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Weight Changes during Early Breast Cancer Treatment and their Association with Survival: An Exploratory Functional Data Analysis of GIM-2 Trial

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INTRODUCTION

Limited evidence is available on the impact of early breast cancer (EBC) treatments on body weight. Notably, robust data quantifying the magnitude and timing of weight changes during treatment are lacking, and existing findings on the association between weight changes and long-term survival outcomes are conflicting [1–3]. Since weight changes may reflect metabolic shifts [4], influence treatment tolerability [5], affect dosing [6], or serve as prognostic markers, our findings could help optimizing both therapeutic and supportive care strategies.

AIMS

We have two objectives. First, to describe how patients' weight changes during the administration of EBC treatments. Second, to explore whether these short-term weight changes are associated with long-term survival outcomes.

METHODS

We used data from the GIM-2 trial, a randomized phase III trial in patients with EBC, which compared the addition of fluorouracil (FEC-P) to standard anthracycline-taxane chemotherapy (EC-P), administered either dose-dense (q14) or at standard intervals (q21). Body weight was recorded at randomization and at each treatment visits. We used Functional

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Data Analysis (FDA) to model individual weight trajectories [7], compare them across subgroups [8], and identify groups of patients with similar trajectories [9]. Two grid search approaches were used: (1) to find the parameters that minimized the generalised cross-validation criterion for curve fitting, and (2) to identify the optimal clustering strategy based on the largest average silhouette score. Long-term outcomes included overall survival (OS), disease-free survival (DFS), and breast cancer–free interval (BCFI), defined according to the STEEP Criteria [10]. Associations between weight changes and outcomes were evaluated using landmark analyses, applying either the standard Cox Proportional Hazard Model (CPH) or its extension [11] to handle functional covariates. In both approaches, models were adjusted for relevant baseline characteristics.

RESULTS

A total of 17,361 weight measurements were analyzed from the 1,978 patients with complete data on treatment administration, stage, and grade. By the end of the treatment, the average weight change from baseline was +0.5%, with 13% of patients experiencing weight changes of ±5% or more. Older and obese patients tended to lose more weight, while tumor characteristics were not associated with weight change. Patients on q21 had a modest but significant weight gain compared to those on q14 (+0.8%, 95% CI: 0.5–1.2), with divergence in mean groups trajectories emerging early during treatment (L2N Test statistic = 1.38, p-value < 0.001). No statistically significant differences were observed between FEC-P and EC-P (L2N Test statistic = 0.01, p-value = 0.76). Conventional CPH models suggested a modest OS benefit associated with weight gain during treatment (HR per 1% increase=0.97; 95%CI=0.94–1.00; p-value=0.039). However, this association was not consistent across all outcomes and appeared to conflict with the observed beneficial treatment effect of the q14 versus q21. FDA revealed a more nuanced picture: the impact of weight gain varied according to its time, with mid-treatment gains appearing less favorable. Notably, a subgroup of patients—more frequently in the q21 treatment group—who experienced weight gain during mid-treatment had significantly increased risk of death compared to those with stable weight (adjusted HR: 1.58, 95% CI: 1.10–2.27). Similarly, patients with mid-treatment weight loss—a pattern more common among older and obese patients—had a higher risk of adverse outcomes across all endpoints (adjusted HR: 1.46, 1.38, and 1.47 for OS, DFS, and BCFI, respectively), and also received reduced dose intensity across all drugs.

CONCLUSIONS

By overcoming the limitations of traditional analyses based on weight changes between two arbitrary fixed timepoints, FDA provided a comprehensive, time-based characterization of weight trajectories. This approach identified distinct patient subgroups with similar longitudinal patterns of weight change, which were also associated with differences in dose intensity and clinical outcomes. These findings support the potential of FDA-informed profiling to guide personalized management strategies in early breast cancer care.

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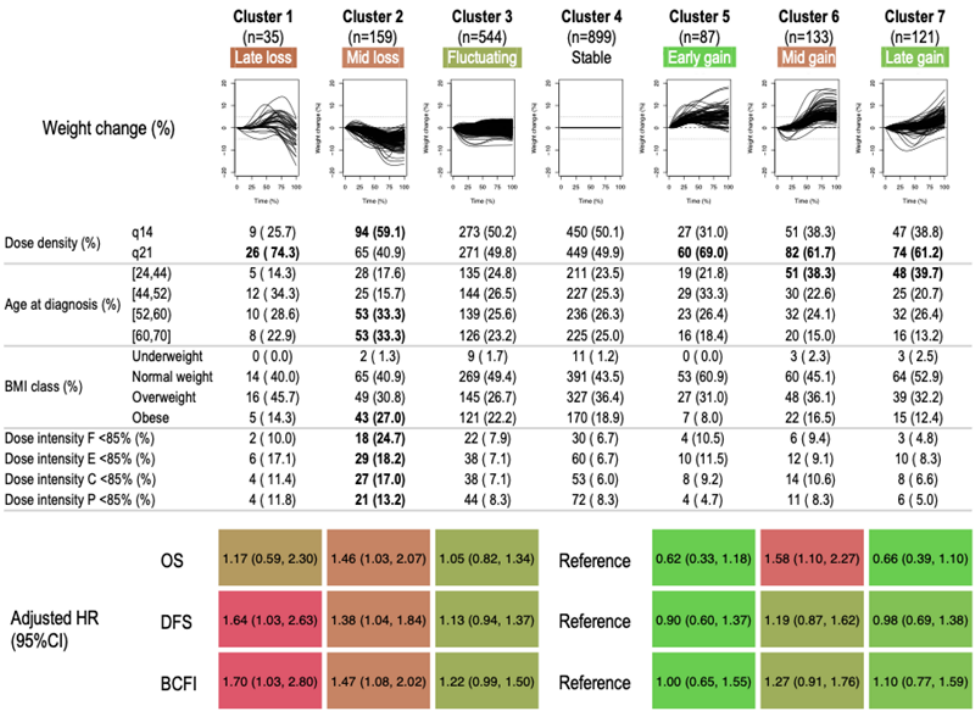

Figure 1. Characteristics associated with patients clusters based on weight changes

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