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Body composition and survival in the early clinical trials setting

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KEYWORDS
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Abstract ***Purpose:*** Delineate the relationships between body composition parameters, 90-day mortality and overall survival, and correlate them with known prognostic factors in an early clinical trials clinic.
Patients and methods: We studied 306 consecutive patients with various tumours; body composition was analysed by computerised tomography images. Survival was measured from the first clinic visit, at 90-day period and until death/last follow-up visit.
Results: Median patient age was 56 years; 159 patients were men. Ninety-day mortality rate was 12%. Median overall survival was 9 months. In multivariate analyses, high MD Anderson Cancer Center (MDACC) score ($p < 0.0001$) [lactate dehydrogenase (LDH) > normal, albumin < normal, Eastern Cooperative Oncology Group (ECOG) performance status > 1, metastatic sites > 2, gastrointestinal (GI) tumours], low skeletal muscle index (SMI) ($p = 0.0406$) and male gender ($p = 0.0077$) were independent predictors of poor survival. If Royal Marsden Hospital (RMH) score (LDH > normal, albumin < normal, metastatic sites > 2) was used in lieu of MDACC score, it was also significant ($p = 0.0003$). Including SMI and gender in the MDACC or RMH score improved the accuracy of the original model ($p = 0.006$ and $p = 0.0037$, respectively).
Conclusion: Patients with low SMI have shorter survival. Gender and SMI strengthens the accuracy of MDACC or RMH scores as prognostic tools. Prospective validation of these findings is warranted.

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1. Introduction

Early clinical trials are designed to determine metabolic and pharmacologic effects of drugs in humans, side-effects associated with increasing doses, maximum tolerated dose, and early evidence of efficacy and response. Patients referred to phase I clinical trials usually present with treatment-refractory, advanced malignancies, and many will not benefit from experimental treatments.[1,2] Therefore, understanding prognostic factors can assist in determining possible outcomes. Personalised therapy that is, matching patients with agents based on an individualised approach is playing an increasingly important role in cancer therapy.[3–6] The significance of host factors such as body composition to this field has not been well studied.

Efforts have been made to delineate objective and reliable prognostic parameters. The Royal Marsden Hospital (RMH) has developed a prognostic scoring system using objectively measured parameters [>2 sites of metastasis, albumin below normal and lactate dehydrogenase (LDH) above normal] that have been validated in multi-institutional studies,[7,8] including the phase I clinic at MD Anderson.[9] Our group has also studied other prognostic factors related to survival in the phase I patient population. Among these are the gastrointestinal (GI) tumour type and poor Eastern Cooperative Oncology Group (ECOG) performance status and, when grouped with the RMH variables, the MD Anderson Cancer Center (MDACC) score[10] may strengthen the ability of the RMH score to predict a poor outcome.

Body weight and body composition (fat and lean mass) play a crucial role in the aetiology, prognosis and treatment outcomes of cancer.[11,12] Sarcopenia, defined as absolute muscle mass below 2 or more standard deviations of the muscle mass in healthy young adults[13] is closely associated with cancer cachexia, and has a significant impact on the prognosis of cancer and other chronic diseases.[14–19] Patients referred to clinical trials usually present with progressive disease despite conventional management. Therefore, they are particularly susceptible to the end-organ effects of cachexia, reflected as changes in body weight and body composition. Clearly, in view of these factors, understanding how body weight and composition impact outcomes and survival in this population is important.

In this study, we analysed body weight and body composition in 306 patients who were referred to the Clinical Center for Targeted Therapy (phase I clinic) of the MD Anderson Cancer Center. Our goal was to delineate the relationships between body composition parameters, including sarcopenia, 90-day mortality and overall survival, and correlate them with known prognostic factors.

2. Patients and methods

A total of 306 consecutive patients with various advanced cancers referred to the phase I clinic starting in December 2004, who met protocol criteria for inclusion, were analysed. These patients were part of a larger pool of patients from a previous study that evaluated survival of patients in the phase I setting.[10] Patients were included if the computed tomography (CT) imaging test had taken place within 5–50 days of their first visit to the phase I clinic. Images were used to assess body composition. All patients received treatment on early clinical trials including cytotoxic and/or targeted agents, systemic and/or local-regional therapy (intra-hepatic arterial infusion).

The study was conducted according to guidelines of the Institutional Review Board at MD Anderson, and written informed consents for all investigational treatments were obtained. Patients were followed up to determine length of survival and relevant variables, including body composition.

2.1. Demographic and laboratory data

Age, gender, cancer diagnosis, height and weight data were collected from patients' electronic medical records (Table 1). Weight measurements were culled from the day closest to the date of CT imaging at the first visit to the phase I clinic; median time from weight to CT imaging was 1 day (range, 10 days before to 20 days after imaging). Laboratory values were collected from the closest day to the first visit to the clinic; median time from laboratory tests to first visit was 0 days (range, 15 days before to 15 days after the first visit). The median time between CT imaging and first clinic visit was 13 days (range, 0–50 days before visit), only 8.2% (25/306) of the patients had imaging done between 31 and 50 days prior to clinic visit.

2.2. Survival data

Overall survival was measured from the day of the first visit to the phase I clinic until death or final follow-up visit. Patients still alive at last follow-up were censored at that date. Ninety-day survival was calculated by censoring alive patients at day 90.

2.3. Body composition assessments

Body mass index (BMI) was calculated dividing patient's weight (kg) by height (m^2). Body composition (muscle and fat body area) was estimated using the validated method described below.

Routine abdominal CT images at the level of the 3rd lumbar vertebra (L3) were chosen for analysis. The use