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Weight loss over time and survival: a landmark analysis of 1000+ prospectively treated and monitored lung cancer patients

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Abstract

Background Eligibility criteria and endpoints for cancer cachexia trials—and whether weight loss should be included—remain controversial. Although most cachexia trials enrol patients after initial cancer diagnosis, few studies have addressed whether weight loss well after a cancer diagnosis is prognostic.

Methods We pooled data from non-small cell lung cancer patients from prospectively conducted trials within the Alliance for Clinical Trials in Oncology (1998–2008), a nationally funded infrastructure. We examined (i) weight data availability and weight changes and (ii) survival.

Results A total of 822 patients were examined. Of these, 659 (80%) were on treatment at the beginning of Cycle 2 of chemotherapy; weight was available for 656 (80%). By Cycles 3 and 4, weight was available for 448 (55%) and 384 (47%), respectively. From baseline to immediately prior to Cycle 2, 208 (32%) gained weight; 225 (34%) lost <2% of baseline weight; and 223 (34% of 656) lost 2% or more. Median survival from the beginning of Cycle 2 was 13.0, 10.9, and 6.9 months for patients with weight gain, weight loss of <2%, and weight loss of 2% or more, respectively. In multivariate analyses, adjusted for age, sex, performance score, type of treatment, and body mass index, weight loss of 2% or more was associated with poor overall survival compared with weight gain [hazard ratio (HR) = 1.66; 95% confidence interval (CI): 1.33–2.07; $P < 0.001$] and compared with weight loss of <2% (HR = 1.57; 95% CI: 1.27–1.95; $P < 0.001$). Although weight loss of <2% was not associated with poorer overall survival compared with weight gain, it was associated with poorer progression-free survival (HR = 1.24; 95% CI: 1.01–1.51; $P = 0.036$). Similar findings were observed in a separate 255-patient validation cohort.

Conclusions Weight should be integrated into cancer cachexia trials because of its ease of frequent measurement and sustained prognostic association.

Keywords Weight loss; Landmark analysis; Prognosis; Survival; Lung cancer

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Introduction

The selection of appropriate eligibility criteria and endpoints for cancer cachexia clinical trials is an area of avid interest and unresolved debate. Cachexia occurs in the majority of patients with advanced, incurable cancer. It is a syndrome characterized by weight loss, poor appetite, attrition of both lean tissue and fat but especially the former, an otherwise inexplicable increase in basal metabolic rate, a decline in patient functional status, and poor survival. Indeed, the

multifaceted nature of this constellation of signs and symptoms only adds to the quandary of choosing the most appropriate clinical trial eligibility criteria and endpoints.[1–3] Not surprisingly, the recent unsuccessful cancer cachexia clinical trials have prompted only further discussion of clinical trial design and choice of appropriate eligibility criteria and endpoints.[4–7]

Simple, unadorned, and inexpensive, weight has, at times, been incorporated into cancer cachexia trials.[8–10] Dewys and others have shown that among 3047 chemotherapy-naïve patients with cancer, self-reported weight loss over the preceding 6 months at clinical trial entry predicts an early demise.[11] Several other studies have confirmed this observation, showing that weight loss at the time of cancer diagnosis or at the time of another hallmark baseline appraisal predicts an early demise. In fact, a large, often-cited, international consensus statement incorporates weight loss into its definition of cancer cachexia.[12]

Despite the above, several investigators have questioned the role of weight in cancer cachexia trials. The complexity of body composition within the context of cancer is such that some investigators have suggested that measurements of specific body compartments with perhaps modalities such as computerized tomography should surpass the role of weight loss in assessing outcomes in cachexia trials. Additionally, although baseline weight loss is associated with a poor prognosis, few studies have addressed whether ongoing weight loss—or weight gain—after the initiation of chemotherapy carries any association with survival. Hence, the current study was undertaken with a twofold set of goals. First, it sought to characterize the weight trajectory of patients with non-small cell lung cancer and to assess patient dropout rates over time in order to speculate on whether a tool such as computerized tomography, typically used to assess tumour response/body composition at 6–8 week intervals in contrast to weight at 3–4 week intervals, appears to generate comparable data for cachexia assessment. Second, the current study sought to determine whether weight change after initiation of chemotherapy—a so-called landmark analysis, with the term 'landmark' used here as a statistical term—is a predictive marker, as opposed to only a baseline marker, of prognosis. Importantly, this study relied on prospectively gathered, multi-institutional, United States' government-funded data to address the foregoing goals.

Methods

Overview

The Mayo Clinic Institutional Review Board and the Alliance for Clinical Trials in Oncology approved the study protocol prior to initiation and reporting of analyses. The current study sought to understand patterns of weight loss during chemotherapy and justification—or lack thereof—for the incorporation of weight data in future cancer cachexia clinical trials as an eligibility criterion and early indicator of long-term outcome.

Clinical trial selection

The current study focused on therapeutic trials in patients with non-small cell lung cancer within the North Central Cancer Treatment Group (now integrated into and renamed the Alliance for Clinical Trials in Oncology), which enrolled patients from 1998 through 2008, with the exception of the following: (i) those that included surgery or concurrent radiation as part of the tested therapeutic intervention, as the inclusion of such studies would have introduced an unacceptable degree of patient and clinical outcome heterogeneity; (ii) those with irretrievable archival information about the study protocol or data set; and (iii) those that had been closed to enrolment prior to completion of planned accrual.

The current study relied on pooled individual patient data from non-small cell lung cancer clinical trials (*Table* 1). This cancer type was chosen because non-small cell lung cancer is the most common cause of cancer-related death in the United States and because it has been the focus of at least two large, multisite cancer cachexia clinical trials.[4–7]

Statistical analyses

Patient demographics and baseline characteristics including age, sex, race, height, weight, body mass index (BMI), performance score (PS), and disease stage were summarized using mean (with standard deviation) or median (with range) values for continuous variables and frequencies (with percentage) for categorical variables. The percentage of patients with weight data and reasons for missing weight data at each treatment cycle were summarized. Percent weight loss at each treatment cycle was summarized using mean (standard deviation) and median values (range) and plotted by number of treatment cycles. Weight measurements were inspected for outliers and corrected in the event of an apparent data entry error (seven cases). Missing weight measurements were imputed by linear interpolation when weight was recorded for the immediately preceding and following cycles (four cases). A linear regression model was built to determine the association between baseline factors and percent weight change between the start of Cycles 1 and 2. Due to the large number of patients dropping off these trials due to death, disease progression, adverse events, and other reasons, a model for weight change beyond Cycle 2 was deemed meaningless and not considered.

Table 1 Included trials

Trial identifier	Dates of accrual	Sample size	Cancer therapy
N0528	08/08/2007–11/24/2008	96	(A) Gemcitabine + carboplatin + cediranib vs. (B) gemcitabine + carboplatin
N0426	07/06/2006–01/25/2007	48	Pemetrexed + bevacizumab
N0326	02/10/2005–06/09/2005	25	Sorafenib
N0323	04/30/2004–10/19/2006	52	Temsirolimus
N0222	12/03/2004–02/22/2006	62	(A) Carboplatin + paclitaxel followed by gefitinib vs. (B) gefitinib
N0026	09/05/2001–05/23/2003	150	(A, B, C) Pemetrexed + gemcitabine (administered via different schedules)
N0022	04/30/2001–03/06/2002	58	Vinorelbine
N9921	02/02/2000–02/07/2001	49	Carboplatin + paclitaxel
982453	12/15/1999–03/30/2001	36	Irinotecan + docetaxel
982452	03/08/1998–06/12/2000	99	(A, B) Docetaxel + gemcitabine (administered via different schedules)
972451	06/01/1999–04/06/2004	147	(A) Carboxy-amino-imidazole (CAI) vs. (B) placebo

Overall survival and progression-free survival were estimated using the Kaplan–Meier estimator. Time to death and to disease progression were measured from the start of Cycle 2. Landmark Cox proportional hazards regression models were used to determine the effect of post-treatment weight change on overall survival and progression-free survival. The proportional hazards assumption was checked using scaled Schoenfeld residuals. All models reported in this study satisfied the proportional hazards assumption. All statistical tests were conducted at the two-sided significance level of 0.05. All analyses were conducted using SAS version 9.4 and R version 3.4.2.

Results

Patient and trial characteristics

Eleven non-small cell lung cancer trials were used for the current study's primary analyses, which encompassed a total of 822 patients (*Table* 1).

Table 2 shows the frequency and percentage of patients with complete weight data by chemotherapy treatment cycle and reasons why weight data were not available. At the beginning of Cycle 2, weight data were available for 656 (80%) patients. Reasons why weight data were not available included the following: 20 (2%) patients died on study, 75 (9%) went off study due to disease progression, and 68 (8%) went off study for other reasons that included adverse events or choice of alternative treatment (*Table* 2). By the beginning of Cycle 3, weight data were available for only 448 (55%) patients. By this time, the number of patients who went off study due to disease progression increased to 229 (28%). At the start of chemotherapy Cycle 4, weight data were available for 384 (47%) patients, while the number of patients who went off treatment due to disease progression increased to 267 (33%). The number of patients on study with missing weight data was negligible across all time points (four patients, 0.5%). *Figure* 1 shows the weight trajectory of patients by availability of weight data. Patients who went off treatment prior to the beginning of chemotherapy Cycle 2 or 3 experienced more weight loss than patients who remained on treatment at Cycle 4.

Weight loss between chemotherapy Cycles 1 and 2

The mean weight change between cycles 1 and 2 of cancer treatment was −1.1% (standard deviation: 3.2) with median −0.8% (range: −15.6% to 11.9%). From baseline to immediately prior to Cycle 2 of cancer treatment, 208 (32% of 656)

Table 2 Reasons for availability and unavailability of patient data (percentages denote the percentage of 822 patients with Cycle 1 weight data)

Status	Start of Cycle 2 (%)	Start of Cycle 3 (%)	Start of Cycle 4 (%)
Available patient data	656 (80)	448 (55)	384 (47)
Unavailable patient data			
Death on study	20 (2.4)	26 (3.2)	31 (3.8)
Disease progression	75 (9.1)	229 (27.9)	267 (32.5)
Adverse events or complications	25 (3.0)	53 (6.4)	66 (8.0)
Other medical complication	4 (0.5)	4 (0.5)	6 (0.7)
Patient withdrawal or refusal	29 (3.5)	43 (5.2)	47 (5.7)
Alternate treatment	2 (0.2)	4 (0.5)	6 (0.7)
Other reason	8 (1.0)	11 (1.3)	11 (1.3)
Missing weight	3 (0.4)	4 (0.5)	4 (0.5)

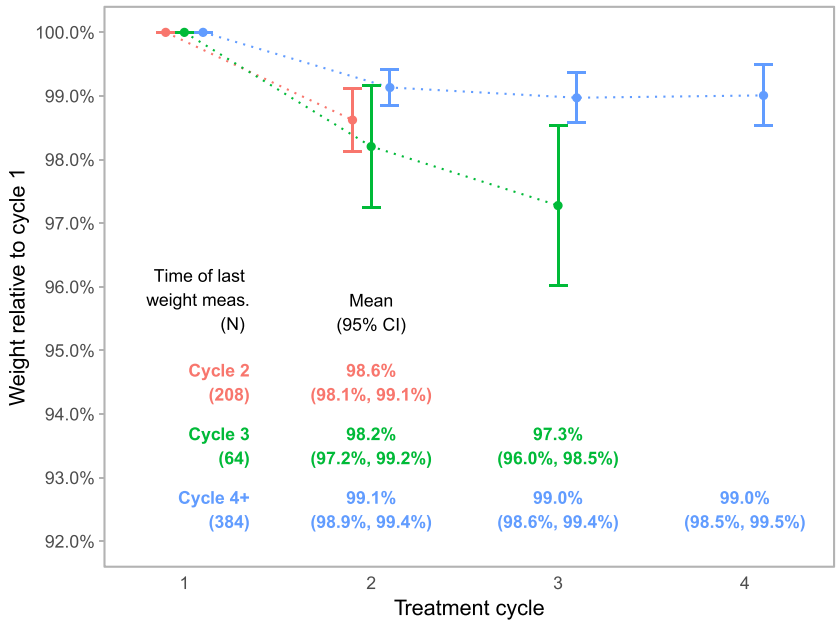

Figure 1 Weight change by treatment cycle. CI, confidence interval.

patients gained weight, 225 (34% of 656) lost between 0 and 2%, and 223 (34% of 656 patients with Cycle 1 weight data) lost more than 2%. *Table* 3 shows patient characteristics by weight change. Linear regression models that examined the associations between weight loss and a variety of variables, specifically age (65 years of age or older versus younger); sex, PS, BMI (categorized as underweight at </=18.5, normal weight at 18.5 to 24.9, overweight at 25 to 29.9, or obese at 30 or greater), and trial and treatment arm (accounting for time effect and type and line of treatment) revealed that baseline BMI classified as overweight was associated with more weight loss [0.7%; 95% confidence interval (CI): 0.14–1.26%; $P = 0.015$] compared with normal BMI. The pattern of weight loss varied according to treatment trial/arm (overall $P < 0.001$).

Weight loss and survival

Weight change in the first cycle of cancer treatment was classified into three categories: any amount of weight gain ($n = 208$), weight loss less than 2% ($n = 225$), and weight loss of 2% or more ($n = 223$). The median survival time from the beginning of Cycle 2 was 13.0, 10.9, and 6.9 months for patients with any weight gain, with weight loss of <2%, and with loss of 2% or more, respectively. Compared with weight gain and to weight loss of <2%, weight loss of 2% or more showed a statistically significant association with poor survival (*Figure* 2). In the multivariate Cox model, risk of overall mortality was higher with weight loss ≥2% compared with weight gain [hazard ratio (HR) = 1.66; 95% CI: 1.33–2.07; $P < 0.001$] and compared with loss of <2% (HR = 1.57; 95% CI: 1.27–1.95; $P < 0.001$) (*Table* 4). There was no statistically significant survival difference between weight gain and weight loss of <2%. Other variables adjusted for in the multivariate Cox model included age (no association with survival); sex (male patients had higher risk of mortality; HR = 1.46; 95% CI: 1.23–1.73; $P < 0.001$ compared with female patients); PS (poorer scores were associated with higher mortality; HR = 1.27; 95% CI: 1.06–1.53; $P = 0.01$; HR = 2.24; 95% CI: 1.60–3.12; $P < 0.001$; for PS of 1 or 2 compared with 0, respectively); baseline BMI (higher BMI was associated with lower mortality; HR = 0.80; 95% CI: 0.66–0.96; $P = 0.02$; HR = 0.73; 95% CI: 0.58–0.93; $P = 0.01$; for overweight or obese compared with normal, respectively).

Similar analyses with progression-free survival indicate that weight loss of 2% or more was associated with poorer outcomes compared with weight loss of <2% (HR = 1.24; 95% CI: 1.01–1.53; $P = 0.037$) and compared with weight gain (HR = 1.54; 95% CI: 1.24–1.91; $P < 0.001$) (*Figure* 3). In contrast to what was observed in overall survival, weight loss of <2% was associated with poorer progression-free survival compared with weight gain of any amount (HR = 1.24; 95% CI: 1.01–1.51; $P = 0.036$) (*Table* 4). Male patients had poorer progression-free survival (HR = 1.36; 95% CI: 1.49–1.60; $P < 0.001$). Patients 65 years of age or older had better progression-free survival (HR = 0.80; 95% CI: 0.66–0.97; $P = 0.02$).

To validate the above observations, we applied these analyses to data from a separate 312-patient trial.[13] Data for weight change after the initiation of cancer therapy were available for 255 (82%) patients enrolled in the trial.

Table 3 Patient demographics based on weight change from Cycle 1 to 2

	Weight gain (N = 208)	Weight loss <2.0% (N = 225)	Weight loss >2.0% (N = 223)	P value
Age				0.9199[a]
Mean (SD)	66.2 (10.15)	66.2 (10.12)	65.7 (10.38)	
Median (range)	67 (38, 91)	67 (33, 91)	67 (37, 90)	
Sex, *n* (%)				0.5782[b]
Female	87 (41.8)	85 (37.8)	94 (42.2)	
Male	121 (58.2)	140 (62.2)	129 (57.8)	
Race, *n* (%)				0.8360[b]
White	185 (96.9)	182 (94.3)	177 (95.2)	
Other	6 (3.1)	11 (5.7)	9 (4.8)	
Missing	17	32	37	
Baseline BMI				0.1543[a]
Mean (SD)	25.9 (4.86)	27.0 (5.95)	26.8 (5.15)	
Median (range)	25.4 (15.1, 41.6)	26.2 (15.8, 47.0)	26.5 (15.5, 48.0)	
Baseline BMI category, *n* (%)				0.1149[b]
Normal weight	84 (41.2)	82 (37.4)	66 (32.0)	
Obese	34 (16.7)	56 (25.6)	45 (21.8)	
Overweight	77 (37.7)	74 (33.8)	90 (43.7)	
Underweight	9 (4.4)	7 (3.2)	5 (2.4)	
Missing	4	6	17	
Performance score, *n* (%)				0.2782[b]
0	95 (45.7)	97 (43.1)	83 (37.2)	
1	103 (49.5)	120 (53.3)	125 (56.1)	
2	10 (4.8)	8 (3.6)	15 (6.7)	
Disease stage, *n* (%)				0.1730[b]
IIIA	0 (0.0)	0 (0.0)	0 (0.0)	
IIIB	32 (16.1)	41 (19.2)	29 (13.6)	
IV	164 (82.4)	171 (80.3)	184 (86.4)	
Other	3 (1.5)	1 (0.5)	0 (0.0)	
Missing	9	12	10	

BMI, body mass index; SD, standard deviation.
[a]Kruskal–Wallis P value.
[b]χ^2 P value.

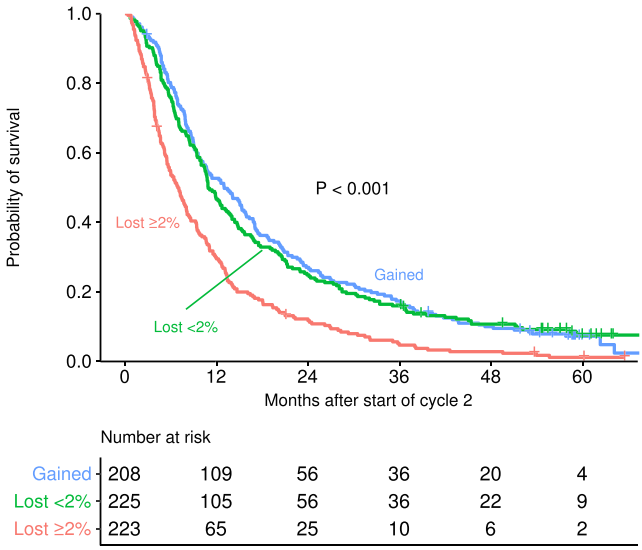

Figure 2 Overall survival curves from beginning of Cycle 2 by weight loss between Cycle 1 and immediately prior to Cycle 2.

Of these 255 patients, 110 (43%) gained weight, 80 (31%) lost <2%, and 65 (26%) lost 2% or more. Kaplan–Meier survival curves were stratified by weight change categories in the same order observed in the analysis above (*Figure* 4). In multivariate Cox model adjusted for age, sex, PS, baseline BMI, and treatment, weight loss of 2% or more in the first cycle was associated with poorer survival compared with weight gain (HR = 1.46; 95% CI: 1.04–2.04; P = 0.03), but presumably because of small numbers and compromised power, no statistically

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Table 4 Results from multivariate cox models

	Overall mortality (inverse of OS)		Treatment failure (inverse of PFS)	
Variables	Hazard ratio (95% confidence interval)	*P* value	Hazard ratio (95% confidence interval)	*P* value
Weight change[c]		<0.001[a]		<0.001[a]
Gained	1		1	
Lost <2%	1.05 (0.86–1.29)	0.625	1.24 (1.01–1.51)	0.036
Lost ≥2%	1.66 (1.33–2.07)	<0.001	1.54 (1.24–1.91)	<0.001
Sex				
Female	1		1	
Male	1.46 (1.23–1.73)	<0.001	1.36 (1.49–1.60)	<0.001
Age				
<65 years	1		1	
≥65 years	0.89 (0.74–1.08)	0.239	0.80 (0.66–097)	0.020
Baseline BMI		0.033[a]		0.246[a]
Normal	1		1	
Underweight	0.92 (0.58–1.44)	0.702	1.14 (0.72–1.78)	0.583
Overweight	0.80 (0.66–0.96)	0.020	0.89 (0.74–1.08)	0.242
Obese	0.73 (0.58–0.93)	0.010	0.82 (0.65–1.02)	0.079
Performance score		0.001[a]		0.059[a]
0	1		1	
1	1.27 (1.06–1.53)	0.011	1.20 (1.00–1.43)	0.046
≥2	2.24 (1.60–3.12)	<0.001	1.37 (0.99–1.89)	0.059
Trial/arm[b]		0.003		0.013

BMI, body mass index; OS, overall survival; PFS, progression-free survival.
[a]Overall *P* value.
[b]Due to a large number of combinations, HRs (hazard ratios) by trial/arm combinations are not listed.
[c]Weight lost ≥2% vs. lost <2%: Overall mortality HR (95% CI) = 1.57 (1.27–1.95), $P < 0.001$; Treatment failure HR (95% CI) = 1.24 (1.01–1.53), $P = 0.037$.

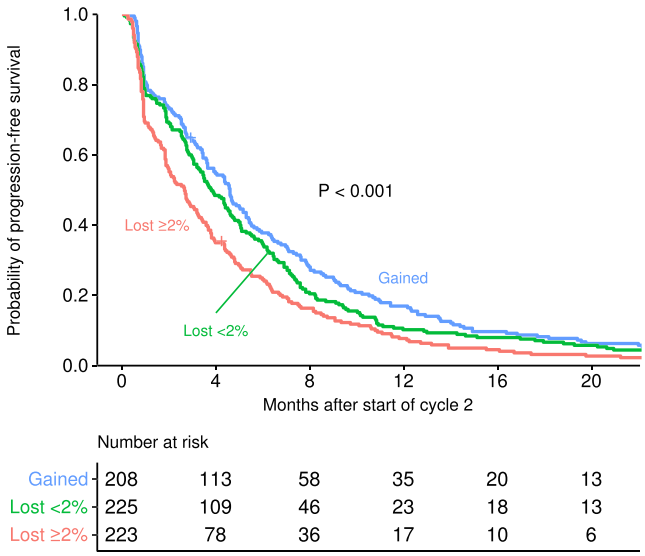

Figure 3 Progression-free survival curves from beginning of Cycle 2 by weight loss between Cycle 1 and immediately prior to Cycle 2.

significant associations with respect to survival were observed with the other weight comparisons.

Discussion

This study shows that weight is a dynamically changing, time-dependent variable in cancer patients, that its decline is associated with poor clinical outcomes, and that enrolling weight-losing patients on cachexia trials well after their initial cancer diagnosis is clinically and prognostically justified. Even a moderate weight loss of 2% or more early in the treatment course can be predictive of poorer overall survival. This association between weight loss of 2% or more and survival were highly significant (<0.001) and robust even when one adjusts for multiple comparisons (three pairwise between weight

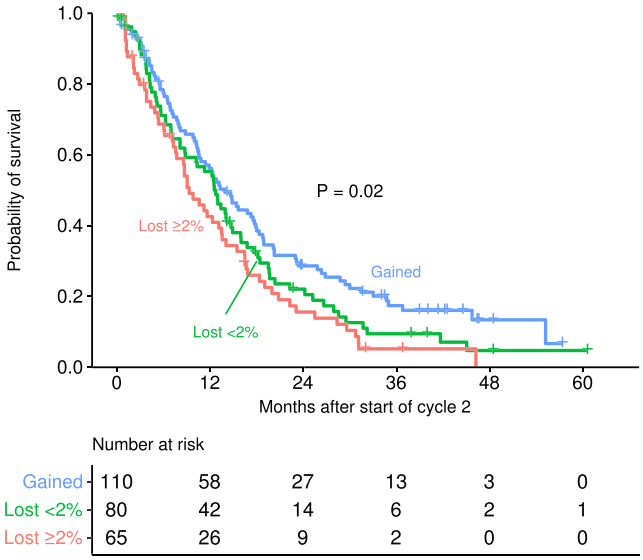

Figure 4 Overall survival curves from beginning of Cycle 2 by weight loss between Cycle 1 and immediately prior to Cycle 2 for the validation cohort.

change categories) with conservative Bonferroni corrections. Furthermore, patients actually did gain weight with cancer therapy, a favourable, previously reported observation that prompted us to evaluate data based on weight gain as the referent.[14] Although computerized tomography scans are increasingly recognized for their ability to measure body compartment-based tissue loss, the data presented here suggest that the simple measurement of weight over time offers advantages.[15,16] Patient dropout rates were extreme to the point of making analyses meaningless around the time that computerized tomography scans are typically obtained (6–8 weeks from start of cancer therapy) and thereby suggest the current practice of commandeering these scans to assess body composition results in high rates of missing data and potentially even flawed conclusions. Taken together, the data presented here show that weight is a reliably trackable endpoint for cancer cachexia trials and that its use carries important, sustained clinical prognostic relevance over time.

The use of a landmark analysis—with the term 'landmark' used here as a statistical term—is important but not unprecedented. Kimura and others used a similar approach when analysing data from 134 non-small cell lung cancer patients.[17] The data presented here build on this important prior work by increasing the sample size by more than sixfold, by using prospectively gathered data (as opposed to retrospective data in the Kimura study) and by integrating a validation set into the study design. In effect, the study reported here serves not only to confirm the findings from Kimura and others but also to provide definitive evidence that weight loss over time is meaningful both from a clinical and research perspective. Weight loss should continue to be an eligibility criterion for cachexia trials post-cancer diagnosis and should be measured in clinical trials aimed at testing new approaches to palliate cancer cachexia.

Interestingly, weight gain appears to be associated with improved progression-free survival compared with even a negligible amount of weight loss (2%). The fact that similar findings were not observed for overall survival is likely reflective of the high likelihood that, over time, patients went on to receive a variety of other cancer treatment that favourably impacted overall survival but would not have impacted the more immediate progression-free survival outcome. This association between weight gain and progression-free survival only further underscores the value of using weight—including weight gain—as a clinically relevant endpoint in cancer cachexia trials.

This study has both strengths and weaknesses. The fact that this study used prospectively gathered data from a multi-institutional setting is a major strength. To our knowledge, such data have been analysed in this manner for the first time. Similarly, although this study did not incorporate clinical trials that tested immunotherapy, it did incorporate a variety of agents that are currently a part of state-of-the-art cancer care. Thus, the observations reported here are relevant to contemporary oncology. With respect to weaknesses, one might argue that a study that focuses on weight lacks the novelty that one might encounter in a study that focuses on a new molecular marker. However, we counter this so-called potential weakness by underscoring the pragmatic nature of these findings. Nearly all patients who visit an oncology clinic are weighed frequently over time; thus, the findings reported here carry widespread clinical relevance. Additionally, the information reported here is critical to the conduct of future cancer cachexia studies and provides justification for enrolling patients who have already

begun chemotherapy and continue to lose weight to such trials. These weight-losing patients carry a poor prognosis, should remain candidates for future cancer cachexia trials, and should be monitored on these trials for changes in weight.

In summary, the findings from this 800+ patient cohort and a 200+ patient validation cohort have value from a clinical and research standpoint. Simple weight measurements should continue to be integrated into clinical care as well as into future cancer cachexia clinical trials.

Author contributions

The authors' responsibilities were as follows. J.L. and A.J. conceived and designed the study; J.L., C.L., and E.W. acquired the data; J.L., C.L., E.W., and A.J. wrote the manuscript; and J.L., C.L., E.W., N.R.F., S.J.M., X.W., R.K., A.A., and A.J. read and approved the final version.

Conflict of interest

None of the authors reported a conflict of interest related to the study.

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Ethical statement

The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[18]

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