (5.0%)	2 (0.2%)	67 (3.2%)	
Gleason score	(n = 605)	(n = 597)	(n = 863)	(n = 2065)	<.001
2–6	101 (16.7%)	102 (17.1%)	484 (56.1%)	687 (33.3%)	
7	504 (83.3%)	495 (82.9%)	272 (31.5%)	1271 (61.5%)	
8–10	0 (0.0%)	0 (0.0%)	107 (12.4%)	107 (5.2%)	
PSA	(n = 605)	(n = 597)	(n = 863)	(n = 2065)	<.001
Median	7.8	7.53	8.4	7.9	
Min–max	0.1–19.9	0.3–19.7	0.1–69.5	0.1–69.5	
Q1–Q3	5.41–10.78	5.26–10.9	5.6–12.8	5.4–11.34	
Induction ADT			(n = 864)	(n = 864)	NA
No	–	–	545 (63.1%)	545 (63.1%)	
Yes	–	–	319 (36.9%)	319 (36.9%)	
Weight			(n = 815)	(n = 815)	NA
Median	–	–	85.3	85.3	
Min–max	–	–	53.1–188.3	53.1–188.3	
Q1–Q3	–	–	76.4–95	76.4–95	

Abbreviations: ADT, androgen deprivation therapy; NA, not available; PSA, prostate-specific antigen; RTOG, Radiation Therapy Oncology Group

[a]Kruskal–Wallis test for continuous variables and χ^2 test for categorical variables.

[b]In NRG/RTOG 9406 race and ethnicity were collected as one variable; patients reported as "Hispanic" are displayed in this table under "ethnicity" and are marked as "unknown" under "race."

[c]Four patients in NRG/RTOG 0126 were missing the comorbidity form and do not have a calculated comorbidity score.

TABLE 2 Summary of body composition assessment

	RTOG 0126 70.2 Gy (n = 605)	RTOG 0126 79.2 Gy (n = 597)	RTOG 9406 (n = 864)	Total (n = 2066)	p[a]
Psoas area					.249
Median	28.12	27.57	27.58	27.69	
Min–max	12.98–52.3	10.23–44.93	9.48–57.97	9.48–57.97	
Q1–Q3	24–31.62	24.37–31.4	23.235–31.16	23.8–31.34	
Psoas area (cat.)					.262
<25.2	191 (31.6%)	187 (31.3%)	304 (35.2%)	682 (33.0%)	
25.2–<29.9	201 (33.2%)	215 (36.0%)	269 (31.1%)	685 (33.2%)	
≥29.9	213 (35.2%)	195 (32.7%)	291 (33.7%)	699 (33.8%)	
SM area					<.001
Median	142.64	140.67	135.35	139.015	
Min–max	67.96–240.2	67.88–232.3	57.9–281.51	57.9–281.51	
Q1–Q3	123.67–161.1	122.5–156.67	116.09–153.19	120.24–156.67	
Bone HU (cont.)					.093
Median	146.76	150.82	155.22	151.36	
Min–max	30.83–429.6	17.11–687.43	14.36–418.88	14.36–687.43	
Q1–Q3	119.11–183.93	114.74–191.7	121.59–189.025	119.34–188.63	
Bone HU (cat.)					.009
<105	102 (16.9%)	107 (17.9%)	105 (12.2%)	314 (15.2%)	
105–<150	216 (35.7%)	189 (31.7%)	296 (34.3%)	701 (33.9%)	
≥150	287 (47.4%)	301 (50.4%)	463 (53.6%)	1051 (50.9%)	
Adipose HU (cont.)					<.001
Median	−101.45	−102.41	−98.885	−100.96	
Min - Max	−145.87 to −57.5	−139.63 to −62.82	−158.65 to −55.2	−158.65 to −55.2	
Q1–Q3	−112.77 to −95.8	−114.23 to −97.25	−108.11 to −92.995	−110.54 to −94.85	
Adipose HU (cat.)					<.001
<−104	244 (40.3%)	261 (43.7%)	298 (34.5%)	803 (38.9%)	
−104 to <−99.5	121 (20.0%)	117 (19.6%)	115 (13.3%)	353 (17.1%)	
−99.5 to <−95	109 (18.0%)	108 (18.1%)	167 (19.3%)	384 (18.6%)	
≥−95	131 (21.7%)	111 (18.6%)	284 (32.9%)	526 (25.5%)	
Psoas HU (cont.)	(n = 588)	(n = 582)	(n = 850)	(n = 2020)	<.001
Median	41.22	40.525	44.155	42.555	
Min–max	−2.05 to 105.7	1.41–108.7	2.42–92.65	−2.05 to 108.7	
Q1–Q3	28.755–48.835	27.58–48.45	35.08–50.66	31.295–49.375	
Psoas HU (cat.)	(n = 588)	(n = 582)	(n = 850)	(n = 2020)	<.001
<35.6	220 (37.4%)	225 (38.7%)	219 (25.8%)	664 (32.9%)	
35.6–<46.9	190 (32.3%)	181 (31.1%)	300 (35.3%)	671 (33.2%)	
≥46.9	178 (30.3%)	176 (30.2%)	331 (38.9%)	685 (33.9%)	

Abbreviations: cat., categorical; cont., continuous; HU, Hounsfield unit; RTOG, Radiation Therapy Oncology Group; SM, skeletal muscle.

[a]Kruskal–Wallis test for continuous variables and χ^2 test for categorical variables.

classification tree. The classification tree was built using NRG/RTOG 0126 data and validated, using Cox proportional hazards models, in NRG/RTOG 9406 data.

RESULTS

Patient characteristics

Of the 2616 men enrolled on the NRG/RTOG 9406 and NRG/RTOG 0126 clinical trials, 2066 (79.0%) had archived CT scans available that were suitable for body composition assessment and were included in this study. Demographic and disease characteristics are presented in Table 1. The summary statistics of the body composition analysis is presented as Table 2. Patients on NRG/RTOG 9406, compared with the NRG/RTOG 0126 70.2-Gy arm and the NRG/RTOG 0126 79.2-Gy arm had lower skeletal muscle area and higher adipose tissue density. NRG/RTOG 9406, compared with the NRG/RTOG 0126 70.2-Gy arm and the NRG/RTOG 0126 79.2-Gy arm, had fewer patients with vertebral body density <105 HU. The correlation matrix of body composition variables is presented as Table S3.

Survival outcomes

A total of 539 deaths were recorded in the NRG/RTOG 0126 cohort and 307 deaths were recorded in the NRG/RTOG 9406 cohort. Cause of death was related to PCa for 68 (8%) men, treatment complications for one (0.1%) man, non-PCa causes for 510 (60.3%) men, and unknown causes for 267 (31.6%) men (Table S4).

Higher psoas area was significantly associated with improved survival in both the unadjusted and adjusted models (HR, 0.770 [95% CI, 0.656–0.904] for 25.2–29.9 cm^2 vs. <25.2 cm^2, $p = .001$ and HR, 0.698 [95% CI, 0.587–0.829] for ≥29.9 cm^2 vs. <25.2 cm^2, $p < .001$ after adjusting for patient characteristics). The highest category of vertebral body density was associated with improved survival when compared with the lowest category (HR, 0.788 [95% CI, 0.653–0.951] for ≥150 HU vs. <105 HU, $p = .013$). Categorical psoas density, skeletal muscle area, and subcutaneous adipose density were not significantly associated for survival in the adjusted models. Figure 1 presents the Kaplan–Meier survival estimates for the study cohort stratified by psoas area, vertebral body density, and adipose density.

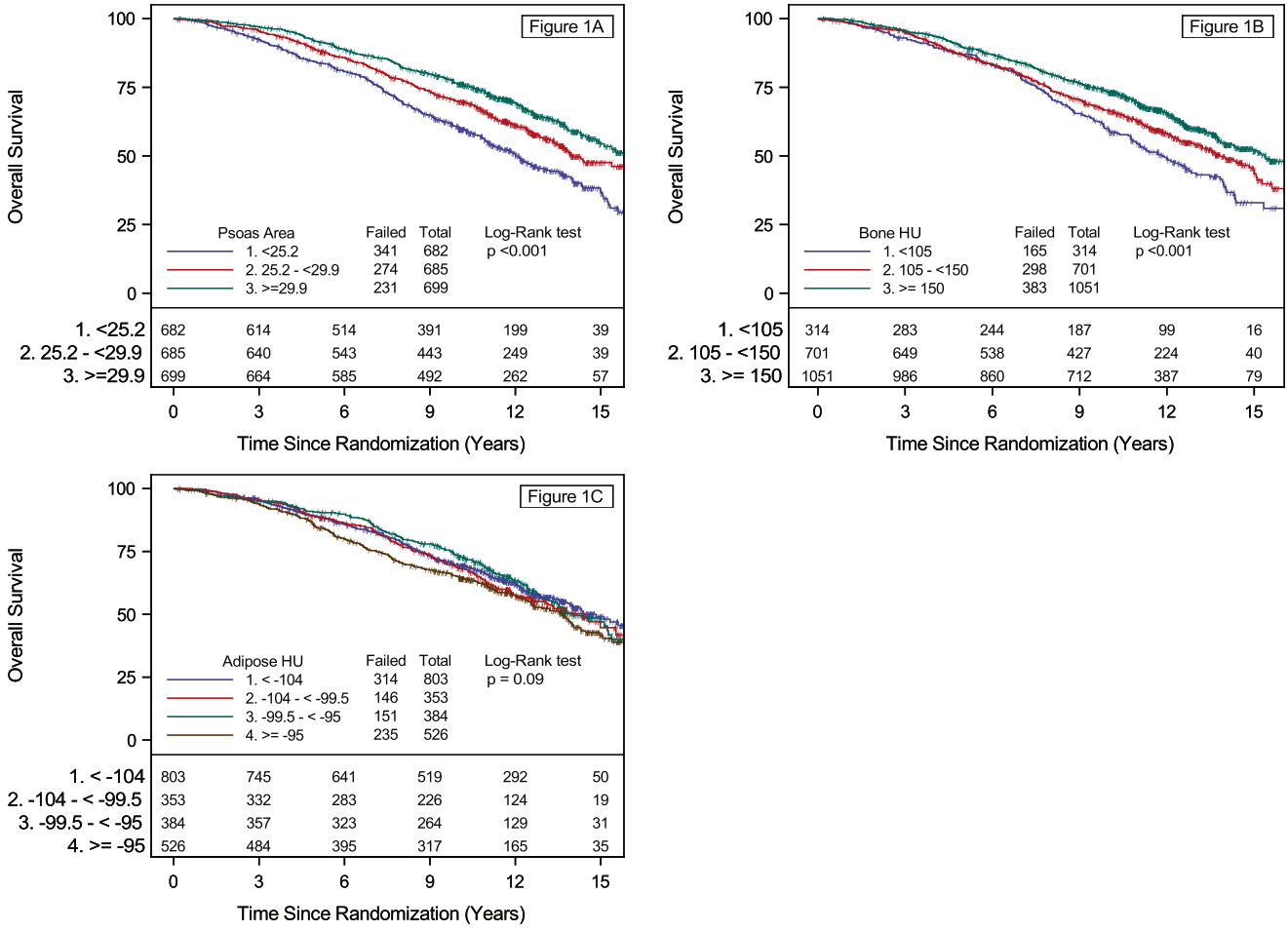

FIGURE 1 Kaplan–Meier survival estimates for the study cohort stratified by (A) psoas area, (B) vertebral body density, and (C) adipose density

The multivariable model of OS is shown in Table 3. Age (continuous, HR, 1.055 [95% CI, 1.043–1.067], $p < .001$), comorbidity score (HR, 1.54 [95% CI, 1.337–1.773] for 1–2 vs. 0, $p < .001$ and HR, 2.573 (95% CI, 1.876–3.529) for 3–5 vs. 0, $p < .001$), psoas area (HR, 0.787 (95% CI, 0.669–0.926) for 25.2–<29.9 cm^2 vs. <25.2 cm^2, $p = .004$ and HR, 0.714 (95% CI, 0.599–0.852) for ≥29.9 cm^2 vs. <25.2 cm^2, $p < .001$), and baseline prostate-specific antigen (continuous, HR, 1.015 [95% CI, 1.004–1.026], $p = .0067$) were each associated with overall mortality. The results of the RPA (Figure 2) classified the NRG/RTOG 0126 cohort into four prognostic subgroups based on risk of death. Notably, the classification into groups 3 and 4 among older (≥70 years) men was determined by psoas area. The Kaplan–Meier estimates of OS stratified by RPA classification group in the NRG/RTOG 0126 cohort and the validation NRG/RTOG 9406 cohort were significant ($p < .001$ for each cohort) are shown in Figure 3. The results of multivariable models for OS, PCSM, and FFBF with continuous body composition variables are shown in Table S5. Adipose density (continuous, HR, 1.006 (95% CI, 1.000–1.011], $p = .035$), vertebral body density (continuous, HR, 0.998 [95% CI, 0.996–0.999], $p < 0.001$), and psoas area (continuous, HR, 0.979 [95% CI, 0.967-0.991], $p < .001$) were each associated with OS when considered as a continuous variable. Adipose density (continuous, HR, 1.027 [95% CI, 1.008-1.048], $p = .007$) was associated with PCSM and no body composition variable was associated with FFBF.

Exploratory analysis of ADT and mortality

The Kaplan–Meier estimates of OS for patients receiving ADT versus no ADT, stratified by RPA classification, is shown in Figure S2. No

TABLE 3 Multivariable Cox proportional hazards model for overall survival with body composition variables as categorical variables ($n = 2061$)

Parameter	Level	HR (95% CI)	p
Adipose HU	<−104	Ref	
	−104 to <−99.5	1.089 (0.892–1.331)	.4017
	−99.5 to < −95	0.979 (0.8–1.197)	.8365
	≥−95	1.165 (0.978–1.387)	.0864
Bone HU	<105	Ref	
	105–<150	0.942 (0.775–1.145)	.5479
	≥150	0.837 (0.688–1.017)	.0739
Psoas area	<25.2	Ref	
	25.2–<29.9	0.787 (0.669–0.926)	.0040
	≥29.9	0.714 (0.599–0.852)	.0002
Treatment group	9406	Ref	
	0126–70.2 Gy	0.861 (0.709–1.046)	.1323
	0126–79.2 Gy	0.909 (0.751–1.101)	.3309
Age		1.055 (1.043–1.068)	<.0001
Comorbidity score	0	Ref	
	1–2	1.54 (1.337–1.773)	<.0001
	3–5	2.573 (1.876–3.529)	<.0001
Baseline PSA		1.015 (1.004–1.026)	.0067
Gleason score	2–6	Ref	
	7	1.119 (0.947–1.323)	.1879
	8-10	0.904 (0.635–1.287)	.5764
Race	White	Ref	
	American Indian or Alaskan Native	0.916 (0.339–2.481)	.8635
	Asian	0.716 (0.296–1.732)	.4584
	Black or African American	1.17 (0.941–1.455)	.1589
	Native Hawaiian or Other Pacific Islander	0.684 (0.219–2.14)	.5143
	Other	0.854 (0.581–1.255)	.4208

Abbreviations: HU, Hounsfield unit; PSA, prostate-specific antigen

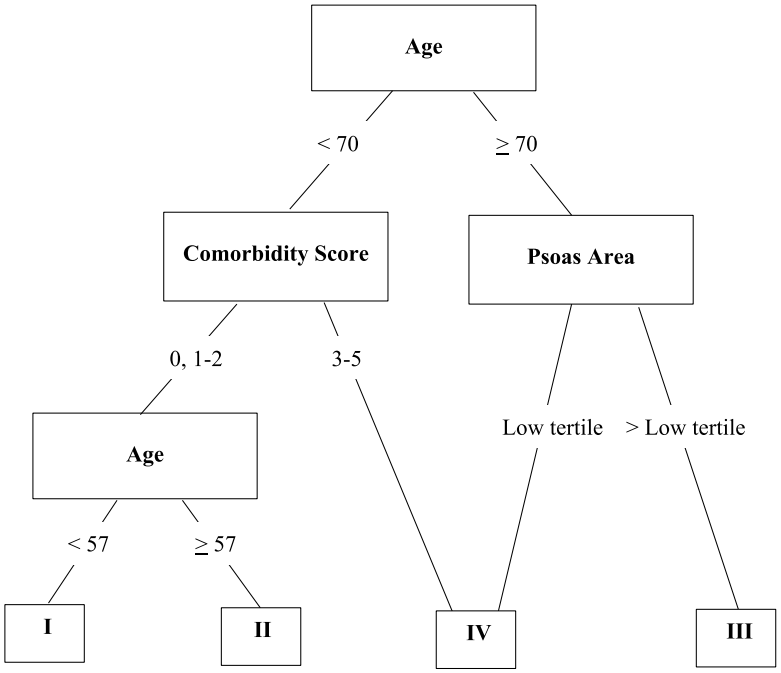

FIGURE 2 Recursive partitioning analysis classification tree using Radiation Therapy Oncology Group 0126 cohort data

significant association between ADT use and mortality was observed within any of the RPA subgroups. No interaction between ADT and psoas area or vertebral body density was observed in a Cox proportional hazards model for OS (Table S6).

DISCUSSION

We performed this study with the goal of expanding our understanding of how body composition and mortality are related in men with PCa. Study results that have investigated the relationship between anthropometry and mortality risk for men with localized PCa have been mixed. An association between BMI and mortality was not observed in a Cleveland Clinic cohort study of men receiving external beam radiation therapy, nor in a separate cohort study of men who were treated with brachytherapy.[11,12] More detailed clinical anthropometry was performed as part of a prospective cohort study of nearly 1000 men in Alberta, Canada, and no association was observed with either BMI, waist circumference, or waist-hip ratio and all-cause mortality.[32] In contrast, in the Cancer Prostate in Sweden study, BMI ≥27.5 kg/m^2 was significantly associated with worse survival in a model incorporated age but not comorbidity status.[33] Nguyen et al. also observed higher rates of all-cause mortality among overweight and obese men with biochemically recurrent PCa, particularly among those with zero to one documented comorbidity.[13]

The body composition descriptive characteristics of the present study cohort should be interpreted with the understanding that NRG/RTOG 9406 and NRG/RTOG 0126 enrolled men who were generally healthy, as opposed to other oncology populations where cachexia, myopenia, and sarcopenia are more common. The mean L5 radiodensity and psoas radiodensity were higher among the cohort of men from NRG/RTOG 9406, which is consistent with the fewer men with comorbidities in that trial as compared to NRG/RTOG 0126. Psoas area and mid-L5 vertebral body radiodensity were both significantly associated with OS when analyzed individually and in models that adjusted for age and comorbidity status. Psoas radiodensity and subcutaneous adipose radiodensity were additional candidate variables that were investigated as measures of myosteatosis and fat quality, respectively, but were not associated with mortality when considered as categorical variables.

Psoas area remained significantly associated with mortality in a multivariable model containing other body composition variables as well as age and comorbidities. L5 density and adipose density were significantly associated with mortality only when considered as continuous variables and not using the predefined categories. When available, predefined categories for body composition variables were used to enhance the validity of the study, but this approach has a risk of masking associations, and further work is needed to understand the relationship between bone density, adiposity, and mortality among men with PCa. Additional models of PCSM and FFBF showed the expected impact of baseline prostate-specific antigen and Gleason score but no clear association with body composition, which is consistent with the hypothesis that the association between body composition and OS is driven by non-PCa mortality. The ability of body composition assessment to enhance patient prognostication was highlighted by the RPA model in which psoas area was selected to discriminate the risk of mortality among men ≥70 years. The selection of psoas area as a decision point to stratify older patients is consistent with prior studies suggesting that muscle mass is an

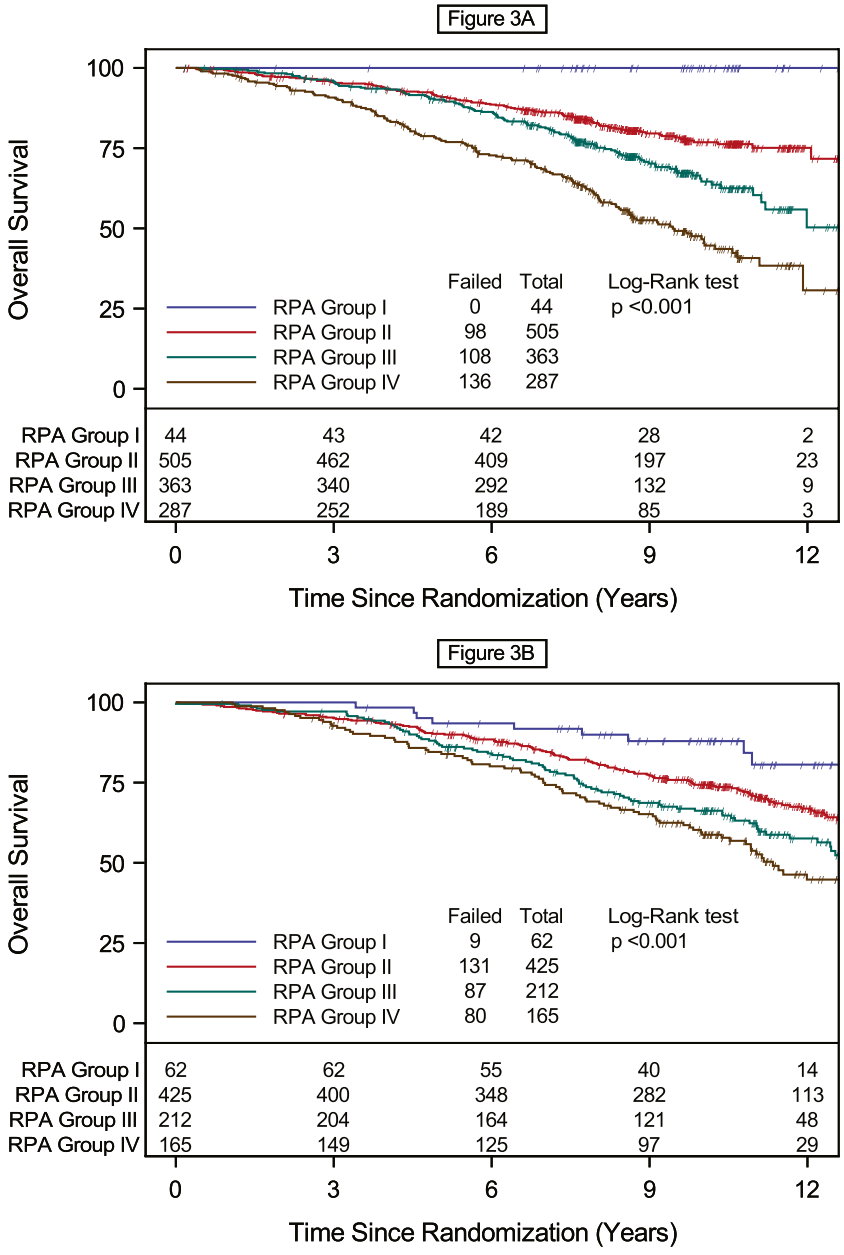

FIGURE 3 Kaplan–Meier estimates of overall survival stratified by RPA classification for (A) NRG/RTOG 0126 and (B) NRG/RTOG 9406. RPA indicates recursive partitioning analysis; RTOG, Radiation Therapy Oncology Group

important factor associated with frailty and overall health among older adults with and without cancer.[34–36]

The ability to classify men with PCa by risk of mortality has important implications for patient care and research. One ongoing debate is whether some men with PCa experience increased mortality when receiving ADT. Men enrolled in a Harvard randomized trial of ADT who had moderate or severe comorbidities experienced worse OS if they received ADT.[15] ADT has also been associated with worse survival among men with cardiac comorbidity in a large multipractice community cohort study[16] and among African American men with intermediate-risk disease treated at one center.[19] However, these findings have been inconsistent, and other studies including the TROG 96.01 clinical trial and a population-based study of men receiving brachytherapy have not observed worse outcomes for men receiving ADT.[17,19] We investigated this topic by comparing survival among participants of NRG/RTOG 9406 who received ADT versus those who did not, stratified by the RPA classification of baseline risk of mortality. We hypothesized that stratification by RPA groups, which include muscle mass and comorbidities, may identify patients whose survival is negatively affected by ADT. However, use of ADT was not associated with survival within any of the RPA subgroups and this remains an important topic for future research.

To our knowledge, this is the largest study of body composition among men with PCa and the first study that has simultaneously considered estimates of muscle mass, muscle quality, fat quality, and bone density. The observed relationship between psoas area and

survival persisted after controlling for age and comorbidities, and the selection of psoas area by the RPA algorithm to classify patients supports that the additional prognostic information gained by assessing body composition is meaningful. Improving mortality risk prediction is not only clinically important but can aid in future research studies because stratifying by competing risks may improve clinical trial design and efficiency.[10] The use of the RPA classification to further investigate the relationship between ADT and mortality, although negative, provides important proof of principle that analysis of archived CT scans can leverage clinical trial data outcomes data to investigate new hypotheses.

A further strength of this study is the quality of the clinical trial data. Pretreatment details were captured in a standardized fashion and patient outcomes were assessed prospectively. The use of data from two separate clinical trials also allowed for a natural division of training and validation cohorts that is less susceptible to bias. One limitation is that information about patient comorbidities was limited to what was available on the trial registration forms. Our approach of summing the number of comorbidities may be viewed as unconventional but is similar to how the Charlson Comorbidity Index score is derived.[37] Analyses of cause-specific mortality were limited by the fact that cause of death was unknown for nearly one-third of decedents. Regarding the measurement of body composition, patient height was not collected for these studies; thus, skeletal muscle area and psoas areas were used for analysis rather than normalizing to skeletal muscle index or psoas index and weight was used instead of BMI. However, the results of the analysis with psoas area in this study were strongly consistent with prior studies that used psoas index, supporting that height information unavailability is unlikely to have altered the results. Because of the nature of CT protocols for PCa simulation scans, this study performed analysis at the level of L4–L5. Although cross-sectional body composition analysis is more commonly performed at L3, measurements at L4–L5 are also validated and perform similarly to measurements at L3.[23]

In summary, this study demonstrated that baseline body composition, namely psoas cross-sectional area as a surrogate for muscle mass, is associated with mortality in men with PCa. The relationship between body composition and mortality may be particularly meaningful among older men. This study also confirmed the feasibility of using archived clinical trial data to investigate new hypotheses related to body composition. No subgroup was identified within this cohort in which ADT increased mortality, but this remains an important area of ongoing research. Though more work is needed to clarify the clinical impact of body composition in men with PCa, recognizing the association between body composition and mortality may assist with patient selection and provide a target for lifestyle interventions to improve outcomes.

AUTHOR CONTRIBUTIONS

Andrew M. McDonald: Conceptualization, investigation, methodology, project administration, supervision, and writing. **Lyudmila DeMora:** Formal analysis, writing, and data curation. **Eddy S. Yang:** Conceptualization and writing. **John M. Hoyle:** Data curation, investigation, and writing. **Andrew Lenzie:** Data curation, investigation, and writing. **Grant R. Williams:** Conceptualization and writing. All other authors: Project administration and writing.

ACKNOWLEDGMENTS

The authors thank the late Dr. James D. Cox of MD Anderson Cancer Center for his guidance and extensive work on the NRG/RTOG 9406 protocol design, development and his expertise in radiation oncology. This project was supported by grants U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), UG1CA189867 (NCORP), and U24CA180803 (IROC) from the National Cancer Institute (NCI).

CONFLICT OF INTEREST

Felix Y. Feng reports consulting fees from Janssen, Bayer, PFS Genomics (termed April 2021), Myovant Sciences, Roivant Sciences, Astellas, Foundation Medicine, Varian, Bristol Meyers Squibb, Exact Sciences, and Novartis; receipt of stock options from Serimmune from serving on their scientific advisory board in 2020; and payment or honoraria from Bristol Meyers Squibb for two educational presentations. Dr. Feng reports his cofounder role at Artera, where he does not receive a salary, funding, or consulting fees from the company, only shares. He reports a leadership position with NRG Oncology, where he serves as the chair of the Genitourinary Cancer Committee. His role at NRG helps investigators design proposals for clinical trials that are then evaluated by the National Cancer Institute (NCI) for funding. All funding decisions are made by the NCI, not by NRG or by Dr. Feng. Mark V. Mishra reports support for attending meetings and/or travel from Varian Medical Systems. Howard M. Sandler reports consulting fees for his role as a member of the clinical trial steering committee for Janssen; he is also a member of the Board of Directors for ASTRO. Luis Souhami reports travel support from Varian Medical Systems and his participation on a Data Safety Monitoring Board or Advisory Board for AbbVie and Janssen. Grant R. Williams reports consulting fees from Cardinal Health and Carevive and payment or honoraria for presentations from Cardinal Health. Eddy S. Yang reports grants or contract from Eli Lilly and Puma Biotechnologies to UAB, and his participation on a Data Safety Monitoring Board or Advisory Board for AstraZeneca, Bayer, and Clovis. The other authors made no disclosures.

ORCID

Grant R. Williams https://orcid.org/0000-0003-4294-5232
Robert Dess https://orcid.org/0000-0003-2331-3758

REFERENCES

1. Siegel DA, O'Neil ME, Richards TB, Dowling NF, Weir HK. Prostate cancer incidence and survival, by stage and race/ethnicity—United States, 2001–2017. *MMWR (Morb Mortal Wkly Rep)*. 2020;69(41):1473-1480. doi:10.15585/mmwr.mm6941a1
2. Lawton CAF, Lin X, Hanks GE, et al. Duration of androgen deprivation in locally advanced prostate cancer: long-term update of NRG Oncology RTOG 9202. *Int J Radiat Oncol Biol Phys*. 2017;98(2):296-303. doi:10.1016/j.ijrobp.2017.02.004

3. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA, J Am Med Assoc*. 2005;294(10):1233-1239. doi:10.1001/jama.294.10.1233
4. Peeters ST, Heemsbergen WD, Koper PC, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol*. 2006;24(13):1990-1996. doi:10.1200/jco.2005.05.2530
5. Michalski J, Winter K, Roach M, et al. Clinical outcome of patients treated with 3D conformal radiation therapy (3D-CRT) for prostate cancer on RTOG 9406. *Int J Radiat Oncol Biol Phys*. 2012;83(3):e363-e370. doi:10.1016/j.ijrobp.2011.12.070
6. Dearnaley DP, Jovic G, Syndikus I, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol*. 2014;15(4):464-473. doi:10.1016/s1470-2045(14)70040-3
7. Kutikov A, Cooperberg MR, Paciorek AT, Uzzo RG, Carroll PR, Boorjian SA. Evaluating prostate cancer mortality and competing risks of death in patients with localized prostate cancer using a comprehensive nomogram. *Prostate Cancer Prostatic Dis*. 2012;15(4):374-379. doi:10.1038/pcan.2012.21
8. Frendl DM, FitzGerald G, Epstein MM, Allison JJ, Sokoloff MH, Ware JE. Predicting the 10-year risk of death from other causes in men with localized prostate cancer using patient-reported factors: development of a tool. *PLoS One*. 2020;15(12):e0240039. doi:10.1371/journal.pone.0240039
9. Daskivich TJ, Chamie K, Kwan L, et al. Comorbidity and competing risks for mortality in men with prostate cancer. *Cancer*. 2011;117(20):4642-4650. doi:10.1002/cncr.26104
10. Zakeri K, Rose BS, Gulaya S, D'Amico AV, Mell LK. Competing event risk stratification may improve the design and efficiency of clinical trials: secondary analysis of SWOG 8794. *Contemp Clin Trials*. 2013;34(1):74-79. doi:10.1016/j.cct.2012.09.008
11. Tendulkar RD, Hunter GK, Reddy CA, et al. Causes of mortality after dose-escalated radiation therapy and androgen deprivation for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2013;87(1):94-99. doi:10.1016/j.ijrobp.2013.05.044
12. Taira AV, Merrick GS, Galbreath RW, Butler WM, Wallner KE. Factors impacting all-cause mortality in prostate cancer brachytherapy patients with or without androgen deprivation therapy. *Brachytherapy*. 2010;9(1):42-49. doi:10.1016/j.brachy.2009.06.008
13. Nguyen PL, Chen MH, Beard CJ, et al. Comorbidity, body mass index, and age and the risk of nonprostate-cancer-specific mortality after a postradiation prostate-specific antigen recurrence. *Cancer*. 2010;116(3):610-615. doi:10.1002/cncr.24818
14. McDonald AM, Swain TA, Mayhew DL, et al. CT measures of bone mineral density and muscle mass can be used to predict noncancer death in men with prostate cancer. *Radiology*. 2017;282(2):475-483. doi:10.1148/radiol.2016160626
15. D'Amico AV, Chen MH, Renshaw A, Loffredo M, Kantoff PW. Long-term follow-up of a randomized trial of radiation with or without androgen deprivation therapy for localized prostate cancer. *JAMA*. 2015;314(12):1291-1293. doi:10.1001/jama.2015.8577
16. Nguyen PL, Chen M-H, Beckman JA, et al. Influence of androgen deprivation therapy on all-cause mortality in men with high-risk prostate cancer and a history of congestive heart failure or myocardial infarction. *Int J Radiat Oncol Biol Phys*. 2012;82(4):1411-1416. doi:10.1016/j.ijrobp.2011.04.067
17. Wilcox C, Kautto A, Steigler A, Denham JW. Androgen deprivation therapy for prostate cancer does not increase cardiovascular mortality in the long term. *Oncology*. 2012;82(1):56-58. doi:10.1159/000334999
18. Rodda S, Miller S, LaPointe V, Hamm J, Morris WJ. Short term androgen deprivation therapy does not increase all-cause mortality in men treated with low-dose-rate prostate brachytherapy: a population-based cohort study. *Brachytherapy*. 2015;14:S34. doi:10.1016/j.brachy.2015.02.242
19. Kovtun KA, Chen M-H, Braccioforte MH, Moran BJ, D'Amico AV. Race and mortality risk after radiation therapy in men treated with or without androgen-suppression therapy for favorable-risk prostate cancer. *Cancer*. 2016;122(23):3608-3614. doi:10.1002/cncr.30224
20. Smith MR, Saad F, Egerdie B, et al. Sarcopenia during androgen-deprivation therapy for prostate cancer. *J Clin Oncol*. 2012;30(26):3271-3276. doi:10.1200/jco.2011.38.8850
21. Berruti A, Dogliotti L, Terrone C, et al. Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J Urol*. 2002;167:2361-2367. discussion 7. doi:10.1097/00005392-200206000-00006
22. Michalski JM, Moughan J, Purdy J, et al. Effect of standard vs dose-escalated radiation therapy for patients with intermediate-risk prostate cancer: the NRG oncology RTOG 0126 randomized clinical trial. *JAMA Oncol*. 2018;4(6):e180039. doi:10.1001/jamaoncol.2018.0039
23. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol*. 2004;97(6):2333-2338. doi:10.1152/japplphysiol.00744.2004
24. Joglekar S, Nau PN, Mezhir JJ. The impact of sarcopenia on survival and complications in surgical oncology: a review of the current literature. *J Surg Oncol*. 2015;112(5):503-509. doi:10.1002/jso.24025
25. Amini B, Boyle SP, Boutin RD, Lenchik L. Approaches to assessment of muscle mass and myosteatosis on computed tomography: a systematic review. *J Gerontol A Biol Sci Med Sci*. 2019;74(10):1671-1678. doi:10.1093/gerona/glz034
26. Pickhardt PJ, Pooler BD, Lauder T, del Rio AM, Bruce RJ, Binkley N. Opportunistic screening for osteoporosis using abdominal computed tomography scans obtained for other indications. *Ann Intern Med*. 2013;158(8):588-595. doi:10.7326/0003-4819-158-8-201304160-00003
27. Murphy RA, Register TC, Shively CA, et al. Adipose tissue density, a novel biomarker predicting mortality risk in older adults. *J Gerontol A Biomed Sci Med Sci*. 2014;69(1):109-117. doi:10.1093/gerona/glt070
28. McDonald AM, Swain TA, Mayhew DL, et al. CT measures of bone mineral density and muscle mass can be used to predict noncancer death in men with prostate cancer. *Radiology*. 2016;282(2):475-483. doi:10.1148/radiol.2016160626
29. McDonald AM, Fiveash JB, Kirkland RS, et al. Subcutaneous adipose tissue characteristics and the risk of biochemical recurrence in men with high-risk prostate cancer. *Urol Oncol*. 2017;35(11):663.e15-663.e21. doi:10.1016/j.urolonc.2017.07.012
30. Roach M, 3rd, Hanks G, Thames H Jr., et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys*. 2006;65(4):965-974. doi:10.1016/j.ijrobp.2006.04.029
31. Therneau T, Atkinson B, Ripley B, Ripley MB. Package 'rpart'; 2015. Accessed April 20, 2016. https://cran.r-project.org/web/packages/rpart/rpart.pdf
32. Farris MS, Courneya KS, Kopciuk KA, McGregor SE, Friedenreich CM. Anthropometric measurements and survival after a prostate cancer diagnosis. *Br J Cancer*. 2018;118(4):607-610. doi:10.1038/bjc.2017.440
33. Cantarutti A, Bonn SE, Adami H-O, Grönberg H, Bellocco R, Bälter K. Body mass index and mortality in men with prostate cancer. *Prostate*. 2015;75(11):1129-1136. doi:10.1002/pros.23001

34. Williams GR, Deal AM, Muss HB, et al. Frailty and skeletal muscle in older adults with cancer. *J Geriatr Oncol*. 2018;9(1):68-73. doi:10.1016/j.jgo.2017.08.002
35. Srikanthan P, Karlamangla AS. Muscle mass index as a predictor of longevity in older adults. *Am J Med*. 2014;127(6):547-553. doi:10.1016/j.amjmed.2014.02.007
36. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: a meta-analysis and systematic review. *Eur J Cancer*. 2016;57:58-67. doi:10.1016/j.ejca.2015.12.030
37. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: McDonald AM, DeMora L, Yang ES, et al. Body composition and mortality in men receiving prostate radiotherapy: a pooled analysis of NRG/RTOG 9406 and NRG/RTOG 0126. *Cancer*. 2023;129(5):685-696. doi:10.1002/cncr.34596