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The Impact of Weight Change During and After Post-Operative Chemotherapy on Breast Cancer Control in Node-Positive Patients Treated With Trimodality Therapy

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Abstract

Objective: The purpose of this investigation was to determine whether an association exists between post-operative chemotherapy weight change and breast cancer control and survival, specifically within a high-risk population of women with node-positive breast cancer diagnosed and treated in the contemporary setting.

Methods: A retrospective investigation with the following eligibility criteria: women who underwent primary surgical therapy for invasive breast cancer, were found to have pathologic evidence of nodal involvement, and were treated with adjuvant chemotherapy and radiation therapy. Demographic, tumor-, and treatment-related data were recorded and analyzed for association with disease control and survival outcomes. The post-operative/pre-chemotherapy weight and BMI served as the baseline comparator for future weight/BMI changes.

Results: From January 2004 through December 2008, 52 patients were identified for inclusion. At a median follow-up of 77.2 months (range 19.9–119.4, with 85% followed $\geq$5 years), 8 patients experienced disease recurrence and 7 patients had died (3 with recurrent disease). Analysis of factors associated with study endpoints identified absolute weight and BMI change at 1, 3, and 4 years post-chemotherapy completion as significantly inversely associated with overall survival, but not associated with freedom from failure. Additionally, a statistically significant association between number of lymph nodes involved and freedom from failure was identified.

Conclusion: This investigation did not detect statistically significant associations between weight or BMI change during chemotherapy and disease control or survival within this high-risk population, while the number of lymph nodes involved was directly related to risk of disease failure. Weight change at intervals following chemotherapy completion demonstrated some association with overall survival.

Keywords: breast neoplasms, chemotherapy, BMI, weight change

1. Introduction

Breast cancer is a devastating disease with significant individual and societal implications. It is the most commonly diagnosed cancer among females in the United States, and currently accounts for an estimated 230,000 new cases each year (Siegel et al., 2013). Data from Surveillance, Epidemiology, and End Results (SEER) database demonstrates that one in eight women in the U.S. will be diagnosed with the disease in their

lifetime (SEER, 2011). Mortality from breast cancer is second only to lung cancer, accounting for over 40,000 deaths each year, and breast cancer is the leading cause of cancer death among women 40-49 years of age (Seigel et al, 2013). The five year survival rates include 98% for localized disease, 84% for locoregionally advanced disease, and 27% for metastatic disease (Newman, 2009). The highest rate of breast cancer is observed in Caucasian women, but it is the most common cancer among women for every major ethnic group.

Obesity is a risk factor for the development of new cases of breast cancer and also affects survival in women who already have been diagnosed with breast cancer (Protani et al., 2010). There is a consistently demonstrated correlation between increased risk for breast cancer and increasing hormone levels (estradiol and estrone) (Key et al., 2002). As peripheral conversion of endogenous estrogens occurs predominately in adipose tissue, increases in body weight have been directly associated with circulating estradiol and estrone, which may fuel tumor growth (6); this is felt to account for the association between obesity and increased risk for breast cancer noted above.

Weight gain is a common problem among patients with breast cancer who receive adjuvant (post-operative) chemotherapy (Demark-Wahnefried et al., 1997; Demark-Wahnefried, Winer, & Rimer, 1993; Ganz et al., 1987; Goodwin et al., 1999; Heasman et al., 1985). This has been a consistent finding since the initial observation made by Dixon et al. (1978). This is especially pronounced in pre-menopausal patients and those who receive multi-agent chemotherapy regimens, with up to 25% of gaining more than 11kg (Demark-Wahnefried et al., 1997; Demark-Wahnefried, Winer, & Rimer, 1993). Weight gain is undesirable in this population for several reasons including negative effect on quality of life and predisposition to obesity-related disorders (hypertension, diabetes, cardiovascular and gallbladder disease, and orthopedic disorders) (Demark-Wahnefried et al., 2001). In addition, studies have shown that chemotherapy-associated weight gain in pre-menopausal women is directly associated with risk of breast cancer relapse and mortality (Camoriano et al., 1990).

The purpose of the present investigation is to determine the impact of the degree of weight change during chemotherapy on breast cancer control within a high-risk population of pre- and post-menopausal women with node-positive breast cancer who underwent contemporary tri-modality therapy, including surgery, chemotherapy, and radiation therapy.

2. Method

2.1 Patient Selection Criteria

This retrospective review was approved by the institutional review boards of the participating institutions. Cases were identified from electronic medical record review, with preliminary selection as women diagnosed with breast cancer between January 2004 and December 2008. Eligible patients were those diagnosed with node-positive breast cancer who received primary surgical therapy followed by adjuvant chemotherapy and radiation therapy. Patients were excluded if any of the following were noted: pre-operative chemotherapy or hormonal therapy, male gender, metastatic cancer at diagnosis, insufficient follow-up (less than 12 months post-chemotherapy completion), and node-negative disease.

Between January 2004 and December 2008, 61 patients diagnosed with node-positive breast adenocarcinoma underwent curative-intent surgical resection, chemotherapy, and radiation therapy. Of these, 52 were eligible for inclusion in the present study. Reasons for exclusion were insufficient/missing records (5 patients) and neoadjuvant (pre-operative) chemotherapy or hormone therapy (4 patients).

2.2 Study Data Collection

Study data were collected from existing quality assurance databases and electronic medical records and included patient demographics, tumor characteristics (including tumor location and laterality, histology, tumor grade, number of disease foci, number of nodes removed and involved, tumor size, presence/absence of lymphovascular or perineural invasion, hormone receptor status, HER-2 status, surgical margin specifics, clinical and pathologic stage), treatment factors (including surgical procedure performed, radiotherapy and systemic therapy specifics), and outcome variables (including disease control and survival status at last follow-up, interval to last follow-up, interval to disease recurrence, location of initial disease recurrence, recurrence work-up studies performed, and salvage therapy specifics.). Specific to weight change, pre-operative and post-operative (pre-chemotherapy) weights and body mass index (BMI) were recorded, as were post-chemotherapy weights (immediate, 6-month, and annually through 5 years post-chemotherapy). The post-operative/pre-chemotherapy weight served as the baseline comparator for change for future weight and BMI levels.

Patients were generally followed every 3–4 months during the first 1–2 years post-chemotherapy, then every 6 months through 5 years, and annually thereafter. Disease control was measured from the date of definitive

surgery (lumpectomy or mastectomy) to the date of disease recurrence or last follow-up. Survival was measured from surgery to the date of death or last follow-up.

2.3 Statistical Analysis

The Kaplan-Meier method was employed to estimate 5-year freedom from failure (with 95% confidence intervals, p-value < 0.05) for the entire population and subsets. Cox proportional hazards model was used to identify continuous, categorical, and dichotomous variable association with disease control. Analyses were performed using SPSS Version 21 (SPSS, Inc.; Chicago, IL, USA).

3. Results

Fifty-two patients were eligible for inclusion in the present study. Patient demographics are outlined in Table 1. Surgical, pathology, and treatment-related data are demonstrated in Table 2.

Table 1. Patient demographics

		N	%
Age (at diagnosis)			
Median	60 yrs		
(Range)	(27-86)		
Race			
White		49	94
Presentation			
Asymptomatic*		20	38
Symptomatic[#]		32	62
Laterality			
Right		26	50
Location			
Central		6	12
Upper Outer		35	67
Lower Outer		6	12
Lower Inner		2	4
Upper Inner		3	6
Histology			
Ductal		38	73
Lobular		12	23
Mixed		2	4
Grade			
1		6	12
2		9	17
3		31	60
4		2	4
Not Recorded		4	8
Molecular Features			
ER+/PR+/HER2+		8	15
ER+/PR+/HER2-		19	37
ER+/PR-/HER2+		5	10
ER+/PR-/HER2-		4	8
ER-/PR+/HER2+		3	6
ER-/PR+/HER2-		3	6
ER-/PR-/HER2+		6	12
ER-/PR-/HER2-		5	10

*Includes 19 patients detected on screening mammography and 1 patient incidental on positron emission tomography. [#]Includes 31 patients detected by self-palpation and 1 patient with nipple discharge without palpable mass.

Table 2. Surgical-, Pathology-, and Treatment-Related Data

		N	%
Interval Biopsy to Surgery			
Median	12 days		
(Range)	(0-63)		
Surgery Type			
Lumpectomy		16	31
Mastectomy		36	69
Primary Tumor Size			
Median	2.7cm		
(Range)	(1-13)		
Pathologic Tumor Stage[$]			
T2a		28	10
T2b		11	4
T2c		169	61
T3a		71	25
Tumor Foci			
Unifocal		42	81
Multifocal		10	19
Lymphovascular Invasion			
Yes		23	44
No		24	46
Not Recorded		5	10
Margin Status			
Involved		7	13
Lymph Node (LN) Evaluation			
Median Removed	12 LNs		
(Range)	(1-49)		
Median Involved	3.5 LNs		
(Range)	(1-23)		
Median % Involved	48%		
(Range)	(6-100%)		
Extranodal Extension		23	44
Pathologic Stage[$]			
IIA		10	19
IIB		14	27
IIIA		17	33
IIIB		1	2
IIIC		10	19
Chemotherapy			
Median Interval Surgery to Chemo	5.1 weeks		
(Range)	(2.2-14.0)		
Anthracycline		42	81
Completed >75% of Planned Chemo		45	87
Hormone Therapy			
Yes*		37	90
Radiation Therapy (RT)			
Median Interval Chemo to RT	28 days		
(Range)	(18-39)		
Median Total RT Dose[#]	6040 cGy		
(Range)	(5240-6640)		

*Excludes 11 hormone-insensitive patients. [$]American Joint Committee on Cancer, TNM Staging Manual, version 7.0. [#]Inclusive of breast/chestwall dose plus boost, when employed.

At a median follow-up of 77.2 months (range 19.9-119.4, with 85% followed ≥5 years), 8 patients had experienced disease recurrence at a median of 49.9 months (14.8-87.7). Patterns of failure included distant-only in 6 patients and locoregional plus distant in 2 patients. Seven patients had died; 3 with recurrent disease, 3 of other cause (1 each of myocardial infarction, end stage renal disease, and acute myelogenous leukemia; all were without recurrent disease at last follow-up), and 1 of unknown cause (probable myocardial infarction, without evidence of disease recurrence 14 months prior). Analysis of factors associated with freedom from failure demonstrated a statistically significant association with number of lymph nodes involved, while absolute weight change and BMI at 1, 3, and 4 years post-chemotherapy completion was associated with overall survival (Table 3; comprehensive analysis in Appendix A).

Table 3. Univariate analyses of factors associated with disease control and survival

	Disease Control		**Overall Survival**	
	exp(b) (95% CI)	p-value	exp(b) (95% CI)	p-value
Number of LNs Involved	**1.119 (1.026-1.221)**	**0.011**	1.051 (0.945-1.168)	0.358
% of LNs Involved	*10.404 (0.983-110.128)*	*0.052*	1.555 (0.157-15.420)	0.706
Absolute Change Weight Post-Op/Pre-Chemo to 1 year Post-Chemo	1.008 (0.947-1.072)	0.803	**0.956 (0.918-0.995)**	**0.026**
Absolute Change BMI Post-Op/Pre-Chemo to 1 year Post-Chemo	1.044 (0.725-1.504)	0.817	**0.770 (0.609-0.974)**	**0.029**
Absolute Change Weight Post-Op/Pre-Chemo to 2 years Post-Chemo	0.990 (0.938-1.046)	0.730	0.934 (0.863-1.011)	0.093
Absolute Change BMI Post-Op/Pre-Chemo to 2 years Post-Chemo	0.959 (0.697-1.320)	0.798	0.669 (0.417-1.076)	0.097
Absolute Change Weight Post-Op/Pre-Chemo to 3 years Post-Chemo	0.962 (0.910-1.017)	0.169	**0.887 (0.812-0.969)**	**0.008**
Absolute Change BMI Post-Op/Pre-Chemo to 3 years Post-Chemo	0.797 (0.575-1.105)	0.173	**0.501 (0.303-0.830)**	**0.007**
Absolute Change Weight Post-Op/Pre-Chemo to 4 years Post-Chemo	0.953 (0.876-1.035)	0.254	**0.869 (0.781-0.966)**	**0.009**
Absolute Change BMI Post-Op/Pre-Chemo to 4 years Post-Chemo	0.741 (0.455-1.209)	0.230	**0.448 (0.248-0.810)**	**0.008**

With respect to weight change during and after chemotherapy, these specific data are demonstrated in Table 4.

Table 4. Weight and Body Mass Index (BMI) change during and after chemotherapy

Interval Post-Chemotherapy (n)	Weight Change	BMI Change	Relative Change
	Median (Range)	Median (Range)	Median (Range)
Immediate (52)	-1.9 lbs (-41.0 to +24.8)	-0.4 cm/m^2 (-7.0 to +4.1)	-1.3% (-18.1 to +14.1)
6-month (52)	+2.4 lbs (-54.0 to +33.6)	+0.4 cm/m^2 (-9.3 to +6.1)	+1.3% (-18.4 to 21.5)
1-year (52)	+4.5 lbs (-54.0 to +30.0)	+0.8 cm/m^2 (-9.3 to +4.8)	+2.4% (-18.4 to +15.0)
2-year (49)	+3.0 lbs (-27.0 to +47.0)	+0.7 cm/m^2 (-4.5 to +7.5)	+2.7% (-15.4 to +23.3)
3-year (48)	+3.5 lbs (-46.0 to +33.0)	+0.7 cm/m^2 (-7.9 to +5.7)	+2.5% (-15.6 to +18.8)
4-year (44)	+1.0 lbs (-62.0 to +33.0)	+0.2 cm/m^2 (-10.6 to +6.1)	+0.8% (-21.1 to +23.7)
5-year (39)	+5.0 lbs (-41.0 to +45.0)	+0.8 cm/m^2 (-6.4 to +7.8)	+3.5% (-19.4 to 33.2)

4. Discussion

The purpose of the present investigation is to determine the impact of weight change during chemotherapy on breast cancer control within a high-risk population of women with node-positive breast cancer who underwent tri-modality therapy, including surgery, chemotherapy, and radiation. Similar to several previously-published studies, we observed that weight gain is a common problem in patients receiving adjuvant chemotherapy (Demark-Wahnefried et al., 1997; Demark-Wahnefried, Winer, & Rimer, 1993; Ganz et al., 1987; Goodwin et al., 1999; Heasman et al., 1985). Obesity is a known risk factor for the development of new cases of breast cancer and has been associated with decreased survival in active breast cancer patients (Protani et al., 2010). A prevailing hypothesis for this is that obese individuals have elevated serum estrogen levels, which has consistently been positively correlated with increased risk for development of breast cancer (Key et al., 2002). Other proposed mechanisms that may link obesity to cancer susceptibility include: diet (caloric excess and positive energy balance), sedentary lifestyle, hyperinsulinemia, insulin-like growth factors (IGF), IGF binding proteins (anabolic and anti-apoptotic effects), increased production of pro-inflammatory molecules (Interleukin-6, adiponectin, and Tumor Necrosis Factor-a), oxidative stress, increased angiogenesis, and obesity-induced hypoxia (De Pergola & Silvestris, 2013).

Specific to recurrence risk in patients with breast cancer, several previously-published studies have investigated the correlation of obesity with outcome. For example, Sparano et al. retrospectively analyzed data from three Eastern Cooperative Oncology Group (ECOG) trials, including approximately 7,000 node-positive and high-risk node-negative patients treated with anthracycline-based chemotherapy (and endocrine therapy, for hormone-sensitive tumors). A strong association was identified between obesity and disease recurrence in hormone-sensitive/HER-2 negative disease, despite adjusting for covariates including age, race, menopausal status, tumor size, number of positive axillary lymph nodes, and type of surgery (Sparano et al., 2012).

Specific to all-cause mortality within a cancer patient population, obesity at diagnosis is inversely associated with overall survival. Dignam et al. (2006) demonstrated higher BMI to be associated with greater overall mortality within a hormone-insensitive, node-negative breast cancer patient population. This was most pronounced in patients with a BMI >35, who were noted to have a two-fold increased risk of non-cancer death, most commonly due to chronic disease. Interestingly, increasing BMI was also associated with secondary primary cancers, excluding the contralateral breast. Specific to our own study population of high-risk, node-positive breast cancer patients treated with uniform contemporary guideline-based management, we did not identify any baseline weight or BMI characteristics which proved predictive of cancer recurrence or survival. One possibility is that the uniformity of treatment, employing optimal locoregional and systemic therapies, has decreased recurrence rates (and thus mortality) such that baseline obesity (or BMI) are no longer stand-alone risk factors. A second possibility is that the pattern of failure in the era of prolonged therapy may be pushed forward, and 10-15 year follow-up may be required to adequately assess these endpoints. For example, The Early Breast Cancer Trialists' Collaborative Group meta-analysis revealed that tamoxifen had a "carry-over effect" of at least

5 years after the completion of 5 years of therapy. Consequently, women who have completed adjuvant tamoxifen are at a significantly lower risk of breast cancer recurrence or death than women who do not receive tamoxifen for up to ten years after surgery (Early Breast Cancer Trialists' Group, 2005). Finally, a third possibility is that the increased risk of recurrence or mortality posed by obesity may be sufficiently small that a larger patient population may be required to detect such risk.

A unique contribution of the present study has been the longitudinal recording of patient weight and BMI before and at several points after chemotherapy. While our primary hypothesis that weight change during chemotherapy would prove to be associated with disease control or survival outcomes did not prove correct, we did identify an increase in all-cause mortality in association with the degree of absolute weight change at specific time points following chemotherapy completion. Absolute weight loss and BMI decreases at years 1, 3, and 4 post-chemotherapy were associated with mortality. As our non-breast cancer causes of death included acute myelogenous leukemia, end-stage renal disease, dementia, and an unknown cause in a patient with chronic diabetes mellitus, we suspect that the weight loss was primarily related to these processes rather than truly independently predictive. Similarly, Adams, Leitzmann, and Ballard-Barbash (2013) observed an increase in mortality risk in those 50-69 years of age who lost weight >0.2 kg per year, particularly in those who rated their health as fair or poor. Within the current study, the median age at diagnosis was 60, with variable baseline health status, such that comorbid conditions were likely to have had a greater impact on the weight change association with mortality independent of treatment and/or recurrence. It is interesting to note that despite the intensity of contemporary multiagent breast cancer-specific chemotherapy, neither weight/BMI changes during nor immediately following chemotherapy were associated with survival, only changes years later. This would suggest potential changes in the severity of the comorbid condition, rather than effects of chemotherapy, though late effects of cytotoxic chemotherapy (e.g., leukemia) certainly cannot be overlooked (Dong & Chen, 2014).

In addition to the post-chemotherapy weight changes, the number of lymph nodes involved was significantly associated with disease control. This has long been demonstrated as perhaps the most important prognostic indicator for disease free survival (Elkhodary et al., 2014; Wiznia et al., 2014; Singletary et al., 2002). More recently, the lymph node ratio (LNR; number of positive lymph nodes divided by the total examined) has been shown to be an alternative means of assessing risk of disease free survival, with some superiority when fewer than 10 lymph nodes are identified within the dissection specimen (Elkhodary et al., 2014; Wiznia et al., 2014; Chagpar, Camp, & Rimm, 2011). While our series did not meet the threshold for statistical significance for LNR association with disease control ($p=0.052$), this may have been due to the low number of cancer recurrence events.

In conclusion, the present investigation did not detect statistically significant associations between weight or BMI change during chemotherapy and disease control or survival. Subsequent decreases in weight or BMI were associated with increased mortality, most commonly from non-breast-cancer causes, though the interaction of treatment with subsequent development and/or severity of comorbid conditions cannot be entirely ruled out. We did not detect a correlation between baseline weight and BMI with breast cancer recurrence or death, noting that despite the high-risk (node-positive) patient population, disease control and survival outcomes at 5 years were favorable. Longer follow-up is required to determine whether baseline weight or BMI (and/or changes during chemotherapy) may have a measurable impact at later time points.

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Appendix A

Supplement to Table 3. Univariate Analyses of Factors Associated with Disease Control and Survival.

	Disease Control		**Overall Survival**	
	exp(b) (95% CI)	p-value	exp(b) (95% CI)	p-value
Age*	1.013 (0.959-1.069)	0.650	*1.071 (0.999-1.148)*	*0.053*
Race[#]	0.045 (0 - >1000)	0.692	3.393 (0.395-29.124)	0.265
How Detected	4.885 (0.600 – 39.726)	0.138	1.700 (0.328-8.809)	0.528
Laterality	2.544 (0.511-12.676)	0.255	0.320 (0.062-1.667)	0.176
Histology	1.067 (0.522-2.179)	0.860	1.035 (0.409-2.618)	0.942
Hormone Receptor Status	2.099 (0.257-17.116)	0.489	1.714 (0.206-14.277)	0.619
HER2 Status	0.582 (0.070-4.800)	0.615	0.035 (0-145.076)	0.429
Pre-Op BMI	1.027 (0.959-1.101)	0.444	1.007 (0.945-1.073)	0.834
Surgery Type	0.748 (0.179-3.133)	0.691	0.342 (0.076-1.531)	0.161
Interval Biopsy to Surgery	1.003 (0.950-1.059)	0.912	1.036 (0.992-1.083)	0.111
Max Tumor Size	1.123 (0.916-1.377)	0.263	1.017 (0.766-1.350)	0.909
Disease Foci	3.325 (0.788-14.032)	0.102	0.927 (0.110-7.821)	0.945
Lymphovascular Invasion	2.545 (0.494-13.123)	0.264	1.064 (0.214-5.285)	0.939
Involved Surgical Margin	0.829 (0.101-6.808)	0.862	1.200 (0.139-10.372)	0.868
Number of LNs Involved	**1.119 (1.026-1.221)**	**0.011**	1.051 (0.945-1.168)	0.358
% of LNs Involved	10.404 (0.983-110.128)	0.052	1.555 (0.157-15.420)	0.706
Extranodal Extension	3.392 (0.649-17.732)	0.148	1.816 (0.399-8.257)	0.440
Max LN Tumor Size	0.840 (0.352-2.004)	0.695	0.762 (0.259-2.248)	0.623
Pathologic AJCC Stage	1.540	0.094	1.084	0.777

	(0.929-2.552)		(0.622-1.887)	
Post-Op/Pre-Chemo BMI	0.983 (0.878-1.102)	0.774	1.045 (0.938-1.165)	0.422
Absolute Change Weight Pre-Op to Post-Op/Pre-Chemo	1.039 (0.895-1.207)	0.611	1.033 (0.872-1.224)	0.708
Absolute Change BMI Pre-Op to Post-Op/Pre-Chemo	1.246 (0.529-2.936)	0.615	1.164 (0.446-3.037)	0.756
Anthracycline	0.383 (0.091-1.605)	0.189	0.592 (0.114-3.060)	0.531
Completed >75% Chemo	1.042 (0.128-8.479)	0.969	0.351 (0.068-1.824)	0.213
Interval Mastectomy to Adjuvant Chemotherapy	0.950 (0.680-1.328)	0.765	1.225 (0.942-1.592)	0.129
Interval Adjuvant Chemotherapy Start to Finish	0.996 (0.978-1.015)	0.627	0.990 (0.971-1.009)	0.290
Post-Chemotherapy BMI	1.000 (0.892-1.121)	0.995	1.027 (0.912-1.155)	0.663
Absolute Change Weight Post-Op/Pre-Chemo to Immediate Post-Chemo	1.039 (0.970-1.112)	0.274	0.952 (0.895-1.013)	0.123
Absolute Change BMI Post-Op/Pre-Chemo to Immediate Post-Chemo	1.248 (0.830-1.879)	0.287	0.758 (0.524-1.099)	0.144
BMI at 6 months Post-Chemo	1.012 (0.904-1.133)	0.834	1.036 (0.920-1.167)	0.561
Absolute Change Weight Post-Op/Pre-Chemo to 6-month Post-Chemo	1.065 (0.985-1.150)	0.112	0.978 (0.930-1.029)	0.390
Absolute Change BMI Post-Op/Pre-Chemo to 6-month Post-Chemo	1.472 (0.932-2.323)	0.097	0.890 (0.657-1.204)	0.449
BMI at 1 year Post-Chemo	0.988 (0.883-1.105)	0.829	1.007 (0.896-1.133)	0.901
Absolute Change Weight Post-Op/Pre-Chemo to 1 year Post-Chemo	1.008 (0.947-1.072)	0.803	**0.956 (0.918-0.995)**	**0.026**
Absolute Change BMI Post-Op/Pre-Chemo to 1 year Post-Chemo	1.044 (0.725-1.504)	0.817	**0.770 (0.609-0.974)**	**0.029**
BMI at 2 years Post-Chemo	0.935 (0.814-1.074)	0.341	0.948 (0.803-1.118)	0.525
Absolute Change Weight Post-Op/Pre-Chemo to 2 years Post-Chemo	0.990 (0.938-1.046)	0.730	0.934 (0.863-1.011)	0.093
Absolute Change BMI Post-Op/Pre-Chemo to 2 years Post-Chemo	0.959 (0.697-1.320)	0.798	0.669 (0.417-1.076)	0.097
BMI at 3 years Post-Chemo	0.902 (0.776-1.048)	0.177	0.900 (0.749-1.081)	0.260
Absolute Change Weight Post-Op/Pre-Chemo to 3 years Post-Chemo	0.962 (0.910-1.017)	0.169	**0.887 (0.812-0.969)**	**0.008**
Absolute Change BMI Post-Op/Pre-Chemo to 3 years Post-Chemo	0.797 (0.575-1.105)	0.173	**0.501 (0.303-0.830)**	**0.007**

BMI at 4 years Post-Chemo	0.924 (0.775-1.102)	0.380	0.950 (0.787-1.147)	0.595
Absolute Change Weight Post-Op/Pre-Chemo to 4 years Post-Chemo	0.953 (0.876-1.035)	0.254	**0.869 (0.781-0.966)**	**0.009**
Absolute Change BMI Post-Op/Pre-Chemo to 4 years Post-Chemo	0.741 (0.455-1.209)	0.230	**0.448 (0.248-0.810)**	**0.008**
BMI at 5 years Post-Chemo	0.950 (0.789-1.145)	0.592	0.942 (0.749-1.185)	0.611
Absolute Change Weight Post-Op/Pre-Chemo to 5 years Post-Chemo	0.974 (0.913-1.040)	0.431	0.863 (0.713-1.044)	0.128
Absolute Change BMI Post-Op/Pre-Chemo to 5 years Post-Chemo	0.833 (0.561-1.238)	0.367	0.242 (0.004-13.283)	0.487
Hormone Therapy[$]	0.530 (0.063-4.446)	0.559	0.477 (0.055-4.134)	0.502
Interval Surgery to Radiotherapy	0.959 (0.837-1.099)	0.547	0.981 (0.851-1.132)	0.798
Interval Chemo to Radiotherapy	0.997 (0.952-1.043)	0.892	1.007 (0.971-1.045)	0.696

*Continuous variable; [#]Categorical variable.[$]Excludes 11 hormone-insensitive patients, for whom hormone therapy was not indicated.