Clinical implication of changes in body composition and weight in patients with early-stage and metastatic breast cancer

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Abstract.

Breast cancer represents the most frequent cancer among women in western countries. Although physicians and patients have witnessed a significant evolution in both treatment strategies and personalized medicine (the identification of featured patients' subsets such as HER2-driven disease), the identification of additional prognostic clinical predictors referring to patients' dietary habits represents a research area aiming to further improve the overall management of this disease. In this regard, body composition (i.e. the relative proportion of fat and muscles) and its changes have recently generated growing interest. A large body of evidence supports the relationship between overweight or weight gain and poor outcome in patients with early-stage breast cancer during adjuvant, and more recently, also neoadjuvant therapy. Nevertheless, a series of data on post-diagnosis weight variations and mortality reports controversial results. Indeed, the limited available data in the metastatic disease do not indicate an impact of body size on the outcome of these patients. With these perspectives, this review aims to elucidate the complex association between weight, body composition and breast cancer outcome, across the different settings of such disease. The more recent and important findings are highlighted, emphasizing the potential role of body composition assessment to predict individualize chemotherapy dosing, toxicity and efficacy, in order to improve the overall health status and prognosis of such still to date growing patients' population.

Key-words: Breast cancer; Body Mass Index; weight gain; body composition; prognosis.

Introduction.

Breast cancer (BC) represents the most common cancer and the second cause of cancer-related mortality among women in developed countries. The number of women living with a BC continues to grow due to advances in early detection and targeted treatment strategies [1].

The discovery of new clinical and biological predictors, in addition to the well-defined prognostic factors, as tumor size, lymph node status, histological type, and immunophenotypical characteristics, represents one of the main goals of ongoing research in order to improve the overall management of BC. In this regard, overweight and obesity, (identified by having a body mass index (BMI) of 25 to 30.0 kg/m^2 and a BMI ≥30.0 kg/m^2, respectively), weight gain and body composition measures have received increasing attention as potential prognostic and predictor factors of toxicity in BC [2-6], besides the well-known role as risk factors for the development of BC, particularly in the postmenopausal setting [7-9].

The results of the National Health Interview Surveys, a cross-sectional survey in the United States from 1997 to 2014, highlighted a statistically significant annual trend in increasing obesity prevalence in BC survivors (3.0%) ($p<0.001$) [10]. Moreover, a series of clinical trials have observed that the excess of weight in pre- and postmenopausal BC patients is associated with higher recurrence rate and poorer survival compared to normal weight [11-13]. This negative prognostic effect of obesity was additionally supported by several meta-analyses [14-16].

The variation of weight represents a frequent condition during and after treatment for BC [17-19], due to changes in metabolism, food intake, decreased energy expenditure and physical activity [20]. Particularly, the weight gain following a diagnosis of early-stage BC seems to predict poor survival [3, 6], despite the impact is not consistent in all studies [21, 22]. In addition, patients do not easily lose the extra weight after the end treatment, with negative consequences on patient self-image, quality of life and overall health [23, 24].

Besides the weight gain, patients affected by BC reported unfavourable changes in body composition, with a significant increase in the percent of adipose tissue and decreases of lean body mass [17, 25]. In this regard, the body composition has emerged as an important prognostic factor in cancer patients [4, 26]. Particularly, a series of studies in BC have explored the association between loss of skeletal muscle and treatment outcomes in early-stage [27] and metastatic disease, raising the potential use of body composition assessment to predict toxicity, tailor dosing and improve treatment planning [28].

Given these perspectives, the aim of this review was to explore the complex association between weight, body composition and BC outcome, across the different settings of such disease. The more recent and relevant findings are highlighted, emphasizing the potential role of body composition assessment to predict outcome, toxicity and individualize chemotherapy dosing.

Weight changes following BC diagnosis.

The majority of patients experience weight changes after BC diagnosis [29]. In this regard, the first reports suggested that 50–96% of women with early-stage disease experience significant weight gain during the

treatment phase [17, 30]. Furthermore, other studies showed that weight change continues progressively for some years after diagnosis, even in patients who remain weight stable during treatment [19]. In this context, a retrospective study of 185 women diagnosed with stage I-III of BC found that the mean weight change across all women was 1.5 kg at year one from diagnosis, 2.7 kg at year two and 2.8 kg at year three, suggesting that weight gain is persistent after diagnosis [23]. This aspect was also observed in a long-term follow-up study in which the risk of weight gain was positively related to the time elapsed since diagnosis (adjusted Odds Ratio (OR)=1.19/year, 95% Confidence Interval (CI) 1.04-1.36) [31].

Despite a large body of literature has reported weight gain in women after diagnosis of BC, the causal factors underlying such change remain unclear [32]. A series of studies suggested that the weight gain may be attributable to the effects of some treatment regimens [33]. Moreover, this effect is highly related to the type and duration of therapies. Several investigations in this area suggested that the weight gain is greater among women who receive chemotherapy as part of their treatment, even if most analyses failed to specify the chemotherapy regimens [31, 34], compared with women who received hormonal treatment or no systemic treatment [35]. Early evidence describing weight gain observed that adjuvant chemotherapy, included long duration treatments of non-anthracycline containing regimens such as CMF, was associated with changes of up to 8-10 kg [36]. The Women's Healthy Eating and Living (WHEL) study, a prospective randomized clinical trial that included 3088 BC patients, reported an association of weight gain with chemotherapy (OR=1.65, 95% CI 1.12-2.43, *p=0.01*), for both anthracycline and non-anthracycline regimens (OR=1.63, *p=0.01* and OR=1.79, *p=0.003*, respectively). In particular, all the chemotherapies (Adriamycin and Cyclophosphamide (AC): OR=1.55, *p=0.01*; Cyclophosphamide, Adriamycin and Fluorouracil: OR=1.83, *p=0.003*; cyclophosphamide, methotrexate, and fluorouracil (CMF): OR=1.76, *p=0.004*) were related to weight gain, without a significant difference between one and the other [24].

In more recent studies, including also taxanes, the weight gain is reported with a lower prevalence (35-85%) and lesser degree than earlier studies, with a weight gain varying between 1.4 to 5.0 kg [36].

The underlying mechanism contributing to the weight change during chemotherapy is unclear. It may be promoted by common treatment-related side effects such as fatigue, changes in dietary eating patterns, induced by alternations in taste and smell, and a significant reduction in physical activity and in basal metabolic rate, which may lead to an impairment in energy balance [37].

Furthermore, a series of evidence suggested that premenopausal status at BC diagnosis may be a strong predictor of weight gain [38, 39]. In this regard, a recent retrospective study, assessing a cohort of 1282 women with a diagnosis of stage I-III, hormone receptor-positive, HER2-negative BC, who had completed 5 years of adjuvant endocrine therapy, identified that women who were premenopausal at diagnosis were 1.40 times more likely than women who were postmenopausal at diagnosis to have a >5% weight gain (OR=1.40, 95% CI 1.01-1.93, *p=0.040*) [32]. This effect seems to be mediated by premature ovarian failure which may produce adverse changes in fat distribution and a decrease in lean body mass, promoting weight gain [38].

Unlike chemotherapy, hormonal treatment seems to be less often associated with significant weight change, even if the evidence is uncertain [31, 40-43]. In this regard, tamoxifen or aromatase inhibitors treatment

alone (without chemotherapy) do not appear to significantly impact on body weight [24, 35, 44, 45]. Moreover, the ATAC trial, a large randomized study of early-stage postmenopausal BC patients, showed no statistically significant differences in weight gain between anastrozole and tamoxifen after 12 months of follow-up (+1.4 kg *vs.* +1.5 kg, *p=0.4*) [46].

Body composition variation following BC diagnosis.

Several studies have identified a shift in body composition, with an increase in adipose tissue and a reduction of lean tissue, with the development of sarcopenic obesity, independent of the amount of weight gain and BMI [38, 47]. The BMI, which can be easily determined, is used in most studies as a simple and reliable surrogate measure for obesity, even if it fails to discriminate between proportions of fat and lean tissues [48, 49].

To further underline this difference, more precise methodologies have been adopted in recent studies, such as the development of image analysis methods (ex. dual X-ray absorptiometry (DXA) scans and computed tomography (CT)), and the bioelectric impedance analyzer (BIA).

In this regard, an observational study, evaluating the body composition by DXA in women receiving chemotherapy (AC or AC followed by paclitaxel), found that patients who were of normal weight at the time of BC diagnosis were more likely to gain in body fat (besides in body weight) than overweight or obese women. Indeed, baseline BMI was inversely related to gains in weight (*p=0.01*) and fat mass in the torso (*p=0.006*) [50]. Moreover, *Freedman et al.[51]* analyzed data from a prospective study in 20 women with Stage I-III BC receiving adjuvant chemotherapy. This small study did not report significant changes in weight during the treatment. However, the investigators showed unfavorable changes in body composition. Indeed, the percentage of body fat, assessed by DXA, increased (+0.9 +/-1.6%; *p=0.02*) and the bone mineral content decreased (-0.02 +/- 0.04 kg; *p=0.02*). Furthermore, using CT, an unfavorable change of decrease in the ratio of visceral adipose tissue to subcutaneous fat was detected (-0.02 +/- 0.05 ml; *p=0.02*).

Besides the adiposity, the evaluation of the depletion of muscle mass (MM), implicated in the definition of sarcopenia, represents a relevant aspect in the nutritional assessment of cancer patients, due to the high prevalence in the oncology setting [52]. In this context, *Villaseñor et al*. [53] investigated the prevalence of sarcopenia, assessed by DXA scans in a cohort of women diagnosed with invasive BC (stages I-IIIA). Sarcopenia was defined as two standard deviations below the young healthy adult female mean of appendicular lean mass divided by height squared (< 5.45 kg/m^2). The authors showed that among the 471 women included in this study, 75 (16%) were sarcopenic, with 38% of these women classified as obese (total body fat percentage, ≥ 38 %) and 61% as not obese (< 38%). In addition, a recent retrospective study, conducted by *Deluche et al.* in patients with early BC, evaluated the prevalence of sarcopenia (defined as skeletal muscle index at the third lumbar vertebra (L3) < 41 cm^2/m^2) by CT used for disease staging. The authors found that among the 119 evaluable patients, 58 (48.8%) were sarcopenic, whose 22 patients had a BMI ≥ 25 kg/m^2 [47]. This study detected a greater prevalence of sarcopenia compared to the results of

Villaseñor et al. probably because DXA scans is less accurate than CT for the evaluation of sarcopenia, although both methods were validated.

Overall, sarcopenia was more common in women who were older at diagnosis, generally in post-menopause [47, 53]. Therefore, the menopause status seems to cause marked changes in body composition, thorough a redistribution of the pattern of adiposity, with an increase in visceral fat mass [54, 55]. In this regard, a retrospective analysis of 172 BC patients who underwent surgery after neoadjuvant chemotherapy, reported a statistically significant reduction of skeletal muscle area and a gain of fat, particularly visceral fat, after menopause and these changes are not reflected in the BMI measures [56]. Besides the menopausal status, adjuvant treatment for BC, including hormone therapy and chemotherapy, are proposed to be the major contributors to the alterations in body composition [57, 58].

In this regard, the majority of evidence in the literature is based mostly on data generated by retrospective studies [59-61], few data are available from prospective analyses.

A recent prospective cohort study, investigating the change in weight and body composition using BIA after current standard adjuvant treatment in 95 women with BC (stage I-III), found that after 18 months, there was an increase in weight of 0.9 kg (95% CI, 0.3-1.5; *p=0.003*) and an average positive association of 0.35 kg/cm increased waist circumference (95% CI, 0.29-0.42 kg; *p<0.0001*). Weight gains associated with increased body fat were observed mainly in premenopausal women receiving chemotherapy (1.4 kg, 95% CI 0.4-2.4; *p=0.007*) [62].

The majority of literature regarding the assessment of body composition in BC patients were conducted in the early stage setting, while few analyses included the metastatic disease. In this regard, a recent analysis compared body composition measures, through CT scans at L3 lumbar segments, between patients with early BC receiving adjuvant chemotherapy and metastatic BC initiating first-line chemotherapy. This study reported that, although mean BMI and body surface area were similar in both groups (29.0 *vs.* 28.8, *p=0.84* and 1.87 *vs.* 1.86 m^2, *p=0.55,* respectively), skeletal muscle index (41.3 *vs.* 44.7 cm^2/m^2, *p=0.009*), skeletal muscle density (29.8 *vs.* 36.4 Hounsfield Units, *p<0.0001*) and lean body mass (LBM, 39.3 *vs.* 41.9 kg, *p=0.024*) were significantly lower in the metastatic cancer patients. Moreover, patients with advanced BC was associated with a higher proportion of sarcopenia (defined as skeletal muscle area/height^2 <41) than early BC (58% *vs.* 31%, *p=0.0016*) [63]. In this regard, the loss of MM is a common condition in patients with advanced cancer. In a meta-analysis, included 7843 patients with solid tumors from 38 studies, the percentage of advanced cancer patients with sarcopenia varied from 19% to 74% [4].

The impact of baseline BMI and weight change on clinical outcome according to the different stages of BC.

Recent evidence has shown that overweight, obesity or underweight are correlated to adverse survival outcome in women with BC [16]. In this regard, *Chan et al*. conducted the most extensive meta-analysis on BMI and BC survival. The authors included 213075 BC patients from 82 prospective cohort studies and analyzed total mortality and BC-specific mortality according to BMI, defined as the World Health

Organization criteria, at baseline and after diagnosis. Compared with normal weight women, the summary relative risk (RR) for total mortality and BC-specific mortality for obese versus normal-weight patients before diagnosis were 1.41 (95% CI 1.29-1.53) and 1.35 (95% CI 1.24-1.47), respectively. Furthermore, the RR for total mortality were 1.07 (95% CI, 1.02-1.12) for overweight women and 1.10 (95% CI 0.92-1.31) for underweight women compared with normal weight patients [64].

A recent study, analyzing data from a prospective cohort of approximately 5000 women with early-BC, reported that high BMI at either pre- or post-diagnosis was associated with a higher risk of BC-specific mortality (pre-diagnosis, HR=1.27, 95% CI 1.14-1.41, *p=0.001*; post-diagnosis, HR=1.19, 95% CI 1.04-1.36, *p=0.02*) only among patients aged 65 years or older [65].

- **The adjuvant setting.**

In patients with resected BC, a growing number of studies indicated that obese women had a poorer prognosis than lean women [2, 13, 66, 67].

In this context, a large study of 18967 patients from Denmark, suggested that obesity is an independent prognostic factor for developing distant metastasis and BC death. Particularly, the investigators found that the increased risk of distant recurrence was significant only in years 5 to 10 after diagnosis, with an HR of 1.42 (95% CI 1.17-1.73, *p<0.001*) and 1.46 (95% CI 1.11-1.92, *p=0.007*) for overweight and obese patients, respectively [68].

Of interest, several evidence suggested that an increase in weight after early BC diagnosis could potentially affect the outcomes of BC survivors, despite this effect is not consistent in all studies [30]. In this regard, a meta-analysis including 12 studies found that weight gain ≥5% compared with maintenance (<±5.0%) was associated with increased all-cause mortality (HR=1.12, 95% CI 1.03-1.22, *p=0.01*). In particular, higher risk of mortality was apparent for weight gain ≥10% after diagnosis (HR=1.23, 95% CI 1.09-1.39, *p<0.001*) [33]. Similarly, the retrospective study of 520 early-stage BC patients by *Fedele et al.*, showed that BMI gain was a significant determinant of recurrence (95% CI 0.163-0.323, *p=0.0008*) [69]. Conversely, the recent study of *Raghavendra et al*. reported that patients with a weight gain of >5% after 5 years of endocrine therapy did not have an increased risk of disease recurrence (HR=0.95, 95% CI 0.62-1.47, *p=0.829*) [32]. These results are consistent with those reported from a study that combined a cohort of the WHEL and the LACE study, which evidenced no effect of weight gain on disease recurrence [70].

With regard to BC histotype, a high BMI and weight gain have been reported to negatively affect the outcome particularly in early BC women with hormone receptor-positive, treated with endocrine therapy [71, 72]. Indeed, *Robison et al.* in a study of 1155 women with luminal, HER2-negative BC, (53.8% had Stage I disease and 88.9% received adjuvant endocrine therapy) reported that obesity was significantly associated with an increased risk of disease recurrence (HR=1.71, 95% CI 1.12-2,62, *p=0.014*) [73].

In a recent study exploring BC recurrence and survival across subtypes defined by PAM50 gene expression, women with Luminal A tumors and class II/III obesity at BC diagnosis had worse outcomes with an HR of 2.24 (95% CI 1.22-4.11) for BC-specific death and 1.24 (95% CI 1.00-1.54) for recurrence [74]. A similar effect has been identified in other previous studies [75, 76].

The analysis of 3385 with hormone receptor-positive BC included in the National Surgical Adjuvant Breast and Bowel Project B-14, a randomised placebo-controlled trial of adjuvant tamoxifen, indicated that obese women had greater all-cause mortality (HR=1.31, 95% CI 1.12-1.54, *p<0.001*) and non-BC mortality (HR=1.49, 95% CI 1.15-1.92, *p<0.001*) compared with normal weight women, without difference in terms of BC-mortality or recurrence. Furthermore, obese women benefited from tamoxifen therapy as much as leaner women [77].

Sparano et al analyzed the relation between BMI and outcome in 3 adjuvant trials coordinated by the Eastern Cooperative Oncology Group that included different anthracyclines-based chemotherapy regimens. They highlighted that BMI ≥30 kg/m^2 was associated with inferior DFS (HR=1.24; 95% CI 1.06-1.46, *p=0.0008*) and OS (HR=1.37; 95% CI 1.13-1.67, *p=0.002*) only in patients with hormone receptor-positive early BC treated with both standard chemotherapy and hormonal therapy [76]. Several studies have also suggested that obesity modulated response to endocrine therapy, in particular, it seems to reduce the response to aromatase inhibitors [78-80].

The negative prognostic effect of obesity may be related to the decrease of sex hormone binding globulin, which can bind and inhibit estradiol, with a consequent increased of circulating unbound estrogen levels [81], that may promote tumor progression. Moreover, excess of adiposity may intensify estrogen production by the conversion of androgens by aromatase in adipose fat [45, 82]. Another potential mechanism through elevated BMI may influence prognosis in tumors includes prolonged hyperinsulinemia, reduced production of insulin-like growth factor binding proteins 3, resulting in elevated circulating insulin-like growth factor and alteration of synthesis of adipokines and cytokines [83].

Recently, *Schvartsman et al.* indicated that BMI increase during adjuvant chemotherapy (within one year from starting chemotherapy) of >0.5 kg/m^2 compared to maintaining BMI was associated with increased locoregional recurrence risk (HR=2.53, 95% CI 1.18-5.45, *p=0.017*), adjusting for grade, stage, and radiation delivery [84].

As opposed to luminal disease, the impact of BMI and weight change on outcome is not well established for triple-negative BC (TNBC) [85-90]. In a recent analysis, overweight was an independent prognostic factor for OS (HR=2.903, 95% CI 1.551-5.432, *p=0.001*) and DFS (HR=1.899, 95% CI 1.05-3.433, *p=0.034*) at 5 years in patients with TNBC. Furthermore, the menopausal status may be a mitigating factor. Indeed, overweight was related to a greater risk of death (HR=2.752, 95% CI 1.267-5.978, *p=0.011*) and recurrence (HR=3.242, 95% CI1.249-8.412, *p=0.016)* only among premenopausal women, but not in postmenopausal women [91]. This results are consistent with data from another analysis by *Turkoz et al*. [92], which evidenced that obesity at diagnosis was associated with worse survival (HR=1.7, 95% CI 1.1-2.5, *p=0.02*) and recurrence (HR=1.4, 95% CI 1.0-2.0, *p=0.04*) among premenopausal TNBC patients. Similar results for TNBC, especially for the premenopausal setting, have been found in other analyses [93, 94].

On the contrary, the largest retrospective study published, including 2311 women with early TNBC, reported no difference in DFS in patients with BMI of 25-29.9 kg/m^2 (HR=1.04, 95% CI 87-1.25, *p=0.66*) and those with BMI ≥ 30 kg/m^2 (HR=0.99, 95% CI 83-1.18; *p=0.89*) compared with patients with BMI <25

kg/m^2[87]. Similarly, no impact of obesity on TNBC was also reported in two retrospective studies [86, 95]. Moreover, a randomized phase III trial of adjuvant chemotherapy with or without anthracyclines in 1066 patients affected by aggressive biological phenotypes (as defined by thymidine labeling index >3%, or histological grade 3 or S-phase >10%, or Ki67/MIB1 >20%) suggested that BMI has not a significant impact on DFS and OS [96].

Given the small size of these studies and the overall poor outcome of TNBC itself, larger studies or meta-analyses are needed to assess whether BMI is linked to survival in women with TNBC or aggressive biological phenotypes [90].

- **The neoadjuvant setting.**

In the BC neoadjuvant setting, current evidence suggested that obese patients treated with neoadjuvant chemotherapy had a significantly lower pathologic complete response (pCR) [97] and worse OS [98-101], in contrast with other previous studies which did not confirm this relationship [102, 103].

A large study of 1169 patients, who have received neoadjuvant chemotherapy, reported an association between the rate of pCR and the BMI. Overweight and the combination of overweight and obese patients were significantly less likely to have a pCR (OR=0.59, 95% CI 0.37-0.95, and OR=0.67, 95% CI 0.45-0.99, respectively, *p=0.03)* [98]. A more recent analysis of 295 Turkish patients with stage II-III BC showed that obesity was an independent adverse predictive factor of pCR compared with normal or underweight patients (OR=0.34, 95% CI 0.13-0.85, *p=0.02*). Moreover, higher BMI was statistically significant related to an increased recurrence rate and a decreased OS [97]. These data were consistent with a prior analysis conducted in the neoadjuvant setting by *Fontanella et al.*, which reported a shorter median DFS and OS in obese patients versus normal-weight patients (87.3 months vs. 91.5 months, *p=0.014* and 94.9 months *vs*. 98.8 months,, *p=0.001*, respectively) [100]. On the contrary, *Farr et al.*, in a retrospective study of women who underwent neoadjuvant anthracycline-taxane-based chemotherapy, found that obesity had an independent positive predictive impact on pCR (OR=4.29, 95% CI 1.42-13.91, *p=0.011*) and a high BMI was associated with longer PFS (HR=0.1, 95% CI 8.448×10^{-4}-0.81, *p=0.025*) [104].

Recently, a retrospective analysis, exploring the impact of BMI on event-free survival (EFS) and OS, according to tumor subtype suggested that, overall, obesity was related to worse EFS (HR=1.71, 95% CI 1.03-2.84, *p=0.04*) without a statically significant difference in OS. The negative impact of obesity in terms of EFS was strongest in TNBC (HR=2.62, 95% CI 1.03-6.66, *p=0.04*), with only a trend in HER2-positive disease (HR=3.37, 95% CI 0.97-11.72, *p=0.06*) [105]. Additionally, *Warner et al.* in a patient cohort of 1797 from 4 clinical trials including neoadjuvant systemic therapy for BC, suggested that the effect of BMI on pCR rate seems to differ according to tumor subtype. In particular, the authors observed a statistically significant inverse relationship between BMI and pCR in estrogen-receptor positive and HER2-positive patients. No significant differences were found in pCR rates according to BMI among patients with estrogen-receptor positive and HER2-negative patients or TNBC [103].

In the context of neoadjuvant setting, a series of studies explored the relationship between weight change and variations in Ki67, a well-established proliferation marker in BC. Overall, weight change during neoadjuvant

chemotherapy seems to not have a significant impact on Ki67 reduction in both estrogen receptor-positive and TNBC [106, 107].

- **The metastatic setting.**

Considering the metastatic setting of BC, limited data focusing on the impact of BMI on survival are available. In a study of 557 patients with BC metastasis, a better prognosis was reported only in women with a BMI<20 kg/m^2 compared with women with normal weight (HR=0.52, 95% CI 0.31-0.87, *p=0.013*), while no difference was seen between normal weight, overweight, and obese patients [108].

A retrospective analysis, conducted by *Drygalski et al. [109]*, in a small cohort of 96 metastatic BC patients who had received high-dose chemotherapy with autologous stem cell support, indicated that BMI>30 kg/m2 was an independent negative predictor of time from initial diagnosis to metastatic disease (HR=1.14, *p=0.04*) and survival at the time of metastasis (HR for progression=2.23, *p=0.005*; HR for death=1.82, *p=0.04*).

Similarly, *Parolin et al.* found that higher BMI was related to poor prognosis in HER2-positive metastatic BC treated with trastuzumab: median OS for normal weight, overweight and obese patients was 67, 54, and 39 months, respectively (*p=0.001*) [110]. The crosstalk between leptin and IGF-1 pathway can potentially modulate the phosphorylation of HER2, reducing the activity of anti-HER2 treatments [111, 112]. However, these findings are in contrast with the results of a recent multicenter retrospective cohort study, including data of 329 women with HER2-positive metastatic BC treated with first-line trastuzumab-based regimens: the BMI was not related with PFS (adjusted-HR=0.88; 95% CI 0.66-1.17; *p=0.387*) and OS (adjusted-HR=0.88, 95% CI 0.59-1.31, *p=0.525*) [113].

Recently, *Pizzuti el al.* [114] analyzed data of 196 women with HER2-negative metastatic BC, a subgroup of patients from the TOURANDOT trial, treated with paclitaxel and bevacizumab in first-line. In this analysis, the BMI showed no impact on PFS, OS and clinical benefit rates, particularly in the luminal subgroup. On the contrary, in TNBC patients with a BMI ≥25 kg/m^2, PFS and OS were significantly longer (6 *vs.* 14 months, *p=0.04* and 25 *vs.* 19 months, *p=0.02*, respectively) and disease control rates were significantly higher (60% *vs.* 91%, *p=0.03*). Similarly, the analysis conducted by *Gennari et al* in 489 women with metastatic BC treated with first-line chemotherapy, indicated that the BMI has not a significant impact on PFS and OS [115].

Moreover, a more recent prospective study suggested that being overweight could improve OS in patients with metastatic BC receiving chemotherapy. Indeed, normal BMI was related to increased risk of death compared with BMI≥ 25 kg/m^2 (HR=0.51, 95% CI 0.26–0.99, *p*=0.047) [116].

Therefore, the majority of the most recent findings in the metastatic BC are in conflict with data from studies in early-stage BC [2, 13, 66-68]. Indeed, the presence of obesity seems to be a paradoxical protective factor in the metastatic setting of BC. This unexpected inverse association between obesity and cancer mortality, called ‘obesity paradox’, represents a recently emerged phenomenon even in other cancer types [117, 118]. However, current evidence suggested that body composition phenotypes may disprove this protective effect

[119]. Additional investigations are needed to clarify the complex relationship between BMI and treatment outcomes in metastatic BC.

The prognostic role of body composition in BC.

Although the obesity represents the main factor included in the majority of studies exploring the prognostic impact of body weight in BC, emerging evidence examines the potential role of body composition parameters such as the sarcopenia in all settings of BC. The results of studies exploring the prognostic role of body composition in the adjuvant and neoadjuvant setting are summarized in Table 1.

- **The adjuvant setting.**

The impact of body composition on prognosis in patients treated in the adjuvant setting for operated BC was mainly explored by DXA and CT scan. The first method was adopted in a study cohort of 471 women with a diagnosis of in situ or stage I–IIIA primary BC enrolled in the Health, Eating, Activity, and Lifestyle (HEAL) study. The prevalence of sarcopenia was 16%, with 38% of sarcopenic women classified as obese. At a median follow-up of 9.2 years, the sarcopenia was an independent poor prognostic factor for OS (HR=2.86, 95% CI 1.67–4.89, $p<0.001$), however not statistically significant for BC related death (HR=1.95, 95% CI, 0.89–4.35) [53]. The images from CT scan, performed for staging, was applied in a retrospective study to evaluate the impact of body composition in 119 BC survivors. Sarcopenia and inter muscular adipose tissue areas were independent poor prognostic factors for DFS (HR=0.3, 95% CI 0.1–0.8, $p= 0.02$ and HR=2.8, 95% CI 1.0-7.8, $p=0.04$, respectively) and OS (HR=0.3, 95% CI 0.1–0.99, $p=0.05$ and HR=3.6, 95% CI 1.2-10.8, $p=0.02$, respectively) [47]. Recently, a study including 3241 patients with stage II-III, evaluated muscle area, muscle radiodensity, and adiposity measured from CT scan within 6 months from diagnosis. At a median follow up of 6 years, patients with sarcopenia presented a 41% greater RR for death compared with patients without sarcopenia and patients in the highest tertile of adiposity had a 35% higher RR for death compared with patients in the lowest tertile. Moreover, the mortality risk was highest among patients with both sarcopenia and high levels of total adiposity, among whom the RR for mortality was 89% higher than that in patients without sarcopenia and with low levels of total adipose tissue. In contrast, low radiodensity and BMI was not significantly associated with survival risk [120] .

With regard to body fat distribution and gain, two prospective observational studies explored its prognostic role in the adjuvant setting. The first suggested that higher abdominal fat distribution, defined as elevated waist-to-hip ratio (WHR), was associated with BC mortality for postmenopausal patients (for highest quartile *vs.* lowest, RR=3.3, 95% CI 1.1-10.4), however not in premenopausal patients (RR=1.2, 95% CI 0.4-3.4) [121]. The second evaluated the relationship between body-fat gain and disease recurrence in Taiwanese women who underwent surgery for stage 0-III BC. Body fat was measured by BIA and its gain was defined by the difference between measures at pre-surgery and 6 months post-surgery. Higher gain in body fat percentage was associated with higher risk of disease metastasis (HR=1.3, 95% CI 1.02–1.72, *p=0.035*) and marginally associated with higher risk of all-cause mortality (HR=1.5, 95% CI 0.94–2.25, *p=0.091*) for postmenopausal patients, but not for premenopausal women [122].

- **The neoadjuvant setting.**

As BMI and obesity [98, 100], body composition seems to play a potential prognostic role in the BC neoadjuvant setting, even if less studies are available. In 2016 *Iwase et al.* found that, in 172 patients who underwent surgery after neoadjuvant chemotherapy, higher amounts of visceral fat (visceral fat area >100 cm^2) correlated with shorter distant DFS (HR=2.36, 95% CI 1.27-4.38, $p<0.05$), especially in postmenopausal women who are likely to accumulate more visceral fat than subcutaneous fat [56]. The authors suggested that a possible explanation of this result relies in the key role of visceral fat in promoting cancer progression through different pathways [123]. In this study just 5 patients had sarcopenia and this did not correlate with the prognosis.

Overall, the role of sarcopenia in the neoadjuvant setting is actually still debated. A study published in 2012 by *Del Fabbro* and colleagues reported that, between patients with operable BC exposed to neoadjuvant chemotherapy, those with lower Skeletal Mass Index (defined as Skeletal Muscle Area/$heigh^2$) had longer OS (HR=1.006, 95% CI 1.001-1.012, p=0.0193*)*. Moreover, sarcopenia was associated with higher pCR rate than normal weight population (p=0.023) [99]. On the other hand, a recent retrospective study found that sarcopenia was associated with shorter DFS intervals (HR=0.3, 95% CI 0.1-0.8, p=0.02), even if none of composition parameter correlated with pCR. This analysis included a remarkable number of patients who received NAC (55/119), but also patients who underwent adjuvant chemotherapy (64/119) [47].

The different results of the impact of sarcopenia through the various researches may be conferred to different definitions of this parameter and different cut-offs. However, although the impact of sarcopenia on the prognosis has been evaluated in many cancer types [49, 124-128], just few analyses are focused on the neoadjuvant setting in patients with BC, so more prospective studies are needed.

The inter-muscular adipose tissue areas (IMAT) index represents a newer body composition parameter that showed an independent prognostic value in patients with early BC. Indeed, higher IMAX index (>3,5 cm^2/m^2) correlated with shorter DFS (HR 2.8, 95% CI 1.0-7.8, p=0.04) and shorter OS (HR 3.6, 95% CI 1.2-10.8, *p=0.02*). A great IMAT was also associated with other body composition variables as sarcopenia, high visceral adipose tissue index and high visceral/subcutaneous adipose tissue ratio, suggesting a potential relative influence of these parameters on the BC outcome [47].

- **The metastatic setting.**

Even if several body composition parameters, like MM, muscle attenuation (MA), sarcopenia and adipose tissue measurements, have been investigated in metastatic BC, their prognostic role remains unclear, as the few available studies reported controversial findings (Table 2).

In 2016 *Rier* and colleagues suggested that, between patients with metastatic BC after first-line chemotherapy, those with low MA had worse outcomes in terms of OS (median OS 15 *vs.* 23 months, p=0.005) and time to the next treatment (HR=1.72, 95% CI 1.14-2.62, p=0.01) compared with patients with normal MA [129]. No significant association was found between low MM or sarcopenic obesity and OS (for low MM median OS 19 *vs.* 18 months, p=0.845; for sarcopenic obesity 20 *vs.* 18 months, p=0.481). These findings are in contrast with the results of a previous study by *Prado et al.* in which sarcopenia adversely

influenced the time to progression (TTP) in women with metastatic BC who received capecitabine treatment (62 days in sarcopenic patients vs. 105 days in non-sarcopenic patients; HR=2.6, 95% CI 1.2-5.6, *p*=0.01) [130]. It is worth noting that this paper included patients with different characteristics from the previous one, in particular patients who failed at least the first chemotherapeutic line; therefore, it is possible that low MM had a prognostic impact in more advanced disease than in first-line chemotherapy.

Anyway, the negative prognostic impact of sarcopenia is sustained also by a meta-analysis, which included patients with advanced solid tumors [4], and by a research investigating the effect of body composition in patients with metastatic BC who received taxane-based chemotherapy [28]. In the last one low skeletal muscle Gauge (a parameter obtained by multiplying skeletal muscle index x skeletal muscle density) correlated with time to treatment failure (HR=0.91, 95% CI 0.84-0.99, *p*=0.03) and had borderline significant association with short OS (HR 0.93, 95% CI 0.87-1, *p*=0.07) suggesting that the quality of the muscle composition may be relevant too.

To our knowledge the more recently published study investigating the changes in body composition and muscle quality was conducted in 98 patients with metastatic BC who received first-line chemotherapy with anthracyclines or taxanes. This analysis reported that in patients who received paclitaxel the median MA significantly decreased (-0.9 HU, *p*=0.03), otherwise in patients who received anthracyclines no significant change in median MA was found. A possible explanation may be found in the specific nature of toxicities related to taxanes, such as the development of neuropathy and myalgia and the effect of administration of co-medication, such as corticosteroids. Furthermore, no significant association was described between decrease in MA, loss of MM or loss of adipose tissue and OS. The authors suggested that maybe the entity of the MA decrease was not enough to impact on the outcome [131].

With regard to fat distribution, a small study of 42 metastatic BC patients treated with aromatase inhibitors suggested that high abdominal fat distribution was associated with better survival: median OS was 472 days *vs.* unreached for patients with a WHR of <0.92 and ≥0.92 (*p=0.002*), respectively. Similarly, the corresponding PFS for patients with a WHR of <0.92 and ≥0.92 were 423 *vs.* 1004 days (*p=0.012*), respectively [132].

The relationship between body composition and prognosis in the metastatic setting still lacks adequate studies. Further investigations are needed to asses in which way the body composition parameters may influence the survival in metastatic BC patients.

Body composition as a key predictor of chemotherapy toxicity.

The obesity and the body composition may influence the development of chemotherapy toxicity, besides their impact in terms of prognosis. A recent prospective observational study by *Greenlee et al.*, included 1237 patients who received taxane-based chemotherapy, observed that overweight and obesity were associated with chemotherapy-induced peripheral neuropathy at 24 months (OR=2.37, 95% CI 1.19 - 4.88, *p=0.02* and OR=3.21, 95% CI 1.52-7.02, *p=0.003*, respectively) [133]. These findings are consistent with a previous study which observed that obesity was related to increased risk of chemotherapy-induced peripheral

neuropathy (adjusted OR=1.94, 95% CI 1.03-3.65, *p=0.039*), compared with normal-weight women, among postmenopausal women with a history of stage I-III hormone receptor-positive BC who received taxanes [134].

In addition, overweight and obesity have recently been related to higher risk of cardiotoxicity after treatment with anthracyclines or sequential anthracyclines and trastuzumab [135, 136]. The mechanisms by which obesity may negatively influence cardiotoxicity are affected by numerous confounding factors, therefore, further studies are needed to establish the independent predictive value of obesity on cardiotoxicity in BC patients.

With regard to hematological toxicity, a systematic review suggested that obese women, receiving adjuvant chemotherapy treatment for BC, tolerated chemotherapy better than lean patients, with lower febrile neutropenia (OR=4.4, 95% CI 1.65–12.01), fewer hospital admissions (OR=0.61, 95% CI 0.38–0.97), and fewer neutropenic events (OR=0.49, 95% CI 0.37–0.66) [137]. However, this effect may be confounded by the use of hematopoietic growth factors and by poorly specified dose capping practices. Indeed, in the clinical practice, chemotherapy doses are frequently capped at a body surface area (BSA) of 2.0 m^2 or adjusted to an ideal weight for obese patients in order to avoid excessive toxicity, which may compromise survival outcome in these patients. However, a retrospective cohort study of 537 women receiving adjuvant chemotherapy, in which obese patients received chemotherapy with proportionally lower mean relative dose intensity than non-obese patients (94 vs. 97% of reference dose, *p=0.03*), showed that there was no significant evidence of increased toxicity among obese women with either full or adjusted chemotherapy doses. Overall, obesity was not statistically related to chemotherapy-related admission risk (OR=1.27, 95% CI 0.78–2.09) or febrile neutropenia risk (OR=0.56, 95% CI 0.28–1.21) [138]. Similarly, a more recent retrospective analysis of 325 early BC patients treated with neoadjuvant or adjuvant chemotherapy, observed that obese women receiving uncapped chemotherapy did not experience a significant difference in febrile neutropenia rate when compared with overweight or normal bodyweight groups [139]. In this regard, ASCO guidelines recommend that obese patients should receive full weight-based chemotherapy doses determined using their actual body weight, particularly when the goal is the cure [140].

Nevertheless, *Furlanetto et al.* reported that a dose adjustment of intense dose-dense chemotherapy should be made to avoid several complications in obese women with early BC. They analysed data of 555 obese women, from patients enrolled in the GAIN study, a randomized phase III adjuvant trial, comparing two types of dose-dense regimens. The obese patients receiving full dose-dense chemotherapy experienced significantly more hematological toxicities, particularly febrile neutropenia and higher-grade thrombopenia, thromboembolic events and higher-grade hot flushes compared with obese patients receiving chemotherapy dose according to an adjusted BSA. Moreover, they observed no differences in DFS and OS between obese patients receiving full-dose chemotherapy or according to an adjusted BSA [141].

The lack of the evaluation of the relationship between body composition parameters and treatment toxicity represents a limit of these studies. Indeed, LBM and others parameters may be better parameters than BMI and BSA for tailoring drug dosages in cancer patients [49, 124, 142].

For what concerns the correlation between body composition parameters and toxicity in BC, the studies available include only chemotherapy regimens (especially anthracyclines and taxanes), while there are no studies regarding tyrosine-kinase inhibitors or monoclonal antibodies (Table 3).

One of the most recent study in early BC showed that neutropenia, hematological grade 3-4 toxicities, dose reductions and delays rates were statistically significant more frequent in patients with sarcopenic obesity. Moreover, hospitalization rate was more frequent in patients with altered body composition, with almost twice RR (RR=1.91, p=0.05) [27]. Another study explored the correlation between body composition and taxanes toxicity in 40 advanced BC patients. In this study, the rate of grade 3-4 toxicities was higher in the sarcopenic group than in the non-sarcopenic patients (57% vs 18%, p=0.02) and frequently since from the first chemotherapy cycle (p=0.04). Moreover, other adverse events, like hospitalizations, delays or dose reductions rates resulted higher in the sarcopenic patients (74% vs 35%, p=0.02) [28].

In an Asiatic analysis of 84 patients from 2 phase II studies, *Wong et al*. tried to demonstrate a link between body composition and toxicity of taxanes and anthracyclines in patients with non-metastatic BC. This analysis showed that that visceral fat was significantly associated with grade 4 leukopenia and also that a low muscle volume was associated with grade 3-4 leukopenia and neutropenia [143]. Another study, evaluating body composition and its association with epirubicin toxicity in a small cohort of 24 patients affected by early BC, suggested that LBM was higher in the toxicity-absent group than in the toxicity-present group (p=0.002). Moreover, the neutrophilic count resulted better in patients with higher LBM (p=0.023) [144]. These studies suggest that the pharmacokinetic profile of anthracyclines may be altered by body fat content and, consequently, associated with a greater myelosuppression.

With regard to other chemotherapy drugs, a prospective study investigated the role of body composition in 55 patients with metastatic BC treated with capecitabine and previously treated with anthracyclines and taxanes. In this study, sarcopenic patients presented a higher risk to have toxicity than non-sarcopenic patients (50% *vs.* 20%, p=0.03), especially diarrhea and stomatitis. Moreover, the TTP resulted better in non-sarcopenic patients, with a difference in over two months (p=0.05) [130].

The paucity of studies and the small number of patients included are not enough to draw precise conclusions regarding the role of body composition parameters in terms of toxicities. Further studies are needed to develop new strategies in dosing cancer therapy according to body composition to reduce toxicities.

Conclusion and future directions.

The obesity seems to be associated with poor disease outcome in the early stage of BC, even if a series of evidence do not support this prognostic impact [145]. In the metastatic setting the prognostic relationship between BMI and prognosis is debatable and only scarce direct evidence supporting or refuting such an impact [108, 109, 115]. Similarly, the association between post-diagnosis weight gain and BC mortality is unclear.

With regard to body composition parameters, the majority of evidence support a prognostic role of muscle and fat mass. Particularly, the sarcopenia, a frequent underrecognized condition in both metastatic and early BC patients, seems to be associated with an increased risk of recurrence and death. Understanding the

relevance of sarcopenia and body composition in BC also highlights the need for timely interventions to increase or prevent further loss of MM during and after treatment [146]. Intervention studies to date has focused on physical exercise, Mediterranean diet, vitamin D and omega-3 fatty acid dietary supplementation, even if the aim of these study is not always focused on BC outcome or treatment toxicity. Further research exploring the impact of these interventions on efficacy and toxicity and how to incorporate them into clinical practice is needed.

The methodological limitations of the majority of studies exploring the role of obesity and body composition in BC, due to the retrospective design, the small sample size, the heterogeneity in terms of patients' characteristics, cut-offs' definitions and methods adopted, may justify the differences in terms of results and make the derived interpretation unreliable. Thus, the development of well-design prospective studies in order to identify reliable prognostic and predictive body composition biomarkers together with the validation of effective intervention strategies, would allow to improve the BC prognosis and reduce treatment toxicity.

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