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# Community Hospital Multidisciplinary Breast Conference Data Analysis - A Pathologist's Perspective

**Alexandre A Vdovenko***

Hartford Pathology Associates, PC Hospital of Central Connecticut, USA

***Corresponding author:** Alexandre A Vdovenko, Hartford Pathology Associates, PC Hospital of Central Connecticut, USA.

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## Abstract

Multidisciplinary breast cancer treatment in a specialized setting has become a standard of care. Breast Cancer conference is a central component of this treatment configuration. Twelve-year experience of a teaching community hospital multidiscipline Breast Cancer Center in the American North-East is analyzed on the Breast Conference material from a Pathologist's perspective. 2185 patients were presented including 1589 patients with primary invasive breast carcinomas, 414 with ductal carcinoma in situ, 18 with other breast malignancies and 164 with other breast lesions. Study confirmed that Breast Conference lists that are composed of all new breast cancer cases are representative of the general population under care and are a valid source for breast cancer analysis. Obtained breast cancer data were in general agreement with the published national and international data. An increasing trend in detection of multiple breast invasive carcinomas was registered. No trends in average age, tumor size or lymph node distant metastases status at presentation were found. Relative overall survival was 94.8% at five and 90.4% at ten years. There was no difference in overall survival between the two subsequent 5-year periods of the Breast Cancer Center operation. Age, tumor size and especially distant metastases at presentation were found to be significant mortality risks. Lymph node metastases may not be significant mortality risk at the present state of care. Conclusion is made that further improvement in breast cancer treatment results requires more efforts aiming at early detection.

**Keywords:** Multidisciplinary; Breast; Cancer; Conference; Data analysis; Survival

## Introduction

Breast cancer is the most common new cancer diagnosis in women. It was estimated that 279,100 women in the US were newly diagnosed with breast cancer in 2020 and that life-long probability of breast cancer in women is 1:8 [1]. Breast cancer treatment attitudes have changed gradually from disfiguring radical mastectomies of the Halsted era to conservative organ-sparing procedures substantiated by the National Surgical Adjuvant Breast Project in the 1970s [2]. The conservative approach implied adjuvant radiation and systemic therapy for control of what was universally accepted as a systemic disease [3,4]. This meant employing a multidisciplinary approach. It was recognized in the 1990s that having breast cancer specialist care meant better survival, and this led to a call at the 1998 Breast Cancer Conference in Florence, Italy, for instituting fully equipped multidisciplinary breast cancer clinics and for every woman having access to specialized multidisciplinary breast care [5]. A specialized multidisciplinary treatment approach was intended to improve treatment results through reconfiguration of cancer care [6]. In the first decade of this century, there was a marked increase in the number of breast centers in Europe and in the US [7]. In 2009, the Breast Cancer Center was established at the Hospital of Central Connecticut (HOCC) with formation of a multidisciplinary team of specialists including Medical and Radiation Oncologists, General and Plastic Surgeons, Radiologist, Pathologist, Genetic Counselor, and Nurse Navigator. HOCC is 446-bed teaching community hospital, which serves the area of Central Connecticut spanning across three counties populated by 456,000 people. The population is predominantly White (69.7%) with smaller proportions of Hispanics (16.6%), Blacks (7.2%), and others (6.5%). Median household income in 2017 was

approximately $61, 000, and according to the State Department of Health (Local Analysis of Selected Health Indicators-2017), 85.5% of adults in the service area were assigned Good or Better General Health Indicators [8].

A key element of the multidisciplinary Breast Cancer Center is the weekly Breast Conference [9]. This conference provides a multispecialty communication platform for discussion of newly diagnosed breast cancers and development of coordinated treatment plans [10]. There are a significant number of reports indicating that all breast cancer patients, especially new patients, should be presented at the breast cancer conference [10-12]. The conference may be considered as providing the "gold standard" in cancer treatment [12]. At its inception, the HOCC Breast Cancer Center adopted this approach.

The role of a Pathologist in the multidisciplinary breast cancer team is critical, as histopathologic tumor assessment determines decisions along many crucial steps in cancer care [14]. As all breast cancer diagnoses are made in the Pathology Department, it is the HOCC Pathologist's responsibility to create patient lists for the Breast Cancer Conferences. The multidisciplinary conference serves its main function as a forum for discussion of breast cancer cases, but there are also very important secondary functions - continuing education, quality assurance, data collection, and research [9,13-15]. It was noted recently that the effect of an established multidisciplinary approach on patient care, survival, and satisfaction is still unclear, and further research is needed [16]. The purpose of this report is to substantiate the utilization of multidisciplinary Breast Cancer Conference lists for breast cancer data analysis at the community hospital level, and to make an assessment of the effects of the HOCC Breast Cancer Center operation on breast cancer parameters and patient survival.

**Materials and Methods**

All weekly HOCC multidisciplinary Breast Cancer Conference lists were compiled by the author, retained in the Pathology Department computer, and retrieved for this study. All cases were reviewed, histologic specimens photographed, and presented at the conference. Over the span of twelve years (2009-2020), 2185 new patients were presented. There were 1589 patients with primary breast invasive carcinomas, 414 with ductal carcinoma *in situ* (DCIS), 18 with other breast malignancies, and 164 with other breast findings.

Final pathologic diagnosis, age at presentation, race/ethnicity, gender, tumor type, grade, size, number of tumors, estrogen receptor (ER), progesterone receptor (PR) and Her2 status, lymph node and distant metastases status, and outcome were obtained from Sunquest CoPathPlus™ and Epic electronic medical record (EMR) systems.

Grading of DCIS and invasive carcinomas was done as described in Van Nuys DCIS Prognostic Index method [17] and Nottingham modification of Bloom-Richardson method [18-20], respectively.

Invasive carcinoma was called multifocal if more than one well-demarcated invasive focus was found and if this focus was separated from the other invasive foci by normal breast tissue or benign lesions by at least one tissue block thickness (3 mm). When evaluating tumor size at presentation in cases with multiple tumors, only the largest (sentinel) tumor was recorded. Average ages at presentation, tumor sizes at presentation, and standard deviations were calculated using Microsoft 365 Excel. Comparisons between mean tumor sizes in three age groups (see below) were conducted by normal tests for large samples [21].

We created an Overall Survival (OS) control group that contained 1000 patients who, in 2009-2020, underwent breast core biopsies for benign conditions and who have never had breast invasive or *in situ* malignancies. This cohort was tailored to the average age of the invasive carcinoma cohort in this study, i.e., 62.

We used Kaplan-Meier analysis to generate the 10-year OS rates for patients with benign breast conditions, with invasive carcinomas, with DCIS, with single invasive carcinoma, and with multiple carcinomas. We performed separate Kaplan-Meier curve analyses to compare "time-to-event" for 2009-2014 and 2015-2020 invasive cancer cohorts (5-year OS). Also, we compared 10-year OS Kaplan-Meier curve analyses for benign breast conditions vs invasive carcinoma, benign breast conditions vs DCIS, DCIS vs invasive carcinoma, and single tumor *vs* multiple tumor cohorts. In addition, we divided the invasive carcinoma group into three groups by age: premenopausal (51 yo and younger, n = 365), 52-64 yo (n = 528), and post-retirement age (65 yo and older, n = 692). We compared the 10-year OS among these three groups. In all analyses "time-to-event" was measured in calendar years from the year of diagnosis. The log-rank test was used to compare mean survival times between the respective groups. Survival curves were plotted and interpreted.

Linear tests of trends of tumor size at presentation, age at presentation, annual rates of tumors presenting with LN or distant metastases from 2009 to 2020 were performed on continuous variables using ANOVA analysis with post hoc testing. The means and standard deviations for the time periods were reported and interpreted. Statistical significance was assumed at $p = 0.05$; Statistical analysis was conducted using SPSS Version 26 (Armonk, NY: IBM Corp.).

Cox proportional hazard analysis of the invasive carcinoma group was conducted using four co-variables assessed at presentation: age, tumor size, lymph node metastases, and distant metastases. For the latter three co-variables, information on most cases was derived from pathology reports. If that information was incomplete, every effort was made to obtain the information

from radiology reports and clinician's notes. If information was still incomplete, the patients were removed from the Cox analysis cohorts. Since premenopausal and 52-64 yo groups demonstrated similar OS, and in order to obtain satisfactory numbers of events per variable [22], these two groups were combined into one group of 858 patients (43 events); the 65+ group included 669 patients (80 events). Analyses were performed using Stata version 17 (StatCorp, Texas). Variables were described as median [IQR] for continuous variables and N (%) for categorical data. Results were presented as hazard ratios (HR) with 95% confidence intervals (CI). HRs were obtained for each variable individually and after adjustment for the other three variables. The HRs describe the effect of a 1-unit increase for continuous variables and the effect of presence or absence for categorical variables. Separate effect estimates were obtained for each age group by fitting interaction terms to the model. The proportional hazards assumption was tested using Schoenfeld residuals. $P < 0.05$ was considered statistically significant. Kaplan-Meier survival curves were constructed with continuous data grouped as above or below the median for each age group.

## Results

HOCC multidisciplinary Breast Conference is a routine weekly meeting. The number of cases presented at each conference varied between one and twenty-three (average = 6.3, mode = 6). There were variations in the number of cases presented annually (range = 197-282). In twelve years (2009-2020), 2185 patients were presented, including eight males (0.37%); 116 patients (5.3%) were presented more than once for different lesions.

Before 2018, cases other than invasive malignancies and DCIS were also presented at the conference (n = 164). These were cases of lobular neoplasia, flat epithelial atypia, atypical ductal hyperplasia, radial scars, benign tumors, etc. (Figure 1). In 2018 we discontinued including such cases in conference lists.

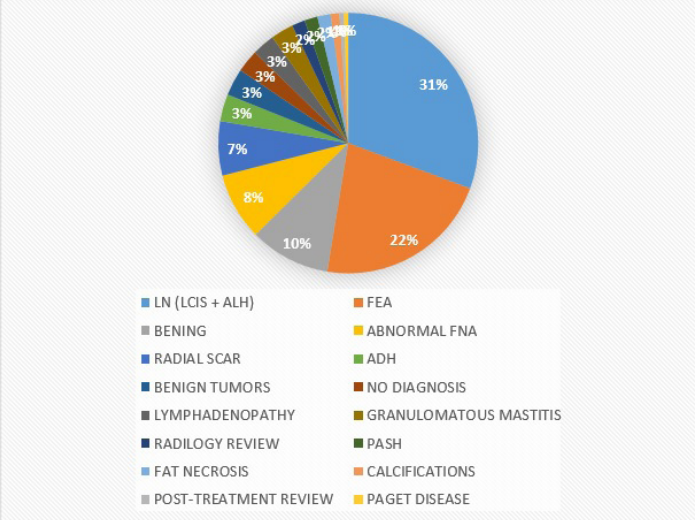


**Figure 1:** Miscellaneous lesions presented at the Breast Conference in 2009-2018.

**DCIS:** This group included 414 patients including one man (0.24%). An additional 31 patients were initially presented as DCIS cases, but on subsequent excision were upgraded to invasive carcinoma (7% upgrade rate). In 26/414 (6.28%) DCIS patients there were microinvasions. In 53/321 (16.5%) patients diagnosed with DCIS on core biopsy, no residual *in situ* carcinoma was found on excision.

Ethnicity/race was known for 374 patients. There were 295 (78.9%) Whites, 49 (13.1%) Hispanics, 16 (4.3%) Blacks, 11 (2.9%) Asians, 2 (0.5%) Middle-Eastern, and 1 (0.3%) South Asian.

Right breast was affected in 198 patients (47.8%), left in 213 patients (51.5%), both in 3 patients (0.7%).

Average age at presentation was 59.37 (SD = 12.38, mode = 52, median = 59). The youngest patient was 22, the oldest was 92. Age at presentation did not exhibit a significant linear trend; $F(11,404) = 1.22$, $p = 0.27$.

Among 414 DCIS cases, 247 (59.2%) were nuclear grade 3, 134 cases (32.1%) were nuclear grade 2, and 36 cases (8.9%) were nuclear grade 1. Comedonecrosis was present in 291 cases (69.7%), 84.8% of cases were ER positive, 74.7% of cases were PR positive. All ER-negative cases (15.2%) were also PR-negative.

Axillary sentinel lymph node sampling was performed on 151/414 (36.5%) patients; in one case of DCIS with microinvasion lymph node metastasis was found.

**Invasive Breast Malignancies:** The primary breast invasive carcinoma group contained 1589 patients, including 6 men (0.38%). The other malignancies group contained 18 patients, all women, including 11 patients with lymphoma, 2 with malignant phyllodes tumor, 2 with angiosarcoma, 2 with metastases to the breast (one melanoma and one ovarian papillary serous carcinoma), 1 with pleomorphic sarcoma, and 1 with primary malignant melanoma (Table 1).

| TYPE OF MALIGNANCY | N =1859 | 100% |
|---|---|---|
| INVASIVE DUCTAL CARCINOMA (NOS) | 1300 | 69.93 |
| INVASIVE LOBULAR CARCINOMA | 234 | 12.59 |
| INVASIVE DUCTAL AND LOBULAR CARCINOMA | 159 | 8.55 |
| MUCINOUS AND DUCTAL WITH MUCINOUS FEATURES | 77 | 4.14 |
| APOCRINE CARCINOMA | 21 | 1.13 |
| TUBULAR CARCINOMA | 20 | 1.08 |
| METAPLASTIC CARCINOMA | 12 | 0.65 |
| ADENOID CYSTIC CARCINOMA | 9 | 0.48 |
| INVASIVE PAPILLARY CARCINOMA | 7 | 0.38 |
| NEUROENDOCRINE CARCINOMA | 1 | 0.05 |
| MICROPAPILLARY CARCINOMA | 1 | 0.05 |
| NON-HODGKIN LYMPHOMA | 10 | 0.54 |
| HODGKIN LYMPHOMA | 1 | 0.05 |
| MALIGNANT PHYLLODES TUMOR | 2 | 0.11 |
| ANGIOSARCOMA | 2 | 0.11 |
| PLEOMORPHIC SARCOMA | 1 | 0.05 |
| METASTASIS TO BREAST | 2 | 0.11 |
| MELANOMA | 1 | 0.05 |

**Table 1:** Breast Conference Malignancies Overall (2009-2020).

There were 87.2% Whites, 6.8% Hispanics, 4% Blacks, 1.5% Asians, 0.4% Middle-Eastern, 0.08% Indians, and 0.08% Native Americans in this group.

In primary breast invasive carcinoma group, the right side was affected in 790 patients (49.9%), left side in 737 patients (46.6%), and both sides in 56 patients (3.5%).

The average age at presentation for breast carcinoma was 62.52 (SD = 14.13, mode = 62, median = 62). The youngest patient was 23, the oldest was 104. Age at presentation did not exhibit a significant linear trend; $F(11,1595) = 1.54$, $p = 0.11$.

Average invasive carcinoma size at presentation was 2.16 cm (SD = 1.84, mode = 1.2 cm, median = 1.7 cm). In the premenopausal group, average tumor size was 2.45 cm (SD = 2.214, mode = 2.5 cm, median = 2 cm), in the 52-64 yo group, average tumor size was 1.96 cm (SD = 1.633, mode = 1.2 cm, median = 1.5 cm), and in the 65+ yo group, average tumor size was 2.16 cm (SD = 1.759, mode = 1.2 cm, median = 1.7 cm). The differences between

average tumor sizes were statistically significant: group 1 *vs* group 2, $p < 0.001$, c.i.= 0.486 ± 0.227; group 2 *vs* group 3, $p < 0.05$, c.i.= 0.2017 ± 0.1631; group 1 *vs* group 3, $p < 0.05$, c.i.= 0.2843 ± 0.223. There was no significant linear trend with respect to invasive breast carcinoma size; $F(11,1420) = 1.18$, $p = 0.30$.

Among the cohort of primary breast carcinoma patients, 206 patients (13%) have had multiple tumors. There was a significant ($p = 0.005$) increasing trend in numbers of multiple breast carcinomas; the rate was 9.7% in 2009 and 19.7% in 2020 (Figure 2).

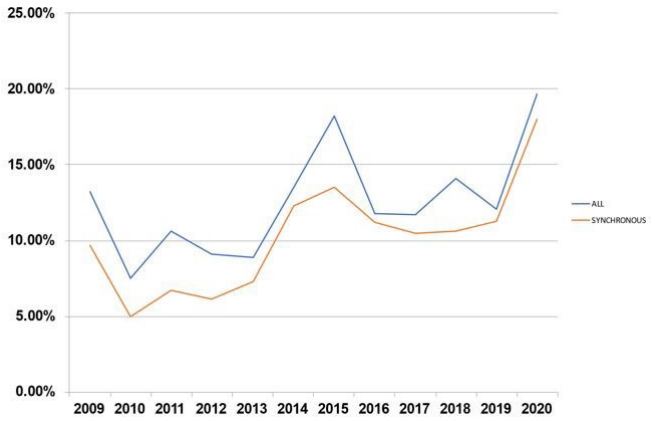


**Figure 2:** Breast Conference Multiple Breast Carcinoma Annual Rates.

In 175 patients (85%), multiple primary breast carcinomas were synchronous (multifocal and multicentric); in 29 patients (14%), tumors were metachronous; in 2 patients (1%) tumors were both synchronous and metachronous. In 153 patients (74%), multiple carcinomas were found in the same breast; in 53 patients (26%), they were found in the opposite breast. In 145 patients (70%), multiple tumors were of the same type. The number of multiple carcinomas varied between 2 and 6, with 82.6% of patients having 2, 13.5% of patients having 3, 1.9% of patients having 4, 1% of patients having 5, and 1% having 6.

There were total of 1841 primary invasive breast carcinomas. The relative frequencies of invasive breast carcinoma subtypes were: no special type (NOS)/ductal, 70.61%; lobular, 12.71%; mixed ductal and lobular, 8.64%; mucinous and ductal with mucinous features, 4.18%; apocrine, 1.14%; tubular, 1.09%; metaplastic, 0.65%; adenoid cystic, 0.49%; invasive papillary, 0.38%; neuroendocrine and micropapillary, 0.05% each. Invasive carcinomas were assigned grade I in 18.9% of cases, grade II in 56.2%, and grade III in 24.9%.

Most common invasive breast carcinomas grades and receptor status distributions are presented in (Table 2).

| GRADE | N | % | ER+ (%) | PR+ (%) | HER2+ (%) | TRIPPLE NEG(%) | HER2 EQUIV (%) |
|---|---|---|---|---|---|---|---|
| I | 291 | 22.8 | 98.2 | 93.2 | 1.4 | 1.1 | 1.1 |
| II | 577 | 45.3 | 91.5 | 81.8 | 11.7 | 5.2 | 1.6 |
| III | 406 | 31.9 | 42.8 | 36.5 | 25.3 | 44.9 | 1.3 |
| ALL | 1274 | | 77.8 | 70.2 | 13.6 | 16.7 | 1.4 |

2A) Incasive Carcinoma of no Special Type/Ductal.

| GRADE | N | % | ER+ (%) | PR+ (%) | HER2+ (%) | TRIPPLE NEG(%) | HER2 EQUIV (%) |
|---|---|---|---|---|---|---|---|
| I | 2 | 0.9 | 100 | 100 | 0 | 0 | 0 |
| II | 212 | 92.2 | 98.5 | 81.5 | 5.1 | 1 | 0 |
| III | 16 | 7 | 87.5 | 62.5 | 31.3 | 6.3 | 6.3 |
| (PLEOMORPHIC) | (16) | 7 | 80 | 66.7 | 33.3 | 6.7 | 6.7 |
| | 230 | | 95.3 | 80.1 | 5.2 | 1.4 | 0.5 |

2B)Invasive Lobular Carcinoma.

| GRADE | N | % | ER+ (%) | PR+ (%) | HER2+ (%) | TRIPPLE NEG(%) | HER2 EQUIV (%) |
|---|---|---|---|---|---|---|---|
| I | 3 | 1.9 | 100 | 100 | 0 | 0 | 0 |
| II | 143 | 91 | 96.4 | 84.2 | 5.8 | 1.4 | 0.7 |
| III | 11 | 7 | 63.6 | 63.6 | 18 | 27.3 | 0 |
| ALL | 157 | | 94.1 | 88.2 | 6.5 | 3.3 | 0.7 |

2C)Invasive mixed Ductal and Lobular Carcinoma

| GRADE | N | % | ER+ (%) | PR+ (%) | HER2+ (%) | TRIPPLE NEG(%) | HER2 EQUIV (%) |
|---|---|---|---|---|---|---|---|
| I | 17 | 23 | 100 | 100 | 0 | 0 | 0 |
| II | 52 | 70.3 | 97.6% | 87.8 | 12.2 | 0 | 0 |
| III | 5 | 6.8 | 66.7 | 33.3 | 66.7 | 0 | 0 |
| ALL | 74 | | 96.7 | 88.5 | 11.5 | 0 | 0 |

2D)Invasive Mucinous Carcinoma Ductal with Mucinous features.

**Table 2: (**2A-2D) HOCC common Breast Carcinoma Grades and Receptor characteristics, A)Incasive Carcinoma of no Special Type/ Ductal B)Invasive Lobular Carcinoma C)Invasive mixed Ductal and Lobular Carcinoma D)Invasive Mucinous Carcinoma Ductal with Mucinous features.

Among apocrine carcinomas, 2/21 (9.5%) were grade I, 13/21 (61.9%) were grade II, and 6/21 (28.6%) were grade III (6/21); 4/21 (19%) cases were ER-positive, 4/21 (19%) were PR-positive, 11/21 (53.4%) were Her2-positive, 9/21 (42.9%) were triple negative, and 1/21 (4.8%) was Her2-equivocal.

All tubular carcinomas were grade I, and all 19 tested cases were receptor-positive, Her2-negative.

All 12 metaplastic carcinomas were triple negative and grade III. Eight cases showed a mesenchymal metaplastic component; three showed squamous metaplasia, and one case showed both.

All 9 adenoid cystic carcinomas were triple negative; two were grade I, 4 were grade II, and 3 were grade III.

All 7 invasive papillary carcinomas were receptor-positive, 6/7 were Her2-negative, and 1/7 was Her2-equivocal; 4/7 cases were grade II, and 3/7 were grade I.

A single case of micropapillary carcinoma was grade II, ER/PR-positive, and Her2-negative; a single case of neuroendocrine carcinoma was grade III, triple negative.

Overall, 80.8% of invasive breast carcinomas were ER-positive, 72.5% were PR-positive, 11.8% were Her2-positive, 14.1% were triple negative, and 1.3% were Her2-equivocal.

Intrinsic molecular subtyping by ER/PR/Her2 expression of 1747 invasive breast carcinomas revealed that 71.8% of cases were luminal A (HR+/Her2-), 14.1% were triple negative (HR-/Her2-), 9.4% were luminal B (HR+/Her2+), and 4.8% were Her2-enriched (HR-/Her2+).

We observed that annual rates of invasive breast carcinoma cases presenting with lymph nodes and/or distant metastases varied between 19% and 34%, with 30% and higher rates observed during the last three years of the study. The apparent increasing trend was not statistically significant (p = 0.08) but may be clinically significant.

Among breast carcinoma distant metastases (n = 172) 32% were to axial skeleton, 15.7% were to liver, 11.6% were to pleura, 11% were to lung, 9.9% were to CSF/brain, 7% were to pericardium, 3.5% were to skin, 1.7% were to mediastinum, 1.7% were to adrenal gland, 1.2% were to peritoneum, 1.2% were to endometrium, and 0.6% each were to stomach, dura, thyroid, uterine cervix, ovary, or soft tissue.

The breast lymphoma group contained one classical Hodgkin lymphoma and ten non-Hodgkin lymphomas. There were three low grade follicular lymphomas, three aggressive B-cell lymphomas (DLBCL, two of which were CD5-positive), one mantle cell lymphoma, one MALT lymphoma (secondary), one breast implant-associated anaplastic large cell lymphoma and one localized monoclonal B-cell periductal infiltrate, likely a MALT lymphoma.

Both angiosarcomas and one pleomorphic sarcoma were post-radiation malignancies arising from treatment of prior breast carcinoma. One of two angiosarcomas and pleomorphic sarcoma developed 11 years after treatment for breast carcinoma. Detailed information for the second angiosarcoma was not available.

**Survival Analysis:** Cumulative survival rates for benign, DCIS, and invasive carcinomas were plotted using a Kaplan-Meier survival curves (Figure 3). The 5-year and 10-year cumulative OS rates for benign breast lesions were 97.0% (standard error (SE) = 0.006) and 93.0% (SE = 0.012), respectively. For DCIS, the 5-year and 10-year cumulative OS were 96.4% (SE = 0.012) and 89.5% (SE = 0.031), respectively. For invasive breast carcinomas, the 5-year and 10-year cumulative OS rates were 92.0% (SE = 0.008) and 84.1% (SE = 0.018), respectively. Relative 5-year and 10-year OS for this last group were 94.8% and 90.4%, respectively. There were no statistically significant differences in OS between benign breast lesions and DCIS, $C^2(1) = 0.31$, $p = 0.58$.

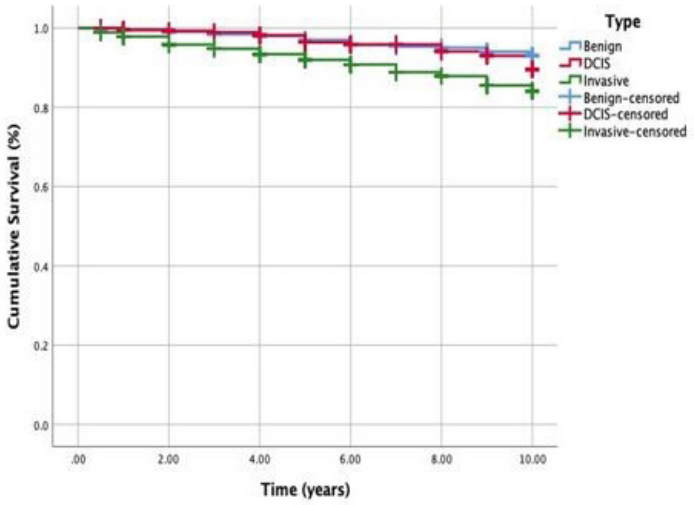


**Figure 3:** 10- years Survival Curves for Benign, DCIS, and Invasive Carcinoma cohorts.

The 5-year cumulative survival for the invasive carcinoma group over the period 2009-2014 (n = 714) was 93.2% (SE = 0.018) and over the period 2015-2020 (n = 875) was 92.5% (SE = 0.013). The log-rank test ($C^2(1) = 0.35$, $p = 0.55$) revealed no statistically significant difference in the mean survival time between these two cohorts (Figure 4).

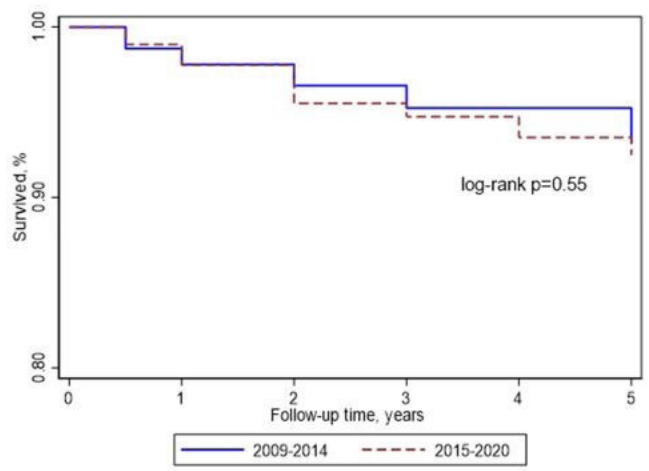


**Figure 4:** Survival Curves for Invasive Breast Carcinomas 2009-2014 and 2015-2020 cohorts.

For the single invasive carcinoma cohort (n = 1383), the 5-year and 10-year cumulative OS were 91.9% (SE = 0.009) and 84.8% (SE = 0.019), respectively. For the multiple invasive carcinomas cohort (n = 206), the 5-year and 10-year cumulative OS were 91.6% and 78.4%, respectively. The difference in OS between these two cohorts was not significant, $C^2(1) = 0.24$, $p = 0.63$.

The Kaplan-Meier analysis did show a statistically significant difference in mean OS between the DCIS and Invasive carcinoma cohorts, $C^2(1) = 10.55$, $p = 0.001$, and between the benign breast lesions and invasive carcinoma cohorts, $C^2(1) = 29.73$, $p < 0.001$.

Kaplan-Meier survival analysis of three age groups (premenopausal, 52-64 yo, and 65+ yo) revealed similar 10-year OS for premenopausal (90.5%) and 52–64 yo (89.8%) groups. OS for the 65+ yo group was significantly worse (74.2%; p < 0.001).

**Mortality Analysis:** For Cox proportional hazard analysis, a total of 1527 patients were followed for 6767.5 person-years, with a median follow-up of 4 years. A total of 123 deaths occurred. The death rate per 1000 person-years of follow-up was 10.8 for those aged < 65 years and 28.5 for those 65+ years old.

In univariate analysis, all variables were significantly associated with mortality in the 65+ yo group, and all variables except age were significantly associated with mortality in the <65 yo group. A significant interaction was found between distant metastases and age, suggesting that the effect of metastases was stronger for the younger age group (p = 0.046) with a 28.19-fold increase in risk for the younger age group compared to a 12.58-fold increase in risk for the older group.

After adjusting each variable for the other three predictors, age, tumor size, and distant metastases were all associated with significantly increased mortality in both age groups. Each one-year increase in age was associated with a 5% increase in mortality for <65 yo and a 6% increase for 65+ yo. Each 1 cm increase in tumor size was associated with a 16% increase in mortality for <65 yo and a 22% increase for 65+ yo. Lymph node status was not significantly associated with mortality after adjustment for the other variables (Table 3).

| | <65 years | | 65 + | |
|---|---|---|---|---|
| Adjusted* | HR (95% CI) | P value | HR (95% CI) | P value |
| Age | 1.05 (1.01-1.09) | 0.01 | 1.06 (1.03-1.09) | <0.001 |
| Tumour size | 1.16 (1.02-1.33) | 0.03 | 1.22 (1.10-1.34) | <0.001 |
| Lymph node | 1.54 (0.73-3.25) | 0.26 | 1.12 (0.66-1.89) | 0.68 |
| Distant metastases | 21.07 (10.79-41.17) | <0.001 | 8.90 (5.28-14.98) | <0.001 |

**A) Multivariable**

A significant interaction remained between metastases and age group, with hazard ratios of 21.07 for <65 yo compared to 8.90 for 65+ yo (interaction p = 0.033).

| | <65 years | | 65 + | |
|---|---|---|---|---|
| Unadjusted | HR (95% CI) | P value | HR (95% CI) | P value |
| Age | 1.03 (0.99-1.07) | 0.10 | 1.07 (1.04-1.10) | <0.001 |
| Tumour size | 1.30 (1.19-1.42) | <0.001 | 1.36 (1.25-1.47) | <0.001 |
| Lymph node | 5.72 (2.98-10.97) | <0.001 | 2.74 (1.75-4.29) | <0.001 |
| distant metastases | 28.19 (14.87-53.42) | <0.001 | 12.58 (7.83-20.22) | <0.001 |

**B) Univaraible.**

**Table 3:** COX Proportional Hazard models each variable adjusted for all other variables. A)Multivariable B) Univaraible.

## Discussion

One of the goals of this study was to test the assumption that with the policy of presenting all new breast cancer cases, the cancer data from Breast Conference lists would be representative of the population under care. The results showed that this assumption is reasonable.

The racial/ethnic distribution of our patient cohort was generally reflective of the Connecticut population, with some overrepresentation of Whites (9% and 17.5% higher for DCIS and invasive malignancy groups, respectively). Males constituted 0.24% of DCIS and 0.38% of invasive carcinoma patients. In the SEER 2017 invasive breast carcinoma report, men comprised 0.99% of patients [23]. We could not find reports on the proportion of men among DCIS patients.

**DCIS:** Our study demonstrated that DCIS comprises 20.7% of all newly diagnosed breast cancers. This is in agreement with national reports from the same time period indicating a 20.6%–24.6% incidence among newly diagnosed breast cancers [23,24]. We found that 84.4% of DCIS was ER-positive and 74.7% was PR-positive, which matches nationally reported rates [25].

Despite the standardized approaches to grading DCIS and invasive carcinoma, there is significant interobserver and interlaboratory variability. Some authors have indicated that the state of DCIS grading agreement is unsatisfactory [26]. A large cohort DCIS study from the Netherlands showed significant interlaboratory variability in reported grades: reported grade 1 ranged from 6.1% to 24.4% of all DCIS, grade 2 ranged from 18.2 to 57.6%, grade 3 ranged from 30.2% to 72.7% [27]. In recently reported US national data, grade 1 comprised 14.3% of all newly diagnosed DCIS, grade 2 comprised 43.4%, and grade 3 comprised 42.3% [25]. In our DCIS cohort, 8.9% were grade 1, 32.1% were grade 2, and 59.2% were grade 3. Comedonecrosis was present in the majority of our DCIS cases (69.7%).

Age at DCIS presentation in our patient group was around 59 (mean and median), and this closely matched the reported age by other authors [27]. There was an apparent trend toward DCIS presenting at younger ages for most of our study period, but that trend was balanced by a higher number of older patients in 2020, consequently, no trend was evident in the final analysis ($p = 0.27$).

Cumulative 10-year OS in DCIS cohort was slightly worse than in the benign breast lesions control group, 89.5% *vs* 93%, but the difference was not significant ($p = 0.58$). Our DCIS cohort contained a small number of cases with microinvasion (6.28%) but these cases did not impact the overall survival since no deaths occurred in this group. Our DCIS survival data is in general agreement with other reports [28-30].

**Invasive Breast Carcinomas:** In the HOCC Breast Conference list, invasive carcinomas constituted 98.9% of all invasive breast malignancies. For comparison, in the 2017 SEER report, this number was 99.5% [23].

The HOCC Breast Conference invasive breast malignancies rates generally match the US national Surveillance, Epidemiology, and End Results data (Table 4). Our rates are also in general agreement with other authors who report 70%–73% for invasive ductal carcinomas (NOS), 6%-11% for invasive lobular carcinomas [31-33] and ~5% for mixed ductal and lobular carcinomas [32].

| Type of malignancy | SEER (2001) | SEER (2017) | Breast conference list |
|---|---|---|---|
| Inv. ductal (NOS) | 75% | 72.4% | 69.9% |
| Inv. lobular | 8.3% | 9.9% | 12.6% |
| Inv. ductal and lobular | 7.1% | 9.7% | 8.5% |
| Mucinous carcinoma | 2.4% | 1.9% | 4.1% |
| Tubular carcinoma | 1.5% | 0.5% | 1.1% |
| Invasive papillary | 0.46% | 0.8% | 0.4% |
| Sarcoma | - | 0.1% | 0.1% |
| Hemangiosarcoma | - | 0.1% | 0.1% |
| Malignant phyllodes | - | 0.2% | 0.1% |

**Table 4:** Breast Malignancies in SEER 2001 [49],SEER 2017 [23] Reports and HOCC Breast Conference List.

The American Cancer Society reported that median age of invasive breast carcinoma diagnosis in 2010-2014 was 62 [34]; our data exactly match that number.

The breast carcinoma grading system sprung from von Hansenmann's general biological concept of anaplasia [35] and was first introduced by Greenough as a practical three-tiered clinico-pathologic system that was informative of prognosis [36]. Bloom and Richardson introduced a streamlined grading method [37], based on scoring tubule formation, nuclear pleomorphism, and mitoses (3 points each). Nottingham Hospital group (United Kingdom) introduced numeric cut-off points into scoring [38], and this latter method of breast cancer grading has become widely accepted. Grade distributions from several studies are presented for comparison in (Table 5). The presented data show that there are substantial population/geographic variations in prevailing grades.

| | Greenough, 1925 (US) n=73 [36] | Bloom-Richardson, 1957 (UK) n=1409 [37] | Nottingham, 1991 (UK) n=2219 [20,38] | Mittendorf et al, 2015(US), N=3138 [39] | Wang et al, 2019 (China) N=4454[40] | Dooijeweert et al, 2020 (Netherlands) N=33043 [41] | Suhani et al, 2020 (India) N=1310 [42] | HOCC, 2021 (US) n=1880 |
|---|---|---|---|---|---|---|---|---|
| Grade 1 | 26% | 26% | 18.6% | 15.6% | 5.04% | 28.1% | 3.1% | 18.9% |
| Grade 2 | 45.2% | 45% | 35.6% | 53.1% | 67.6% | 47.6% | 83.7% | 56.2% |
| Grade 3 | 28.8% | 29% | 45.6% | 31.3% | 15.2% | 24.3% | 13.2% | 24.9% |

**Table 5:** Breast Carcinoma grades Distribution in Different Studies.

It was noted that the rate of invasive lobular carcinoma increased from 6.2% in 1987 to 9% in 1999, and the increase was attributed to hormone replacement therapy [39]. The median incidence of invasive lobular carcinoma is about 11% in Western countries [40]. These tumors are predominantly ER- and PR-positive and Her2-negative [41-46] and the majority of Her2-positive lobular carcinomas are pleomorphic variants [44,45]. We report a 12.7% rate of lobular carcinomas. Pleomorphic variants constituted 7%, and a third of them were Her2-positive.

Invasive carcinomas with mixed ductal and lobular features represent 3.8%-5% of breast cancer cases [33]. Mixed carcinomas in the breast are called when a second recognizable type of carcinoma is present in 10%-90% of the tumor [47]. Mixed ductal and lobular breast carcinomas show variable admixtures of ductal and lobular patterns; the lobular component usually expresses E-Cadherin. These carcinomas show receptor and grade characteristics similar to classical lobular carcinoma, usually grade II, ER/PR-positive, and Her2-negative [45]. Results of our study are consistent with these prior reports, although our mixed ductal and lobular carcinoma rate was somewhat higher at 8.6%.

The reported rate of mucinous breast carcinoma is about 4% (1%-7% range) [23,33,48]. A significant proportion of these tumors are not pure mucinous carcinomas, i.e., composed of > 90% mucinous component [46,49,50]. Most of them are grade II; HR and Her2 status distribution is close to that of invasive ductal carcinoma (NOS) [46], which was demonstrated in our study, as well. In our experience, mucinous carcinoma of the breast behaves in similar fashion to invasive ductal carcinoma (NOS) counterparts (grade and stage dependent); 15.3% of our mucinous carcinoma cases developed metastases to LN and 4.1% to distant sites. Therefore, treatment approaches to this type of tumor should be similar to that for invasive ductal carcinoma (NOS).

Apocrine carcinoma constitutes < 1% of all breast carcinomas. Apocrine carcinomas in our study were designated by morphologic criteria, no androgen receptor tests were done, and 5/21 cases were ER- or PR-positive, and hence, they may be, by strict criteria, designated as "apocrine-like" invasive carcinomas [51]. When adjusted for these cases, the apocrine breast carcinoma rate constituted 0.8% of all breast carcinomas, as has been reported by other authors [52].

Tubular carcinoma is considered to be a low-risk breast cancer [54], having an incidence of 1.2%-2.1% [33,46,53]. It is nearly always ER-positive and is about 80% PR-positive [54]. Although receptor-negative cases were included by some authors in tubular carcinoma cohorts [53,54], all of our tubular carcinoma cases were HR-positive, Her2-negative, and we would be hesitant to assign HR-negative cases to the tubular carcinoma category. Tubular carcinoma patients demonstrate OS similar to that of the general population. There are reports of tubular carcinomas presenting with LN metastases in 5%–12% of cases [53-55]. In our cohort the tubular carcinoma incidence was 1.08%; no LN metastases were observed. A large European tubular carcinoma study cohort [53] revealed no survival benefit from hormonal or chemotherapy but did identify a benefit from breast irradiation. Another large tubular carcinoma study from Europe reported a limited benefit from hormone or radiation treatment [55]. Diagnosis of tubular carcinoma rests mostly on morphologic grounds, and in our experience disagreements on whether a tumor is grade I invasive ductal carcinoma (NOS) or tubular carcinoma is not unusual. Given the prognostic and treatment implications of this type of carcinoma, a fresh look on diagnostic criteria may be useful.

The metaplastic carcinoma incidence is reported to be between 0.2% and 5% of all breast carcinomas [33,45,56,57]. This is a heterogeneous group of triple-negative breast tumors including low- and high-grade variants [56,58]. Our metaplastic carcinoma group was all grade III and triple-negative; 9 of 12 cases contained a malignant mesenchymal component.

Adenoid cystic carcinoma accounts for 0.06%-1% of breast cancers [33,59,60]. It is usually a triple-negative, basaloid carcinoma with a peculiar morphologic pattern similar to its salivary gland or skin counterparts [61]. It has combined epithelial/myoepithelial features with the corresponding immunophenotype. In addition, adenoid cystic carcinoma expresses *c-kit* [60], and we found that CD117 staining was helpful in making the diagnosis in less differentiated, high-grade cases. This tumor is described as being associated with excellent survival [60-62]. Our experience was less encouraging; two out of nine cases developed distant metastases and were lost to follow-up within three years from diagnosis.

Invasive papillary carcinoma comprises 0.2%-3.4% of all breast carcinomas [33,63-65]. Several authors state that this diagnosis is reserved for tumors with 90%-100% papillary morphology [63,65]. In our limited experience (seven cases in this study, five of which were reported previously [66]), these lesions may show a cribriform pattern in addition to papillary, and may also show abundant psammoma bodies and apocrine differentiation. These tumors have been considered as having better prognosis than invasive ductal carcinoma (NOS), but some authors have indicated that papillary morphology is not associated with a significant survival advantage [64].

Neuroendocrine breast carcinoma is a rare entity with a reported incidence from less than 0.1% to 5% of invasive breast carcinomas [67,68]. These tumors, unlike our single case in this cohort, are usually luminal, receptor-positive type with worse prognosis than ductal carcinoma (NOS) [67].

Invasive micropapillary carcinoma is another rare type of breast carcinoma with characteristic "exfoliative" or "inside-out", reverse polarity infiltrative growth [69]. The reported incidence of these tumors is 0.81%-8% of all breast cancers [46,70,71]. They demonstrate propensity for lympho-vascular invasion and lymph node metastases, as was the case with our patient, but overall survival is similar to that of invasive ductal carcinoma patients [70,71]. Our patient was alive at 9 years of follow-up.

The incidence of multiple breast carcinomas varies in reports depending on inclusion criteria and methods of pathologic sampling, from 1.75% to 60%, but the incidence is increasing due to better detection techniques, especially MRI [72-74]. For the purpose of this study, we did not segregate synchronous and metachronous tumors, but the majority (85%) of multiple breast carcinomas cases were synchronous; therefore, we extrapolated general conclusions and comparisons for multifocal/multicentric carcinomas. Better radiological/ultrasound detection may play a role in the increasing incidence, but also improved specimen processing and sampling techniques are crucial for finding additional synchronous tumors [73]. We analyzed the rate of multiple breast biopsies per patient for the period 2009-2018 and found no increasing trend (data not presented). Therefore, we conclude that a significant contribution to finding multiple synchronous tumors is made by efforts of gross pathologists to improve specimen processing and sampling techniques.

Some authors report worse survival for multifocal/multicentric breast cancers [74], others show no significant difference in survival between unifocal and multifocal/multicentric breast carcinomas [72]. The latter view is prevailing at this time, and this is reflected in the current breast cancer staging scheme. We found that 10-year OS was 78.4% for the multiple breast cancers group and 84.8% for the single cancer group, but the difference was not statistically significant ($p = 0.63$). This may be due to the relatively small number of cases of multiple tumors (206 multifocal/multicentric *vs* 1383 unifocal).

Breast cancer gene profiling two decades ago revealed that its biology with direct clinical implications is driven by hormone receptor and Her2-related genes [76]. Invasive breast carcinomas have been divided into four molecular subtypes with characteristic, mutually exclusive hormone receptor patterns: luminal A (HR+/Her2-), triple negative (HR-/Her-), luminal B (HR+/Her2+) and Her2-enriched (HR-/Her2+) [34,75,76].

For Connecticut in 2010, the molecular subtype cancer distribution was 76.1% luminal A, 10.1% triple negative, 10.2% luminal B, and 3.6% Her2-enriched. For the period 2017-2018, American Cancer Society reported the distribution was 71% luminal A, 12% triple negative, 12% luminal B, and 5% Her2-enriched [34]. Our Breast Conference list contained 71.8% luminal A, 14.1% triple negative, 9.4% luminal B, and 4.8% Her2-enriched carcinomas.

An MD Anderson Cancer Center Study of 3138 breast cancer patients in stages IA-IIA reported 79.3% ER-positive tumors, 64% PR-positive tumors, and 11.5% Her2-positive tumors [39]. A study of 2214 consecutive breast cancer cases in Switzerland between 2015 and 2018 revealed 88.16% ER-positive, 77.46% PR-positive, 8.85% triple negative, and 12.88% Her2-positive cancers [78]. Our breast carcinoma cohort contained 80.8% ER-positive, 72.5% PR-positive, 14.1% triple negative, and 11.8% Her2-positive tumors.

The most common breast carcinoma metastatic sites in our study were bones, liver, pleura, lung, and brain. This is in general agreement with published data [78].

Our study results are in agreement with universally accepted importance of invasive breast carcinoma size as a powerful prognostic factor. New diagnostic modalities and surveillance health care algorithms made much improvement in detection of small size breast cancers. Still, our findings showed that these efforts in the community under study are not sufficient. Although the median tumor size for the entire study cohort was 1.7 cm, the average tumor size was more than 2 cm in premenopausal and postretirement age groups, particularly in the former group (nearly 2.5 cm average tumor size).

**Other Breast Malignancies:** In 1962, The Memorial Hospital for Cancer and Allied Diseases, New York, NY reported the first estimate of the incidence of primary breast lymphoma as 0.18% of all breast malignancies [79]. Wiseman and Liao (1972) reported the incidence rate of primary breast non-Hodgkin lymphoma as 0.53% [80]. One out of ten of our non-Hodgkin lymphoma cases was secondary, therefore, we report an incidence rate of 0.48% for primary breast non-Hodgkin lymphomas. One primary Hodgkin lymphoma case presented as a nodular sclerosing classical variant that started in the breast and two years later progressed to supraclavicular lymph nodes and then to mediastinal and abdominal lymph nodes. Our breast primary Hodgkin lymphoma rate is 0.05% of all invasive breast malignancies.

Breast sarcomas are rare and, excluding phyllodes tumor, are reported to comprise from less than 0.1% to 1% of all breast malignancies [33,81-84]. The incidence of angiosarcomas is reported to be 0.04%-0.2% [33,81,84].

The majority of angiosarcomas arise in breast of patients with a prior history of breast carcinoma occurring with a peak incidence 5-10 years after the initial diagnosis [81-83]. The same is true for sarcomas, and for both tumors is usually attributed to breast irradiation [81]. In our study cohort, angiosarcoma and pleiomorphic sarcoma of the breast comprised 0.11% and 0.05% of all breast malignancies, respectively, and two out three occurred 11 years after ipsilateral breast carcinoma treated with irradiation.

Mammary phyllodes tumors account for 0.3%-1% of all primary breast tumors [85], and 12%-18% of them are malignant [85,86]. As well, there are reports indicating that malignant phyllodes tumors comprise 0.3% of all breast malignancies [33]. In our dataset, malignant phyllodes tumors represent 0.11% of all breast malignancies. We found the same incidence (0.11%) for breast metastases from extramammary malignancies. This does not contradict other reports indicating a 2% or less incidence rate of malignancies metastatic to the breast because the majority of these are metastases from the opposite breast [87,88].

Primary breast malignant melanoma is rare, accounting for < 0.5% of breast cancers and 3%-5% of all malignant melanomas [89,90]. Our single case in this study occurred in 77-year-old man.

Our results presented here are in general agreement with published data from other studies and support the conclusion that Breast Conference lists containing every new breast cancer case may serve as a valuable source for accurate breast cancer data analysis in the population under care.

**Breast Cancer Center Survival Analysis:** Our data demonstrated very good overall survival of 92% at 5 years and 84.1% at 10 years. Relative overall survival was 94.8% and 90.4%, respectively. For comparison, a large cohort study from Germany in 2014 reported 79.3% 5-year overall survival [54], and the US SEER data from 2017 reported relative overall survival of 91.4% at 5 years and 86.2% at 10 years [23.34].

We could not compare our OS to OS determinations made prior to introduction of the HOCC multidisciplinary Breast Cancer Center because follow-up data was not available in EMR for most patients treated before 2009. Instead, we compared OS of breast cancer patients over two consecutive five-year periods of Breast Cancer Center operation, and identified no significant difference - 93.2% and 92.5%, respectively.

The breast cancer death rate in the US decreased between 1990 and 2006 by 28.3% [91] and has continued to decline between 2006 and 2020 by an additional 11.7% [1]. Improving breast cancer overall survival was documented in Europe between 1999 and 201 [31] 2. The decline in breast cancer mortality was attributed to improved adjuvant therapy and early detection/screening, with therapy playing a slightly more important role [92]. Our study showed no trends regarding age or average tumor size at presentation. At the same time there was an increasing trend (albeit not statistically significant, $p = 0.08$) in the rate of cancers presenting with lymph node and distant metastases. We conclude that the demonstrated good overall survival in our study cohort was due to improved treatment and not due to improved detection. Premenopausal women, constituting 23% of our study cohort, had the largest average tumors at presentation (2.45 cm) in comparison to the 52-64 yo group (1.96 cm) and the >65 yo group (2.16 cm).

Mortality analysis revealed that age at diagnosis, tumor size, and distant metastases at diagnosis were all associated with significantly increased mortality for all studied age groups. In particular, distant metastases at diagnosis was associated with an HR of 21.07 for the <65 yo group and 8.9 for the 65+ yo group. Lymph node metastases that were shown as risk factors on univariate Cox analysis were no longer statistically significant risk factors on multivariate analysis. Degree of lymph node involvement is an important prognostic factor in breast cancer [31,93]. Also, it has been reported that with application of chemotherapy in T1 patients with micrometastases their survival is similar to node-negative patients [39]. In our study, we made no attempt to stratify the degree of lymph node involvement, and on multivariable analysis found that it did not represent a statistically significant risk factor in all age groups. It is our presumption that this finding represents the effects of treatment instituted to node-positive patients.

Breast cancer size and distant metastases status are important prognostic factors, and their influence on survival is well documented [34,78]. Our findings are in agreement with these generally established facts. Comparisons of plots of average tumor sizes and rates of LN/distant metastases showed that peaks do overlap. Increasing age at presentation was also reported to be associated with high breast cancer mortality [94]. Our study also showed that advancing age was a significant risk factor for all breast cancer age groups.

## Conclusions

1. Breast conference lists that include all new breast cancer cases are a valuable source for accurate breast cancer analysis in the population under care.
2. Multidisciplinary Breast Cancer Center care is associated with above average cancer patient OS.
3. No difference in OS at present found between single tumor and multiple tumors groups.
4. As prognostic factors, lymph node metastases may not be as significant as tumor size, distant metastases, and age.
5. More attention ought to be called to early breast cancer detection particularly in premenopausal and postretirement age groups.
6. At present, multidisciplinary breast cancer care alone may not lead to further improvements in survival. Improvements in early breast cancer detection, would seem to have the greatest promise for improving survival.

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