AMERICAN UNIVERSITY OF BEIRUT

PRESENTATION, TREATMENT MODALITIES, AND OUTCOMES OF BREAST CANCER IN YOUNG FEMALES: A COMPARISON WITH OLDER AGE GROUP IN LEBANON

by
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ABSTRACT
OF THE THESIS OF

Mohamad Othman El Helou for Master in Health sciences (SHARP)

Title: Presentation, Treatment Modalities, and Outcomes of Breast Cancer in Young Females: A Comparison with Older Age Group in Lebanon

Background: Breast cancer is the most prevalent cancer in women worldwide. Young breast cancer is not as frequent yet is the most common cancer in females aged 15 to 39 years. To add, young breast cancer is more common in developing countries like Lebanon highlighting the importance of investigating this disease in the region. Nonetheless, studies investigating this entity in Lebanon and the region are scarce.

Objectives: In this study we aim to investigate the differences between young breast cancer patients (<40 years old) and older breast cancer patients (≥40) in terms of tumor characteristics, treatment modalities, and outcomes

Methods: We reviewed charts of female patients with biopsy proven invasive breast cancer who received part of their treatment at AUBMC between 2010 and 2016. Data on patient demographics, tumor characteristics, treatment modalities, and patient outcomes were collected. Follow up was limited to March 2020. Patients were then divided into two age groups: young (<40) and older (≥40) breast cancer patients. The chi-squared test was used to compare categorical variables and the independent t-test was used to compare continuous variables between the two age groups. Univariate and multivariate logistic regression models were conducted to investigate the trends of undergoing complete mastectomy and chemotherapy administration in both age groups. Odds ratios were used to report trends for different variables. A sensitivity analysis was undertaken by recoding the missing values in each categorical variable as an unknown category in that variable. Overall survival and Disease-Free survival curves were computed using the Kaplan Meier method and compared across both age groups using the log rank test. IBM SPSS version 28.0 was used to conduct all statistical analyses. Significance level was set at the 5% level.

Results: We identified 745 patients diagnosed with breast cancer between 2010 and 2016. 126 patients (17%) were younger than 40 years of age. Young breast cancer patients were found to have significantly higher proportion of multiple masses on imagining (38.1% vs 27.2%, P: 0.017), more multifocal and multicentric tumors (39.2% vs 27.3%, P: 0.001), more calcifications on mammography (72.4% vs 51.9%, P:0.001), higher proportion of grade 3 tumors (52% vs 34.2%, P<0.001), higher HER-2 positive disease (30.6% vs 21.6%, P:0.033), and higher lymphovascular invasion (46.7% vs 40.1%, P:0.028). Moreover, the young age group was also found to have higher proportion of stage III

cancer (23.8% vs 15.8%, P:0.095), greater tumor size on imaging (2.62 $\pm$ 1.63 cm vs 2.29 $\pm$ 1.64 cm, P:0.052), and lower Luminal A subtype (30.6% vs 41.8%, P:0.126) but these results did not reach statistical significance. In terms of treatment young breast cancer patients were found to take more chemotherapy (90.2% vs 75.8%: P:0.003), especially neoadjuvant chemotherapy (37.4% vs 24.6%, P:0.028) and anthracycline based chemotherapy (90.2% vs 75.8%, P:0.003). Young patients were also found to take more Trastuzumab (Anti-Her2) treatment (37.3% vs 24.6%; P:0.029). No difference in breast surgery type, axillary surgery, radiotherapy, and hormonal therapy was noted between both groups. Univariate and multivariate logistic regression revealed similar trends in both age groups with positive lymph nodes, multiple tumors on imaging, higher tumor grade, more aggressive molecular subtypes (Luminal B, HER 2, and TN), and higher tumor stage being all associated with greater odds of undergoing complete mastectomy A second model that included in addition to the variables in the first mode the calcification on mammography variable and the sensitivity analysis revealed similar trends with the calcifications on imaging (when present) being associated with higher odds of complete mastectomy. Similarly, the univariate and multivariate analysis for chemotherapy indications revealed that higher tumor size, positive lymph node status, multiple tumors on imaging, higher grade, higher stage, and complete mastectomy were all associated with higher odds of chemotherapy.All patients with HER 2 and Triple negative subtypes were found to take chemotherapy. The second model and the sensitivity analysis revealed similar results with calcifications on mammography (when present) being linked to higher odds of chemotherapy only in the older age group. As for outcomes, young breast cancer patients were found to have a significantly higher proportion of recurrence (16.7% vs 10%, P:0.031) and particularly distant recurrence (14.3% vs 8.2%, P:0.033). Furthermore, there was a statistically significant difference in DFS curves (log rank: 0.012) but not OS curves.

Conclusion: Our results are in line with previous studies on young breast cancer. Our study revealed that young breast cancer patients had more aggressive presentation, more aggressive chemotherapy treatment, similar surgical treatment, and worse recurrence outcomes. We are to our knowledge the first study to investigate all three aspects: tumor characteristics, treatment modalities, and outcomes in Lebanon and the region. There is a need for larger prospective studies, to investigate this disease further to better guide physicians to tailor therapies in the region, avoiding over or under treatment.

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ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
AUB	American University of Beirut
AUBMC	American University of Beirut Medical Center
AYA	Adolescent and Young Adult
BCS	Breast Conservation Surgery
BCT	Breast Conservation Therapy
BMI	Body Mass Index
BC	Breast Cancer
CI	Confidence Interval
CPM	Contralateral Prophylactic Mastectomy
DFS	Disease Free Survival
DM	Diabetes Mellitus
EBCTCG	Early Breast Cancer Trialists' Collaborative group
ER	Estrogen Receptor
FH	Family History
FISH	Fluorescence in situ hybridization
GBD	Global Burden of Disease
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
IRB	International Review Board
NSABP	National Surgical Adjuvant Breast and Bowel Project

LR	Local Recurrence
OBC	Older Breast Cancer
OR	Odds Ratio
OS	Overall Survival
PR	Progesterone Receptor
RCT	Randomized Controlled Trials
RR	Relative Risk
TEXT	Tamoxifen and Exemestane Trial
TN	Triple Negative
TM	Total Mastectomy
SEER	Surveillance, Epidemiology, and End Results Program
SOFT	Suppression of Ovarian Function Trial
YBC	Young Breast Cancer

CHAPTER 1

BACKGROUND

1.1. Female Breast Cancer Overview:

1.1.1. Epidemiology:

According to the WHO, female breast cancer ranks first worldwide in terms of incidence and prevalence with 7.8 million women living with breast cancer by the end of 2020 [1]. Furthermore, breast cancer is the fifth leading cause of cancer related mortality in females with 685,000 deaths [2]. In the US, female breast cancer has the highest estimated incidence in 2022 with 287,850 cases constituting 31% of all cancer cases in women[3]. This trend can be seen in other countries as well, for breast cancer ranks first in terms of incidence in 159 out of 185 countries and first in mortality in 110 out of 185 countries [2]. Australia has the highest incidence rate worldwide (80 per 100,000), with higher incidence rates recorded in developed countries (55.9 per 100,000) compared to developing countries (29.7 per 100,000 [2]. These striking statistics highlight the burden of female breast cancer globally.

1.1.2. Molecular and clinico-pathological subtypes:

At the beginning of the 20th century, breast cancer patients were all managed with uniform treatment; however, over time it became clear that patients with the same type of cancer have varying prognosis despite receiving the same treatment. This indicates that breast cancer is a heterogenous disease in nature and should be treated as such. To match this evolving understanding of the disease, the era of the “Molecular Classification” emerged to replace the traditional “Morphological classification” [4]. This new classification is not only beneficial in terms of determining prognosis, but also aids in

tailoring the management plan for individualized patients. With multiple factors and criteria being taken into consideration including hormone receptor status, human epidermal growth factor 2 (ERBB2; formerly known as HER2/neu) overexpression, and Ki67 proliferation rate; breast cancer patients can be sub grouped into four main categories depending on gene expression [5]. Luminal A subtype that is Estrogen Receptor (ER) and Progesterone receptor (PR) positive with low histologic grade and low ki67 proliferation rate. Luminal B subtype that is ER positive tumors with higher histologic grade, progesterone receptor negative, her-2 positive or high Ki67. HER 2 subtype which has HER2 overexpression with negative ER and PR receptors. Finally, basal, or triple negative cancer that is negative for all three receptors (ER, PR, and HER2/neu), and has the worst prognosis among these subtypes [6, 7].

1.1.3. Treatment modalities:

Treatment modalities in breast cancer can be divided into local and systemic therapies. Local therapies include surgery and radiation; while systemic therapies includes chemotherapy, hormonal therapy, and targeted therapy.

1.1.3.1 Surgical Treatment:

The two main surgical treatments for breast cancer can be divided into breast conserving therapy (BCT) - partial mastectomy- and total mastectomy (TM). Several randomized clinical trials comparing TM to BCT showed that BCT has comparable survival outcomes to mastectomy in early breast cancer [8]. One of the first clinical trials comparing recurrence and survival outcomes between the two surgical techniques is the “Milan trial” by Veronesi et al. conducted between 1973 and 1980. This study included

701 patients with tumors less than 2cm in diameter and no palpable axillary lymph nodes. These patients were randomized to quadrantectomy (partial mastectomy) with radiation therapy or "Halsted" (total) mastectomy in a 1:1 ratio. Follow up results in 2002 (20 years later), revealed greater local recurrence in the partial mastectomy group compared to total mastectomy (8.8% vs 2%; P<0.001), with long term overall survival being similar between the two groups (58% vs 59%, p:1.0)[9]. Similarly, the National Surgical Adjuvant Breast and Bowel Project B-06 trial (NSABP-06), initiated in 1973, included 1,851 eligible patients randomized into one of three groups: total mastectomy, partial mastectomy, or partial mastectomy with irradiation. Outcomes from 20 year follow up revealed no significant difference between the three groups in terms of overall survival, disease free survival, and distant free survival[8]. The Hazard ratio of death between the lumpectomy group compared to the mastectomy group was 1.05 (P:0.51) and that between lumpectomy with irradiation and complete mastectomy was 0.97 (P:0.74). Similarly, the hazard ratios for disease free survival were 1.05 (P:0.47) for the lumpectomy alone group and 0.94 (P:0.41) in the lumpectomy with irradiation group when both were compared to the complete mastectomy group. The same goes for the distant disease free survival that was 1.11 (P:0.21) in the lumpectomy alone group and 1.01 (P:0.95) in the lumpectomy with irradiation group when compared to total mastectomy[8].

1.1.3.2. Radiation therapy:

With the implementation of mammography screening for asymptomatic women, tumors were detected at an earlier stage (smaller size), making them candidates for conservative therapy. Radiation therapy is an integral part of BCT and can be directed to

the breast (if a lumpectomy is performed), the chest wall in case of a complete mastectomy, and axillary lymph nodes. Randomized clinical trials showed similar survival rates between conservative therapy and complete mastectomy [10]. One trial is the (NSABP) B-06 randomized clinical trial discussed above that also highlighted the beneficial role of radiotherapy on outcomes as the local recurrence rate in the lumpectomy group with radiation was the lowest at 20 years with 8.1% compared to 17.5 % in the Lumpectomy alone group, and 14.8% in the mastectomy group [8]. Similarly, the Early Breast Cancer Trialists' Collaboraxtive group (EBCTCG) meta-analysis which included around 20,000 breast cancer patients divided into surgical treatment with and without radiotherapy revealed similar beneficial results [11]. In this study, adjuvant radiotherapy was found to decrease yearly odds of recurrence by 3 times, lead to a 20 % absolute reduction in Loco-regional failure, and a 5% improvement in long term breast cancer specific survival [11]. The studies above highlight the importance of radiotherapy and its positive therapeutic effects in all age groups including young breast cancer patients.

1.1.3.3. Chemotherapy:

Chemotherapy is considered the cornerstone in the systemic treatment of breast cancer, as it plays a role in the improvement of both survival and recurrence outcomes. In one prospective study, that included 32,502 women with non-metastatic breast cancer that were propensity scored matched to 2 groups (with and without chemotherapy), the chemotherapy group had improved 5- and 10-year overall survival (92.1 and 81.9) compared to (87.6 % and 75%) in the no chemotherapy group respectively. The multivariate logistic regression also revealed that chemotherapy was significantly associated with improved Overall Survival by 25% [HR=0.75, P:<0.0001)[12]. In

addition to improving survival, chemotherapeutic agents play an integral role in decreasing recurrence rates in patients with non-metastatic breast cancer. This was highlighted in a study by the EBCTCG group, that revealed that the use of polychemotherapy in patients less than 50 years of age was found to decrease 5 year recurrence rates (24.6% vs 37.1% in control group), 10 year recurrence rates (35.5% vs 47.9% in control group), and 15 year recurrence rates (41.1% vs 53.5% in control)[13]. These studies highlight the important role that chemotherapy in improving long term outcomes particularly in the young breast cancer group, especially when used in addition to hormonal therapy in (ER+) tumors and to targeted (anti-Her-2) therapy in patients with Her2/neu overexpression. Moreover, chemotherapy is the only systemic treatment that is effective in triple negative breast cancer patients [14]. Several chemotherapy regimens are available for the treatment of breast cancer. A systematic review published in JAMA oncology, compared different chemotherapy combinations including Anthracyclines with and without Taxanes, Docetaxel and cyclophosphamide, cyclophosphamide with methotrexate and fluorouracil, and platinum containing regimens. The conclusion of the study was that the sequential use of Anthracyclines and Taxanes (i.e anthracycline/cyclophosphamide and Taxanes) is more effective than the other combinations for the treatment of early-stage breast cancer regardless of hormone status [15]. To add chemotherapy can be used as both an adjuvant treatment (after delivering the surgical treatment) and as a neoadjuvant treatment (before delivering the surgical treatment). In the neoadjuvant setting, studies have shown that the use of neoadjuvant chemotherapy in large locally advanced tumors decreases tumor size, helps patients avoid radical surgeries, and improves outcomes. This was confirmed in a meta-analysis containing 3776 patients that revealed that neoadjuvant chemotherapy combined with

pathological complete response significantly increased the odds of overall survival by 3.44 times [95% CI:2.45-4.84], the odds of disease free survival by 3.41 times[95%CI: 2.54-4.58], and the odds of relapse free survival by 2.45 times [95%CI: 1.59-3.80] [16].

1.1.3.4. Hormonal Therapy:

In Hormone receptor positive tumors, the use of hormonal (antiestrogen) treatment is a mainstay therapy. Furthermore, the hormonal treatment choice depends on the patients menopausal status, with the standard treatment consisting of using daily antiestrogen medications for five years [14]. The two main treatments that can be used include tamoxifen (selective estrogen receptor modulator) and aromatase inhibitors (letrozole, anastrozole, exemestane) which decrease the circulating estrogen level [14]. Tamoxifen can be used in both premenopausal and menopausal women, while aromatase inhibitors are mainly effective in post-menopausal women [14]. In premenopausal women, a meta-analysis of 20 randomized clinical trials conducted by the Early Breast cancer Trialists Collaborative group (EBCTG), revealed that tamoxifen significantly decreased the 15-year risk of recurrence and death (compared to the no tamoxifen group) with ER receptor status being a major predictor for response to treatment [17]. The RR for recurrence was 0.53 (P:<0.001) for the first 4 years and 0.68 (P:<0.001) between 5-9 years in the tamoxifen group compared to no tamoxifen [17]. Meanwhile in older women, a randomized clinical trial (RCT) published in the New England Journal of Medicine, comparing tamoxifen to aromatase inhibitors in postmenopausal women, showed that aromatase inhibitors significantly decreased the risk of recurrence by 19 % [HR=0.81, P:0.03] and particularly recurrence at distant sites by 27% [HR=0.73, p-value:0.001] compared to Tamoxifen group [18].This is consistent with other studies that favor

aromatase inhibitors over tamoxifen in postmenopausal women [14]. Furthermore, a major factor in the choice of hormonal therapy is the side effect profile of the drugs used with endometrial cancer and venous thromboembolism being major concerns in the tamoxifen group, while osteoporosis and joint pains being a worrisome factor in the aromatase group [19]. That's why studies are investigating the sequential use of hormonal therapies that are found to improve Disease Free Survival (DFS) compared to tamoxifen as a method to decrease systemic toxicities of the hormonal agents [19].

1.1.3.5. HER 2 targeted therapy:

Targeting the HER2 receptor has been considered the greatest advancement in the treatment of HER 2 positive tumors. Treatment options include monoclonal antibodies (like trastuzumab) and tyrosine kinase inhibitors (like lapatinib, neratinib, afatinib). The therapeutic effect of trastuzumab was investigated in a randomized clinical trial that included 469 women with metastatic breast cancer randomized into two groups: standard chemotherapy with and without trastuzumab [20]. In this study by Slamon et al, the trastuzumab plus standard chemotherapy group was found to have improved overall-survival (25 months compared to 20 months in the standard chemotherapy group), increased response rate by 18% (50% compared to 32%in the no trastuzumab group), and extended time to progression (7.4 months compared to 4.6 months in the no trastuzumab group) [20]. Dual therapy - combination of trastuzumab with other targeted agents like Pertuzumab (monoclonal antibody) and Neratinib (tyrosine kinase inhibitor)- also demonstrated improved efficacy in cancers with HER2/neu overexpression compared to standard trastuzumab and chemotherapy treatment. In a placebo-controlled phase III clinical trial that included 4805 patients, the addition of pertuzumab to the standard

combination therapy was found to improve 3 year invasive free survival (HR:0.77, 95%CI:0.62,0.92) and disease recurrence (HR:0.81, 95%CI:0.66,1, P:0.045) [21]. Similarly, Neratinib demonstrated an improved 5 year invasive disease free survival in a placebo controlled phase III randomized clinical trial that included 2840 patients randomized into: standard therapy with the addition of Neratinib daily for 1 year or placebo [5-year recurrence free rates: 90.2% with neratinib vs 87.7% with placebo (HR:0.73, 95%CI:0.57,0.92)] [22].

1.1.4. Prognosis and Outcomes:

When it comes to prognosis and long-term outcomes it is essential to talk about survival and recurrence rates. Survival rates reflect the percentage of women that are alive at a certain time point following diagnosis. While recurrence rates reflect the percentage of females that experience breast cancer recurrence at a certain time point following diagnosis. Moreover, the National Cancer Institute defines Overall Survival (OS) as the "time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive" and Disease Free Survival (DFS) as: "the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of the cancer" which are both essential components for oncologic outcomes [23, 24]. In terms of outcomes, more advanced tumors are associated with worse outcomes and many factors come into place when evaluating the risk of breast cancer death or recurrence like high grade, larger tumor size, negative hormone receptor status, and axillary lymph node involvement. For instance, higher stage is linked to worse survival rates. In a study done containing 3,873 females with breast cancer the 5-year survival rates were found to decrease significantly as the

stage of cancer increased that were 94.4% (stage I), 85% (stage II), 56.6% (stage III), and 28.3% (stage IV). In a population-based analysis of cancer registries, including 29,833 women, breast cancer survival was compared across the different molecular subtypes. In the unadjusted analysis the survival curve was best for the luminal A subtype, followed by luminal B, Her 2 overexpressed, and finally the Triple negative subtype that had the worse survival of all (P:<0.001)[25]. In the multivariate cox regression across molecular subtypes, a dose dependent increase in Hazard ratio was noted across increasing age and stage. The most prominent of which was in the HER 2 subtype with up to 8 times the Hazard for age [95%CI: 3.68-11.81] and 37 times the Hazard with increasing stage [95%CI: 34.64-41.27] [25].

1.2. Overview of Young Female Breast Cancer:

1.2.1. Age cutoff:

Several age cutoffs were used by investigators when studying young breast cancer including the ages of 30, 35 ,40, 45, and 50 years. The most frequently used to define young breast cancer is the age of 40, with some investigators defining "very young" breast cancer patients under the age of 35. A study by Collins et al demonstrated no difference in prognosis and molecular subtype distribution even after dividing the young breast patients into 5-year increments (≤ 30 years, 31 to 35 years, and 36 to 40 years)[26]. Which could support the use of the 40 years cutoff to define young breast cancer.

1.2.2. Epidemiology:

Even though the incidence of breast cancer increases with age, breast cancer is the most common cancer in adolescent and young adult (AYA's) women aged 15 to 39 [27]. Worldwide, approximately 6.6% of all breast cancers are diagnosed in women less than 40 years of age, accounting for 15% of all invasive cancers and 30% of cancers in

young females [28, 29]. In the US, young breast cancer (<40) accounts for around 5.6 % of all invasive breast cancer in females [28]. But in developing countries higher proportions of young breast cancer are reported compared to developed countries with countries in the middle east recording up to 33% of breast cancer cases under the age of 40 [30]. The reasons for this difference can be explained by demographical differences, in particular the bigger proportion of younger people in developing countries compared to developed countries, and can be due to genetic and environmental factors [31]. Furthermore, the incidence of young breast cancer at very young ages is even lower with statistics from the CDC highlighting that the age specific rate of young female breast cancer increases from 10.3 per 100,000 in females between 25 and 29 years to 30.5 per 100,000 in females aged between 30-34 years to 62 per 100,000 women in women aged 35 to 39 years [32].

1.2.3. Initial Presentation:

In terms of initial presentation, young breast cancer patients identify asymptomatic tumors upon self-examination while older age groups are more likely to identify the cancer on imaging [33]. A study by Partidge et al highlighted that, younger women are more likely to present with symptomatic disease rather than screening detected disease (89.5% in young vs 52.1 % in older females) [34]. Similarly, Several descriptive studies highlighted that most young women detect their disease through self-examination (80%), followed by imaging (12%), and finally by clinical exam (6%) [35].

1.2.4. Pathologic features and molecular subtypes:

It is believed that young breast cancer in females has a more aggressive presentation compared to the older age groups with data from prospective and

retrospective studies supporting this claim. In a large retrospective study conducted by Gnerlich et al, that included 243,012 patients who survived between 1998-2003 (out of which 15,548 patients were younger than 40 years of age) young breast cancer was found to be associated with worse biological features like larger tumor size, greater lymph node involvement, poor differentiation, and ER negative tumors (p-value<0.001) [36]. In terms of more aggressive staging and grading, a study conducted by Gomez et al highlighted that young breast cancer is more likely to be diagnosed at regional and distant stages compared to older age groups [37]. Furthermore, the proportion of Stage III and IV cancers was more than 50% in women age <35 in all ethnic groups and was found to decrease in proportion with increasing age, compared to an increase in proportion of Stage I and II tumors [37]. A retrospective chart review of 8892 patients between the years 1980 and 2002, studied nodal status and tumor size of 925 young breast cancer patients (<40 years) and 2362 older breast cancer patients (50 to 60 years of age) are compared. No significant difference between tumor size and nodal status was identified between the two age groups from the years 1980 and 1990 [38]. However, from 1990 to 2002 young breast cancer patients had significantly larger mean tumor size of 2.4 cm (compared to 1.8 cm in the older group; P: <0.01) and higher percentage with positive lymph nodes of 35.2% (vs 23.9%, P-value: <0.001) [38]. In terms of Molecular subtypes distribution, a large retrospective study conducted by Azim et al, revealed that younger patients have the greatest percentage of basal like tumors with 34.3% (p<0.0001) and the lowest percentage of Luminal A tumors with 17.2% (p-value< 0.0001) [39]. This is in concordance with another retrospective study that includes 4467 patients diagnosed below the age of 40. This study demonstrated an increase in the Luminal A subtype with age (P<0.001),

compared to a decrease in triple negative (P<0.001) and HER 2 positive (P=0.001) subtypes with no significant change in Luminal B subtype [40].

1.2.4.1. Is age an independent risk factor for more aggressive breast cancer?

Whether the more aggressive presentation of young breast cancer is an indirect consequence of more aggressive tumors at a younger age or is the direct effect of age as an independent prognostic factor has been studied in the literature. Some studies indicated that the more aggressive features in young breast cancer patients are due to the higher proportions of poorly differentiated cancers in younger age group and are not a direct consequence of age itself [41]. Similarly, other studies demonstrated that the worse prognosis in young breast cancer is the result of both a more advanced disease and the tumor biology in this age group [42]. On the other hand, studies investigating the independent effect of age after stratification by molecular subtypes demonstrated that age is an independent prognostic factor especially in Luminal subtypes (Luminal A and Luminal B(HER2- subtypes)) but not in HER 2+ve, and triple negative disease [43]. In addition, a retrospective study conducted by Azim et al that included 3,522 patients from 39 published data sets on young breast cancer revealed that young breast cancer patients are associated with worse Recurrence free survival (HR: 1.34, 95%CI:1.1-1.63, P=0.004) even after adjusting for tumor characteristics (cancer subtype, nodal status, tumor size, and histological grade) and stratifying by treatment modality used [39]. Thus, suggesting that breast cancer in young females have distinct biological features that should be studied further.

1.2.5. Treatment modalities:

1.2.5.1. Loco-Regional Treatment:

Despite the reported more aggressive presentation of young breast cancer, young age should not be an indication for more aggressive surgical treatment. Thus, both surgical options (breast conservative therapy or mastectomy) are still feasible options for the younger age group. Especially that studies reveal similar survival rates between both surgical treatments [44]. In a retrospective study of 1930 patients with triple negative breast cancer, no difference in 5-year local recurrence was noted between the younger age group (<40 years) (LR: 3.9%; 95%CI:1.5-6.2) and the older cohort (≥ 40 years) (4.5%; 95%CI:3.5-5.6) [45]. Similarly, no difference in 5 years Disease free survival was noted between young and older patients (DFS:75.3% vs 77.7% respectively; P:0.94); despite the more aggressive treatment in the younger age group (mastectomy, axillary lymph node dissection, and chemotherapy) [41]. In addition, on multivariate logistic regression age (HR:0.91, P:0.79) and type of surgery (HR:0.62, P: 0.15) were not significantly associated with the outcomes [45]. This is in concordance with other studies that demonstrated no additional survival benefits for mastectomy over Breast conservative therapy in the younger age group [46, 47]. Nonetheless, younger breast cancer patients are not only opting for mastectomy over breast conservative therapy; but are also choosing to go for contralateral prophylactic mastectomy (CPM). This increasing trend in contralateral prophylactic mastectomy is noted in a large retrospective study between 1998 and 2011 from the California cancer registry that showed an increase in patients undergoing CPM from 3.6% in 1998 to 33% in 2011 [48]. Furthermore, young breast cancer patients have 4.3 times the odds of undergoing reconstruction following mastectomy compared to their older counterparts [49]. In the Arab world a study by El

Saghir et al, highlighted that mastectomy is still the most common procedure performed in more than 80% of breast cancer patients; however, in recent years a decrease in proportion of mastectomies was noted in some Arab countries like in Lebanon [50]. A major factor for the overutilization of mastectomies in the Arab world is due to the limited availability of radiation therapy resources (technicians, physicians, and centers) in regions of the Arab world [50].

1.2.5.2. Systemic therapy:

The chemotherapy agents used in young breast cancer patients are like those in older age groups with anthracycline and Taxanes based chemotherapies forming a major component. In a meta-analysis by the EBCTCG group, the anthracycline chemotherapy combination was found to have a greater impact in reducing the annual breast cancer death rate in women younger than 50 compared to those between 50 and 69 years of age (38 % vs 20 % reduction respectively) [51]. Moreover, threefold improvement in recurrence and mortality was found in the chemotherapy group (compared to no chemotherapy group) in women less than 50 years compared to those older [51].

The use of tamoxifen for 5 years is favored in premenopausal females for hormone sensitive cancers. To add when treating premenopausal females, the addition of ovarian suppression either using medications or oophorectomy has been studied in the suppression of ovarian function trial (SOFT). This study revealed that in young high-risk patients the combination of ovarian suppression and tamoxifen is superior to tamoxifen alone in terms of 5-year freedom from breast cancer (HR: 0.65; 95%CI:0.49-0.87) [52]. Another Randomized clinical trial discussing ovarian suppression is the Tamoxifen and Exemestane trial (TEXT). In a meta- analysis using both trials tamoxifen in combination

with ovarian survival was found to be superior to tamoxifen alone in terms of 8 year survival rate (83.2% vs 78.9% for tamoxifen alone group; P:0.009) and 8-year overall survival (93.3% vs 91.5% for tamoxifen alone; P:0.01) [53].

1.2.5.3. Special Considerations in Treatment of Premenopausal Women:

1.2.5.3.1. Fertility:

The risk of infertility in young women is dependent on several factors including age at diagnosis, ovarian reserve, type of chemotherapy and duration of treatment [54]. That's why premenopausal women interested in childbearing should be referred to a fertility specialist to discuss fertility preservation options. Chemotherapy leads to infertility by inducing ovarian failure (temporary or permanent) due to alkylating agent injury [55]. In an RCT by the Prevention for early menopause study (POEMS)/SWOG Intergroup S0230, patients on the combination of chemotherapy and Gonadotropin releasing hormone agonist (GNRH- agonist) compared to patients on standard chemotherapy alone were found to have a significantly higher cumulative incidence of pregnancy (23.1% vs 12.2% respectively; OR:2.34; P:0.03) [56]. Even though patients can regain the ability to conceive after chemotherapy, long term chemotherapy seems to complicate the odds. Moreover, hormone therapy doesn't cause direct infertility, but is highly teratogenic and therefore pregnancy should be avoided during time of treatment [54].

1.2.6. Outcomes:

There is no clear-cut answer whether young breast cancer has worse or similar outcomes compared to older age groups, but available studies favor the worse outcomes

[57-60] In a SEER retrospective study comparing young patients (35 years or less; n:4616) to older age group (55 to 60 years; n:20319), 5 year survival in the young age group (74.3%) was worse than the older age group (85.1%) with worse survival in all stage groups except stage IV cancer [59]. Furthermore, another study demonstrated the younger age remained a significant predictor for death even after adjusting for patient demographics, tumor characteristics, and treatment received (HR= 1.095; 95% CI: 1.013, 1.183; P: 0.022) [59]. Similarly, a pooled analysis from two large European randomized clinical trials (n:1772 patients) revealed that young age (35 or younger) is an independent risk factor for both local recurrence (HR: 9.24, 95%CI: 3.74, 22.81) and distant disease after breast conservative therapy (HR: 2.24; 1.26-3.96; P:0.006) [60]. These studies combined illustrate how younger age had worse survival outcomes even when taking into consideration the aggressive presentation and treatment modalities making the effect of age on survival and recurrence an interesting area for future studies.

1.3. Arab World and Lebanon:

1.3.1. Burden of Disease in the region:

The burden of breast cancer is understudied in the middle east compared to the west. In a retrospective study from the Global burden of Disease (GBD) database in Washington which includes data from 22 Arab countries between the years of 1990 and 2016. An increasing trend in the incidence of breast cancer in the study was reported in the region with an incidence rate of 28/100,000 in 2016 and a mortality rate of 11/100,000 [61]. In terms of country specific incidence and death rates, Lebanon was found to be ranked first with 84/100,000 and 21/100,000 respectively [61]. It's important to note that the study results should be analyzed with caution because of the limited quality of

information reported and the lack of proper registries in the region [61]. Moreover, breast cancer in Arab countries is by far the most prevalent cancer in women constituting 50% of the cancers in 2012 with a multitude of factors coming to explain the increasing incidence including genetic, lifestyle factors (smoking, alcohol, decreased activity, unhealthy diet), emotional stress, environmental stress, and air pollution [62].

1.3.2. Molecular subtypes and Tumor Characteristics:

The distribution of molecular subtypes in the Middle east and North Africa (MENA) is discussed in articles from different countries in the region. The majority of those studies were from single institutions and a common theme in the majority was the earlier age of presentation of breast cancer compared to the west, the predominance of the Luminal A subtype, the increased proportion of triple negative subtypes in younger age groups, and the association between triple negative subtype and aggressive tumor features [63-67]. Thus, as in the west young breast cancer patients in the region have more aggressive features and consequently worse prognosis. In a retrospective study done in the Kingdom of Saudi Arabia, 708 patients with breast cancer were included, out of which 173 (24.4%) were younger than 40 years of age [68]. The young age group was found to have greater tumor size (4.5 cm vs 3.7 cm in the older age group; P: 0.046), higher proportion of Grade III tumors (55.2% vs 35.3% in older age group; P:<0.0001), greater lymph vascular invasion (67.5% vs 37.4%; P: <0.0001), and more distant metastasis (64.3% vs 31.8%; P: <0.0001) [68]. Moreover, tumors in the young age group were found to have less ER positive status (48.3% vs 65.9%; P: 0.0001), PR positive status (43.1% vs 67.1%; P: <0.0001), higher HER2/neu receptor status (44.7% vs 31% ; P:0.002), and were more likely to be triple negative cancers (P: 0.008) [68].

1.3.3. Burden of Disease in Lebanon

Compared to western countries, the average age of breast cancer in Lebanon and Arab countries is found to be around 10 years younger [69]. In Lebanon, the incidence of breast cancer in women is among the highest in the world, with Lebanon ranking 6th internationally in terms of breast cancer rate according to the World Cancer Research Funds with an Age standardized rate of 97,6 per 100,000 [70]. Furthermore, Incidence of breast cancer in younger age groups and premenopausal women is reported to be higher than that in the West, with around half of breast cancer cases reported under the age of 50, 21% of which are under the age of 40 [71]. This is also confirmed in a study conducted by Lakkis et al, that revealed that five-year age specific incidence rates of breast cancer in Lebanon is among the highest worldwide with (67,7/100,000) in the 35 to 39 age group, (163.7/100,000) in 40-44 age group, and (209.3/100,000) in 45-49 age group [72].

In addition, the proportion of breast cancer subtypes in Lebanon was reported in study conducted at the American University of Beirut Medical Center (AUBMC), and was found to be similar to the distribution of molecular subtypes in the west and the region with Luminal A being the most common subtype, followed by Luminal B subtype, HER 2 positive, and basal subtypes respectively [73]. On the genetic level, Lebanese women are found to have similar gene expression pattern to western molecular subtypes [73]. These findings emphasize the need for more studies to further investigate the distribution of molecular subtypes and particularly at the young age group in Lebanon.

In a literature review and analysis of available registries conducted in 2006 by El Saghir et al, the scarcity of data was noted to be remarkable, with most counties having either a national or regional registry while some countries have no data [50]. From the

available data, almost 50% of the patients are younger than 50 years of age, with a median age of 49-52 which is more than 10 years younger than the median age in developed countries (63 years) [50].

Despite the high prevalence of the disease in the region, quality research investigating characteristics and therapy of breast cancer diagnosed in young females in the Middle East and developing countries is scarce. The aim of our study is to better understand the incidence of young breast cancer (≤ 40), stage of disease at presentation, distribution of molecular subtypes, choice of treatment by specialists for this subgroup, and outcomes in young women in a tertiary hospital in Beirut Lebanon. This will help physicians get a better understanding of the characteristics of breast cancer in young females in the region and how they compare with older females (>40) to better guide physicians to tailor therapies in this population, avoiding over or under treatment.

CHAPTER 2

RESEARCH QUESTION AND OBJECTIVES

2.1. Research question

How do young females (<40) with breast cancer compare to older age (≥40) groups in terms of clinical and pathologic tumor characteristics, treatment modalities, and outcomes.

2.2. Primary Objectives

1- Investigate the modes of presentation in young and older breast cancer patients (Compare the clinical and pathological tumor characteristics between young and older breast cancer patients).

2- Investigate the treatment modalities used in young and older breast cancer patients (Compare treatment modalities used in young and older breast cancer patients).

2.3. Secondary Objectives

1- Compare Overall survival and Disease-free survival between young and older breast cancer patients.

2- Investigate the trends in indicators for chemotherapy and mastectomy across young and older breast cancer patients.

2.4. Hypothesis/es

We hypothesize that breast cancer in young females will be more advanced at presentation and will receive more aggressive treatment modalities compared to older age groups.

CHAPTER 3

METHODS

3.1. Study design and data sources:

Our study is a retrospective review conducted at the American University of Beirut Medical Center (AUBMC). We included female patients with biopsy proven invasive breast cancer who had at least one part of their treatment at AUBMC between the years 2010 and 2016. After we obtained IRB approval, we reviewed charts of eligible patients. We collected data on relevant patient demographics, tumor characteristics, treatment modalities, and patient outcomes (survival and recurrence) up to March 2020.

3.2. Eligibility Criteria:

Inclusion criteria:

- Biopsy proven breast cancer
- Females more than 18 years of age
- At least one part of their treatment at AUBMC between the years 2010 and 2016
- Non-metastatic breast cancer

Exclusion criteria:

- Patients who did not receive any treatment at AUBMC
- Male breast cancer patients
- Patients with stage IV breast cancer

3.3. Outcome Measures:

3.3.1. Primary Outcomes:

- Difference in baseline clinical and pathological tumor characteristics (tumor size, tumor stage, tumor grade, molecular subtypes, number of masses, and nodal status) between young (<40) and older (≥40) breast cancer patients.
- Difference in use of systemic treatment modalities (neoadjuvant chemotherapy, adjuvant chemotherapy, hormonal therapy, targeted therapy) and local treatment modalities (breast surgery type (partial vs total), lymph node surgery (sentinel lymph node biopsy vs axillary lymph node dissection), and radiotherapy) in young (<40) vs older (≥40) breast cancer patients.

3.3.2. Secondary Outcomes:

- Difference in Overall survival and Disease-Free Survival in young (<40) vs older (≥40) breast cancer patients.
- Identify predictors for choice of total mastectomy and chemotherapy in young (<40) vs older (≥40) breast cancer patients.

3.4. Data Collection:

3.4.1. Sources and methods of selection:

Patients with biopsy proven breast cancer receiving part of their treatment at AUBMC between 2010 and 2016 were identified and their IDs were extracted by the IT team. The electronic charts were then reviewed by research fellows under the supervision of Dr Eman Sbaity, to extract relevant information onto a comprehensive data collection sheet that was previously IRB approved. Access to data collection sheets was restricted to study members. All sheets were stored on password protected computers. Participants

who didn't meet the eligibility criteria were excluded from the study sample. The patients follow up information including mortality and recurrence were updated using the "epic software".

3.4.2. Study Variables:

We collected and analyzed information relating to patient demographics (age at diagnosis, weight, height, comorbidities (Hypertension, Diabetes), smoking status (yes/no), and family History of Breast cancer (yes/no)), clinical tumor characteristics (size of tumor on imaging (in cm), number of masses (single vs multiple), focality (unifocal, multifocal, or multicentric), clinical nodal status (yes/no)), and pathologic tumor characteristics (including type of cancer on biopsy, tumor size, tumor stage, tumor grade, molecular subtypes, hormone receptor status (estrogen and progesterone), HER 2 receptor status, Ki67 proliferation rate, nodal status, and lymph vascular invasion)). Furthermore, we collected information on systemic and local treatment modalities received including breast surgery type, neoadjuvant chemotherapy, adjuvant chemotherapy, chemotherapy regimen, hormonal therapy, targeted therapy, radiotherapy, and axillary surgery received. Finally, we collected follow up information including patient status at last follow up (alive or deceased), date of last follow up, recurrence (yes/no), type of recurrence (loco-regional vs distant recurrence), date of recurrence.

3.4.3 Definition of Variables:

Age at diagnosis was calculated based on the date of core breast biopsy retrieved from the original pathology reports, for patients whom we were unable to find the core biopsy reports, the date of the surgical pathology report was used to calculate the age at

diagnosis. For patients whom we were unable to find both reports the physicians' notes were reviewed to extract the age at diagnosis.

Data on pre-operative tumor size, tumor number on imaging, focality, and clinical nodal status were obtained from the original radiology reports. Furthermore, pathological tumor characteristics including tumor size, tumor grade, immunohistology characteristics, and nodal status were obtained from the original pathology reports. Tumor grade was assigned according to the Nottingham combined histologic grade. If pathology and radiology reports are not present, data were collected from the notes of the treating physician. T, N, and M stages were classified according to the American Joint Committee on Cancer (AJCC) 8^{th} staging system that was introduced in 2018. Patients with stage IA and IB were grouped together under stage I, patients with stages IIA, IIB, and IIC were grouped as stage II, and patients with stage IIIA, IIIB, and IIIC were grouped as stage III. For variables like Multifocality and tumor count regrouping was done as (unifocal or multifocal and multicentric) and (single versus multiple tumors) respectively in concordance with other similar studies.

Molecular subtypes were determined based on the immunohistology evaluation of the tumor. This included the assessment of the Estrogen (ER) and progesterone (PR) receptor status, HER2/NEU overexpression, and Ki-67 proliferation index. In concordance with the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) guidelines, our pathology department used the 1% of tumor nuclei positivity as a threshold to classify a positive ER/PR status. We considered HER2/Neu to be overexpressed when the score is +3 and negative if score is 0 or +1. In case the Her2 neu receptor had a score of +2, it was considered equivocal, and the fluorescence in situ hybridization (FISH) test was reviewed to determine overexpression.

We then used the Ki-67 proliferation rate, tumor grade, and receptor status results (positive/negative) to classify the tumors into one of the four molecular subtypes (Luminal A, Luminal B, Her2 positive, and Triple Negative). Luminal A subtype was classified as ER receptor positive, HER2/neu negative and low ki67 (<15); if ki67 was not present we checked for low tumor grade (Grade 1 and 2). Luminal B was classified as one of the ER/PR positive with high Ki67 (>15) with either negative HER/neu receptor or positive HER2/Neu receptor (bad prognosis), if ki67 was not present we checked for high tumor grade. HER2 positive subtype was classified as ER and PR negative receptors with HER 2 positive receptors. Triple negative was classified as negative ER, PR, and HER 2 receptors.

Information on breast surgery type and lymph node surgery were obtained from the operative reports, and if not found we relied on the physician notes. Chemotherapy treatment (both neoadjuvant and adjuvant therapy) and regimens were obtained from chemotherapy admission reports and physician notes. For other treatment modalities -like hormonal therapy, targeted therapy, and radiotherapy- physician notes, discharge instructions, and medications lists were reviewed for accurate data collection.

Data on demographic variables like Body Mass Index, Comorbidities (Hypertension, Diabetes), Smoking Status (Yes/No), and family history of breast cancer were collected from admission history, physician notes, and clinic visits.

3.4.4 Follow up Data

Data on Follow up were collected using the Health Electronic records and epic software. In case of mortality, we searched for the death certificate if present to confirm the results. If the death certificates were not present, we searched the patients charts to

certify the date of death). For recurrence, data on recurrence type and site were obtained from the follow up radiology reports, in case the reports were not present we searched the physician notes for the date and site of recurrence. The date of last follow up was obtained from the last interaction recorded in the patient charts at AUBMC. All time to event variables were calculated from the time of diagnosis.

Overall survival was defined as time from treatment to date of death or date of last follow up if alive. While disease free survival was defined as the time from treatment till time of any recurrence or date of last follow up if no recurrence occurred.

3.5. Data auditing:

To minimize any potential mistakes during data collection multiple data audits were introduced to ensure the integrity of the data. In case of any suspected mistakes, the charts were reviewed to make sure the data was entered correctly.

3.6. Missing Data:

Most of our variables had low proportion of missing data with only 5 variables having a proportion of missing data higher than 10%. For these variables: FH of breast cancer (11.5%), tumor size on imaging (13.8%), Calcifications (36.8%), Tumor size on pathology (16.9%) and lymph vascular invasion (15.2%) similar distributions were found across both age groups as can be seen in Appendix 3. Furthermore, the use and interpretation of such variables was done with caution. Apart from tumor size on imaging none of the other variables were used in our main model. Patients with missing variables were excluded from our main univariate and multivariate logistic regression models. Missing categorical variables were then included in the sensitivity analysis as a third

category, to increase sample size and compare results to primary analysis. No other imputation methods were used in our analysis. We decided to include the extent of calcifications in a separate model (Model 2), due to the high percentage of missing data and we compared the results to our main analysis.

3.7. Statistical Analysis:

We started by stratifying the data set into two groups based on age: younger breast cancer group (<40) and older breast cancer group (≥40). After testing for normality, we reported the descriptive statistics for both groups including baseline characteristics, clinical tumor characteristics, pathological tumor characteristics, and treatment modalities used. We used means and standard deviations to report continuous variables (median and Inter-Quartile range if data is not normally distributed) and frequencies/percentages to report categorical variables. Prognostic factors including clinical tumor characteristics, pathological tumor characteristics, and treatment modalities were compared between both age groups using chi-squared test for categorical variables and independent t-test for continuous variables. Furthermore, we reported patient outcomes in both age groups including (mortality rate, recurrence rate, local recurrence rate, nodal recurrence rate, and metastasis). We did not adjust our alpha level when reporting the p-values for this comparison because they are exploratory in nature. Univariate and multivariate logistic regressions was done for the indicators of mastectomy and chemotherapy. Variables of interest were number of tumors on imaging (categorized as single or multiple), tumor size on imaging (in cm), tumor grade, molecular subtypes, tumor stage, and nodal status. The odds ratios of these variables were reported for each variable across age groups to examine trends, we did

not include p-values when comparing trends across age groups because this will make our analysis prone to false positives due to multiplicity of testing. Similarly in our multivariate analysis we adjusted for the variables pre-operative tumor size, lymph node status on imaging, number of tumors on imaging, tumor grade, tumor stage, and molecular subtypes in our main model for mastectomy indications with the addition of (breast surgery type) variable for the indicators of chemotherapy (Model 1). This was followed by a sensitivity analysis where we recorded the missing values in each categorical variable as an unknown category in the variable to increase sample size. We also included a second model that contained in addition to the variables in the first model the calcifications on mammography variable and categorical missing variables included in the analysis to examine the effect of presence of calcifications on mammography (highest proportion of missing data) on outcomes. Finally, overall survival and disease-free survival were computed using the Kaplan Meir method and compared between both age groups using the log rank test. Overall survival was calculated as time from curative breast surgery to date of death or last follow-up. While Disease free survival was calculated as the time from breast surgery to date of recurrence or last follow-up. We used IBM SPSS version 28.0 to conduct all statistical analysis. Significance level was set at the 5% level.

CHAPTER 4

RESULTS

4.1 General description of the data set

Our data set contains 745 patients diagnosed with breast cancer between the years 2010 and 2016 with a follow up period until March 2020. The mean age of the patients in the entire data set is 52 $\pm$ 12.17 years, with 126 patients (17%) in the younger breast cancer group (<40) and 619 patients (83%) in the older breast cancer group (≥40) group. The median age for follow up in the entire data set is 4.5 $\pm$ 2.98 years, with 25 (3.4%) deaths recorded and 83 cases of recurrence (11.1%) observed in both groups during the follow up period.

4.2. Comparison of baseline characteristics between young and older breast cancer patients

The baseline characteristics at the sample population level and across age groups can be seen in table 1. The mean age of the young breast cancer (YBC) group is 35.44$\pm$3.84 years which is significantly lower than the mean age of the older age group (OBC) 55 $\pm$ 10.5 years (P: 0.001). Furthermore, 211 patients (29%) are found to have hypertension and 83 patients (11%) have diabetes in our sample. The older age group has higher percentages of hypertension (209 (34.7%) compared to 2 (1.6 %) in YBC group) and diabetes (79 (13.3%) compared to 4 (3.2 %) in the YBC group) and the differences are statistically significant (P:<0.001). Furthermore, out of the 214 (32.5%) cases with positive family history of breast cancer, the younger breast cancer group has a higher proportion of positive FH of breast cancer in 40 (35.7%) participants compared to 174 (31.8%) in the older age group but this didn't reach statistical significance (P: 0.421).

4.3. Comparison of clinical and pathological tumor characteristics between young and older breast cancer groups

The clinical and pathological tumor characteristics in the sample population and across age groups can be seen in tables 2 and 3. The mean tumor size of all patients is 2.35 ± 1.65 cm, the young breast cancer group have a higher mean tumor size on imaging with 2.62 ± 1.63 cm compared to 2.29 ± 1.64 cm in the older age group but this failed to reach statistical significance (P: 0.052). In the overall population the distribution of tumor stage is 247 patients (34.8%) with stage I, 341 (48%) with stage II, and 122 (17.2%) with stage III cancers. In terms of lymph node status on imaging, 251 patients (36.1%) from our cohort have positive lymph nodes with the young breast cancer group having a higher proportion of positive lymph nodes on imaging (49 (39.8%) vs 202 (35.5%) in older group), but this did not reach statistical significance. Moreover, out of the 296 patients (41.2%) with positive lymph nodes on pathology, the younger group also have a higher proportion of positive lymph nodes on pathology with 55 patients (46.7%) compared to 240 (40.1%) in OBC group, but the difference did not reach statistical significance. The distribution of tumor stage in the younger age group is 37 patients (30.3%) with stage I, 56 (45.9%) with stage II, and 29 (23.8%) for stage III cancers. The young BC group has a higher proportion of stage III cancers and lower proportions of stage I cancer compared to the older age group who have 210 patients (35.7%) with stage I, 285 (48.5%) with stage II, and 94 (15.8%) with stage III cancers, but these differences did not reach statistical significance (P:0.095). Furthermore, the distribution of tumor grade in the overall population was 129 patients (18.2%) with grade 1, 316 (44.5%) with grade 2, and 265 (37.3%) with grade 3 tumors. The distribution of tumor grade in the younger breast cancer group is as follows 18 (14.6%) patients with grade 1, 41 (33.3%) with grade 2, and 64 (52%) with grade 3 tumors. The younger age group has a higher proportion of grade

3 tumors compared to the older age group with a tumor grade distribution of 111 patients (18.9%) with grade 1, 275 (46.8%) with grade 2, and 201 patients (34.2%) with grade 3 tumors, and this difference is statistically significant (P<0.001). Overall, the Luminal molecular subtypes were the most common subtypes in our cohort with 290 (39.9%) patients with Luminal A subtype, 310 patients with Luminal B subtype (42.6%), followed by 74 patients (10.2%) with TN molecular subtype and 53 patients (7.3%) with Her 2 molecular subtypes. The younger age group are found to have a lower proportion of Luminal A subtype compared to older age group (38 (30.6%) vs 252 (41.8%) in OBC), a higher proportion of Luminal B molecular subtype (63 (50.8%) vs 247(41%) in OBC), and similar distribution in HER 2 positive subtype (9(7.3%) vs 44 (7.3%) in OBC) and Triple negative subtype (14 patients (11.3%) vs 60 (10%) in OBC) but the differences are not statistically significant. In terms of estrogen receptors, 607 patients (81.9%) have positive ER receptors, with the younger age group having a lower proportion ER positive receptor status with 98 patients (78.4%) compared to 509 (82.6%) in the older age group, but this difference didn't reach statistical difference (P: 0.263). There was no difference in the distribution of PR positive receptor status between the young and older breast cancer groups, with 546 (73.6%), 92 (73.6%) and 454 (73.6%) patients with positive PR receptors in the overall, young, and older patients respectively. Overall, 171 patients (23.1%) had positive HER 2 receptor status, with the younger age group found to have higher proportions of positive HER 2 receptor status with 38 (30.6%) compared to 133 (21.6%) patients in the older age group and the result is statistically significant (P:0.033). In our cohort, 199 patients (29.1%) have multiple masses on imaging on the population level and 486 (70.9%) of patients have single tumors. The young BC group has a higher proportion of multiple tumors on imaging with 45 (38.1%) vs 154 (27.2%) in the older

age group (P:0.017). Similarly, 200 patients (29.4%) have multifocal or multicentric tumors while 480 (70.6%) have unifocal tumors on the population level. The younger breast cancer group have a greater proportion of multifocal and multicentric tumors with 47 patients (39.2%) compared to 153 patients (27.3%) in the older age group and the results is statistically significant (P:0.001). In addition, the presence of calcifications on mammography on the population level is 260 patients (55.2%) and is higher in the younger breast cancer group 55 (72.4%) compared to the older age group 205 (51.9%) with the difference being statistically significant (P:0.001). Finally, out of the 190 patients (30.1%) with lymph vascular invasion, the younger breast cancer group have a significantly higher proportion of lymph vascular invasion (43 (38.7%) vs 147 (28.2%) in OBC group; P:0.028)..

4.4. Comparison in treatment modalities between young and older breast cancer groups

The information on treatment modalities used at the level of the sample population, younger, and older age groups can be seen in Table 4. Most of the patients 742 (99.6%) underwent surgery with 428 patients (57.7%) undergoing partial mastectomy and 314 patients (42.3%) undergoing total mastectomy. The younger breast cancer group has similar percentage of total mastectomy (57 (45.6%) compared to 257 (41.7%) in the older age group). Similarly, 471 patients (64.6%) underwent sentinel lymph node biopsy and 258 patients (35.4%) underwent axillary lymph node dissection in our cohort, with the young breast cancer group undergoing similar axillary lymph node dissection surgery (47 (37.9%) compared to 211 (34.9%) in OBC group). In terms of radiotherapy 546 patients (76.9%) underwent radiotherapy treatment, with the young BC patients undergoing radiotherapy less frequently in 91 patients (74.0%) compared to 455

patients (77.5%) in the older breast cancer group, but this result did not reach statistical significance. In terms of systemic therapy, 580 patients (80.8%) took chemotherapy, the young breast cancer group had significantly higher rates of chemotherapy with 111 patients (90.2 %) compared to 469 (75.8%) in the older age group (P:0.003). Out of the 580 patients that took chemotherapy, the younger age group patients are found to have higher proportion of Anthracycline (92 (90.2%) vs 355 (81.1%) in OBC) and Taxanes based chemotherapy with (94 (92.2%) compared to 372 (84.9%) in OBC group) but the result only reached statistical significance for the anthracycline regimen (P: 0.028). Furthermore, in terms of type of chemotherapy the younger age group is found to have significantly higher proportions of neoadjuvant chemotherapy (47 (37.3%) vs 151 (24.6%) in the OBC group; P: 0.003), but not adjuvant chemotherapy (72 (60.5%) vs 343 (59.1%); P: 0.782). As for other systemic treatments, the younger age group is found to have significantly higher rates of Trastuzumab (Anti-Her2) therapy with 47 patients (37.3%) compared to 151 patients (24.6%) in the older age group (P:0.029). As for hormonal therapy, 404 patients (60%) took hormonal therapy with the younger age group taking a lower proportion of this treatment in 60 patients (54.5%) compared to 344 (61.1%) in OBC group, but this result did not reach statistical significance.

4.5. Comparison of outcomes between younger and older breast cancer patients

The outcomes at the population, younger, and older age groups can be found in table 5. The overall median follow up period in our cohort is 4.52 $\pm$ 2.98 years, and it is found to be similar between the younger (4.59 $\pm$ 3.55) and older (4.52 $\pm$ 2.95) age groups (P:0.83). Out of the 25 (3.4%) deaths recorded, the young breast cancer patients were found to have a higher proportion of mortality recorded with 7 patients (5.6%) compared

to 18 patients (2.9%) in the OBC group, but this result did not reach statistical significance. As for recurrence, out of the 83 cases (11.1%) with breast cancer recurrence, the young BC patients were found to have a higher proportion of BC recurrence (21 (16.7%) in YBC group compared to 62 (10%) in the OBC; P:0.031). In particular, the younger age group had higher proportions of distant recurrence with 18 participants (14.3%) compared to 51 (8.2 %) in the older age group (P:0.033) and higher proportion of locoregional recurrence (8 patients (6.3%) in YBC compared to 21 patients (3.4%) in OBC but this difference did not reach statistical significance. The Overall survival graph (figure 1) shows similar survival curves for both younger and older age groups; however, the disease-free survival graph (figure 2) shows significantly higher recurrence for the younger breast cancer group compared to the older breast cancer group (log rank: 0.012).

4.6. Indicators for Mastectomy in younger and older breast cancer patients

The univariate logistic regression for mastectomy indications (Table 6) reveals similar trends in the younger and older age group. Preoperative tumor size is associated with greater odds of undergoing complete mastectomy (OR= 1.107 and OR=1.472 for younger and older groups respectively, but the result is only significant for the older age group; P:<0.001). Similarly, having positive lymph nodes or multiple tumors on imaging are both found to be associated with significantly higher odds of undergoing complete mastectomy (OR=4.435 (YBC) and 2.78 (OBC) for lymph node status, OR= 5.679 (YBC) and 2.981 (OBC) for multiple tumors; P<0.001). Similarly, higher tumor grades are associated with higher odds of undergoing complete mastectomy for both younger and older breast cancer groups by 1.818 and 1.670 times respectively. Luminal B, HER 2, and Triple negative subtypes are all found to be associated with higher odds of having

complete mastectomy, but the result is only significant for Luminal B and Her 2 subtypes in the older age groups (OR= 1.554 for Luminal B subtype in OBC; P:0.017, and OR= 4.185 for HER 2 subtype in OBC; P:<0.001). For the tumor stage the higher the stage the higher the odds of complete mastectomy for both younger and older breast cancer patient, reaching up to 4.22 times in younger breast cancer group and 9.859 times in older breast cancer group (P:0.007 and P:<0.001 respectively).

For our multivariate logistic regression (Table 7) we adjusted for all the variables included in the univariate analysis (pre-operative tumor size, lymph node status on imaging, number of tumors on imaging, tumor grade, tumor stage, and molecular subtypes). As in our univariate analysis, the larger the tumor size by 1 cm, the higher the odds of undergoing mastectomy in the older age group by 1.272 times (P:0.002). Similarly, having positive lymph nodes on imaging is associated with significantly higher odds of undergoing mastectomy in both age groups with up to 3.686 times in YBC (P:0.02) and 1.66 times in OBC (P:0.038) after adjusting for the other variables in our model. Having multiple tumors on imaging as compared to having a single tumor was also significantly associated with higher odds of undergoing complete mastectomy in both younger breast cancer (OR= 6.593; P:<0.001) and older breast cancer groups (OR=2.736; P:<0.001). However, the tumor grade shows different trends among both age groups with the younger breast cancer group having higher odds of complete mastectomy rather than lumpectomy with increasing tumor grades (although non reached significance) compared to the older age group patients that have a significant decrease in the odds of having a complete mastectomy in grade 3 tumors as compared to the grade 1 tumors (OR= 0.443; P:0.0046). In terms of molecular subtypes, the triple negative subtype is associated with significantly higher odds of complete mastectomy compared

to the Luminal A subtype by 3.314 times in the younger BC group and 2.26 times in the older BC group, but the results are not statistically significant. Higher stage is also associated with higher odds of undergoing complete mastectomy reaching up to 2.3 times in the younger breast cancer group and 2.95 times the odds in the older breast cancer group. A sensitivity analysis for the indicators of mastectomy with the same variables but with categorical missing variables included in the analysis reveals similar results to our multivariate regression model as can be seen in table 8. For our second model we included the same indicators of mastectomy with the addition of the calcifications on mammography variable and with categorical missing variables included in the analysis (Table 9). We found similar trends for mastectomy indicators compared to our primary analysis. As for the presence of calcifications on mammography significantly higher odds of undergoing complete mastectomy in both young (OR=6.54; P:0.021) and older age groups (OR=2.404; P<0.001) is noted in those with positive calcifications.

4.7. Indications for Chemotherapy in younger and older breast cancer patients

In the univariate logistic regression for chemotherapy indications (Table 10) similar trends among indicators are noted between the younger and older breast cancer groups. Every 1 cm increase in preoperative tumor size increases the odds of taking chemotherapy by 2 times in YBC and 3.218 times in the OBC group but only the latter achieved statistical significance (P:<0.001). Similarly positive lymph node status on imaging is associated with higher odds of chemotherapy administration (OR= 3.852 for YBC and OR= 8.620 for OBC), but only reached significance in the older age group (P:<0.001). Similarly having multiple tumors on imaging increases the odds of taking chemotherapy by 1.323 times in the young breast cancer group and 2.6 times in the older

breast cancer group and this result is only significant in the latter (P:<0.001). In addition, higher grade is significantly associated with statistically significant higher odds of chemotherapy administration especially in grade 3 tumors that were found -compared to grade 1 tumors- to be 11.731 times higher in the younger breast cancer group and 20.6 times higher in the older breast cancer groups (P:0.006 and <0.001 respectively). For molecular subtypes Luminal B subtypes is found to be significantly associated with higher odds of chemotherapy administration compared to Luminal A in both younger and older groups (OR= 5.06 and 3.129 respectively). However, the odds ratios for the HER 2 subtype and TN subtype are not estimated in the older and younger breast groups because all the patients in these subtypes took chemotherapy as can be seen in Appendix 1. Similarly, the higher the stage the higher the odds of chemotherapy administration reaching up to 76 times in the older breast cancer group and cannot be estimated for stage III cancer in the young BC as all patients in this subgroup took chemotherapy as can be seen in Appendix 2. Moreover, patients who underwent complete mastectomy are found to take more chemotherapy by 2.8 times in the younger breast cancer group and 4.6 times in the older breast cancer group, but is only significant in the latter (P:<0.001)..

In the multivariate logistic regression (table 11) and after adjusting for all the variables in the univariate analysis, greater tumor size is associated with higher odds of chemotherapy administration in both the younger and older group (OR= 1.329 and 1.886 respectively for every 1 cm increase in size). Meanwhile, positive lymph nodes on imaging are associated with higher odds of chemotherapy administration only in the older breast cancer group but this result did not reach statistical significance (OR=2.356; 95%CI: 0.977- 5.685; P: 0.056). Multiple tumors on imaging are also associated with higher odds of chemotherapy administration compared to single tumors by 2.46 times in

the Younger BC group and 1.395 times in the older BC group but this result did not achieve statistical significance in either group. Furthermore, the higher the grade the higher the odds of taking chemotherapy with grade 3 tumors - compared to grade 1 tumors - having up to 8.6 times the odds in the young BC group and 14.5 times the odds in the older breast cancer group. In addition, higher stages are associated with higher odds of chemotherapy administration, with stage III cancers - compared to stage I cancers - reaching up to 9.586 times the odds in the older breast cancer. Similarly, complete mastectomy is associated with higher odds of chemotherapy administration in both young and older groups but is more prominent in the latter reaching up to 2.3 times the odds. A sensitivity analysis with the same variables in our primary model but with categorical missing data included in the analysis reveals similar results as can be seen in Table 12. Finally, a second model including the same variables in model 1 but with the addition of the calcification on mammography variable reveals similar results (Table 13). As for the calcification variable, presence of calcification on imaging is found to be linked to significant higher odds of chemotherapy administration only in the older age group as can be seen in table 13 (OR=2.11, 95%CI:1.082 – 4.113, P:0.028).

CHAPTER 5

DISCUSSION

5.1. Young breast cancer in Lebanon and developing countries compared to the west

In this study, the proportion of young breast cancer patients (<40 years) was 126 patients (17%). Which coincides with the results of a previous study by El Saghir et al that reported that the proportion of young breast cancer patients in Lebanon ranged from 8.1% in those less than 35 years to 48% in those less than 50 years of age[74]. These numbers are similar to those reported in neighboring Arab and Asian countries like KSA (24.4%), Iran (19.5%) China (17.6%), and Morocco (22%)[68, 75-77]. Interestingly, developing countries have a greater proportion of young breast cancer compared to only around 3 to 7% reported in the West, [78]. However, it's important to interpret these numbers with caution especially that lack of national registries in many developing countries (including Lebanon) limit the generalizability of the results compared to the West. Some studies attributed the difference in proportion to the lack of massive mammography screening in developing countries compared to the west, so less screen-detected breast cancer is reported in the older age groups but this cause is unlikely to be the only explanation [79]. Other, studies attributed the younger mean age of breast cancer patients in developing countries - which is around a decade earlier than developing countries – to a combination of genetic (ethnicity/race, mutations) and environmental factors (lifestyle and dietary habits, westernized lifestyle, active and passive smoking)[68, 76, 80]. This might explain part of the picture as well but not all, for other studies highlighted that the younger age distribution/pyramid in developing counties could be a possible reason for the higher incidence of YBC compared to the older western

populations. Studies from KSA and Hong Kong attributed the incidence of young breast cancer to the age structure in these populations [68, 76]. Similarly, a study done in Lebanon by Lakkis et al, that estimated the crude and age standardized incidence rates in Lebanon highlighted that the skewed distribution towards the younger age groups, and some genetic traits can explain the higher proportion of young breast cancer [72]. It is also important to note that the use of multiple age cutoffs for young breast cancer including (35, 40, 45, and 50 years), due to the lack of a clear definition of “young age" could explain some of the variability in different study results and pose a challenge toward drawing definite conclusions about the disease in this population.

5.2. Comparison of clinical characteristics between young and older breast cancer patients

In our study, we found features indicative of more aggressive presentation in young females including significantly larger tumor size on imaging. In a study by Charati et al, young breast cancer patients were more likely to have greater tumors ($OR_{T2+/T1}$:2.13; P:0.007) that were also indicators of increased malignancy[75]. Similarly, a study in Saudi Arabia revealed a significantly higher tumor size in young breast cancer patients compared to older (4.5 cm vs 3.7; P:0.046)[68]. In the literature, the detection of more advanced disease with larger tumor size was attributed to the absence of early breast cancer detection because screening programs prior to age 40 are not routinely recommended [81]. This was also emphasized in a study by Gajdos et al, that highlighted that young breast cancer patients (<36 years) had larger tumor diameters (2.0 vs 1.5 cm in older age groups; P<0.001) and this could be attributed to the lack of mammography screening and patients being diagnosed after presenting with a palpable mass [82]. Other studies failed to find a significant difference in tumor size between the two age groups,

with the main reason attributed to the limited sample size in the study and the inclusion of premenopausal patients in the older age (control) group which could be a source of heterogeneity [83].

In our study young breast cancer was found to have higher proportion of Stage III cancer compared to the older age group but this did not reach statistical significance probably due to insufficient sample size. Gajdos et al, found that young breast cancer patients (<36 years) are more likely to have higher stage II and stage III tumors (60% vs 43% in older patients, P<0.001) and higher grade tumors (80% vs 44% in older age groups, P<0.001)[82]. Similarly, the trend of more aggressive stage at young age was noted in several studies including the AMAZONA III study done in Brazil that showed that younger patients were more likely to have stage III disease (36.8% vs 25.1%; P:<0.001), greater tumor size (T3: 24.1% vs 13.9%; P<0.001), and grade III tumors (43.1% vs 30.1%; P:<0.001) compared to older breast cancer patients [84]. A possible explanation for the authors was that young patients often go undetected until they reach more advanced stages of cancer [84]. Moreover, Azim et al, revealed that young breast cancer includes mutation leading to immature mammary cells like BRCA-1, c-kit, and RANKL as well as mutations in growth factor signaling (PI3K and MAPK) which could explain the “immature” presentation in the young age group[39]. Similarly, a study by Chen et al, that utilized the SEER criteria revealed decreasing trends in tumor stage and grade as the patients age increased from 30 to 80+ years [81].

In our study young breast cancer patients were significantly more likely to have multifocal or multicentric / multiple tumors on imaging and calcifications present on imaging. This trend was highlighted in several studies, one of which is by Langman et al, whom revealed that young breast cancer patients (<40 years of age) were likely to present

with calcifications in 49.1 % of the cases and multiple tumors on imaging in 40.9% of the patients[85]. Both sample size and the retrospective nature of the study were major limitations of that study[85]. Even though calcifications can indicate DCIS, certain presentations and types of calcifications when linked to more aggressive tumor features like negative hormone receptors, high grade, comedo necrosis in DCIS, and positive lymph nodes can be indicative of invasive cancer[86-88]. Moreover, other studies highlighted the importance of examining the results according to the calcification specific BI-RADS; unfortunately, this was not readily available in our data set, so we were unable to examine the full picture [89]. Causes of these calcifications include inflammation, tissue necrosis, scar tissue following biopsy or surgery, epithelial proliferation, and fluid accumulation [89].

5.3 Comparison of pathologic characteristics between young and older breast cancer patients

In our study, invasive ductal carcinoma was the most common cancer in both young and older breast cancer patients. This result is like that reported in other studies including the AMAZONA III study that showed that IDC constituted around 94.7% and 87.6% in the YBC and OBC groups respectively[68, 84]. Moreover, the authors also noted that the older breast cancer group was found to have higher proportion of Invasive lobular cancer types which can also be visualized in our study[90].

In our study, we found a trend of higher nodal involvement in young patients, but this did not reach statistical significance. In the literature, some studies identified no significant difference in terms of nodal status positivity between younger and older age groups[83, 85]. While others like Kroman et al reported a significantly higher rate of lymph node positivity in YBC compared to OBC (51% vs 46%; P:0.02)[91]. Similarly,

a study done in Saudi Arabia highlighted that young breast cancer patients were likely to have higher lymph node involvement (75.4% vs 33.2%) and lymph vascular invasion (84.1%vs 65.7%) compared to patients greater than 40 years of age[68]. With authors speculating that this result could be due to more aggressive tumor biology[92]. In a study by Chakraboty et al the authors investigated tumor characteristics affecting lymph node positivity, they found that greater tumor size (OR:14.675; P: <0.001), higher tumor grade (5.140, P<0.001), lymph vascular invasion (OR:3.58, P:<0.001), and HER2/neu positivity (OR: 5.296, P<0.001) were all associated with higher odds of positive lymph nodes, highlighting how the tumor characteristics are interrelated and should be taken together to understand the full picture[93].

Moreover, in our study young breast cancer patients were found to have higher Her 2/Neu receptor positivity and lower ER receptor positivity, but the latter result did not reach statistical significance. This difference can be explained by a study by Andres et al, who identified 367 genes that are distinctive in the young cancer group compared to the older breast cancer patients [94].These mutations include lower mRNA expression of ER alpha (7.2 vs 9.8 in OAG;P:0.0001), ER beta (5.6 vs 5.9 in OAG; P:0.02) and PR (4.1 vs 5 in OAG; P:0.001) [94]. In addition, the young age group was also found to have high HER2 Neu expression compared to older patients (11.1 vs 9.4; P:0.0001) [94]. These result were also seen in larger studies that included 6,668 YBC patients compared to around 150,000 OBC patient revealed high hormone receptor negative tumors [(35.2% vs 22.9%) for ER receptor and (42.9% vs 31.3%) for PR receptor; P:<0.001] , and a high expression of HER2/neu (11.1% vs 7.9; P<0.001) in the young breast cancer group [95, 96].

5.4. Comparison of Molecular subtype distribution in young and older age groups

As for molecular subtypes, our study found no significant difference in distribution between the two age groups. It was interesting to see a higher proportion of Luminal B subtype and lower luminal A subtype in the young breast cancer group compared to the older population. In the literature some studies reported that young breast cancer patients have greater proportion of TN and HER 2 positive cancer subtypes [68, 97]. Other studies identified the Luminal B subtype to be more common in the young age group[98]. But what most studies agreed on is that the Luminal A subtype was the least common in the young breast cancer group[68, 80, 84, 97]. In a study by Avci et al in turkey, 137 breast cancer patients 60 of which are YBC (<35 years), the luminal B subtype was found in 16.8% in the OBC group compared to 40% in the YBC group[98]. Other studies also revealed a higher rate of Luminal B subtypes in developing countries compared to developed countries in the young age group[26, 90, 98]. Moreover, in our cohort the proportion of triple negative breast cancer was 11.3% which is significantly lower than that of other studies in westernized countries like Europe and USA (21%-38%)[26, 99]. Similarly, a higher proportion of (Luminal A and B subtypes) compared to triple negative subtypes was noted in some developing countries, the reason for which is still not fully understood[98]. It is hypothesized that high calorie intake, increased exposure to pollutants, and decreased childbearing age can be among the factors that explain the phenomenon [100].

5.5 Comparison of Surgical treatment between young and older breast cancer patients

In our study almost all patients 742 (99.6%) underwent breast cancer surgery which is the gold standard for treatment of invasive stage I to III breast cancer. Out of the

3 cases that did not undergo surgery, the young breast cancer patient didn't follow up on treatment while the two older were not eligible for breast cancer surgery. In term of breast surgery type, there was no significant difference between the two age groups, despite the younger group having a slightly higher proportion of total mastectomy. This goes with the results of some studies that identified that young breast cancer patients undergo more aggressive treatments compared to the older breast cancer group (Mastectomy rate 116 (54.7%) in YBC vs 630 (45.7%) in OBC, P<0.001)[84, 96]. Other studies found no difference in surgical treatments between the two groups mainly because the surgical indications are the same (Mastectomy rate 211 (82.4%) in YBC vs 1482 (83.1%), P:0.796)[83, 96]. Some studies even questioned whether breast conservative therapy is considered an optimal therapy in young breast cancer patients given the higher local recurrence rates reported when undergoing breast conservative therapy (10 year Local recurrence free survival (85.3% vs 92.3% in OBC, P<0.001)[60, 101-103]. Nevertheless, none of the studies demonstrated a survival disadvantage in the young group compared to the older group. Several factors explain the more aggressive surgical treatment reported in the younger population including tumor characteristics, germline mutations, and patient preference [96].

5.5.1 What factors favor complete mastectomy over partial mastectomy

In our study, similar trends were found to increase the odds of undergoing complete mastectomy in both age groups, including greater tumor size, positive lymph nodes, multiple tumors on imaging, high grade, Luminal B subtype, hormone receptive tumors, and higher stage. This stems from the reason that the indications of mastectomy are the same for both age groups, as young age is not a contraindication for breast

conservative surgery[104]. Indications for mastectomy include multifocal/ multicentric tumors due to higher volume of distribution, patients with large primary tumors (more than 5 cm), patients with advanced locoregional disease, and chest or skin involvement in some cases [105, 106].

5.5.2, Effect of tumor size on surgical choice:

In our study, larger preoperative tumor size was linked to higher odds of of undergoing complete mastectomy. This is similar to results from previous studies revealing that higher tumor size was associated with higher odds of complete mastectomy with up to 3.8 times the odds in tumors greater than 4 cm compared to tumors 1cm or less[107]. However, tumor size should be taken with other factors before choosing the most suitable treatment choice for the patient. In a study done by Kwong et al that included 1,485 women, the authors highlighted that the choice of surgical treatment differed among different ethnicities with the Asian population being less likely to undergo breast conservative therapy compared to Caucasians[18]. This was explained by the relatively smaller breast size in the Asian population who were more likely to undergo complete mastectomy if the tumor size is greater than 2cm [108]. Similarly, other studies highlighted that surgical treatment should be case specific, and should involve the tumor to breast ratio, with breast conservative therapy being a feasible option for large tumors if the tumor can be removed with negative margins and the patient can undergo radiotherapy[106].

5.5.3. Effect of lymph node involvement on surgical choice:

In our study, positive lymph nodes were associated with greater odds of mastectomy. Similarly, a study by Tonellotto et al that included 628 women with node positive breast cancer revealed that N2 and N3 tumors were more likely to recur compared to N1 tumors (HR: 2.47 and 2.42 respectively, P:<0.001)[109].Even though positive lymph nodes are managed with Axillary lymph node surgery and are not an absolute indication for undergoing mastectomy. Positive lymph nodes have been associated with more aggressive tumor features including greater stage, lymph vascular invasion, and metastasis leading to worse outcomes in the patient including increased hazard of death and recurrence rates [109, 110]. These aggressive features could explain the higher reliance on more aggressive surgical treatments for patients with positive lymph nodes.

5.5.4. Effect of tumor stage and grade on surgical choice:

In our study higher stage was associated with greater odds of mastectomy compared to stage I tumors. A similar result was noted by freedman et al, who reported that stage III cancers had a higher risk of bilateral mastectomy (OR: 8.28, 95%CI: 2.32-29.5) compared to stage 0 disease, and patients with stage II and III had significant higher odds of undergoing unilateral mastectomy (OR:2.21, 95%CI: 1.19-4.11 and OR:5.31, 95%CI: 2.2-12.8 for stage II and III respectively) compared to stage 0 disease [111]. In a study by Dragun et al, that contained 21.869 women who underwent breast surgery to treat stage 0, I and II tumors, patients with higher stage (compared to stage 0) and poorly differentiated tumors (high grade compared to grade 1) were more likely to undergo mastectomy by 2.8 times and 1.5 times respectively[107]. It is interesting that in our study the older age group patients with grade 3 tumors had lower odds of undergoing

mastectomy which could be due to the significantly higher odds of neoadjuvant chemotherapy that help decrease tumor size making BCS a feasible option.

5.5.5. Effect of Molecular Subtypes on surgical choice:

In our study the Luminal B subtype and the hormone receptor negative subtypes were all found to have a greater odd of complete mastectomy compared to the more benign Luminal A molecular subtype. However, several studies identified that even though HER 2 and triple negative tumors are associated with more aggressive features like multicentric and multifocal tumors which are also predictors for complete mastectomy, no difference in Local recurrence rates was noted between both surgical techniques highlighting that more aggressive surgical treatment does not overcome more aggressive tumor biology and that surgical treatment should be tailored on a more individual level [112, 113]. In a SEER population-based study that included 8656 young BC patients (< 40 years), the authors wanted to test whether type of surgical treatment plays a role in outcomes of different molecular subtypes[114]. The authors found that the BCS group actually had significantly improved survival compared to the mastectomy group in the Luminal subtype (HR: 0.637, 95% CI: 0.448-0.905, P:0.012) and TN subtype (HR: 0.64, 95%CI: 0.455-0.901, P:0.01), but not HER 2 positive subtypes (HR:0.791,P:0.262)[114].

5.5.6. Effect of Imaging features on surgical choice:

In our study, multifocal and multicentric tumors were associated with higher odds of undergoing mastectomy in both age groups. Similarly, a study by Neri et al that included 1158 cases found that patients with multifocal and multicentric tumors are

significantly more likely to be treated with complete mastectomy than with breast conservative therapy (81.2 vs 18.9%, P:<0.001)[115]. In the literature, multifocal and multicentric tumors tend to have larger tumor size, more lymph nodes involvement, and more lymph vascular invasion which all warrant more aggressive treatment[116]. Moreover, when choosing the appropriate surgical approach for the patient the best cosmetic choice and negative margins is the favorable option, that's why BCS in the case of multicentric tumors will not be the suitable cosmetic option for the patient[117].

In our study the presence of calcifications on mammography was associated with higher trends of mastectomy in both young and older age groups. In previous studies it was noted that presence of calcifications on mammography is not a contraindication for BCS; however, if there is diffuse presence of malignant appearing calcifications it is not advised to undergo BCS[118]. In addition, several studies discussed whether the presence of calcifications is associated with worse outcomes in breast cancer, but this topic is still controversial[119, 120]. Unfortunately, we were not able to collect information on the calcification characteristics of our patients, so we were not able to investigate this point further.

5.5.7. What other factors play a role in surgical choice:

Previous studies highlighted that patients who underwent breast conservative surgery were found to have higher body image satisfaction scores compared to those with complete mastectomy but breast reconstruction can help improve the scores in the mastectomy group [121]. That's why if BCS is an available option the patient can choose the surgery she prefers, but her choice can be biased by physician's recommendations who might be more inclined to advise young BC patients to undergo BCS or mastectomy

with reconstruction due to higher patient satisfaction rates [122]. Furthermore, results from the National Health Cancer Institute revealed that young patients are favoring complete mastectomy because young age is considered as a negative prognostic factor that requires more aggressive treatments[123]. Moreover, young patients are more likely to opt for more radical treatments for "peace of mind", fear from undergoing another surgery, or inability to attend radiotherapy session due to familial or work-related commitments[123, 124]. However, like other studies no survival advantage was found in patients undergoing complete mastectomy [123, 125].

5.6. Comparison of radiotherapy between young and older breast cancer patients

In our study there was no significant difference in radiotherapy between the younger and older group. This in concordance with other studies that discussed how the use of radiotherapy is linked to the surgical treatment choice as radiotherapy is a cornerstone in breast conservative therapy for it boosts local control [104]. One study revealed that the young age group were likely to be treated with radiation therapy in 61% of cases in young age group which is similar to that recorded in our study (70%)[85]. Furthermore, common indications for radiation therapy in young women include one to three lymph node involvement, or nodal negative disease with positive margins, tumor size greater than 2cm, and lymph vascular invasion[104].

5.7. Comparison of Chemotherapy between young and older breast cancer patients

In our study, the young breast cancer group was found to have more chemotherapy administration and particularly neoadjuvant chemotherapy. This is similar to a study by El Saghir et al found that patients younger than 35 years and patients between 35 and 50 were more likely to take chemotherapy (76.5% and 72.8% respectively) compared to

patients more than 50 years ((53.1%)[74]. Moreover, the younger age groups were found to take more anthracycline-based chemotherapy compared to the older age group (56%-68.3% vs 50.6% in patients older than 50; $p<0.001$) which reflected the more aggressive treatment in the young age group[74]. Similarly, a study using an Argentinian cancer registry with 7,105 patients revealed that young patients (<40) were more likely to take adjuvant chemotherapy in 66% of the cases compared to 36.6% in the older patients [96]. A third study by Han et al, that included 2042 breast cancer patients, also revealed that young breast cancer patients (<35 years of age) were more likely to be administered chemotherapy compared to the older breast cancer group (68% vs 58.7%) with anthracycline and CMF as the most common cancer agents used[83]. Furthermore, Langman et al also highlighted that the young breast cancer patients are likely to receive neoadjuvant chemotherapy in 88.9% which is a high percentage similar to the one reported in our study favoring the more aggressive treatment [85].

However, Bouferraa et al highlighted no difference in adjuvant and neoadjuvant treatments including chemotherapy, hormonal therapy, and radiation therapy was found[126]. Similarly , other studies including Kwong et al, did not find a difference in terms of adjuvant chemotherapy between the two age group [76]. However, this study had a small sample size which affects the power of the study, treatments were not standardized, and missing treatment information including the duration of treatment limited the certainty in the results [126].

Studies attributed the increased reliance on chemotherapy regimens in young patients to the increased proportion of hormone negative tumors that need more aggressive chemotherapy instead of hormonal therapy [127]. Moreover, reliance on

anthracycline-based chemotherapy in young patients was attributed to the regimens characteristics as it is usually recommended for patients at high risk of recurrence[128].

5.8. What factors play a role in chemotherapy choice

In our study, increasing tumor size, positive lymph nodes, advanced tumors (higher stage and grade), more aggressive molecular subtypes, and complete mastectomy were all associated with higher odds of chemotherapy administration. This is in concordance guidelines that support the use of chemotherapy and particularly neoadjuvant chemotherapy in operable breast cancer as the standard of care to downsize the tumor in the breast and axilla prior to surgery and to help make inoperable breast cancers operable [129, 130]. Moreover, axillary lymph node involvement is an indication for adjuvant systemic therapy like chemotherapy, hormonal therapy, and targeted therapy[131]. In addition, Stage I and II patients are usually treated with surgery and radiation; however, Stage III disease requires more aggressive treatment with chemotherapy administration, surgery (breast and axilla if indicated), and radiation therapy (if indicated)[131].

In our study, all patients with HER 2 and TN subtypes underwent chemotherapy administration, and the trends were similar in both groups because the indications are the same. This is in concordance with the essential role neoadjuvant chemotherapy has in treating HER2 and Triple negative molecular subtypes[130]. In a meta-analysis, patients were treated with either neoadjuvant or adjuvant chemotherapy, no significant difference in local recurrence (was noted between the two groups or survival (HR: 0.98, 95%CI: 0.87-1.09) at 5-year follow up; however, the rate of mastectomy dropped by 17% in patients receiving NACT. This is an underrepresentation because many of the patients

were eligible for BCT and weren't eligible for NACT[132]. These numbers highlight how NACT can help decrease treatment aggressiveness while still maintaining similar recurrence profiles.

5.9. Comparison of Hormone and Trastuzumab therapy between young and older age group

In our study, there was no significant difference in hormonal therapy between the young and older age groups. This is like other studies that identified that the use of hormonal therapy in both premenopausal and postmenopausal women improves survival for hormone positive tumors[133]. As for targeted therapy, in our study we found a significantly higher use of trastuzumab therapy in the young age group which is in concordance with the higher proportion of HER 2 positive receptors in the young age group. This is similar to prior research that revealed that patients with HER 2 positive receptors benefit from adjuvant targeted therapy in both young and older age groups[104]. Moreover, in young women that addition of targeted therapy further helps decrease the chemotherapy related amenorrhea, which favors the use in HER 2 positive tumors[104].

5.10. Comparison of outcomes between young and older breast cancer patients

In our study, young breast cancer patients were found to have worse recurrence and mortality outcomes compared to older age group, but this only reached significance for recurrence and particularly distant recurrence. Similarly, Bouferraa et al reported that young breast cancer patients have worse overall survival (77.4% vs 98.6% in older age group) and DFS (70.4% vs 90% in older age group)[126]. In a study by El Saghir in Lebanon, young breast cancer patients (<35years of age) had significantly worse survival curves compared to older age groups (P:0.03)[74]. Similarly, a study by Chediak et al

that included 123 patients at AUBMC revealed worse DFS curves in the young breast cancer group (<40) with a recurrence rate of 19.4% compared to 5.2 % in patients more than 40 years of age[134]. Furthermore, a study by Avci et al, revealed that 3.8% of the patients recurred locoregionally and there was no significant difference between the two age groups[98]. However, distant metastasis occurred more frequently in 24.6% with a significantly higher incidence in the young breast cancer group (31% vs 11%; P:0.004)[98]. Small sample size was a considerable limitation in the study. However, another study by wang et al, that included around 483 patients (<35 years) and 739 patients (>35 years) also found a significant difference in 5-year Disease free survival between the two groups (73.7% in YBC vs 83.4% in OBC; P: 0.001) but not 5 year overall survival (91.7% in YBC vs 91.7% in OBC, P:0.721)[135]. Moreover, young BC patients had significantly higher 5-year locoregional (8.9% vs 4.3%) and distant recurrence (18.8% vs 9.5%)[135]. Some studies from developing countries like Singapore and Saudi Arabia demonstrated that young breast cancer patients had better survival, or no effect compared to older counterparts [136, 137]. But sample size and study design are limitations that should alarm us to interpret these results with caution. In Lebanon. El Saghir et al concluded that young breast cancer is a bad prognostic factor on patient outcomes. Reason for these worse outcomes include prognostic factors like multifocal and multicentric tumors, greater tumor size, increased lymph node involvement, and molecular subtypes [80, 83, 116].

5.11. Limitations and strengths

Our study is not without limitations, first the limited sample size especially in the young breast cancer group might have affected the power to detect significant differences

for some variables in our analysis. Furthermore, the retrospective of our study might be considered inferior to a prospective study design; however, data were collected through chart review and hospital reports decreasing the chance of bias. Moreover, missing data in some variables (pathologic tumor size, Family History, and calcification) limited the use of such variables in our study. In addition, our study occurred in one institution (AUBMC) which could limit the generalizability of our study. However, AUBMC is a tertiary care center and is a referral center for cancer patient across Lebanon. In a study by El Saghir et al, the authors highlighted that the distribution of patients receiving treatment at AUBMC is similar to the population distribution[74]. Also, the lack of a national registry limits the generalizability of our results as we couldn't compare the characteristics of our group to national data to determine if it is a representative sample.

Concerning, the strengths our study, this is to our knowledge the first study to compare presentation, treatment modalities, and outcomes simultaneously in young and older breast cancer patients in Lebanon and the region. Moreover, a major advantage of our study is that unlike older studies that experienced variability due to the use of different AJCC criteria for staging, heterogenous treatments, and outdated grading systems (Bloom and Richardson) , our study occurred over a short period of time in a single center (between 2010 and 2016) using the same AJCC criteria for staging, original pathology reports for reporting tumor features, original radiology reports for reporting tumor image features, and homogeneous treatment modalities for patients. Which help address many of the limitations in previous studies.

CHAPTER 6

CONCLUSION AND FUTURE IMPLICATIONS

In conclusion, in this study we investigated the presentation, treatments, and outcomes of young breast cancer compared to older breast cancer patients in Lebanon. We found that young breast cancer was associated with more aggressive features including greater tumor size, multifocal and multicentric tumors, presence of calcifications on imaging, higher grade, HER2 positive receptors, and greater lymph vascular invasion. No difference in treatment modalities was noted between the two age groups except for higher use of chemotherapy and particularly in the neoadjuvant setting between both groups. Young patients had worse recurrence outcomes and particularly distant metastasis. Furthermore, we found similar trends in the indications of mastectomy and chemotherapy in both age groups. We believe that our study will provide a cornerstone for future research on the topic with greater sample size and possibly prospective studies in nature.

APPENDIX

Table 1: Baseline Characteristics Between Young (<40) and Older Breast Cancer (≥40)

Variable	Population (N=745)	Young Breast Cancer (N=126)	Older Breast Cancer (N=619)	P-value
Age in years	51.64 ± 12.17	35.44 ± 3.84	54.94 ± 10.53	< 0.001
BMI	27.53± 5.17	25.93± 4.75	27.86 ± 5.19	< 0.001
Hypertension Yes No	 211 (29.0%) 517 (71.0%)	 2 (1.6%) 123 (98.4%)	 209 (34.7%) 394 (65.3%)	< 0.001
Diabetes Yes No	 83 (11.5%) 636 (88.5%)	 4 (3.2%) 121 (96.8%)	 79 (13.3%) 515 (86.7%)	0.001
Smoking Non smoker Smoker Ex-smoker	 433 (61.6%) 223 (31.7%) 47 (6.7%)	 75 (62.5%) 39 (32.5%) 6 (5.0%)	 358 (61.4%) 184 (31.6%) 41 (7.0%)	0.749
FH of Breast Cancer Yes No	 214 (32.5%) 445 (67.5%)	 40 (35.7%) 72 (64.3%)	 174 (31.8%) 373 (68.2%)	0.421

Table 2: Clinical Tumor Characteristics Between Young (<40) and Older Breast Cancer (≥40)

Variable	Population (N=745)	Young Breast Cancer (N=126)	Older Breast Cancer (N=619)	P-value
Tumor Size on Imaging in cm	2.35 ± 1.65	2.62 ± 1.63	2.29 ± 1.64	0.052
Number of Masses on Imaging Single Multiple	 486 (70.9%) 199 (29.1%)	 73 (61.9%) 45 (38.1%)	 413 (72.8%) 154 (27.2%)	0.017
Multifocality Unifocal Multifocal or multicentric	 480 (70.6%) 200 (29.4%)	 73 (60.8%) 47 (39.2%)	 407 (72.7%) 153 (27.3%)	0.01
Calcifications Yes No	 260 (55.2%) 211 (44.8%)	 55 (72.4%) 21 (27.6%)	 205 (51.9%) 190 (48.1%)	0.001
Clinical Tumor Stage 1 2 3	 247 (34.8%) 341 (48%) 122 (17.2%)	 37 (30.3%) 56 (45.9%) 29 (23.8%)	 210 (35.7%) 285 (48.5%) 93 (15.8%)	0.095
Clinical Nodal Status on Imaging Yes No	 251 (36.1%) 444 (63.9%)	 49 (39.8%) 74 (60.2%)	 202 (35.5%) 370 (64.7%)	0.343

Table 3: Pathological Tumor Characteristics Between Young (<40) and Older Breast Cancer (≥40)

Variable	Population (N=745)	Young Breast Cancer (N=126)	Older Breast Cancer (N=619)	P-value
Type of Invasive Breast Cancer				0.448
IDC	651 (88.5%)	115 (92.0%)	536 (87.7%)	
ILC	67 (9.1%)	8 (6.4%)	59 (9.7%)	
IDC and ILC	8 (1.1%)	0 (0.0%)	8 (1.3%)	
Others	10 (1.4%)	2 (1.6%)	8 (1.3%)	
Tumor Grade				<0.001
1	129 (18.2%)	18 (14.6%)	111 (18.9%)	
2	316 (44.5%)	41 (33.3%)	275 (46.8%)	
3	265 (37.3%)	64 (52.0%)	201 (34.2%)	
Tumor Size on Pathology	2.22 ± 1.78	2.22 ± 1.55	2.22 ± 1.82	0.984
Estrogen Receptor Status				0.263
Positive	607 (81.9%)	98 (78.4%)	509 (82.6%)	
Negative	134 (18.1%)	27 (21.6%)	107 (17.4%)	
Progesterone Receptor Status				0.997
Positive	546 (73.6%)	92 (73.6%)	454 (73.6%)	
Negative	196 (26.4%)	33 (26.4%)	163 (26.4%)	
HER 2 Receptor Status				0.033
Positive	171 (23.1%)	38 (30.6%)	133 (21.6%)	
Negative	570 (76.9%)	87 (69.6%)	483 (78.4%)	
Molecular subtypes				0.126
Luminal A	290 (39.9%)	38 (30.6%)	252 (41.8%)	
Luminal B	310 (42.6%)	63 (50.8%)	247 (41.0%)	
HER 2	53 (7.3%)	9 (7.3%)	44 (7.3%)	
TN	74 (10.2%)	14 (11.3%)	60 (10.0%)	
Lymph vascular Invasion				0.028
Yes	190 (30.1%)	43 (38.7%)	147 (28.2%)	
No	442 (69.9%)	68 (61.3%)	374 (71.8%)	
Lymph node status on pathology				0.180
Positive	296 (41.2%)	56 (46.7%)	240 (40.1%)	
Negative	423 (58.8%)	64 (53.3%)	359 (59.9%)	

Table 4: Treatment Modalities Between Young (<40) and Older Breast Cancer (≥40)

Variable	Population (N=745)	Young Breast Cancer (N=126)	Older Breast Cancer (N=619)	P-value
Surgery				0.427
Yes	742 (99.6%)	125 (99.2%)	617 (99.7%)	
No	3 (0.4%)	1 (0.8%)	2 (0.3%)	
Surgery Type				0.428
Partial	428 (57.7%)	68 (54.4%)	360 (58.3%)	
Total	314 (42.3%)	57 (45.6%)	257 (41.7%)	
Axilla Surgery Type				0.116
SLNB	471(64.6%)	77 (62.1%)	394 (65.1%)	
ALND	258 (35.4%)	47 (37.9%)	211 (34.9%)	
Radiotherapy				0.398
Yes	546 (76.9%)	91 (74.0%)	455 (77.5%)	
No	164 (23.1%)	32 (26.0%)	132 (22.5%)	
Chemotherapy (both)				0.003
Yes	580 (80.8%)	111 (90.2%)	469 (75.8%)	
No	138 (19.2%)	12 (9.8%)	126 (20.4%)	
Anthracycline (N=580)				0.028
Yes	447 (82.8%)	92 (90.2%)	355 (81.1%)	
No	93 (17.2%)	10 (9.8%)	83 (18.9%)	
Taxanes (N=580)				0.056
Yes	466 (86.3%)	94 (92.2%)	372 (84.9%)	
No	74 (13.7%)	8 (7.8%)	66 (15.1%)	
Neoadjuvant Chemotherapy				0.003
Yes	198 (26.8%)	47 (37.3%)	151 (24.6%)	
No	542 (73.2%)	79 (62.7%)	463 (75.4%)	
Adjuvant Chemotherapy				0.782
Yes	415 (59.4%)	72 (60.5%)	343 (59.1%)	
No	284 (40.6%)	47 (39.5%)	237 (40.9%)	
Trastuzumab Therapy				0.029
Yes	146 (21.3%)	47 (37.3%)	151 (24.6%)	
No	539 (78.7%)	79 (62.7%)	463 (75.4%)	
Hormonal Therapy				0.199
Yes	404 (60.0%)	60 (54.5%)	344 (61.1%)	
No	269 (40.0%)	50 (45.5%)	219 (38.9%)	

Table 5: Outcomes Between Young (<40) and Older (≥40) Breast Cancer

Variable	Population (N=745)	Young Breast Cancer (N=126)	Older Breast Cancer (N=619)	P-value
Median Follow up (in years)	4.52± 2.98	4.59 ± 3.55	4.52 ± 2.95	0.831
Death Yes No	 25 (3.4%) 720 (96.6%)	 7 (5.6%) 119 (94.4%)	 18 (2.9%) 601 (97.1%)	0.169
Recurrence Yes No	 83 (11.1%) 662 (88.9%)	 21 (16.7%) 105 (83.3%)	 62 (10%) 557 (90%)	0.031
Loco-regional Recurrence Yes No	 29 (3.9%) 716 (96.1%)	 8 (6.3%) 118 (93.7%)	 21 (3.4%) 598 (96.6%)	0.118
Distant Recurrence Yes No	 69 (9.3%) 676 (90.7%)	 18 (14.3%) 108 (85.7%)	 51(8.2%) 568 (91.8%)	0.033

Table 6: Univariate Logistic Regression for mastectomy indications

Variable	Young BC			Older BC		
	OR	95% CI	P-value	OR	[95% CI]	P-value
Pre- operative tumor size	1.107	0.875 – 1.400	0.396	**1.472**	**1.291 – 1.678**	**<0.001**
Positive Lymph node status	**4.435**	**2.041 – 9.638**	**<0.001**	**2.788**	**1.955 – 3.977**	**<0.001**
Multiple tumors on Imaging	**5.679**	**2.509 – 12.851**	**<0.001**	**2.981**	**2.036 – 4.367**	**<0.001**
Grade						
1	1			1		
2	1.565	0.492 – 4.983	0.448	1.484	0.933 – 2.362	0.095
3	1.818	0.607 – 5.449	0.286	1.670	**1.028 – 2.714**	**0.038**
Molecular Subtype						
Luminal A	1			1		
Luminal B	1.308	0.577 – 2.2963	0.520	**1.554**	**1.081 – 2.233**	**0.017**
HER2 Positive	1.917	0.442 – 8.310	0.385	**4.185**	**2.107 – 8.311**	**<0.001**
Triple Negative	1.314	0.369 – 4.679	0.673	1.302	0.730 – 2.323	0.372
Stage						
1	1			**1**		
2	1.562	0.656 – 3.723	0.314	**3.620**	**2.407 – 5.443**	**<0.001**
3	**4.222**	**1.473 – 12.104**	**0.007**	**9.859**	**5.608 – 17.331**	**<0.001**

Table 7: Multivariate logistic regression for mastectomy indications

Variable	Model 1 (Young BC- N= 108) *			Model 1 (Older BC- N=475) *		
	OR	95% CI	P-value	OR	[95% CI]	P-value
Pre- operative tumor size	0.941	0.68 – 1.31	0.757	**1.272**	**1.093 – 1.480**	**0.002**
Positive Lymph node status	**3.686**	**1.241 – 10.945**	**0.020**	**1.661**	**1.028 – 2.685**	**0.038**
Multiple tumors on Imaging	**6.593**	**2.413 – 18.01**	**<0.001**	**2.736**	**1.761 – 4.252**	**<0.001**
Grade						
1	1			1		
2	2.403	0.465 – 12.404	0.240	1.103	0.596 – 2.043	0.755
3	2.031	0.296 – 13.916	0.417	**0.443**	**0.199 – 0.987**	**0.046**
Molecular Subtype						
Luminal A	1			1		
Luminal B	1.488	0.339 – 6.526	0.584	1.580	0.904 – 2.760	0.108
HER2 Positive	0.713	0.076 – 6.646	0.785	**4.479**	**1.757 – 11.417**	**0.002**
Triple Negative	3.314	0.423 – 25.963	0.254	2.266	0.928 – 5.535	0.073
Stage						
1	1			**1**		
2	1.108	0.351 – 3.595	0.704	**1.836**	**1.050 – 3.209**	**0.033**
3	2.300	0.465 – 11.362	0.261	**2.953**	**1.284 – 6.789**	**0.011**

*Model 1 adjusted for tumor size, lymph node status, number of tumors on imaging, tumor grade, tumor stage, and molecular subtype with unknown missing variables excluded from the analysis.

Table 8: Sensitivity Analysis for mastectomy indications with categorical missing variables included in the analysis

Variable	Model 1 (Young BC- N= 115) *			Model 1 (Older BC- N=525) *		
	OR	95% CI	P-value	OR	[95% CI]	P-value
Pre- operative tumor size	0.949	0.681 – 1.322	0.757	**1.259**	**1.076 - 1.473**	**0.004**
Positive Lymph node status	**3.680**	**1.231 – 10.997**	**0.020**	**1.677**	**1.019 - 2.761**	**0.042**
Multiple tumors on Imaging	**6.990**	**2.539 – 19.243**	**<0.001**	**2.654**	**1.686 – 4.178**	**<0.001**
Grade						
1	1			1		
2	2.704	0.515 – 14.185	0.240	1.229	0.675 – 2.236	0.500
3	2.232	0.321 – 15.528	0.417	0.555	0.258 – 1.190	0.130
Molecular Subtype						
Luminal A	1			1		
Luminal B	1.518	0.341 – 6.797	0.584	1.341	0.786 – 2.290	0.282
HER2 Positive	0.732	0.078 – 6.850	0.785	**3.664**	**1.474 – 9.105**	**0.005**
Triple Negative	3.353	0.420 – 26.791	0.254	1.554	0.681 – 3.543	0.295
Stage						
1	1			**1**		
2	1.248	0.399 – 3.904	0.704	**1.972**	**1.148 – 3.388**	**0.014**
3	2.505	0.505 – 12.435	0.261	**3.062**	**1.363 – 6.878**	**0.007**

*Model 1 adjusted for tumor size, lymph node status, number of tumors on imaging, tumor grade, tumor stage, and molecular subtype with categorical missing variables included in the analysis

Table 9: Multivariate logistic regression for mastectomy indications with calcifications variable and categorical missing variables included in the analysis

Variable	Model 2 (Young BC- N= 115) *			Model 2 (Older BC- N=525) *		
	OR	95% CI	P-value	OR	[95% CI]	P-value
Pre- operative tumor size	0.912	0.636 - 1.307	0.615	**1.274**	**1.095 - 1.482**	**0.002**
Positive Lymph node status	**5.538**	**1.664 – 18.438**	**0.005**	**1.693**	**1.047 - 2.756**	**0.034**
Multiple tumors on Imaging	**8.070**	**2.792 – 23.330**	**<0.001**	**2.903**	**1.841 – 4.579**	**<0.001**
Grade						
1	1			1		
2	2.149	0.382 – 12.074	0.385	1.184	0.644 – 2.177	0.587
3	1.976	0.250 – 15.616	0.519	0.504	0.232 – 1.098	0.085
Molecular Subtype						
Luminal A	1			1		
Luminal B	1.407	0.287 – 6.904	0.674	1.312	0.760 – 2.263	0.329
HER2 Positive	0.604	0.059 – 6.224	0.672	**3.829**	**1.518 – 9.658**	**0.004**
Triple Negative	2.584	0.280 – 23.816	0.402	1.702	0.732 – 3.959	0.217
Stage						
1	1			**1**		
2	1.364	0.410 – 4.538	0.613	**1.940**	**1.124 – 3.350**	**0.017**
3	1.891	0.356 – 10.031	0.454	**2.846**	**1.253 – 6.466**	**0.012**
Presence of calcifications on Mammography	**6.544**	**1.333 – 32.118**	**0.021**	**2.404**	**1.449 – 3.981**	**<0.001**

*Model 2 adjusted for tumor size, lymph node status, number of tumors on imaging, tumor grade, tumor stage, molecular subtype, and calcifications on mammography with categorical missing variables included in the analysis

Table 10: Univariate logistic regression for chemotherapy indications

Variable	Young BC			Older BC		
	OR	95% CI	P-value	OR	[95% CI]	P-value
Pre- operative tumor size	1.990	0.960 – 4.126	0.064	**3.218**	**2.369 – 4.370**	**<0.001**
Positive Lymph node status	3.852	0.805 – 18.427	0.091	**8.620**	**4.392 – 16.920**	**<0.001**
Multiple tumors on Imaging	1.323	0.374 – 4.679	0.664	**2.589**	**1.507 – 4.446**	**<0.001**
Grade						
1	1			1		
2	2.615	0.648 –	0.177	**3.978**	**2.462 – 6.428**	**<0.001**
3	**11.731**	10.549 **2.047 – 67.217**	**0.006**	**20.608**	**9.813 – 43.276**	**<0.001**
Molecular Subtype						
Luminal A	1			1		
Luminal B	**5.067**	**1.251 –**	**0.023**	**3.129**	**2.019 – 4.850**	**<0.001**
HER2 Positive	>>>1[a]	**20.518**		>>>1 [a]		
Triple Negative	3.467	0.393 – 30.616	0.263	>>>1 [a]		
Stage						
1	1			**1**		
2	**4.000**	**1.102 –**	**0.035**	**7.531**	**4.690 –**	**<0.001**
3	>>>1 [a]	**14.520**		**76.355**	**12.095** **10.431 – 558.911**	**<0.001**
Complete Mastectomy	2.789	0.717 – 10.859	0.139	**4.639**	**2.781 – 7.735**	**<0.001**

[a]The effect estimate is very large and could not be estimated because all patients took chemotherapy.

Table 11: Multivariate logistic regression for chemotherapy indications

Variable	Model 1 (Young BC- N= 105) *			Model 1 (Older BC- N=465) *		
	OR	95% CI	P-value	OR	[95% CI]	P-value
Pre- operative tumor size	1.329	0.621 – 2.845	0.464	**1.886**	**1.286 – 2.766**	**0.001**
Positive Lymph node status	0.320	0.023 – 4.518	0.399	2.356	0.977 – 5.685	0.056
Multiple tumors on Imaging	2.460	0.259 – 23.387	0.433	1.395	0.646 – 3.016	0.397
Grade						
1	1			1		
2	3.578	0.570 – 22.436	0.174	**4.509**	**2.195 – 9.260**	**<0.001**
3	8.629	0.459 – 162.269	0.150	**14.504**	**4.436 – 47.419**	**<0.001**
Molecular Subtype						
Luminal A	1			1		
Luminal B	1.900	0.228 – 15.831	0.553	0.973	0.489 – 1.934	0.937
HER2 Positive	>>>1[a]			>>>1 [a]		
Triple Negative	>>>1[a]			>>>1 [a]		
Stage						
1	1			**1**		
2	**8.073**	**1.067 – 61.099**	**0.043**	**3.189**	**1.559 – 6.524**	**0.001**
3	>>>1[a]			**9.586**	**1.124 – 81.736**	**0.039**
Complete Mastectomy	1.140	0.154 – 8.41	0.898	**2.328**	**1.062 – 5.105**	**0.035**

*Model 1 adjusted for tumor size, lymph node status, number of tumors on imaging, tumor grade, tumor stage, molecular subtype, and breast surgery type with unknown missing variables excluded from the analysis.

[a]The effect estimate is very large and could not be estimated because all patients took chemotherapy.

Table 12: Sensitivity Analysis for chemotherapy indications with categorical missing variables included in the analysis

Variable	Model 1 (Young BC- N= 113) *			Model 1 (Older BC- N=512) *		
	OR	95% CI	P-value	OR	[95% CI]	P-value
Pre- operative tumor size	1.329	0.621 – 2.845	0.464	**1.956**	**1.334 – 2.869**	**<0.001**
Positive Lymph node status	0.320	0.023 – 4.518	0.399	2.385	0.991 – 5.740	0.053
Multiple tumors on Imaging	2.460	0.259 – 23.387	0.433	1.374	0.642 – 2.938	0.413
Grade						
1	1			1		
2	3.578	0.570 – 22.436	0.174	**4.506**	**2.194 – 9.257**	**<0.001**
3	8.629	0.459 – 162.269	0.150	**15.158**	**4.640 – 49.525**	**<0.001**
Molecular Subtype						
Luminal A	1			1		
Luminal B	1.900	0.228 – 15.831	0.553	0.978	0.494 – 1.935	0.949
HER2 Positive	>>>1[a]		0.766	>>>1 [a]		
Triple Negative	>>>1[a]		0.254	>>>1 [a]		
Stage						
1	1			**1**		
2	**8.073**	**1.067 – 61.099**	**0.043**	**3.146**	**1.563 – 6.334**	**0.001**
3	>>>1[a]			**9.466**	**1.112 – 80.604**	**0.040**
Complete Mastectomy	1.140	0.154 – 8.41	0.898	**2.214**	**1.035 – 4.739**	**0.041**

*Model 1 adjusted for tumor size, lymph node status, number of tumors on imaging, tumor grade, tumor stage, molecular subtype, and breast surgery type with categorical missing variables included in the analysis

[a]The effect estimate is very large and could not be estimated because all patients took chemotherapy.

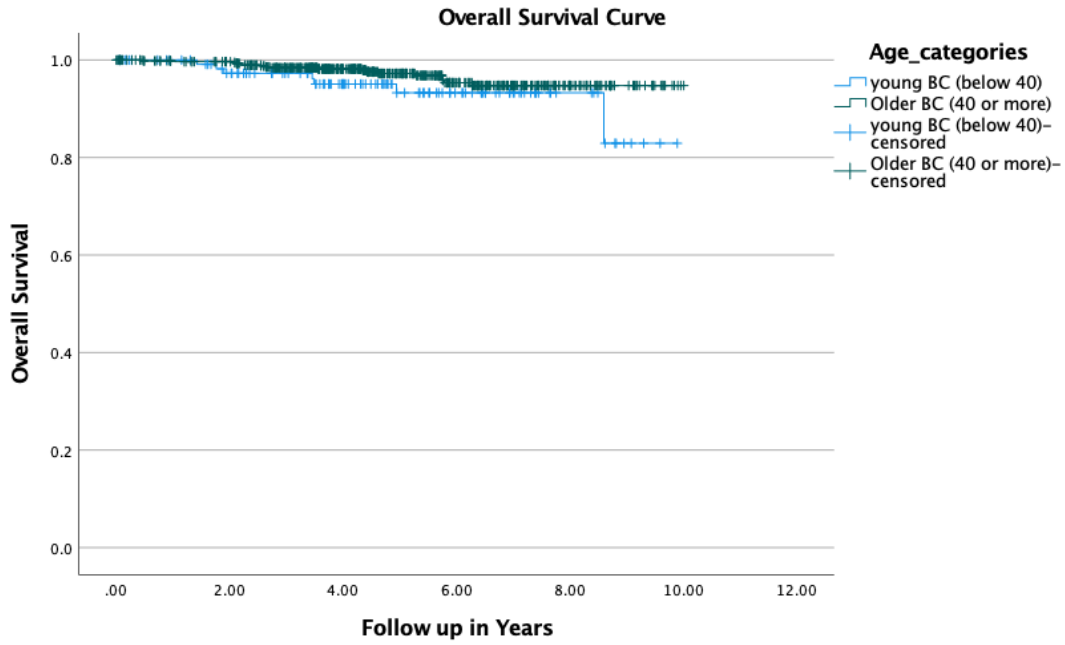
Table 13: Multivariate logistic regression for chemotherapy indications with calcifications variable and categorical missing variables included in the analysis

Variable	Model 2 (Young BC- N= 113)			Model 2 (Older BC- N=512)		
	OR	95% CI	P-value	OR	[95% CI]	P-value
Pre- operative tumor size	1.215	0.454 – 3.250	0.698	**1.847**	**1.249 – 2.731**	**0.002**
Positive Lymph node status	0.054	0.002 – 1.812	0.103	2.304	0.940 – 5.647	0.068
Multiple tumors on Imaging	6.946	0.317 – 152.223	0.219	1.632	0.748 – 3.560	0.218
Grade						
1	1			1		
2	**15.248**	**1.261 – 184.342**	**0.032**	**4.236**	**2.039 – 8.803**	**<0.001**
3	14.605	0.76 – 448.121	0.125	**13.137**	**3.944 – 43.753**	**<0.001**
Molecular Subtype						
Luminal A	1			1		
Luminal B	4.633	0.266 – 80.759	0.293	1.104	0.549 – 2.223	0.781
HER2 Positive	>>>1 [a]			>>>1[a]		
Triple Negative	>>>1 [a]			>>>1[a]		
Stage						
1	1			**1**		
2	**46.461**	**2.273 – 949.513**	**0.013**	**3.248**	**1.581 – 6.674**	**0.001**
3	>>>1[a]			8.420	0.961 – 73.748	0.054
Complete Mastectomy	0.658	0.052 – 8.388	0.898	1.960	0.898 – 4.276	0.091
Presence of calcifications on Mammography	0.519	0.033 – 8.139	0.640	**2.110**	**1.082 – 4.113**	**0.028**

*Model 2 adjusted for tumor size, lymph node status, number of tumors on imaging, tumor grade, tumor stage, molecular subtype, breast surgery type, and calcifications on mammography with categorical missing variables included in the analysis

[a]The effect estimate is very large and could not be estimated because all patients took chemotherapy.

Figure 1: Overall Survival Curve



Overall Comparisons

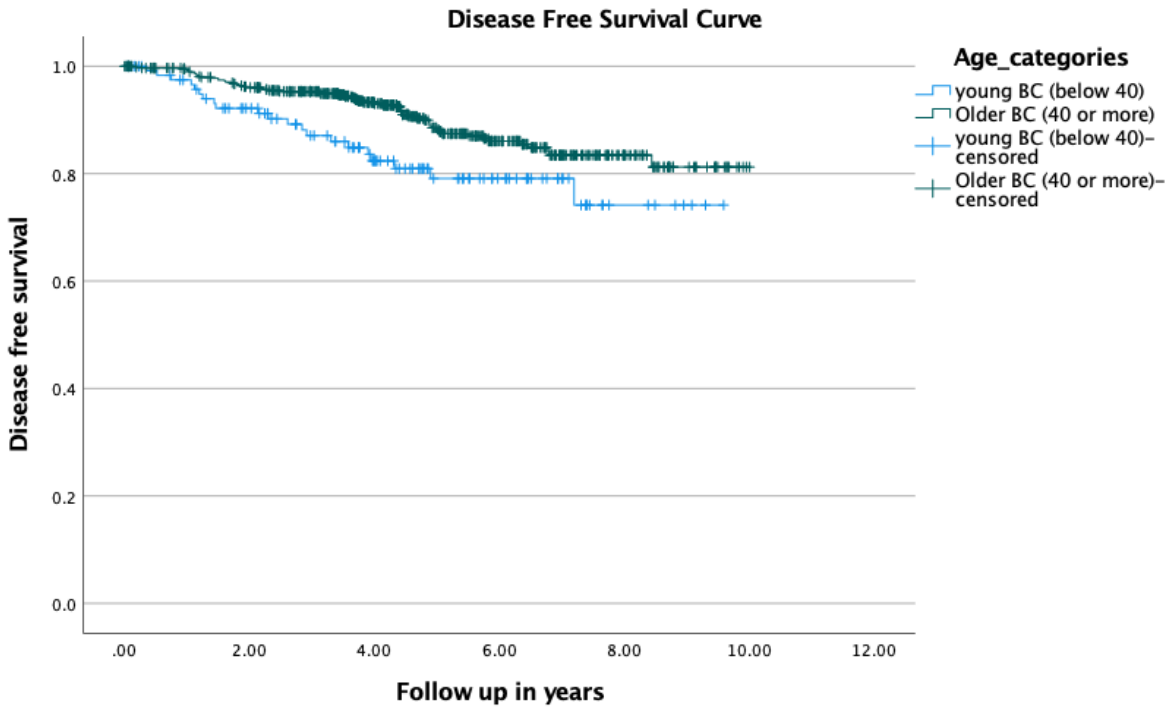
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	2.390	1	.122
Breslow (Generalized Wilcoxon)	2.412	1	.120
Tarone-Ware	2.280	1	.131

Test of equality of survival distributions for the different levels of Age_categories.

Case Processing Summary

			Censored	
Age_categories	Total N	N of Events	N	Percent
young BC (below 40)	124	7	117	94.4%
Older BC (40 or more)	613	18	595	97.1%
Overall	737	25	712	96.6%

Figure 2: Disease Free Survival Curve



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	6.303	1	.012
Breslow (Generalized Wilcoxon)	9.438	1	.002
Tarone-Ware	8.249	1	.004

Test of equality of survival distributions for the different levels of Age_categories.

Case Processing Summary

Age_categories	Total N	N of Events	Censored N	Censored Percent
young BC (below 40)	124	21	103	83.1%
Older BC (40 or more)	613	62	551	89.9%
Overall	737	83	654	88.7%

Appendix 1: Chemotherapy distribution among molecular subtypes and across younger and older age groups:

Molecular Subtypes and Chemotherapy (Younger Breast Cancer)[a]

			Chemotherapy_coded		
			no	yes	Total
Molecular Subtypes	Luminal A	Count	8	30	38
		% within Luminal Type (A,B,TN,HER-2)_coded	21.1%	78.9%	100.0%
	Luminal B	Count	3	57	60
		% within Luminal Type (A,B,TN,HER-2)_coded	5.0%	95.0%	100.0%
	HER 2	Count	0	9	9
		% within Luminal Type (A,B,TN,HER-2)_coded	0.0%	100.0%	100.0%
	TN	Count	1	13	14
		% within Luminal Type (A,B,TN,HER-2)_coded	7.1%	92.9%	100.0%
Total		Count	12	109	121
		% within Luminal Type (A,B,TN,HER-2)_coded	9.9%	90.1%	100.0%

a. Age_categories = young BC (below 40)

Molecular Subtypes and Chemotherapy (Older Breast Cancer)[a]

			Chemotherapy_coded		
			no	yes	Total
Molecular Subtypes	Luminal A	Count	88	152	240
		% within Luminal Type (A,B,TN,HER-2)_coded	36.7%	63.3%	100.0%
	Luminal B	Count	37	200	237
		% within Luminal Type (A,B,TN,HER-2)_coded	15.6%	84.4%	100.0%
	HER 2	Count	0	43	43
		% within Luminal Type (A,B,TN,HER-2)_coded	0.0%	100.0%	100.0%
	TN	Count	0	60	60
		% within Luminal Type (A,B,TN,HER-2)_coded	0.0%	100.0%	100.0%
Total		Count	125	455	580
		% within Luminal Type (A,B,TN,HER-2)_coded	21.6%	78.4%	100.0%

a. Age_categories = Older BC (40 or more)

Appendix 2: Stage and Chemotherapy across age groups

Stage and Chemotherapy (YBC)[a]

			Chemotherapy_coded		
			no	yes	Total
Stage	1	Count	8	26	34
		% within Clinical Stage_coded	23.5%	76.5%	100.0%
	2	Count	4	52	56
		% within Clinical Stage_coded	7.1%	92.9%	100.0%
	3	Count	0	29	29
		% within Clinical Stage_coded	0.0%	100.0%	100.0%
Total		Count	12	107	119
		% within Clinical Stage_coded	10.1%	89.9%	100.0%

a. Age_categories = young BC (below 40)

Stage and Chemotherapy (OBC)[a]

			Chemotherapy_coded		
			no	yes	Total
Stage	1	Count	95	107	202
		% within Clinical Stage_coded	47.0%	53.0%	100.0%
	2	Count	29	246	275
		% within Clinical Stage_coded	10.5%	89.5%	100.0%
	3	Count	1	86	87
		% within Clinical Stage_coded	1.1%	98.9%	100.0%
Total		Count	125	439	564
		% within Clinical Stage_coded	22.2%	77.8%	100.0%

a. Age_categories = Older BC (40 or more)

Appendix 3: Missing Data Table

Variable	Population (N=745)	Young BC	Older BC
BMI (in kg/m^2) Missing	14 (1.8%)	2(1.6%)	12(1.9%)
Hypertension	17 (2.3%)	1 (0.8%)	16(2.6%)
Diabetes	25 (3.5%)	1(0.8%)	25 (4%)
Smoking	42 (5.6%)	6 (4.8%)	36 (5.8%)
Family History of Breast Cancer	86 (11.5%)	14 (11.1%)	72(11.6%)
Tumor Size on Imaging (in cm)	103 (13.8%)	10 (7.9%)	93(15%)
Number of tumors on imaging	60 (8.1%)	8 (6.3%)	52 (8.4%)
Multifocality	68 (8.7%)	6 (4.8%)	59 (9.5%)
Calcifications	274 (36.8%)	50 (39.7%)	224 (36.2%)
Tumor Stage (Clinical)	35(4.7%)	4 (3.2%)	31 (5%)
Clinical Nodal Status	50 (6.7%)	3 (2.4%)	47 (7.6%)
Type of Invasive Breast Cancer	9 (1.2%)	1 (0.8%)	8 (1.3%)
Tumor Grade	35 (4.7%)	3 (2.4%)	32 (5.2%)
Tumor Size on Pathology (in cm)	126 (16.9%)	23 (18.2%)	103 (16.6%)
Estrogen Receptor Status	4 (0.5%)	1(0.8%)	3(0.5%)
Progesterone Receptor Status	3 (0.4%)	1(0.8%)	2 (0.3%)
HER 2 Receptor Status	4 (0.5%)	1 (0.8%)	3 (0.5%)
Molecular subtypes	18 (2.4%)	2(1.6%)	16 (2.6%)
Lymph vascular Invasion	113 (15.2%)	15 (11.9%)	98 (15.8%)
Lymph node status on pathology	26 (3.5%)	6 (4.8%)	20 (3.2%)
Chemotherapy	27 (3.6%)	3 (2.4%)	24 (3.9%)
Anthracyclines	40 (6.9%)	9 (8.1%)	31 (6%)

Taxanes	40 (6.9%)	9 (8.1%)	31 (6%)
Others	40 (6.9%)	9 (8.1%)	31 (6%)
Neoadjuvant Chemotherapy	5 (0.7%)	0 (0%)	5 (0.8%)
Adjuvant Chemotherapy	46 (6.2%)	7 (5.6%)	39 (6.3%)
Targeted Therapy (adjuvant Herceptin)	60 (8.1%)	8 (6.3%)	52 (8.4%)
Hormonal Therapy	72 (9.7%)	16 (12.7%)	56 (9%)
Radiotherapy	35 (4.7%)	3 (2.4%)	32 (5.2%)
Surgery (Y/N)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Surgery Type (Partial vs Total mastectomy)	3 (0.4%)	1 (0.8%)	2 (0.3%)
Axilla Surgery Type	16 (2.1%)	2 (1.6%)	14 (2.3%)
Mean follow up (in years)	8 (1.1%)	2 (1.6%)	6 (1.0%)
Death	0 (0%)	0 (0%)	0 (0%)
Recurrence	0 (0%)	0 (0%)	0 (0%)
Local Breast Recurrence	0(0%)	0 (0%)	0 (0%)
Nodal Breast Recurrence	0 (0%)	0 (0%)	0 (0%)
Distant Recurrence	0 (0%)	0 (0%)	0 (0%)

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