

Practical and theoretical implications of weight gain in advanced non-small cell lung cancer patients

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Involuntary weight loss occurs frequently in individuals with many types of cancers and was shown to be associated with inferior survival almost 40 years ago (1). More recently, there is evidence that weight loss prior to initiation of systemic anti-cancer therapies is associated with increased treatment related side effects (2,3). The majority of these patients are suffering from the cancer anorexia cachexia syndrome. In 2011, a panel of cancer cachexia experts published a consensus statement which defined and classified cancer cachexia (4). This group pointed out that the predominant feature of this syndrome includes loss of skeletal muscle mass which cannot be reversed by conventional nutritional support and which may or may not be accompanied by loss of body fat. Their consensus for diagnostic criteria for cancer cachexia are weight loss greater than 5% in individuals with body mass index (BMI) of ≥ 20 during the preceding 6 months and 2% weight loss in individuals with BMI < 20 . They also defined stages of cachexia as pre cachexia ($< 5\%$ weight loss), cachexia as defined above, and refractory cachexia which is usually associated with progressive cancer and poor performance status.

Recent investigators have worked to define cancer cachexia and its prognostic value more precisely (5,6). Investigators at the University of Alberta conducted studies in which they used routine computed tomography (CT) scans to measure skeletal muscle index (SMI) and muscle attenuation in cancer patients (5). They developed a multi-variate survival model that included weight loss, body mass index (BMI), SMI

and muscle attenuation. They found that this model using parameters associated with cancer cachexia had a higher C-statistic (concordance statistic) than a survival model which evaluated conventional parameters (type of cancer, stage, age, and performance status). Their observations suggest that including muscle measurements refined the definition of cancer cachexia and enhanced its prognostic value. Currently measuring these muscle parameters requires special software and increases time for measuring the CT parameters, it is likely that this methodology will be used primarily as a research tool unless automation is developed.

An alternate strategy, also out of the University of Alberta, subsequently reported used a grading system which included percent weight loss and BMI in more than 8,000 cancer patients. Similar to performance status, their grading system consists of levels 0 through 4 with the longest survival being associated with grade 0. This favorable group of patients has no weight loss and a BMI ≥ 25 kg/m². In contrast, the shortest survival was observed in grade 4 patients who have $\geq 15\%$ weight loss and BMI < 20 . With increasing use of electronic records these important measurements will be available immediately prior to and at the time of diagnosis for every cancer patient and can be readily incorporated into prognostic models.

Weight loss at the time of study entry has been the primary body weight consideration in NSCLC clinical trials. This parameter served both as a stratification factor and as an eligibility criterion. While weight changes have been used to

recalculate treatment doses in advanced non-small cell lung cancer (NSCLC) clinical trials, weight variation duration treatment has not been reported in relation to NSCLC patient outcomes. Giolda *et al.* (7) reported preliminary evidence that weight gain during treatment with chest radiation and concurrent platinum based chemotherapy was associated with longer survival. They evaluated body weight change after completion of chest radiation and concurrent chemotherapy in 54 NSCLC patients who subsequently had resection of their pulmonary neoplasms. They found that 48% of the patients gained weight and in multivariate analysis only initial stage and any weight gain were significantly related to overall survival.

Subsequently, Sher *et al.* (2013) reported results of weight gain and its relationship to overall survival in 92 stage III B NSCLC patients treated with definitive split course chest radiation and concurrent platinum containing chemotherapy at Rush University Medical Center. They compared patients in the highest quartile of weight gain (>4.5 pounds) and found that patients who gained more than 4.5 pounds had a 3-year survival rate of 55% *vs.* 31% for patients who do not achieve this level of weight gain. In addition, weight gain was the only significant predictor of survival in multivariate analysis.

While these combined observations (7,8) suggest that there is a positive relationship between weight gain during treatment and overall survival in locally stage III NSCLC patients, these were small, retrospective, exploratory, single institution studies which did not define weight changes as a percentage of body weight. Topkan and his colleagues at Baskent University (9) reported results of weight gain and outcome in a retrospective study of 425 good risk stage IIIB NSCLC patients treated with definitive chest radiation and concurrent platinum based chemotherapy. In addition to being a significantly larger study, this group of investigators also defined weight change more specifically. They evaluated changes in BMI, expressed as weight in kgs divided by height expressed as m^2 , and they considered a change of $0.5 \text{ kg}/m^2$ to be significant. They observed the following changes in BMI: decrease in 59% of patients, stable in 20, and increase in 21% of patients. Overall survival was significantly longer in patients with increased or stable BMI with a hazard ratio of 0.603 ($P < 0.001$). The investigators suggested that weight change in locally advanced NSCLC patients during treatment with radiation and chemotherapy could be considered a surrogate marker for outcomes in this group of patients (9), and Topkan has suggested that weight gain during chemoradiation in locally

advanced NSCLC be added to conventional prognostic and predictive factors (10).

The results of the Radiation Therapy Oncology Group's (RTOG) phase III 0617 trial comparing platinum based regimens and two doses (60 *vs.* 74 Gy) of concurrent chest radiation were surprising in showing significantly shorter in patients that received the higher dose (10). The median survival was 28.7 months for patients who received 60 Gy and 20.3 months for patients who received 74 Gy. The hazard ratio for overall survival was 1.38 ($P = 0.004$). The rate of grade 3 esophagitis was significantly increased with the higher dose of radiation—21% *vs.* 7%, $P = 0.0001$ (11). Conducting phase III combined modality trials in locally advanced NSCLC requires a great deal of effort and team work. If serial body weights are available in the data base for the RTOG 0617 trial, it would be interesting to compare this information at 6 and 12 weeks for patients treated with 74 *vs.* 60 Gy. If there a negative effect on body weight occurred with the higher dose of radiation in RTOG 0617, it suggests that evaluating weight changes in phase I/II trials testing novel chemoradiation treatments might be useful for selecting regimens for inclusion in future phase III locally advanced NSCLC studies.

The relationship between serial body weights and outcomes has also been evaluated in stage IV NSCLC patients. Patel *et al.* (12) reported results regarding the relationship between weight and outcomes in 2301 stage IV non-squamous NSCLC patients who received first line platinum-based chemotherapy in three international randomized clinical trials. They found that body weight increased by more than 5% in 18.3% of the patients and that survival was significantly longer compared to patients who do not achieve this level of weight gain with a hazard ratio of 0.54 ($P < 0.001$). It was interesting to see that any degree of weight gain was also associated with significantly longer survival with a similar hazard ratio—0.51. Weight gain was also associated with a higher chemotherapy response rate with a 50% response rate in the group with weight >5% versus 25% response rate in the remaining patients. The investigators suggested that tumor regression might inhibit the mechanisms which promote cachexia and enable mechanisms which enhance weight gain.

Although multiple factors effect weight changes in lung cancer patients who are receiving chemotherapy with or without chest radiation, we believe that tumor status and treatment related side effects are the major determinants of weight loss versus weight gain. If our assumption is correct, serial weight determinations have practical implications

NSCLC cancer patients. With increasing availability of electronic medical records, this clinical parameter can be easily tracked, and stable or increasing weight during treatment is reassuring and likely means that tumor is not progressing and that treatment is tolerable. In contrast, progressive weight loss should prompt investigation of cancer progression and careful assessment of treatment side effects. This especially has implications for clinical trials and it is somewhat surprising that the report by Patel *et al.* (12) appears to be the first description of serial body weight information and its relationship to progression free and overall survival in advanced NSCLC patients on a clinical trial. We believe that serial body weights will have more clinical significance than the large amount of data for low grades of hematologic, renal, hepatic, neurologic, and dermatologic toxicities which are currently reported for most clinical trials.

We also suspect that weight change impacts each patient's quality of life, with weight loss being a source of distress for many patients and their families (13). While important patient reported outcomes are provided by quality of life instruments, this process is labor intensive and increases clinical trial cost. Correlating weight changes with quality of life changes in clinical trials is a relatively unexplored area of research.

Assessing serial weights in NSCLC patients may also have implications for increasing our understanding of the mechanisms involved in cancer cachexia. In reviews of cancer cachexia (13,14), the authors propose that cancer cachexia is an energy balance disorder which involves reduced ingestion of nutrients and increased catabolism of normal tissues. Inflammation which occurs in the tumor microenvironment is believed to be a major driver of anorexia and catabolic events which include muscle proteolysis and adipose tissue lipolysis. There is increasing information regarding molecular mediators of cachexia (15). Pro-inflammatory cytokines including TNF- α , IL-1, and IL-6 are associated with skeletal muscle breakdown in cachexia (15-17). Muscle mass also depends upon the balance between regulators of myogenesis, with IGF-I promoting myogenesis and with myostatin and activin inhibiting myogenesis (15). Comparing serum levels of these proteins in patients who gained weight versus those who lost weight during antineoplastic therapy might provide insights regarding the mechanisms of cachexia. Similarly, longitudinal study of serum protein patterns and body weights in individual patients might be informative. These study designs might

also identify other mediators of cachexia and provide ideas for novel strategies for treating cachexia.

Although studies exploring the relationship between tumor regression and weight gain during anti-cancer therapy are needed, the observations that weight gain in NSCLC patients who received concurrent chest radiation and chemotherapy (7-9) or chemotherapy alone (12) suggest that tumor control reverses mechanisms involved in cancer cachexia. Stene *et al.* have also suggested that achieving tumor control might reverse the catabolic processes involved in cancer cachexia (18). Although their study was small, they observed that 16 of 35 stage IV NSCLC patients maintained or gained cross sectional muscle mass at the level of the third lumbar vertebra while receiving chemotherapy, and it's interesting that almost all of these patients (14 of 16) had tumor remission as defined by RECIST v 1.1 criteria (18). If tumor regression/control reverse cancer cachexia, it's conceivable that treatments which target cachexia might inhibit a tumor's growth by reducing its energy sources and precursors of macromolecules (19). Since cachexia is also associated with increased treatment toxicity (2,3), it's possible that treatments targeting cachexia will also reduce side effects from tumor specific therapies.

In summary, there are relatively few reports regarding body weight change in patients being treated for stage III/IV NSCLC. However, with increasing use of electronic medical records, this information should be readily available for every NSCLC patient. This information is likely to be useful in providing care of advanced NSCLC patients on a daily basis and as a global assessment of the effectiveness and tolerability regimens being tested in randomized trials. As suggested by Topkan and his colleagues (9,10), these data could serve as a surrogate for outcomes in stage III NSCLC patients being treated with combined modality regimens in phase I/II trials. Finally, correlating longitudinal weight changes and molecular markers could enhance our understanding of the mechanisms of anorexia-cachexia and lead to novel treatment strategies for this common and devastating syndrome.

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Footnote

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