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Relationship between efficacy outcomes and weight gain during treatment of advanced, non-squamous, non-small-cell lung cancer patients

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Background: Unintentional weight loss occurs among advanced non-small-cell lung cancer (NSCLC) patients and is associated with worse survival. Small studies have suggested that weight gain during treatment is associated with superior survival.

Patients and methods: A retrospective analysis analyzed data from three international phase III studies comprising 2301 advanced, non-squamous NSCLC patients who received a platinum-based, first-line doublet, with or without bevacizumab and maintenance therapy. Body weight was recorded before and after treatment by each study's schedule. The relationship between weight gain and overall survival (OS) and progression-free survival (PFS) was assessed using log-rank test and adjusted Cox modeling. Logistic regression assessed the association between baseline covariates and post-baseline weight gain.

Results: Four hundred and twenty-one (18.3%) patients had >5% weight gain after baseline. More than half of the weight gain cohort exhibited initial weight gain by 3 weeks. The median OS was 16.7 months versus 10.7 months for the >5% versus ≤5% weight gain subgroup ($n = 1880$) ($P < 0.001$). PFS was 6.9 versus 4.8 months, respectively ($P < 0.001$). Differences in overall tumor response rate (50.8% versus 25.4%, respectively) and disease control rate (tumor response or stable disease) (91.5% versus 63.6%, respectively) were also significant ($P < 0.001$). The Cox modeling revealed the >5% subgroup had longer survival [hazard ratio (HR) = 0.54, 95% confidence interval (CI) 0.47–0.62; $P < 0.001$] than the ≤5% subgroup after adjusting for baseline factors. Similar significant results were found for PFS (HR = 0.59, 95% CI 0.52–0.67; $P < 0.001$). Unadjusted logistic regression indicated a significant association between weight gain (>5% versus ≤5%) and age, and BMI.

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Conclusions: Weight gain during treatment may be an early indicator of clinical benefit. If confirmed in prospective studies, monitoring weight change may provide important information regarding survival outcomes in NSCLC and may provide ideas for new therapeutic strategies.

Key words: NSCLC, weight gain, retrospective analysis, phase III clinical trial, cachexia

Introduction

Lung cancer represents ~13% of the global cancer burden [1]; the mortality rate is among the highest of all cancers, in part due to the late stage at diagnosis [1]. Performance status and disease stage are two well-established non-small-cell lung cancer (NSCLC) prognostic factors [2, 3]. The loss of appetite and weight loss at presentation have also been identified as adverse prognostic factors in some advanced NSCLC studies [2, 4–8].

A retrospective analysis of lung cancer patients at diagnosis reported ~60% of patients had already experienced weight loss [6]. Whether weight loss continued or stabilized during therapy correlated with progression-free survival (PFS) and overall survival (OS). NSCLC patients with weight stabilization experienced 2 months longer median PFS ($P = 0.01$) and OS ($P = 0.006$). Two small retrospective studies of locally advanced NSCLC patients showed that weight gain was associated with superior survival [9, 10]. Similarly, in a larger retrospective study, patients with stage III NSCLC who maintained or gained weight after chemoradiation survived significantly longer [11]. The investigators suggested future study of weight loss during treatment might provide the basis for new treatment strategies for patients with stage III NSCLC. The objective of our study was to evaluate potential relationships between serial weight changes and outcomes in patients with advanced non-squamous NSCLC treated with chemotherapy. Our analyses focused on weight gain defined as >5% post-baseline since prior studies of the prognostic impact of weight loss have used this threshold [3, 4], and since higher thresholds (10%, 15%) result in too few patients.

Methods

Patients and study design

Patients included in these retrospective analyses had stage IIIB or IV NSCLC and had received a platinum doublet, with or without bevacizumab, as first-line treatment in one of three phase III clinical trials: JMDB (pemetrexed/cisplatin versus gemcitabine/cisplatin) [12]; S380 (pemetrexed/carboplatin versus docetaxel/carboplatin) [13]; and PointBreak (JMHD) (carboplatin/pemetrexed/bevacizumab followed by maintenance pemetrexed/bevacizumab versus carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab) [14].

The analysis set met the following criteria: (i) non-squamous NSCLC confirmed by histology data; (ii) received at least one dose of treatment; (iii) had at least one recorded pretreatment and post-treatment body weight; (iv) available survival data. Patients excluded from the analyses for reasons of histology or treatment are summarized (supplementary Appendix Table SA, available at *Annals of Oncology* online). Overall, a total of 2301 treated non-squamous patients were included in the pooled analysis set: JMDB trial, $n = 1208$; S380 trial, $n = 209$; PointBreak trial, $n = 884$. To maximize the size of the analysis set, all analyses used the three-trial pooled analysis set with the exception of time-to-weight-gain analysis (Table 1); there, Pointbreak data were presented separately due to a salient difference in study design.

Baseline and treatment assessments

Efficacy measures included OS, PFS, and best overall tumor response (per RECIST 1.0 guidelines). In general, body weight was recorded at baseline, at the onset of every treatment cycle, and at the 30-day post-study discontinuation follow-up visit.

Statistical analyses

Baseline body weight was defined as the last non-missing weight measure before first treatment. Post-baseline body weight was defined as the maximum weight during treatment or at the 30-day post-study discontinuation follow-up visit. The analysis set was divided into two groups: those with >5% weight gain and those with ≤5% weight gain. Unadjusted logistic regression was used to assess the association between baseline covariates and post-baseline weight gain.

Patient data were analyzed using graphs of the Kaplan–Meier estimates, log-rank test, and adjusted Cox modeling to assess the relationship between weight gain and OS and PFS. Fisher's exact test was used to compare the overall response rate (ORR, percentage of patients with either a complete or partial tumor response) and disease control rate (DCR, percentage of patients with either stable disease or a tumor response) between weight gain groups. Adjusted logistic regression was used to assess the relationship between weight gain and ORR and DCR. Patients without smoking status at baseline ($n = 148$) were excluded from the adjusted Cox and logistic modeling.

As an exploratory BMI analysis, we categorized patients into six mutually exclusive groups based on their baseline BMI and post-baseline weight gain, and investigated the impact on OS using the Kaplan–Meier estimates, the log-rank test, and adjusted Cox modeling.

SAS (Version 9.2, SAS Institute, Cary, NC) was used for all analyses. All the statistical tests were two-sided. A P -value of 0.05 was the statistical significance threshold.

Results

Patient demographics are reported (supplementary Appendix Table SB, available at *Annals of Oncology* online). A total of 421 patients (18%) had a >5% increase in weight (>5% subgroup) over baseline weight measurement at ≥1 time point during the study. Among those patients achieving >5% weight gain in the analysis set derived from studies S380 and JMDB, two-thirds (67.8%) of them achieved this threshold after 9 weeks of treatment (Table 1). In the PointBreak study in which all patients were randomized to induction therapy and eligible patients continued to maintenance therapy after four cycles of induction therapy, approximately half (54.0%) of the patients who achieved >5% weight gain did so after 12 weeks of treatment (4 induction cycles). A similar analysis examined when >5% subgroup patients reached their maximum post-baseline weight (Table 1).

Unadjusted logistic regression indicated a significant association between weight gain (>5% versus ≤5%) and age and BMI,

Table 1. Timing of the earliest and maximum post-baseline patient weight gain

Cycle number at which weight was recorded ^a	Weeks of treatment preceding measuring weight	Timing at which earliest >5% post-baseline patient weight gain observed		Timing at which maximum post-baseline weight gain observed among patients achieving >5% weight gain	
		Cumulative frequency	Cumulative percent	Cumulative frequency	Cumulative percent
Combined JMDB and S380 trial patients (<i>n</i> = 1417) ^b					
2	3	36	14.0	17	6.6
3	6	95	36.8	37	14.3
4	9	175	67.8	78	30.2
5	12	221	85.7	139	53.9
6	15	251	97.3	240	93.0
Post-study	19 ^c	258	100	258	100
PointBreak (JMHD) trial patients (<i>n</i> = 884) ^b					
2	3	7	4.3	3	1.8
3	6	42	25.8	10	6.1
4	9	74	45.4	25	15.3
501	12	88	54.0	32	19.6
502	15	106	65.0	44	27.0
503	18	120	73.6	56	34.4
504	21	127	77.9	78	47.9
505	24	140	85.9	95	58.3
506	27	149	91.4	110	67.5
507	30	152	93.3	118	72.4
508	33	155	95.1	125	76.7
509–532	≥36	163	100	163	100

^aWeight was recorded at the beginning of each scheduled 3-week cycle. Baseline weight was defined as the last non-missing weight measure before first treatment at cycle 1.

^bData from PointBreak are presented separately from JMDB and S380 because the study was structured differently. Patients participating in the JMDB and S380 studies received the same treatment for up to six 3-week cycles. PointBreak patients received four 3-week cycles of induction therapy (cycles 1–4), and then the eligible patients continued to receive 3-week cycles of maintenance therapy until progressive disease or treatment discontinuation. PointBreak maintenance cycles are designated 501, 502, and so on, beginning with the first maintenance cycle.

^cWeight was recorded during the 30-day (~4 weeks) post-final treatment visit for the S380 trial patients. There was no corresponding time point for JMDB trial patients.

among baseline covariates. More patients aged <65, or with a BMI ≤25 had a >5% weight gain ($P < 0.001$) after treatment. In addition, there was no significant weight gain association ($P = 0.983$) between patients with a BMI <20 and those with a BMI between 20 and 25.

The >5% weight gain subgroup from the three study pooled analysis set exhibited a median OS of 16.7 months versus the median OS in the ≤5% weight gain subgroup (‘≤5% subgroup’) of 10.7 months [$P < 0.001$; unadjusted hazard ratio (HR) = 0.57, 95% confidence interval (CI) 0.50–0.65] (Figure 1A). An additional analysis using ‘any weight gain’ rather than 5% as the cutoff (1066 of the 2301 patients in this group) found similar results (median OS = 15.2 and 8.6 months, respectively; HR = 0.51, 95% CI 0.46–0.56).

The median PFS was also statistically longer for the >5% subgroup (6.9 versus 4.8 months, $P < 0.001$; unadjusted HR = 0.61, 95% CI 0.55–0.69) (Figure 1B). When the analysis was repeated for the three-trial intent-to-treat (randomized) population ($n = 2924$, supplementary Appendix Table SA, available at *Annals of Oncology* online), near identical results were obtained (data not shown).

There was also a statistically significant difference between the ORR and DCR of the >5% subgroup and that of the ≤5% subgroup. (50.8% versus 25.4%, $P < 0.001$; 91.5% versus 63.6%, $P < 0.001$) (Table 2).

Adjusted Cox modeling revealed that patients in the >5% subgroup had significantly longer survival (HR = 0.54, 95% CI 0.47–0.62; $P < 0.001$) than those in the ≤5% subgroup, after adjusting for baseline age (<65 versus ≥65), sex, ECOG PS (0 versus 1/2), histology (adenocarcinoma versus others), disease stage (IIIB versus IV), smoking (yes versus no), BMI (<20, 20–25, >25), and study. Similar significant results were found for PFS, with patients in the >5% subgroup exhibiting significantly longer PFS (HR = 0.59, 95% CI 0.52–0.67; $P < 0.001$) than those in the ≤5% subgroup after adjusting for the other covariates.

Except for age in the OS model and sex in the PFS model, all other baseline covariates were identified as significant prognostic factors for survival outcomes, after adjusting for other covariates in the model. For BMI, the group of BMI >25 had significantly longer OS and PFS than the other two BMI groups.

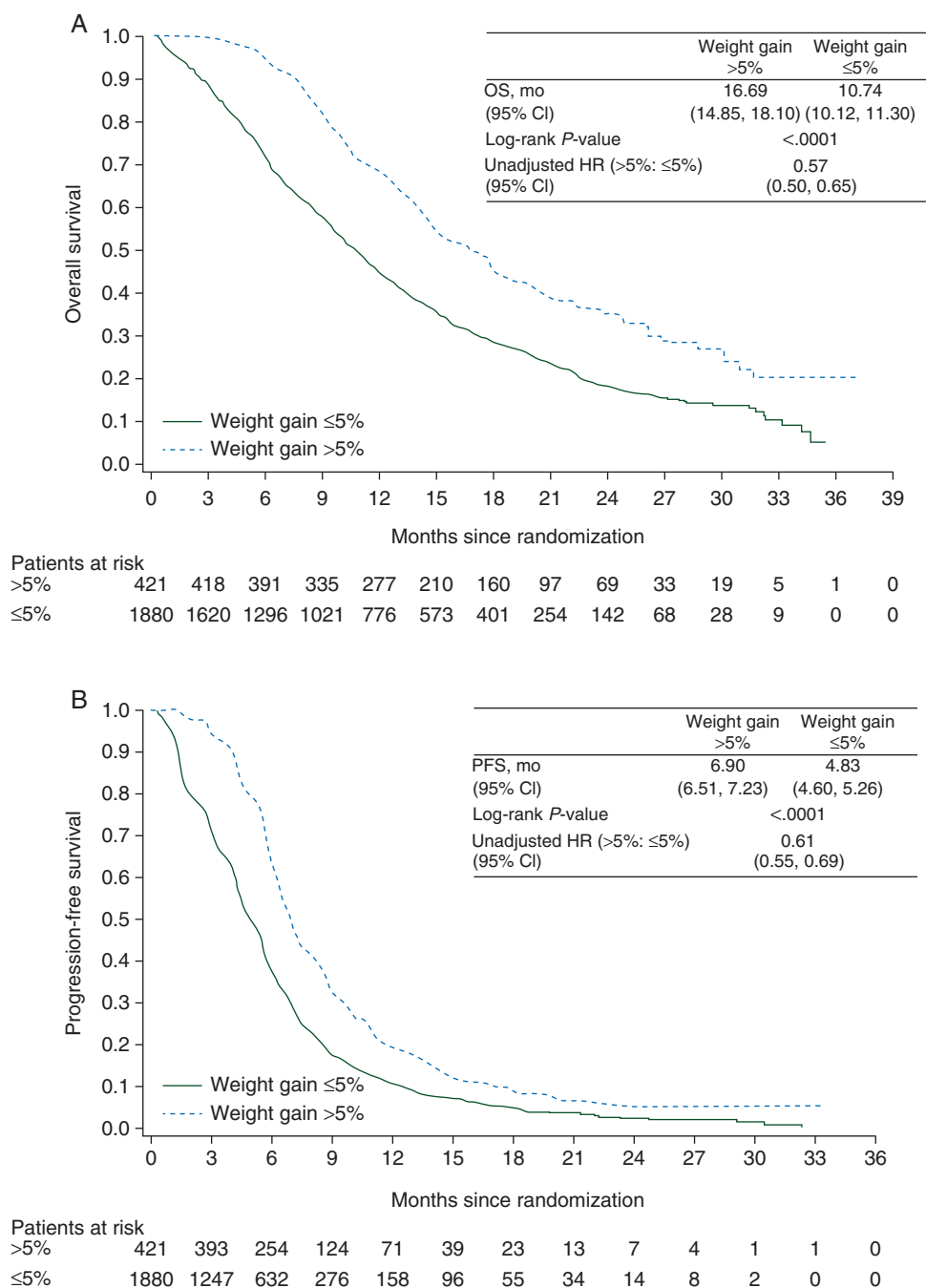


Figure 1. Graphs of the Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival by >5% weight gain and ≤5% weight gain in the three-trial non-squamous analysis set. CI, confidence interval; HR, hazard ratio; *n*, number of patients; mOS, median overall survival (months); mPFS, median progression-free survival (months).

The Forest plot (Figure 2) demonstrates the median OS differences between patients with or without a >5% weight gain by baseline characteristics (age, sex, histology type, ECOG PS, disease stage, smoking history, BMI, and study). The plot shows the statistically significant improvement in survival with weight gain in all subgroups.

Logistic regression models with multiple covariates were used to ascertain if patients displaying weight gain were more or less likely to display a tumor response or disease control. Adjusting

for the baseline covariates (age, gender, non-squamous histology type, ECOG PS, stage, smoking history, BMI, and study), patients in the >5% subgroup were significantly more likely to exhibit a complete or partial tumor response (OR = 2.55, 95% CI 2.02–3.22; *P* < 0.001) and disease control (CR + PR + SD) (OR = 4.28, 95% CI 2.89–6.35; *P* < 0.001).

For the exploratory BMI analysis, patients were grouped based on their baseline BMI and post-baseline weight gain status: BMI >25 and weight gain >5% (*n* = 144, median

Table 2. Best overall response rate in the three-trial analysis set

Variable	All combined All (n = 2301)	All strata		P-value*
		>5% Gain (n = 421)	≤5% Gain (n = 1880)	
Complete response (CR) (%)	0.4	0.7	0.4	
95% CI	(0.2, 0.8)	(0.2, 2.1)	(0.2, 0.8)	
Partial response (PR) (%)	29.6	50.1	25.1	
95% CI	(27.8, 31.6)	(45.2, 55.0)	(23.1, 27.1)	
Stable disease (SD) (%)	38.6	40.6	38.1	
95% CI	(36.6, 40.6)	(35.9, 45.5)	(35.9, 40.4)	
Progressive disease (%)	19.4	7.6	22.1	
95% CI	(17.8, 21.1)	(5.3, 10.6)	(20.2, 24.0)	
Unknown/missing (%)	11.91	1.0	14.4	
95% CI	(10.6, 13.3)	(0.3, 2.4)	(12.8, 16.0)	
ORR (CR + PR) (%)	30.1	50.8	25.4	<0.001
95% CI	(28.2, 32.0)	(46.0, 55.7)	(23.5, 27.5)	
DCR (CR + PR + SD) (%)	68.7	91.5	63.6	<0.001
95% CI	(66.7, 70.6)	(88.4, 93.9)	(61.3, 65.7)	

*P-value: Fisher's exact test to compare >5% gain versus ≤5% gain.

CI, confidence interval; ORR, overall response rate; DCR, disease control rate.

OS = 20.6 months, 95% CI 17.08–26.78); $20 \leq \text{BMI} \leq 25$ and weight gain >5% ($n = 214$, median OS = 14.7 months, 95% CI 13.86–17.74); BMI <20 and weight gain >5% ($n = 63$, median OS = 15.7 months, 95% CI 10.32–16.99); BMI >25 and weight gain ≤5% ($n = 941$, median OS = 11.6 months, 95% CI 10.78–12.42); $20 \leq \text{BMI} \leq 25$ and weight gain ≤5% ($n = 726$, median OS = 10.2 months, 95% CI 9.4–11.27); and BMI <20 and weight gain ≤5% ($n = 213$, median OS = 7.8 months, 95% CI 6.28–9.63). The log-rank tests show that the group of BMI >25 and weight gain >5% had significantly longer survival than other groups. In an adjusted Cox model with the BMI by weight gain group included as a categorical variable, this group variable was shown to be a significant factor for OS ($P < 0.001$), after adjusting for baseline covariates (age, sex, histology type, ECOG PS, disease stage, smoking history, and study). Moreover, the group BMI >25 and weight gain >5% had significantly longer survival than other BMI and weight gain groups, after adjusting for baseline covariates.

discussion

In this retrospective study, weight gain during chemotherapy was compared with outcomes in patients with advanced non-squamous NSCLC using pooled data from three phase III clinical trials. A weight gain of >5% occurred after initiation of platinum-based chemotherapy in 18% of patients (421 patients). This subgroup of patients exhibited a positive correlation between weight gain and improved OS, PFS, and tumor response. Although this association was also observed when weight gain was defined as 'any weight gain' (rather than >5%), our analyses focused on patients with >5% weight gain since the lower cutoff likely includes patients with small increases in weight due to daily fluctuations in hydration and standard error variances.

Weight loss exhibited by cancer patients may be due to the physical inability to ingest or digest food (e.g. due to nausea). However, across all types of cancer, associated weight loss is more frequently an outcome of cachexia syndrome, that is, the cancer-induced metabolic shift that results in an involuntary loss of body mass (fat and muscle) that cannot be reversed nutritionally [15]. This metabolic shift is characterized by increased lipolysis and alterations in skeletal muscle metabolism including increased resting energy expenditure, decreased protein synthesis, and increased protein degradation [15]. Patients also exhibit hypoalbuminemia and evidence of inflammation (e.g. elevated C-reactive protein). Cachexia decreases patients' quality of life, reduces physical activity, causes greater susceptibility to infection, and is the cause of death in at least 20% of all cancer patients [16].

The association of weight gain with disease control and superior survival suggests that treatment-induced tumor regression/stabilization may inhibit molecular pathways involved in cachexia. This observation raises the possibility that therapeutic strategies specifically targeting mechanisms of cachexia might reduce tumor growth rate and prolong survival. Although previous nutritional and pharmacologic anti-cachexia interventions have not been successful, there is increasing information regarding the mechanisms that mediate cancer cachexia. Ongoing sarcopenia, a dominant feature of cancer cachexia, serves as a source of energy and molecules for synthesis of macromolecules in tumors. Recently, anamorelin, a ghrelin agonist [17], and enobosarm [18], a selective androgen receptor modulator, have been shown to increase lean body mass in advanced lung cancer patients. Evaluation of OS was not a primary end point on these studies.

While the mechanisms that mediate cancer cachexia are incompletely defined, substantial evidence suggests the involvement of inflammatory cytokines released either by the tumor or host inflammatory cells responding to the tumor [15, 16].

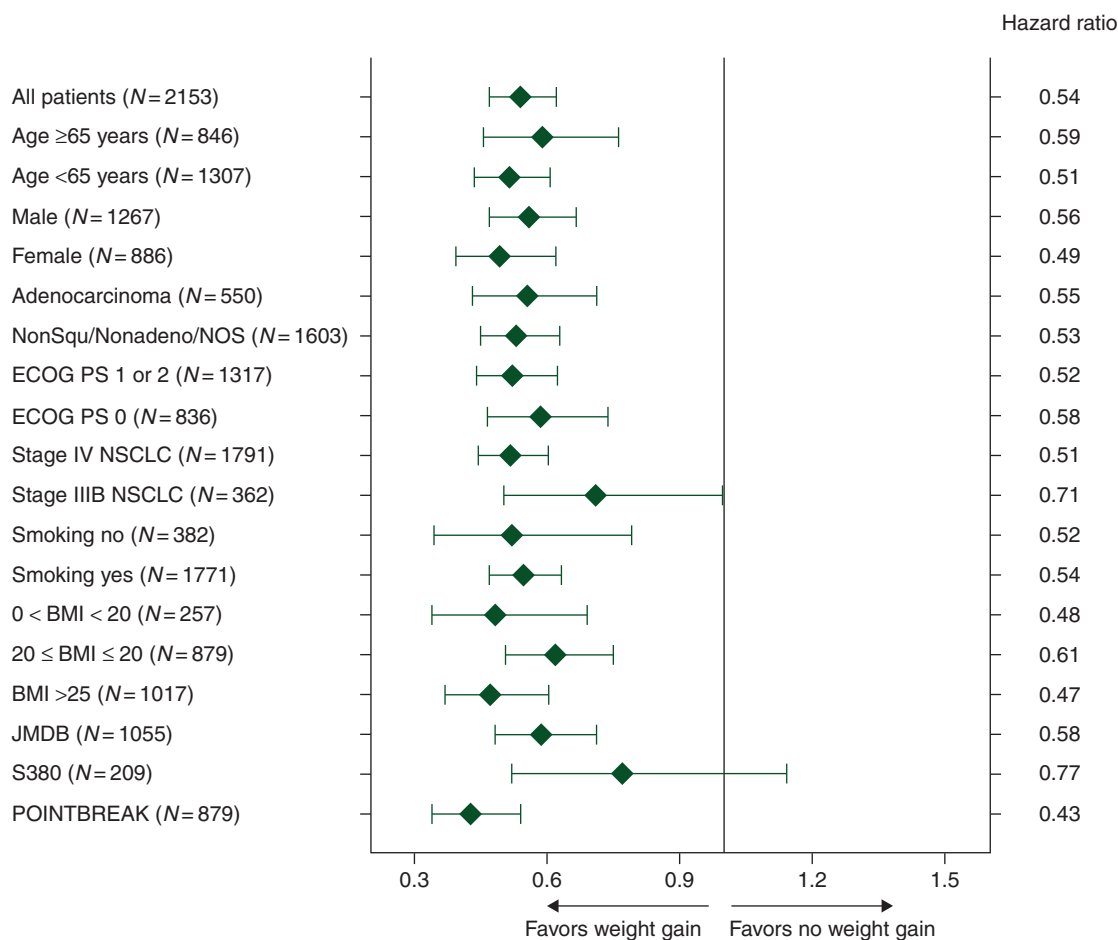


Figure 2. Overall survival hazard ratios (>5% weight gain/≤5% weight gain) in subgroups according to baseline characteristics. Survival hazard ratios (weight gain >5% versus weight gain ≤5%) are shown for subgroups of the analysis set as defined by baseline characteristics. Ninety-five percentage confidence intervals are depicted; *P*-values are <0.001 except for the S380 subgroup (*P* = 0.019), stage IIIB subgroup (*P* = 0.047), and Smoking No (*P* = 0.002). This analysis used the non-squamous-treated patient set used by other analyses, but excluded 148 patients who did not have smoking status at baseline. For each subgroup, an adjusted Cox model was fitted to obtain the hazard ratio and *P*-value for the weight gain group comparison. The controlling covariates that were included in the models were age, gender, histology, ECOG performance status, disease stage, BMI, smoking history, and study. The covariate used to select the patient subgroup to be analyzed was excluded in the adjusted Cox model. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; NonSqu/Nonadeno/NOS, non-squamous/non-adenocarcinoma/not otherwise specified histology; PS, performance status.

Tumor necrosis factor α (TNF α), interleukin-6 (IL-6), interferon γ (IFN γ), and transforming growth factor β superfamily member MIC-1/GDF15 have been implicated as cachexia mediators [15, 19, 20]. Interestingly, elevated levels of circulating inflammatory cytokines have also been shown to occur with age [21, 22]. Specifically, elevated levels of TNF α , IL-6, and IL-1 have been associated with increased morbidity and mortality in older patients, with TNF α and IL-6 markers of mortality in frail elderly patients [22]. This higher basal level of inflammatory cytokines in older patients may in part explain why the univariate logistic regression analysis identified younger patients as more likely to gain weight after treatment than older patients. The positive association between younger age and gaining weight observed in our Cox analyses does not necessarily mean younger patients will also have a significantly better survival outcome since there may be some interactive effect between age and other covariates such as this low level elevation of inflammatory cytokines. Our logistic regression analysis also found

that patients with a better PS (0 versus 1/2) were more likely to gain weight. A similar association was also found in a study in which a heightened inflammatory response in advanced NSCLC patients was accompanied by poorer performance status, greater weight loss, and poorer survival [23]. Although our studies did not collect samples required to study inflammatory cytokines, future studies might explore their contribution to weight loss and gain. Studies might also collect data on serum albumin levels before and after chemotherapy to determine whether low albumin is a predictive factor for chemotherapy benefit and risk of toxicity. If albumin is a predictive factor for weight gain, patients who have had greater weight loss, or weight loss over a longer time period, might have lower albumin levels more suggestive of cachexia than those with more normal albumin levels.

Our analyses of the non-squamous NSCLC patients found similar HRs associated with all three BMI subgroups, suggesting a similar survival advantage among individuals who gain weight, independent of their initial weight. This included those

in the 20–25 BMI (ideal weight range), >25 BMI (overweight), and <20 BMI (approaching underweight). The low BMI subgroup is noteworthy because these individuals may have already experienced cachexia-induced weight loss or have comorbidities that interfere with weight gain. The high BMI weight group is also interesting in that they did as well as the ideal BMI weight group. Given that proinflammatory cytokines including TNF α and IL-6 are secreted by adipose tissue, this similar outcome of the high and ideal BMI groups suggests that mechanisms other than inflammatory cytokines may be involved in weight loss [22].

The adjusted Cox modeling showed that after adjusting for other covariates, patients with high (>25) baseline BMI had a statistically significant longer OS and PFS. A recently published analysis has investigated the impact of baseline BMI and weight loss on OS [24]. In the absence of pretreatment weight loss data in our studies, we carried out an exploratory analysis investigating the impact of baseline BMI and post-baseline weight gain on OS. The results show that baseline BMI and post-baseline weight gain are significant predictors for OS, after adjusting for other baseline covariates. Particularly, the group of BMI >25 and weight gain >5% had significantly longer median OS compared with other BMI and weight gain groups. Interestingly, a recent analysis of ECOG trials also showed an association of high BMI (≥ 30 , obese) with longer survival relative to a combined group of normal weight (18.5–25 BMI) and overweight (>25–30 BMI) patients [25]. The ECOG trial analysis also observed that the ≥ 30 BMI subgroup exhibited a significant increase in OS HR relative to the normal/overweight subgroup when time on study exceeded 16 months.

The analyses presented here are retrospective and thus would benefit from confirmation by additional prospective studies. An additional limitation of these analyses was the absence of data regarding the percentage of weight loss each patient had experienced before study therapy. These data would clarify if the patients who gained weight were the same as those who experienced pretreatment weight loss. If pretreatment weight loss correlated with on-treatment weight gain, this finding could support the hypothesis that longer survival was at least in part the result of reversing cachexia. Our data were also limited and potentially skewed because the analyses did not factor in that patients with progressive disease discontinued from study treatment earlier than those who have stable or responding disease. Patient drop out would give the stable/responding patients more time on study in which to gain weight and thus magnify the contribution of weight gain on treatment outcome. Finally, our analyses did not separate the high BMI subgroup into obese (≥ 30) and overweight (≥ 25 –30 BMI) groupings. Doing so in future analyses will allow further observation of subgroup trends while enabling and accounting for the larger weight gain necessary for the obese population to achieve a 5% weight gain.

Serial weight measurement is a readily accomplished assessment. If additional prospective studies confirm weight gain as prognostic for survival, its assessment will provide an additional tool for the treating physician. Stable or increasing weight might be cause to continue with the treatment regimen; conversely, declining weight might alert the physician to the need for a different therapeutic approach. While serial weight measurement will not replace NSCLC tumor assessment as the definitive measure of treatment efficacy,

stable or increasing weight may be practical indicators of clinical benefit related to tumor control and treatment tolerability.

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disclosure

GS reports honoraria from Eli Lilly, AstraZeneca, Pfizer, Roche, and Clovis Oncology; service as a consultant for Eli Lilly, and speakers' bureau participation for Eli Lilly, AstraZeneca, and Roche. PDB reports honoraria and service as a consultant for Eli Lilly, Pfizer, Merck, and Helsinn, and travel funds from Eli Lilly and Helsinn. JC, JL, SCG, WJJ, and MO are employees of Eli Lilly and Company. All remaining authors have declared no conflicts of interest.

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The role of oral hygiene in head and neck cancer: results from International Head and Neck Cancer Epidemiology (INHANCE) consortium

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Background: Poor oral hygiene has been proposed to contribute to head and neck cancer (HNC) risk, although causality and independency of some indicators are uncertain. This study investigates the relationship of five oral hygiene indicators with incident HNCs.

Methods: In a pooled analysis of 8925 HNC cases and 12 527 controls from 13 studies participating in the International Head and Neck Cancer Epidemiology Consortium, comparable data on good oral hygiene indicators were harmonized.

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