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Clinicopathologic Presentation of Asian-Indian American (AIA) Women with Stage 0, I & II Breast Cancer

Malay Rao,

Department of Radiation Oncology, The Cancer Institute of New Jersey & UMDNJ/Robert Wood Johnson Medical School, 195 Little Albany Street, New Brunswick, NJ 08903, USA

Atif J. Khan,

Department of Radiation Oncology, The Cancer Institute of New Jersey & UMDNJ/Robert Wood Johnson Medical School, 195 Little Albany Street, New Brunswick, NJ 08903, USA

Meena S. Moran,

Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, CT, USA

Kim M. Hirshfield,

Department of Medicine, Division of Medical Oncology, The Cancer Institute of New Jersey & UMDNJ/Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Shridar Ganesan,

Department of Medicine, Division of Medical Oncology, The Cancer Institute of New Jersey & UMDNJ/Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Bruce G. Haffty, and

Department of Radiation Oncology, The Cancer Institute of New Jersey & UMDNJ/Robert Wood Johnson Medical School, 195 Little Albany Street, New Brunswick, NJ 08903, USA

Sharad Goyal

Department of Radiation Oncology, The Cancer Institute of New Jersey & UMDNJ/Robert Wood Johnson Medical School, 195 Little Albany Street, New Brunswick, NJ 08903, USA

Sharad Goyal: goyalsh@umdnj.edu

Abstract

Although numerous studies have looked at cancer incidence and survival in Asian Indian-American (AIA) patients, there is a paucity of data regarding clinicopathologic presentation of cancer in this ethnically diverse population. After receiving IRB approval, AIA patients of Indian and Pakistani descent who presented with Stage 0, I, & II breast cancer to our facility were identified. Charts were extracted for clinical and pathologic variables in addition to outcomes data. Standard statistical analyses were performed using SAS (v 9.1). The population ($n = 50$) consisted of 86% Indian ($n = 43$) and 14% Pakistani ($n = 7$). The median age at diagnosis was 52 (range 25–79). Sixty-three percent of tumors were detected after discovery of a palpable mass while 36% had a mammographically detected mass. Stage 0, I & II distribution was 14, 42 and 44%, respectively. The median tumor size was 1.5 cm (range 0.2–4.5 cm). ER, PR, and HER2 were positive in 69, 67, and 24% of AIA patients, respectively; 21% were triple-negative. Treatment data shows that 60% underwent lumpectomy ($n = 29$), 39% underwent mastectomy ($n = 19$), 74% received hormonal therapy ($n = 26$) and 55% received chemotherapy ($n = 30$). To our knowledge, this is the

first detailed report of the clinicopathologic presentation of Asian-Indian American women with breast cancer at a single institution. Of note, AIA women were more likely to present with palpable masses and at a younger age. This differs from Caucasian women and may indicate a social or cultural barrier to routine screening mammograms and possibly a biologically more aggressive tumor.

Keywords

Asian-Indian American; Ethnic disparity; Early stage breast cancer; Radiation therapy (RT); Breast conserving therapy (BCT)

Background

In 2009, the incidence of breast cancer is estimated to be 182,460, representing nearly 25% of all newly diagnosed malignancies. Further, breast cancer is responsible for nearly 15% of all cancer deaths with an estimated 40,480 deaths in 2008, making it the second leading cause of death after lung cancer [1].

To our knowledge, females of all ethnicities share the burden of breast cancer, including Caucasians, African-Americans, Hispanics and Asian-Americans. Among Asian-American women, the most common malignancy and the second leading cause of cancer mortality is breast cancer [2, 3]. However, Asian-American is an umbrella term that encompasses various nationalities and geographic locales—Chinese, Filipino, Korean, Japanese, Vietnamese, Indian, Pakistani, and more. Currently there are more than two million people in the United States who identify themselves as Asian Indian or Pakistani, and this number is rapidly growing [4]. There is a paucity of ethnicity based cancer data and it is unreasonable to assume data derived from largely Caucasian populations is directly congruent with an AIA population. In fact, in an effort to eliminate statistical discrepancies, starting in the year 1988, the Surveillance Epidemiology and End Results (SEER) Cancer database has established a separate subcategory under race and ethnicity to identify the incidence of cancer specific to the Asian Indian and Pakistani population living in the United States [5].

A recent American Community Survey revealed that from 2000 to 2007, the AIA population in the United States grew 53%, the highest for any Asian American community. Furthermore, according the 2007 Census Bureau, AIAs are the highest-educated and highest-paid ethnic minority in the US, with close to 35,000 Indian American doctors. However, despite their high socioeconomic status, the majority of AIA women report having inadequate breast cancer knowledge [6]. It therefore becomes important to learn breast cancer presentation in AIA women to identify possible reasons for limited breast cancer knowledge in a well-educated and economically stable minority group.

In order to develop a better understanding of their disease presentation, the purpose of this project was to determine the clinicopathologic characteristics of Asian-Indian American (AIA) women with stage 0, I & II breast cancer. We then compared the subgroup of AIA patients that underwent breast conserving therapy consisting of lumpectomy followed by radiation therapy to Caucasian and African American controls.

Materials and Methods

After approval by the institutional review board, we identified a total of 50 Asian Indian American (AIA) patients that presented with Stage 0, I or II breast cancer to The Cancer Institute of New Jersey (CINJ) between 1997 and 2009 using the institutional tumor registry

and radiation oncology database. Inclusion criteria was described as Asian Indian and Pakistani women of any age, currently residing in New Jersey with a known diagnosis of breast cancer Stage 0, I or II. Data extracted included demographic information, breast cancer risk factors, pathologic information, and treatment received, including type of surgery, use of chemotherapy or hormonal therapy, and use of radiotherapy. When available, we collected the initial method of tumor detection, specifically whether the tumor was detected using screening mammography or by physical exam (either physician or self breast exam).

The date of diagnosis was defined as the date of last definitive surgical procedure. The size of the primary tumor was considered to be the largest tumor diameter reported by the pathologist after surgical excision. Lymph node status was determined by histological evidence of lymph node metastasis. Data regarding presence or absence of a positive sentinel lymph node and the number of nodes positive from the total number of lymph nodes examined was noted. Breast cancer was staged according to the current breast cancer staging/classification using the TNM system. The tumor grade was identified based on pathology report and given an overall designation of either Grade 1, 2 or 3 consistent with the following definitions: Grade 1—low grade/well differentiated tissue (default); Grade 2—moderately differentiated tissue; Grade 3—poorly differentiated tissue. Grading was based on both nuclear and histological features of the tumor—in case of discrepancies between the two grades, the higher of the two grades was assigned to the patient's overall grade status. Histology, such as invasive lobular, invasive ductal, medullary, colloid/mucinous, adenocarcinoma, metaplastic, ductal carcinoma in situ and lobular carcinoma in situ, were also noted. The margin status was recorded “positive” if the tumor cells were found within 1 mm of the tumor's excised border, “negative” if the tumor cells were at least two or more mm away from the specimen's border and “close” if tumor cells were found between 1 and 2 mm of the specimen's excision boundary.

Tumor characteristics such as status of estrogen receptor (ER), progesterone receptor (PR), HER2 receptor, BRCA 1/2 mutation status, lymphovascular invasion (LVI) and extracapsular extension (ECE) was recorded based on surgical pathology report. Presenting features such as laterality (left, right, bilateral), multicentricity (presence of more than one, noncontiguous, tumor within the same breast at the same time) and the quadrant location of the tumor was also recorded.

Further, we examined the nature of therapy the patient received with particular attention to the type of surgery performed (simple mastectomy, modified radical mastectomy, lumpectomy) and the type of axillary surgery performed (sentinel node, full dissection, or both sentinel node and full dissection). The combination and regimen of drugs used for administration of systemic chemotherapy and/or adjuvant hormone therapy and its sequence in relation to surgery (adjuvant vs. neoadjuvant) was collected. We also identified any instances in which the patient was recommended chemotherapy but refused treatment. However, the reason for refusal was not available. Likewise, data on adjuvant radiation therapy was gathered from the patient's charts to include radiation fields, radiation dose and start date of radiation therapy.

Of the 50 AIA patients, those that received breast conserving therapy followed by radiation therapy were matched with Caucasian and African American case-controls that also received breast conserving therapy followed by radiation therapy. The radiation oncology database at Yale University was the source used to match the controls based on their age at the time of cancer diagnosis and stage of breast cancer and these reports have been previously published [7].

Statistical analysis was only performed on the known data points. All unknown data values are indicated in Tables 1 and 2. A computer program package SAS (Version 9.1, SAS Institute, Cary, NC) was used for all statistical testing and management of the database.

Results

Demographics and Clinical Data

The population ($n = 50$) consisted of 86% Indian ($n = 43$) and 14% Pakistani ($n = 7$). The median age at diagnosis was 52 (range 25–79). Forty-four percent of patients were younger than 50 years of age (refer to Table 1 for details).

At time of presentation, 63% of patients had a palpable mass ($n = 27$) while 36% ($n = 16$) had a mammographically detected mass. The initial detection method was unknown in 14% patients ($n = 7$). Four patients reported a prior history of contralateral breast cancer (three in the right breast, one in the left breast). Only one of these patients had their second cancer diagnosis detected by mammography and the other three were detected upon physical exam. The majority of patients (67%) did not have a family history of cancer, 16% of patients had a first-degree relative with breast, ovarian or uterine cancer and 18% ($n = 8$) of patients had a second-degree relative with these cancers. Thirty-one percent ($n = 10$) of AIA patients reported to have used oral contraceptives and/or hormone replacement therapy. The median age of menarche was 13. The cause of menopause when known ($n = 22$), was physiologic in most women 55% ($n = 12$), with surgical or chemotherapy induced menopause in 10 patients, making the median age at menopause 50.

AIA patients presented as stage 0, I & II in 14% ($n = 7$), 42% ($n = 21$) and 44% ($n = 22$), respectively at our institution. Among those with Stage II disease, 17 presented with Stage IIa disease and six with Stage IIb disease. About 22% ($n = 11$) of patients had lymph node-positive disease. Tumors were more likely to present unilaterally in the right breast 71% ($n = 34$) than in the left breast 29% ($n = 14$) with no incidence of bilateral tumors in our population. The most common location of the tumor was in the upper outer quadrant (51%). Eighteen percent ($n = 8$) presented with multi-centric disease of the breast.

Pathologic and Molecular Features

The tumor characteristics of our AIA women with early stage breast cancer are as follows (Table 2). The median tumor size was 1.50 cm (range 0.2–4.5 cm). All patients had histological evidence of invasive breast carcinoma with early stage (I/II) disease.

Invasive ductal carcinoma and ductal carcinoma in situ (DCIS) were found in 82 and 13% of patients, respectively; there were no cases of invasive lobular carcinoma in our population. Nuclear & histological grade 1, 2 & 3 features were present in 7, 36 and 57% of patients. Lymphovascular invasion (LVI) was present in 23% of patients. Estrogen receptor (ER), progesterone receptor (PR), and HER2 were positive in 69, 67, and 23% of AIA patients, respectively; 21% were triple-negative ($n = 8$). Two patients were found to have a positive BRCA mutation; both of whom presented with Stage II disease.

Treatment Statistics

For surgical treatment of tumors, the overall majority of patients, 60% ($n = 29$), underwent lumpectomy and 39% ($n = 19$) underwent mastectomy. In particular, 14 were modified radical mastectomy and five were simple mastectomy procedures. Hormonal therapy and chemotherapy was administered in 74% ($n = 26$) and 55% ($n = 27$) patients, respectively. Four patients refused chemotherapy although it was recommended. Likewise, there was no

data on administration of hormonal therapy in four patients with positive estrogen or progesterone receptor status.

BCS + RT Subgroup and Matched Controls

Twenty-eight AIA patients out of the total 50 received breast conserving surgery followed by radiation therapy. After matching this subgroup by their age and stage to Caucasians and African Americans (AAs) that had also undergone BCS + RT, the following was observed (Table 3). Forty-six percent of tumors were detected via physical exam in the AIA subgroup compared to the 14% in Caucasians and 11% in AAs. Invasive ductal carcinoma with intraductal features was found in 64% ($n = 18$) AIA, 43% Caucasians ($n = 12$) and 43% African Americans ($n = 12$). An additional 18% AIAs ($n = 5$), 36% Caucasians ($n = 10$) and 43% African Americans ($n = 12$) had infiltrating ductal carcinoma without DCIS features. Adenocarcinoma was seen only in an AIA patient ($n = 1$) while infiltrating lobular carcinoma ($n = 2$) was found only in Caucasian patients.

Estrogen receptor positivity was seen in 74% ($n = 20$), 71% ($n = 20$) and 55% ($n = 11$) of AIAs, Caucasians and AAs, respectively. Progesterone receptor positivity was seen in 69% ($n = 18$), 63% ($n = 17$) and 55% ($n = 11$) of AIAs, Caucasians and AAs, respectively. Her2 positivity was found in 13% AIAs ($n = 3$), 13% Caucasians ($n = 1$) and 17% AAs ($n = 1$). Adjunctive chemotherapy was administered to 54, 50 and 41% of AIAs ($n = 15$), Caucasians ($n = 14$) and AAs ($n = 11$), respectively. Likewise, adjunctive hormonal therapy was administered to 69, 57 and 29% of AIAs ($n = 18$), Caucasians ($n = 16$) and AAs ($n = 8$), respectively. Final margin status was positive in 6% of AIAs, 7% Caucasians and 11% AAs and final margin status was close (within 2 mm) in 39% of AIAs, 11% of Caucasians and 14% of AAs. Strong family history of breast cancer was seen in 14% AIAs, 15% Caucasians and 19% AAs while another 11% AIAs, 19% Caucasians and 27% AAs had moderate family history of breast cancer.

Discussion

In India, one out of forty women develops breast cancer, but in the US, one out of every eight Asian Indian women will get the disease, the highest incidence in the world [8]. Studies have reported that, after emigration from South Asia, breast cancer rates in AIA women have steadily increased to mimic breast cancer incidence in the general US population. This is more commonly seen when AIA women have lived in US for longer periods of time and adapt to US lifestyle and diets [9, 10]. Hence, it is imperative to identify and understand disparities in breast cancer within AIA population.

To our knowledge, this is the first study that examined the clinicopathologic presentation of breast cancer in an Asian-Indian American (AIA) population. Studying the clinical characteristics and biological aspects of this disease in AIA women will allow us to uncover prognostic factors that may affect screening, treatment and outcomes in this ethnically diverse subgroup. The high density of AIA minorities in the state of New Jersey provides us with a geographic advantage to study the development of breast cancer within this population.

A previous study on breast cancer in Caucasians and African Americans with the same ability to access health care, reported the median age of breast cancer diagnosis at 50 years in AA versus 58 years in Caucasians [11]. A younger age of presentation (median age 52 years) in our study can go along with a more aggressive tumor (grade) or it may be that there is a genetic counterpart in AIA patients such as BRCA mutations or other susceptibility gene mutations. Two patients from our study that tested positive for BRCA mutation were retained in our analysis of median age at diagnosis, although, the number of patients offered

BRCA testing and the clinical indication for offering the test is unknown. Additional studies that examine genetic information in Asian Indian and Pakistani women would be useful. Indeed, Rashid et al. reported a high rate of BRCA mutations in Pakistani women with family histories of breast or ovarian cancer [12].

In an effort to increase early detection of breast cancer, the American Cancer society recommends yearly mammograms at age 40 and continuing as long as the woman is in good health [13]. Results from our institution show that in AIA women, only 36% of breast cancers were detected via mammography screening versus 63% were detected by physical exam, performed either by the patient or by the physician. In the BCS + RT matched subgroup, again we see that AIA women (54%) are less likely to have their tumors detected via mammography screening than are Caucasians (86%) and African Americans (89%). Data from our AIA population in entirety and from the comparison group emphasizes that the mammography-screening rate in AIA population is still well below the Healthy People 2010 target rate of 70% [14].

We consider language and cultural barrier as a potential issue that may inhibit AIA women from seeking mammographic screening. However, given the large number AIA physicians in the US (35,000) that can help AIA women overcome the language and cultural issues, it seems counterintuitive for AIA women to lag behind their Caucasian counterparts in accessing preventive measures for breast cancer care. Socioeconomic status (SES) may directly affect patient's access and financial affordability to health care. Hence, we explored socioeconomic status (SES) as a potential cause of underutilization of mammographic screening in AIA women. The US Census Bureau reports the median income for the average AIA household at \$63,669, which is well above the median income for Caucasian population (\$44,687) and other minority groups including African Americans [15]. Therefore, it is unlikely that SES is a cause for screening delay and advanced presentation in AIA women. Similarly, other studies have reported that despite higher income, more education and better insurance coverage, AIA women still have lower rates of breast cancer screening [16, 17]. In addition, Asian women diagnosed with breast cancer were more likely to receive a diagnosis at a later stage and to have larger tumors at the site than white women [16, 17]. Wu et al. have studied the health beliefs and practices related to breast cancer screening in AIA and have found that fewer AIA women perceived themselves as being vulnerable to getting breast cancer and did not view breast cancer as a serious illness. Common barriers to screening for AIA women are being examined by a male practitioner, having breast touched by a stranger and being exposed to unnecessary radiation [14].

Another reason for AIA patients to present with larger breast masses compared to Caucasians, could be poor self detection methods. A study of breast cancer screening practices in Asian Americans found that only 5% of Asian Indian women practiced monthly breast self-examination, as compared with 23 and 51% of Chinese and Filipino women, respectively [18]. Whether or not the possibility of a monthly breast self-exam improving outcomes of breast cancer in AIA needs to be further examined.

While our study focuses on early stage breast cancer (Stages 0, I and II) in AIA women, it is worthwhile to consider the properties of late stage breast cancer (Stages III and IV) and of overall breast cancer survival in AIA women. Hossain et al. analyzed the US National Cancer Institute Surveillance Epidemiology and End Results (SEER) database from 1988 to 2003, and found that breast cancer is the most common cancer in both non-Hispanic white females (32%) and Asian Indian American females (38%) in the US [5]. This study also reported better overall survival among the AIA subgroup compared to Caucasians for breast and other common cancers—including colon, lung, and prostate.

On the contrary, another study that analyzed the same SEER database found that among common cancers sites, survival was generally better among AIA than Caucasians with the notable exception of breast cancer, for which Caucasians had slightly better survival [19]. Hence, the issue of how breast cancer survival in AIA women compares with Caucasian women is currently unresolved because of the conflicting results from the two preceding studies. That said, consideration should still be given to the SEER data since the relatively poor breast cancer survival for Asian Indian/Pakistani women appears to result from their tendency to present with more advanced disease.

A closer look at the case-control results shows that AIA patients (25%) are more likely to align with Caucasians (34%) than with AAs (46%) when examining the presence of strong or moderate family history. Both AIA (73%) and Caucasian (75%) subgroups are more likely to present with tumor in the right breast than the AA subgroup (56%). Intra-ductal carcinoma is more likely to present with ductal carcinoma in situ features in AIA (64%) than in either Caucasians (43%) or AAs (43%). The AIA subgroup's estrogen and progesterone receptor positivity is more similar to that of the Caucasian subgroup than the AA subgroup. No major difference in Her2 positivity is seen in either subgroups (Table 3). Treatment analysis shows that AIA are just as likely as Caucasians to have received chemotherapy, however, both Caucasians and AIA women were more likely than AA women to have received chemotherapy. Additional treatment data reveals that AIA women (69%) were the most likely to have received hormonal therapy followed by Caucasians (57%) and AAs (29%) (Table 3).

However, it is important to note several limitations of this study. First, patients were seen at a National Cancer Institute Designated Comprehensive Cancer Center and this may reflect bias in terms of patients who choose to seek care or who were referred to a tertiary cancer care center. Furthermore, patients treated at the Yale University Department of Radiation Oncology were used for case-controls as the data was readily available. In comparison, data from our institution may reflect regional differences in socio-economic status, breast cancer presentation or care after diagnosis. Further, the case-control subgroup offers limited data for comparison of the remaining pathologic and molecular features. In particular, characteristics such as pathologic grade, nodal status, lympho-vascular invasion, BRCA mutation status and risk factors (age of menarche and menopause, history of oral contraceptive use and prior history of breast cancer) were not available for the case-controls. Hence, additional studies that include these parameters are needed in order to compare the biological aggressiveness of breast tumors in AIA women to Caucasian and AA women.

Conclusions

This study adds to our overall understanding of breast cancer presentation in the AIA minority subgroup. Further, results from the case-control match in the subset that underwent BCS + RT emphasize critical differences and similarities in breast cancer presentation in AIA women. Our data on breast cancer detection method supports findings from earlier studies that report underutilization of screening mammography in AIA women. This calls for a need to increase awareness of breast cancer in AIA women, education in technique for proper breast self-exam and stress the importance of prevention with mammography screening. Through active patient participation, it may be possible to reduce advanced stage or larger size presentation of breast cancer in AIA women.

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Table 1

Clinical features of early stage breast cancer in Asian Indian American Women

Features	Subset	Number of patients (<i>n</i>)	Percent (%)
Race	Indian	43	86
	Pakistani	7	14
Age at diagnosis	Mean 51.7	Median 52	Range 25–79
	20–29	1	2
	30–39	6	12
	40–49	15	30
	50–59	17	34
	60–69	7	14
	70–79	4	8
Prior history of breast cancer	Yes	4	9
	No	41	91
	Unknown	5	
Family history of cancer	Strong	7	16
	Moderate	8	18
	None	30	67
	Unknown	5	
Initial detection method	Physical exam ^a	27	63
	Screening mammogram	16	36
Laterality	Right	34	71
	Left	14	29
	Unknown	2	
Quadrant	Upper outer	19	51
	Upper inner	5	14
	Upper mid	4	11
	Other quadrants	9	24
	Unknown	13	

^aPhysical exam is defined as a breast self-exam and/or breast exam performed by a physician

Table 2

Pathologic and molecular features with adjuvant treatment statistics of early stage breast cancer in Asian Indian American Women

Features	Subset	Patients (n)	Percent
Tumor size (range 0.2–4.5 cm)	Mean 1.75 cm, median 1.50 cm, mode 1.50 cm	49	
	Unknown	1	
T stage	Tis	7	14
	T ₁	27	54
	T ₂	16	32
Nodal status	Negative	39	78
	Positive	11	22
Staging of primary	Stage 0	7	14
	Stage I	21	42
	Stage IIa	17	34
	Stage IIb	5	10
Surgical procedure	Lumpectomy	29	60
	MRM	14	29
	SM	5	10
	None	1	
	Unknown	1	
Final margins	Negative	12	26
	Positive	19	41
	Close	15	33
	Unknown	4	
Tumor type	DCIS	7	14
	LCIS	1	2
	IDC with DCIS	32	64
	IDC without DCIS	8	16
	Adenocarcinoma	1	2
	Mucinous/colloid	1	2
IDC grade	1	4	8
	2	15	31
	3	29	60
	Unknown	2	
ER status	Positive	33	69
	Negative	15	31
	Unknown	2	
PR status	Positive	32	67
	Negative	16	33
	Unknown	2	
HER2 status	Positive	9	24
	Negative	29	76

Features	Subset	Patients (n)	Percent
BRCA status	Unknown	12	
	Positive	2	4
LVI	Present	12	26
	Absent	34	74
Chemotherapy	Unknown	4	
	Administered	27	55
	Not administered	18	37
	Recommended but refused	4	8
	Unknown	1	
Hormonal therapy in those with known receptor positivity	Administered	26	74
	Not administered but indicated	4	11
	Unknown	5	14

DCIS ductal carcinoma in situ; *ECE* extracapsular extension; *ER* estrogen receptor; *HER2* Herceptin receptor; *IDC* infiltrating ductal carcinoma; *LCIS* lobular carcinoma in situ; *LVI* lymphovascular invasion; *MRM* modified radical mastectomy; *OCP* oral contraceptive use; *PR* progesterone receptor; *SM* simple mastectomy

Table 3

Comparison of clinicopathologic characteristics of breast cancer in AIA, Caucasian and African American women in the BCS + RT subgroup after matching for age and stage

Features	AIA % patients (n)	Caucasian % patients (n)	AA % patients (n)
Initial detection method			
Physical	46 (11)	14 (3)	11 (2)
Mammography	54 (13)	86 (17)	89 (17)
Unknown	(4)	(8)	(9)
Laterality			
Right	73 (19)	75 (21)	56 (15)
Left	27 (7)	25 (7)	44 (12)
Unknown	(2)	(0)	(1)
Family history			
Strong	14 (4)	15 (4)	19 (5)
Moderate	11 (3)	19 (5)	27 (7)
None	75 (21)	66 (18)	54 (14)
Unknown	(0)	(1)	(2)
Histology			
DCIS	14 (4)	14 (4)	14 (4)
IDC with DCIS	64 (18)	43 (12)	43 (12)
IDC without DCIS	18 (5)	36 (10)	43 (12)
ILC	0 (0)	7 (2)	(0)
Adenocarcinoma	4 (1)	0	(0)
Estrogen receptor			
Positive	74 (20)	71 (20)	55 (11)
Negative	26 (7)	29 (8)	45 (9)
Unknown	(1)	(0)	(8)
Progesterone receptor			
Positive	69 (18)	63 (17)	55 (11)
Negative	31 (8)	37 (10)	45 (9)
Unknown	(2)	(1)	(7)
Her2			
Positive	13 (3)	13 (1)	17 (1)
Negative	87 (20)	87 (7)	83 (5)
Unknown	(5)	(20)	(22)
Chemotherapy			
Administered	54 (15)	50 (14)	41 (11)
Not administered	46 (13)	50 (14)	59 (16)
Unknown	(0)	(0)	(1)
Hormonal therapy			
Administered	69 (18)	57 (16)	29 (8)
Not administered	31 (8)	43 (12)	71 (20)

Features	AIA % patients (<i>n</i>)	Caucasian % patients (<i>n</i>)	AA % patients (<i>n</i>)
Unknown	(2)	(0)	(0)
Final margin status			
Positive	6 (5)	7 (2)	11 (3)
Negative	55 (11)	82 (19)	75 (18)
Close	39 (11)	11 (3)	14 (4)
Unknown	(1)	(4)	(3)