Weight gain as a surrogate marker of longer survival in advanced non-small cell lung cancer patients

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Abstract: Weight loss (WL), as a key step of the irreversible and fatal cancer-related anorexia cachexia syndrome is present to some degree in 80% of non-small cell lung cancer (NSCLC) patients upon diagnosis which has been clearly proved to negatively alter patients' performance status, quality of life (QOL), response to treatment, and prognosis. However, WL is not a problem encountered only upon diagnosis but is also commonly reported during the course of aggressive chemotherapy, radiotherapy (RT) and particularly the concurrent chemoradiotherapy (C-CRT) which may further diminish QOL measures and clinical outcomes. In general, the NSCLC literature has concentrated on WL during the treatment course, but recent studies have demonstrated that it is possible to preserve or even experience weight gain (WG) during or just short after the discontinuation of various cancer treatments in approximately 40% to 45% NSCLC patients. Considering the fact that recent evidence suggest a prognostic and predictive role for WG in anticipation of longer survival times and better response rates in weight gainers, this current manuscript will specifically aim to realize the actual value of WG in locally advanced and metastatic NSCLC patients which may potentially be added to the conventional prognostic and predictive factors as a novel surrogate marker of outcomes in such patients.

Keywords: Weight gain (WG); cancer treatment; non-small cell lung cancer (NSCLC); prognosis

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Since the earliest report of Hippocrates (460–377 BC), weight loss (WL) has been perceived as a condition that is closely associated with poor prognosis in patients presenting with chronic illnesses, including the cancer. As a pivotal component of the irreversible and fatal cancer-related anorexia cachexia syndrome (CACS), WL ,is present to some degree in 80% of non-small cell lung cancer (NSCLC) patients at presentation which has been clearly proved to negatively alter patients' performance status, quality of life (QOL), response to treatment, and prognosis (1,2). However, WL is not a problem encountered only upon diagnosis but is also commonly reported during the course of aggressive chemotherapy, radiotherapy (RT), and particularly the concurrent chemoradiotherapy (C-CRT), which may further diminish QOL measures and clinical outcomes. WL during NSCLC treatment may be associated with side effects including fatigue, anorexia, nausea, vomiting, esophagitis, early satiety, dysphagia, diarrhea, and infections (3).

In the August 2016 issue of *Annals of Oncology* Patel *et al*. (4) reported the outcomes of retrospective analysis of 2,301 stage IIIB or IV non-squamous NSCLC patients enrolled on three previous phase III clinical trials (5-7) with the primary endpoint of the impact of weight gain (WG) experienced during the treatment or at the 30-day post-study discontinuation follow-up visit. In this commendable study the authors divided the 421 (18.3%) patients with WG into two groups: those with >5% *vs*. ≤5% WG. Majority of these patients had stage IV disease (n=340; 81%). Their results demonstrated a significant association between superior median overall survival (OS) and >5% WG (16.7 *vs*.10.7 months; HR: 0.57; P<0.001). Likewise, the patients who experienced >5% WG had approximately 2 months superior median progression-free survival (PFS;

6.9 *vs*. 4.8 months; HR: 0.61; P<0.001) and 25% superior overall response rate (50.8 *vs*. 25.4%; P<0.001). The authors also reported that these positive relationships were independent of other confounding variables.

Current standard treatment options for metastatic and locally-advanced NSCLC (LA-NSCLC) include systemic chemotherapy, targeted therapies, and palliative RT for metastatic and C-CRT for LA-NSCLC patients, respectively (8,9). However, starkly contrasting with the significant improvements in diagnostic tools and treatment options in the last three decades, the survival rates remained poor and almost constant for both the metastatic (range, 8–12 months) and locally advanced (range, 16–24 months) disease stages (8-10). Given the poor outcomes in this patient populace, it is essential to determine prognostic factors beyond the conventionally utilized performance status, T, N, M stages, pretreatment WL, and objective response to treatment. Therefore, the impressive results of the Patel's large retrospective review are of vital significance with respect to that it confirms the suggested novel prognostic and predictive roles for WG in NSCLC patients (10-12).

The particular prognostic significance of weight preservation or gain has previously been addressed in three retrospective cohort series as aforementioned above (10-12). In the first study reported by Sher *et al*. from Rush University Medical Center (11), the authors evaluated the prognostic significance of WG during the split course chemoradiotherapy in 92 LA-NSCLC patients with the primary endpoint of OS. In this study the WG was defined as the any weight change greater than the highest quartile of change (4.5 lb) between the initiation and completion of the CRT. The authors reported that the WG was the unique factor to associate with enhanced median OS times (51 *vs*. 23 months; HR: 0.5; P=0.04). At long-term, the OS probability was more profound in favor of the WG group with respective 5-year OS estimates of 50% *vs*. 12%. Second study was a smaller preoperative split-course CRT study again from Rush University Medical Center (12) which included 54 patients with locally advanced (n=51) or oligometastatic (n=3) LA-NSCLC patients. Results of multivariate analysis revealed that the initial stage (HR: 2.94; P=0.02) and percent weight change during the CRT course (HR: 0.79; P<0.01) were the factors to associate with OS outcomes. Accordingly patients who experienced WG (n=26) had significantly longer median OS time compared to dose who did not (not reached yet *vs*. 16.3 months; P=0.001) and 3-year OS probability (71.4% *vs*. 21.9%). Although these studies suggested a survival enhancing function for WG during CRT course, one may contend that both studies utilized split-course CRT which does not reflect the current standard treatment paradigm for such patients, namely the C-CRT. In this regard, the third study reported by our group represents the largest of ever its kind study which particularly researched the impact of weight change during the course of exclusive radical C-CRT in 425 stage IIIB NSCLC patients (10). In this study, in order to prevent uncontrollable feeding-related measurement biases, any WC was accepted as significant only if the calculated difference came upon a positive or negative body mass index (BMI) change of 0.5 kg/m^2 relative to pretreatment levels. Therefore, the study population was divided into 3 groups: group 1: WL (BMI reduction >0.5 kg/m^2); group 2: weight preservation (WP: BMI reduction/increment <0.5 kg/m^2); and group 3: WG gain (BMI increment >0.5 kg/m^2). However, for comparative analysis groups 2 and 3 were consolidated as WP/G. As indicated by this definition, 252 patients (59.3%) experienced WL, while 89 patients (20.9%) and 84 patients (19.8%) demonstrated weight preservation or gain during C-CRT. Survival analysis revealed that WP/G group had significantly superior median OS time (27.3 *vs*. 17.8 months; P<0.001) and 3-year OS rate (42.3% *vs*. 0%). Another important finding of our study was the demonstration of significantly longer median locoregional PFS (LRPFS: 17.4 *vs*. 11.5 months) and distant metastasis free survival (DMFS 14.1 *vs*. 9.3 months), which translated into longer PFS (8.7 *vs*. 13.3 months) in WL patients.

Interpreting the three previous reports together with the more recent one by Patel *et al*. (4), available results suggest the WG experienced during C-CRT as a surrogate marker of superior OS times either in the preoperative split-course induction CRT, definitive split-course induction CRT, or radical C-CRT settings independent of the chemotherapy regimen or RT protocol in use. These results may be influenced by the decreased toxicity rates (particularly the esophagitis, nausea and vomiting) by use of more sophisticated RT techniques such as intensity-modulated or image-guided RT, earlier diagnosis and intervention of treatment related toxicities, and more common use of supportive measures. However, it is obvious that these complications have not been eliminated totally yet by utilization of more sophisticated RT techniques or available pharmaceutical or nutritional additives. Additionally, as some patients with severe toxicity do not experience WL and as currently available nutritional additives have

questionable influence on prevention or treatment of WL, such survival gain cannot be explained uniquely by decreased rates of toxicity and indicates presence of other potential factors to be identified. More reasonably these findings rather designate higher response to chemotherapy both as a radiosensitizer at locoregional sites and as a systemic treatment at distant microscopically involved sites (10).

Despite the exact cause(s) of association between WL and poorer locoregional and distant control rates is not fully investigated yet, impaired nutritional status, anti-tumoral immunity, existence of potentially unaltered chronic inflammatory milieu, and more aggressive tumor phenotype with poor or no response to any oncologic treatment may sensibly have assumed a part (13,14). Additionally, unaltered or even increased secretion of cachectic factors by poor or nonresponding tumors may have further contributed to unfavorable outcomes observed in these patients (15). Therefore, WG experienced during the treatment course may have mirrored the reversal of poor immunity, blockade of secretion of cachectic factors, and alteration of chronic inflammatory milieu in a group of NSCLC patients treated with various oncologic interventions. However, in order to conclude more reliably on this subject of critical importance further studies addressing this issue are urgently needed.

The value of degree of clinically significant WL has been clearly defined in consensus statements in order to create a three-stage classification specific for cancer; namely precachexia, cachexia, and refractory cachexia (16). For this purpose, the criteria for cachexia incorporates body WL >5% over the past 6 months or a BMI of <20 in combination with WL >2% over the past 6 months (16). However, our knowledge about the importance of degree of WG experienced during the cancer treatment is scarce. In general, previous reports did not search for a significant WG cutoff specific to NSCLC patients and grouped patients into two respective groups: those with WL or WG (including the weight preservers). In this respect Patel *et al*. defined "clinically significant WG" as any gain >5% with the aim of prevention of false measurements which potentially caused by daily fluctuations in hydration and standard error variances (4). However, authors' additional analysis using "any WG" rather than 5% as the cutoff (n=1,066; 46.3%) demonstrated similar superior median OS outcomes (15.2 and 8.6 months; HR: 0.51) favoring the group of patients with any WG over those without. Comparing the HRs of two different dichotomization methods (0.51 *vs*. 0.57; for any WG *vs*. >5% WG, respectively) reveals that preservation or gain of any body weight is even more important than WG >5%. Despite the fact that it is hard to allocate this finding to a single cause, yet it is rationale to hypothesize that even minor and clinically insignificant WG is the representative of the early reversal of the molecular pathways of the irreversible and fatal CACS.

In the two largest studies Patel *et al*. (4) and Topkan *et al*. (10) respectively demonstrated that it is possible to preserve pretreatment body weight or induce WG in 46.3% and 40.7% of all metastatic or locally advanced NSCLC patients undergoing chemotherapy or C-CRT. Concentrating on this point, Topkan's study is intriguing by exhibiting striking long-term survival rate differences at 3-year OS (42.3 *vs*. 0%), LRPFS (31.2 *vs*. 0%), PFS (25.3% *vs*. 0%), and DMFS (26.2 *vs*. 0%) time points between the WG and WL groups, favoring the former (10). Despite suggesting a surrogate role for WG during C-CRT in accurate anticipation of outcomes in LA-NSCLC, these observations may further hint at tailoring adjuvant or salvage treatments of such patients. Because the response and survival outcomes were poor in the WL cohort, such finding may be suggestive of the need for more intense and efficient but less toxic adjuvant chemotherapeutics. Additionally, it may further suggest closer follow-up of such patients for earlier detection and timely management of resistant or recurrent local disease and/or already existing or *de novo* metastases. In the presence of stereotactic radiation therapy facilities, some of these patients may further experience tumor control, QOL, and potential survival benefits. On the other hand, favorable results in WG cohort may also raise the question about the need for potentially toxic and currently debated consolidation chemotherapies, which may not yield further clinical gain in such patients.

In conclusion, outcomes of available studies (4,10-12), particularly the largest of ever one by Patel *et al*. (4), are important by demonstration of a clear survival benefit with prevention of WL in approximately 40–45% of all NSCLC patients (*Table 1*). However, looking at the other side of the coin, it is dramatic to see that more than 50% of all NSCLC patients are continuing to lose weight despite of aggressive treatment. Therefore, although the potential therapeutic implications have not been fully exploited in humans, it is imperative to continue on clinical research of CACS for improving patients' tolerance to treatment and QOL. The main goal should incorporate the development of both preventive and therapeutic measures for WL on a multidisciplinary approach basis. For this purpose,

Table 1 Studies specifically addressing the impact of weight change during treatment in NSCLC patients

Reference	Patients (n)	Stage	WG patients, n (%)	Median OS, WG *vs*. WL	P value
Sher *et al*. (11)	92	IIIA/B	51 (55.0)	51.0 *vs*. 23.0 mo	0.030
Gielda *et al*. (12)	54	III–IV	26 (48.1)	Not reached yet *vs*. 16.3 mo	0.001
Topkan *et al*. (10)	425	IIIB	173 (40.7)	27.3 *vs*. 17.8 mo	<0.001
Patel *et al*. (4)	2,301	III–IV	421 (18.3)*	16.7 *vs*. 10.7 mo	0.001
			1,066 (46.3)	15.2 *vs*. 8.6 mo	0.001

*, patients with >5% WG. NSCLC, non-small cell lung cancer; WG, weight gain; OS, overall survival; WL, weight loss; mo, months.

considering the multifactorial nature of WL on the way of fatal CACS, targeting the multiple steps of CACS including the hypothalamic pathways, tumor-secreted factors, and chronic inflammation status rather than a single potential target appears to be of vital importance on the way of success.

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Footnote

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