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CLINICAL STUDY

# Body mass index and treatment outcomes following neoadjuvant therapy in women aged 45 y or younger: Evidence from a historic cohort

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**ABSTRACT**

Purpose: Large and consistent evidence supports the role of body mass index (BMI) as a prognostic and predictive indicator in breast cancer. However, there is paucity of data specifically referred to women diagnosed at a young age across the different disease settings. We investigated the impact of BMI on treatment outcomes in 86 breast cancer patients aged 45 y or less treated with neoadjuvant chemotherapy (CT) followed by surgery.

Methods: Pathologic complete response (pCR) was defined as the eradication of cancer from both breast and lymph nodes. Overall survival (OS) and disease-free survival (DFS) were calculated using the Kaplan-Meier product-limit method. Curves were compared by long rank test for significance. Potential predictors of survival were tested in Cox models.

Results: We observed a pCR in 19 patients (22%). Lower values of BMI were more commonly associated with pCR ($p = 0.05$). Results from univariate, but not multivariate, models were somewhat supportive of higher pCR rates in leaner women ($p = 0.06$). None of the variables impacted DFS. OS was longer in leaner patients (medians and 95%CI: 74.6 months, 66.2–82.9 and 58.5 months, 49.6–67.4, $p = 0.009$). Longer OS was also related to lower T-stage, adjuvant radiotherapy (RT), and non triple negative (TN) subtype ($p = 0.046$, $p = 0.024$, and $p = 0.015$, respectively). Cox models confirmed the protective role of lower BMI (Hazard Ratios: 0.30, 95%CI: 0.12–0.71, $p = 0.007$), non TN subtype and adjuvant RT ($p = 0.008$ and $p = 0.024$).

Conclusions: In young breast cancer patients treated with neoadjuvant CT followed by surgery, lower values of BMI are associated with longer OS. Our data also showed longer OS in association with a non TN molecular subtype and adjuvant RT. The modifiable nature of BMI and aggressive biologic behavior of the disease diagnosed at a young age encourage further studies to corroborate our findings.

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Body mass index; breast cancer; neoadjuvant setting; young age

## Background

Body mass index (BMI) is an anthropometric parameter widely used for medical purposes. Its applicability both in clinical routine and research spans across several and heterogeneous areas including major chronic diseases and common causes of death.[1-5] BMI is by nature an easily assessable indicator and, if standardized operative procedures are applied at the time of data collection, a highly reproducible measure.[6] Medical oncologists have first relied on BMI to fulfill dose definition needs in patients treated with chemotherapeutic agents. Since then, the potential value of this anthropometric factor has significantly evolved until its role as a prognostic and/or predictive determinant has consistently emerged in breast and other cancers.[7-8] The growing interest of the cancer research community toward BMI is further enhanced by its modifiable nature and encouraging results from trials of life-style modifications and/or administration of drugs acting on energy metabolism in breast cancer patients.[9-13]

Breast cancer tends to assume a particularly aggressive behavior in younger patients.[14-15] Given the rarity of these events in the overall population, young patients do not benefit from specifically tailored screening initiatives, neither have they been stably placed within pre-existing breast cancer screening programs mostly conceived for women aged 50 and older. This translates into worse outcomes which are comparable to those of older women not participating in the screening programs.[16] The barely sustainable physical, social and lifestyle challenges faced by young women diagnosed with breast cancer makes it particularly meaningful investigating factors with a prognostic and/or predictive role.[17]

The impact of BMI on treatment outcomes in breast cancer has been recently addressed in the pooled analysis of

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data from 8 neoadjuvant trials performed by Fontanella and colleagues. According to their results, a higher BMI was associated with a lower rate of complete pathologic response (pCR) and had a detrimental impact on survival outcomes.[18] Subsequently, in a further combined individual patient data analysis, women aged less than 40 y appeared significantly more likely to achieve pCR following neoadjuvant chemotherapy (CT) compared to their older counterpart, particularly if diagnosed with hormone receptor (HR) positive, human epidermal growth factor receptor 2 negative (HR+/HER2-), or triple negative (TN) breast cancers.[19]

Based on these findings, we investigated whether BMI impacts treatment outcomes following neoadjuvant chemotherapy (CT) in a historic cohort of women aged ≤45 seeking clinical and instrumental breast examination.

## Patients and methods

Data included in the present analysis are from 86 patients aged ≤45 years who received pre-operative CT followed by surgery between October 2007 and August 2013. Most of these women were part of a larger cohort participating in the initiative called "Underforty Women Breast Cancer Care," which was supported by the Campania Region jointly with the Italian Cancer League (LILT from the Italian "Lega Italiana per la Lotta Tumori").[20] The overall initiative was approved by the Institutional Ethical Board of the institutions involved. All patients released a written consent for participating in the study and allowing the collection of data and their anonymized use for scientific purposes. Records concerning demographics, anthropometrics, pathological and clinical features, therapy administered and treatment outcomes were gathered, filed and analyzed by qualified research assistants working in strict collaboration with the surgeons, oncologists and pathologists from our team. For all the study patients, medical therapy was established and administered in full agreement with the current indications and recommendations in both the neoadjuvant and adjuvant phase of treatment. Decisions on breast surgery were informed by the most updated evidence and oriented by the disease characteristics and patient individual needs. Adjuvant radiotherapy was administered to patients having undergone breast conserving surgery (BCS) and, eventually, to women treated with mastectomy based on an individual patient evaluation including axillary lymph node involvement, primary tumor size, margins invasion, grade and age.[21-24]

## Statistical methods

Descriptive statistics were computed for all the variables of interest. Means and ranges were used for continuous data while frequencies and percentage values for categorical variables. Existing differences between medians were evaluated using the T- Student or One Way Anova test according to the number (2 or more) of groups compared. Similarly, depending upon the number and size of groups compared, we used the Pearson's Chi-squared test of independence or Fisher's exact test (2-tailed) to assess the relationship between categorical variables.

BMI was computed as weight in kilograms divided by the square of height in meters (kg/m2) and considered as a categorical variable whose modalities were defined according to a cut off value of 26, namely, the mean BMI computed at this study population level. pCR was defined as no invasive residual tumor in breast and lymph nodes (ypT0/is ypN0) [25] and analyzed for the entire study population and in subgroups defined upon BMI, mean age, molecular subtypes,[26] type of neoadjuvant regimen, and surgical approach. Given the study focus, results from analysis testing age, molecular subtype, and surgery were further stratified by BMI. We also tested these variables for association with pCR using univariate logistic regression analysis. Multivariate models were then built by including those factors testing significant at the univariate analysis and/or for which evidence of a putative role on the association of interest was supported by the available literature.

Overall survival (OS) and disease-free survival (DFS) were calculated using the Kaplan-Meier product-limit method and curves were compared by long rank test for significance. DFS was defined as the time from the starting date of pre-surgical chemotherapy to the date of disease progression or last follow-up evaluation. OS was calculated as the time from the commencement of pre-operative CT to the date of death from any cause or last contact. Cox proportional hazards models were used to test the impact of features related to the patients, disease and administered treatment on survival outcomes in multivariate analyses. The variable choice was oriented by the evidence emerged from univariate analysis and previous studies. The level of significance was set at $p<0.05$. SPSS software was used for all statistical evaluations (SPSS version 21.0, SPSS Inc., Chicago, Illinois, USA).

## Results

Main descriptive characteristics of the study participants are reported in Table 1. Mean age was 38 y and ranged between 20 and 45 y. A BMI value equal to or greater than (≥) 26 was slightly more common and observed in 46 patients (53.5%). Luminal B breast cancers were the most commonly represented subtype [39(45.3)]. At cancer diagnosis, our patients most frequently exhibited a T3-4 and/or N0-1stage [58(67.4) and 48 (55.8), respectively]. The greatest majority of our study participants underwent a pre-surgical neoadjuvant therapy based on an anthracycline- and/or taxane-including regimen [79(91,9)]. In about 49%(42 patients) of our study population breast surgery was performed according to a conservative approach. Adjuvant RT and HT were administered in about 65.0% (56) and 62.8%(54) of patients. Nineteen (22.0%) patients received adjuvant trastuzumab. The median follow up was 45.0 months (range:8.0–90.0).

In Table 2, pCR is described for the overall study population and in groups differing by disease- and patient-related features including age, BMI, intrinsic molecular subtypes (IMS) and treatment administered. Overall, we recorded a pCR in 19 patients over 86, namely, in about 22% of our study population. Lower BMI values were more often associated with pCR compared to what observed for the heavier counterpart, though at a not fully significant extent ($p = 0.05$). Stratification by BMI did not significantly affect results from descriptive analyses

**Table 1.** Descriptive characteristics of the study participants (N:86).

| | | Mean (range) |
|---|---|---|
| Age (years) | | 38(20–45) |
| | | N(%) |
| [a]BMI (Kg/m2) | *<26* | 40(46.5) |
| | *≥26* | 46(53.5) |
| [b]IMS | Luminal A | 13(15.1) |
| | Luminal B | 39(45.3) |
| | HER2 positive | 19(22.0) |
| | Triple negative | 15(17.4) |
| T Stage | *T1-2* | 28(32.6) |
| | *T3-4* | 58(67.4) |
| N Stage | *N0-1* | 48(55.8) |
| | *N2-3* | 38(44.2) |
| Neoadjvant CT | [c]*Anthra. and/or tax.* | 79(91.9) |
| Sugery | [d]*BCS* | 42(48.8) |
| | *Mastectomy* | 44(51.2) |
| Adjuvant CT | *Anthra. and/or tax* | |
| [e]RT | *Yes* | 56(65.1) |
| [f]HT | *Yes* | 54(62.8) |

[a]BMI: Body mass index. BMI categories were defined upon the mean value computed for this study population, i.e., 26
[b]IMS (Intrinsic Molecular Subtype): Clinico-pathologic surrogate definition of intrinsic subtypes of breast cancer (26 in the reference list)
[c]Neoadjuvant CT: Anthra. and/or tax.: Anthracycline-and/or Taxane-based regimen
[d]BCS: Breast Conservative Surgery
[e]RT: Adjuvant radiotherapy
[f] HT: Adjuvant hormone therapy.

(Supplementary Table 1). Results from univariate models were somewhat supportive of higher pCR rates in women with lower BMI (p = 0.06). However, this result was not confirmed in multivariate models (Supplementary Table 2).

None of the variables tested impacted DFS significantly (available upon request). Conversely, OS was affected by BMI (p=0.009) (Fig. 1). A significantly longer OS was also observed in patients with lower stage at diagnosis (p = 0.046, available upon request), and in women who received adjuvant RT (72.4 months, 64.6–80.2 and 55.3 months, 43.6–67.0, (p = 0.024) (Fig. 2). A longer OS was also conditioned by IMS (p = 0.015, Fig. 3) and, at some extent, by the chances of being treated with HT (71.2 months, 63.5–79.0 vs 54.3 months, 43.8–64.8, p = 0.05) (available upon request). Results from multivariate analysis are shown in Table 3. In Cox models, the protective role of lower BMI was confirmed (HR: 0.30, 95%CI: 0.12–0.71, p = 0.007). In addition, women lived significantly longer if diagnosed with a non TN breast cancer, that is, if the disease was molecularly characterized as luminal A, B or HER2+ (p = 0.008), and if having received adjuvant RT (p = 0.024).

## Discussion

In this observational study, we analyzed data from a moderately sized cohort including 86 women aged 45 y or less treated with neoadjvant CT followed by surgery. Our scope was to address an increasingly debated issue, that is, the impact of BMI on short- and long-term treatment outcomes. Our study cohort was essentially characterized by 2 distinctive features, namely, the young age and neoadjuvant setting. We observed a pCR in about 22% of our cohort, with a suggestion in support of the association between favorable outcomes and lower BMI. This was somewhat confirmed in univariate, but not in multivariate, analysis. The role of BMI emerged more clearly from survival analysis, with the inherent data showing a significantly prolonged OS in women whose BMI fell in the lowest category. The impact of BMI on OS was confirmed in multivariate analysis, along with the influence of the molecular characteristics and adjuvant RT.

To the best of our knowledge, no previous study has addressed the role of BMI in the neo-adjuvant setting with a focus on young age at diagnosis. Indeed, 2 groups of colleagues have separately worked on the impact of BMI on neoadjuvant treatment outcomes in breast cancer [18] and on the outcomes of neoadjuvant chemotherapy in young breast cancer patients.[19] The pCR rate observed in our cohort was about 22%. This is consistent with what reported by Fontanella and co-authors in their individual data pooled analysis on BMI and neoadjuvant treatment outcomes, wherein a pCR rate of 21.3% was observed, i.e., 1,890/8,872.[18] Our results are also consistent with those from the work of Loibl and colleagues, who focused on young breast cancer patients and found evidence of an inverse association between age at diagnosis and pCR rate. When compared across groups differing by age, the pCR rates were 20.9 (303/1,453), 17.7 (545/3,073) and 13.7% (608/4,423) for women aged less than 40 years, between 40 and 49 years, and at least 50 years, respectively.[19]

Results from our analysis provide some support to the association between lower BMI and higher chances of pCR achievement. This is in key with what described by Fontanella and co-authors, who observed a higher pCR rate in normal weight

**Table 2.** Pathologic complete response(pCR) in the overall study population and in subgroups defined by participant- and disease-related features (N:19 pCR out of 86 study participants).

| | | | N(%) | p |
|---|---|---|---|---|
| pCR | | | 19(22.1) | |
| | Age | *<38* | 9 (47.4) | .52 |
| | | *≥38* | 10 (52.6) | |
| | [a]BMI | *<26* | 12(63.2) | 0.05 |
| | | *≥26* | 7(36.8) | |
| | [b]Intrinsic Molecular Subtypes | *Luminal ALuminal BHER2 positiveTriple negative* | 2(10.5)9(47.4)3(15.8)5(26.3) | .593 |
| | T Stage N Stage | *1-23-40-12-3* | 7(36.8)12(63.2)10(52.6)9(47.4) | .424.430 |
| | Neoadj. CT | [c]*Ant.and/orTax.* | 12(63.2) | .200 |
| | | *Other* | 7(36.8) | |

[a]BMI: Body mass index (Kg/m2), BMI categories were defined upon the mean value computed for this study population, i.e., 26
[b]IMS (Intrinsic Molecular Subtype): Clinico-pathologic surrogate definition of intrinsic subtypes of breast cancer (Reference 26)
[c]Neoadjuvant CT: Anthra. and/or tax.: Anthracycline-and/or Taxane-based regimens.

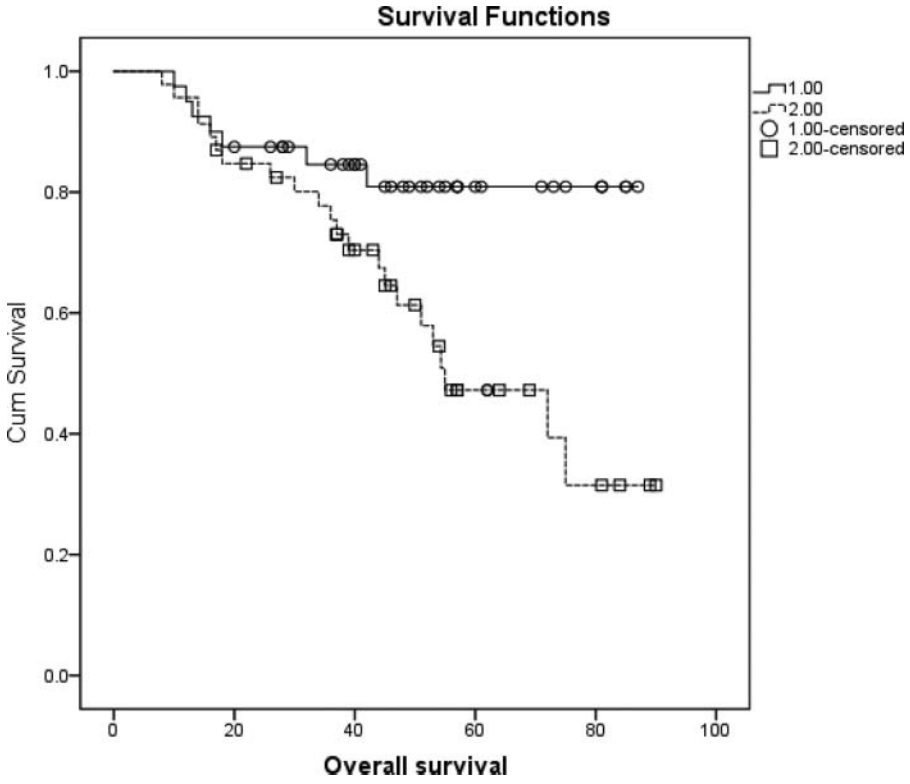


**Figure 1.** Overall survival (OS) by subgroups defined upon BMI, i.e., BMI: <26 and BMI≥26.

patients, namely, in women whose BMI was between 18.5 and 25, compared with other BMI groups.[18] In our work, BMI groups were defined based on the mean value computed at the study population level, namely, 26. This latter cut off is slightly higher than that suggested by the world health organization (WHO) to distinguish between normal weight and overweight patients.[27] However, when BMI categories were re-defined according to this same cut off, i.e. Twenty-five rather than 26, the 57.9% (11/19) of pCR still fell in the lowest BMI categories ($p = 0.14$).

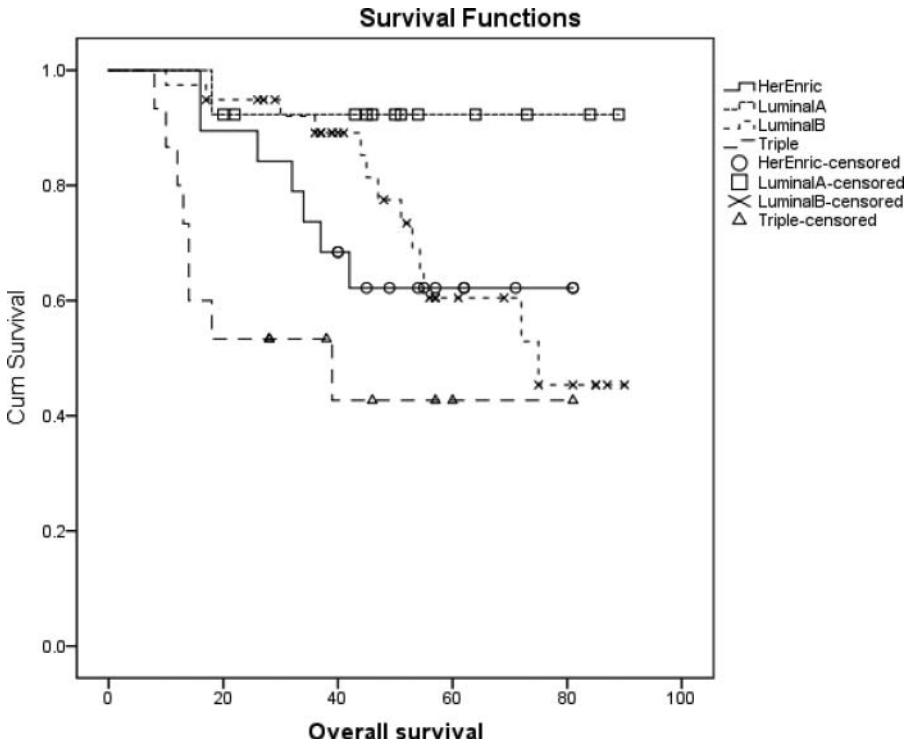


**Figure 2.** Overall survival (OS) by subgroups defined upon intrinsic molecular subtype (IMS).

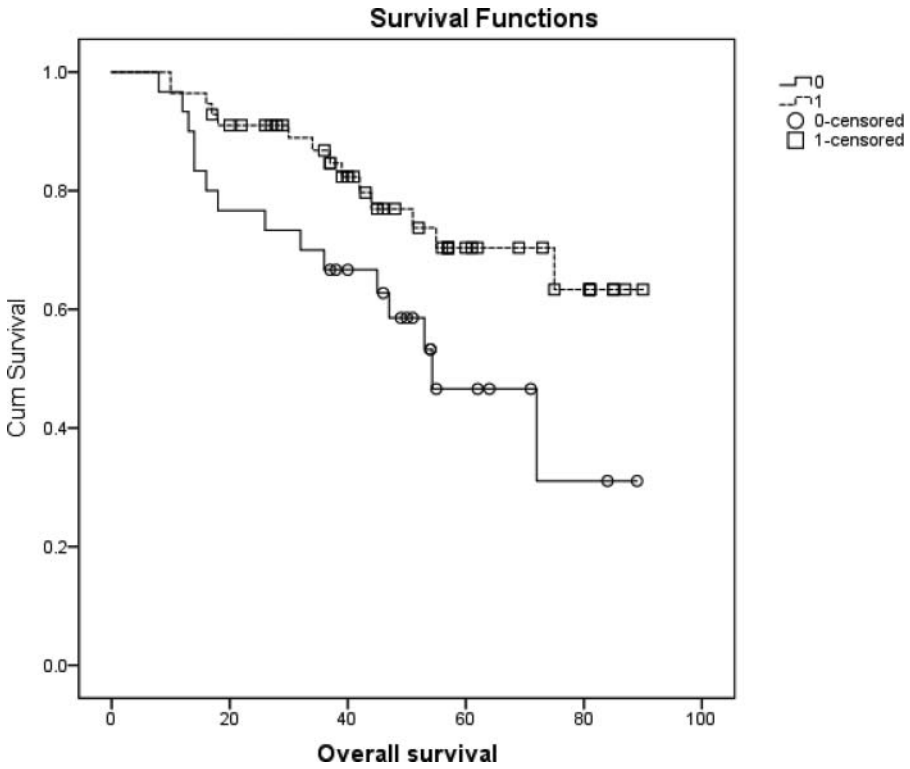


**Figure 3.** Overall survival (OS) by subgroups defined upon adjuvant radiotherapy (RT).

Overall survival was significantly longer in patients within the lowest BMI category. The detrimental effect of BMI on OS in the neoadjuvant setting was also reported by Fontanella and co-authors. In addition, large and consistent evidence links poorer survival outcomes to higher BMI values not only in the neoadjuvant setting but also in the metastatic and adjuvant settings (28-29-30). A number of mechanisms may actually concur to provide a biological rationale for the role of BMI on treatment outcomes in the neoadjuvant and other breast cancer settings. In regard to survival outcomes, several and heterogeneous determinants may potentially be involved. Hormones, adipocytokines, and meaditors of inflammatory processes such as cytokines are all related to key aspects of cell survival or apoptosis, migration, and proliferation. Though in premenopausal women estrogens are mainly of gonadic origin, adipose tissues represent an adjunctive source of these hormones via aromatization from androgens. Higher levels of insulin are commonly observed in overweight and obese women and related to poorer prognosis in breast cancer patients. Possible interactions have been described between leptin and insulin, and obesity-related markers of inflammation have also been described in association with breast cancer outcomes. Further mechanisms could include obesity-related co-morbidities which may act as contraindications to the most effective treatment at the individual patient level.[31-35]

Several studies have shown that young breast cancer patients are more likely to exhibit a TN subtype (36–37). As shown by Anders and colleagues, in breast cancer arising at a young age, specific biologic differences may be subtype dependent.[37] In our cohort, OS was negatively associated with TN breast cancer. This finding replicates what observed by Chen and colleagues in 187 chinese breast cancer patients aged less than 40 y old. In Cox models including lymph node status and molecular subtype, young patients with TN breast cancer showed significantly worse OS compared to other molecular subgroups ($p = 0.048$).[38]

**Table 3.** Cox proportional hazards models of factors associated with Overall Survival (N:86).

| | Hazard Ratios | 95%CI[a] | p |
|---|---|---|---|
| BMI[2] | 0.30 | 0.12-0.71 | 0.007 |
| IMS[3] | | | 0.008 |
| *I* | 0.43 | 0.15-1.21 | 0.011 |
| *II* | 0.04 | 0.01-0.35 | 0.003 |
| *III* | 0.30 | 0.12-0.75 | 0.010 |
| T Stage | 0.58 | 0.23-1.46 | 0.247 |
| RT[4] | 2.41 | 1.12-5.18 | 0.024 |

[1]95%CI: 95% Confidence Interval
[2]BMI: Body mass index
[3]IMS: Intrinsic molecular subtype: the reference category is the triple negative (TN) subtype (reference: 26)
[4]RT: radiotherapy.

In our case series, women who did not undergo adjuvant RT showed a significant disadvantage in terms of OS. According to the results from descriptive analysis, 56 women (65.1%) received RT. Among them, 42 (48.8%) had previously been treated with BCS, while only 14 (31.8%) of those having undergone mastectomy received adjuvant RT. Recently, the administration of postmastectomy radiotherapy (PMRT) has increasingly attracted the researchers' attention. However, we still lack data from randomized trials which may clearly orient toward the delivery or omission of PMRT in patients who had been treated with neoadjuvant chemotherapy, which is now an progressively more common approach. Neither are the available data specifically referred to women diagnosed with breast cancer at a young age.[39]

Our study has limitations. In first place, the observational nature of the study design makes *per sè* our research more prone to confounding and bias compared to randomized clinical trials. However, thus far, the association of interest has not been addressed using data from trials. In addition, evidence from a real world population may fairly suit the clinicians' needs and integrate knowledge from future randomized studies. Indeed, due to the strict selection criteria applied at the time of enrollment, patients from trials may significantly differ from patients from the clinical practice. This fuels doubts concerning the external validity of the results from randomized trials and their applicability to a definable group of patients in routine practice.[40]

Our study also has some important strengths. In first place, novelty of findings should be considered. We observed first time evidence on the role of BMI, an increasingly used anthropometric indicator of general obesity, on treatment outcomes in a well characterized cohort of women with an indication to neoadjuvant treatment due to breast cancer diagnosed at a young age. Similarly, to the best of our knowledge, this is the very first source of data concerning PMRT in young women having undergone neoadjuvant systemic treatment. In addition, when considering the rarity of the condition,[41] our series size appears only limitedly restricted and quite well characterized concerning patients' molecular and clinical features.

In summary, we carried out an observational study focused on the role of BMI on the short- and long-term outcomes of 86 women aged 45 or younger who received neoadjuvant CT followed by surgery. We found borderline evidence of higher pCR rates in women within the lowest BMI category compared to their heavier counterpart. The evidence emerged from survival analysis of OS was more robust, with lower values of BMI being associated with significantly longer OS. Results from the univariate were confirmed in Cox models. These latter were also confirmative for more favorable survival outcomes (OS) in patients with non TN breast cancer and in women who have received adjuvant RT. It is notable that every social group is vulnerable to the familial, health and economic burden of cancer. However, current evidence indicates that physical and emotional distress are significantly amplified in patients diagnosed at a young age.[42] In this view, further evidence collected throughout ad hoc, prospective studies is urgently needed to confirm our findings and eventually explore interventions targeting BMI for their impact on treatment outcomes in breast cancer patients diagnosed at a young age.

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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