Breast Cancer Survival in Sri Lanka

Jayantha Balawardena, MBBS, MD[1]; Thurairajah Skandarajah, MBBS, MD[2,3]; Wasantha Rathnayake, MBBS, MD[2,3]; and Nuradh Joseph, MBBS, MD[3,4]

abstract

PURPOSE In this study, we report survival data of the largest cohort of patients with breast cancer in Sri Lanka.

PATIENTS AND METHODS All female patients with histologically confirmed breast cancer treated at a single unit at the National Cancer Institute of Sri Lanka between 1994 and 2006 were included in the study. Clinical records were reviewed and data obtained on the following clinical and pathologic factors: age, histology, stage at presentation, grade, and immunohistochemistry profile. Treatment details such as type of surgery and use of systemic chemotherapy, hormonal therapy, trastuzumab, and radiation therapy were also collected. In localized cancer, disease-free survival (DFS) was the primary end point, while in patients who presented with de novo metastases, progression-free survival (PFS) was the primary end point.

RESULTS A significant proportion of patients presented with de novo metastases (14%) and locally advanced disease (18%). While 57% of patients had hormone-sensitive tumors, human epidermal growth factor receptor 2 overexpression was seen in 14%, and 29% had triple-negative tumors. Only 3% of patients with localized disease were treated with breast-conserving surgery, with the rest undergoing modified radical mastectomy. The 5- year DFS rate was 71.6% (95% CI, 69.2 to 74.0) in patients with localized disease. The median PFS in patients with metastatic disease was 20 months (95% CI, 18 to 22 months), while the median overall survival was 30 months (95% CI, 32 to 35 months). On multivariable analysis, immunohistochemical group and stage were prognostic factors in localized disease, while in patients with metastases, immunohistochemical group and tumor grade were associated with PFS.

CONCLUSION More effective screening and early detection programs along with increasing breast-conserving surgery will improve breast cancer outcomes in Sri Lanka.

INTRODUCTION

Breast cancer is the most common cancer among females in Sri Lanka.[1,2] According to registry data, its incidence is rising, and approximately 3,000 new cases are diagnosed each year.[2] Cancer services have expanded significantly within the public-funded state health system in Sri Lanka, with general surgical and medical oncology centers being available in district general hospitals throughout the island, but radiation facilities are restricted to seven provincial hospitals in the country.[1,3] There are no dedicated breast surgical units in the country, although nine surgical oncology departments in provincial hospitals deliver specialized care to patients with breast cancer. Systemic treatment and radiation therapy are delivered by clinical oncologists who are trained in both medical and radiation oncology.[3]

There is no established mammography screening program in Sri Lanka. Early detection with clinical breast examination is offered to all women between 50 and 70 years of age through well women clinics conducted by public health midwives, but its use is low.[1]

There are a paucity of data on survival of patients with breast cancer in Sri Lanka in addition to the distribution and prognostic significance of variables such as immunohistochemistry parameters, stage at presentation, histology type, tumor grade, and type of surgery in the local setting. A higher prevalence (30%-40%) of triple-negative and high-grade tumors have been reported in Sri Lankan patients with breast cancer, a finding that is consistent with data from other South Asian countries.[4-7] Although previously, the prognostic significance of Nottingham grade and St Gallen risk stratification groups have been validated in a cohort of patients with breast cancer treated in the Southern Province of Sri Lanka,[6,7] these studies were limited to patients with localized disease.

CONTEXT

Key Objective

In this study, we report clinical, pathologic, and therapeutic data as well as survival outcomes of a cohort of > 2,000 patients with breast cancer treated at the National Cancer Institute from 1994 to 2006, representing the largest analysis of breast cancer survival in Sri Lanka.

Knowledge Generated

We report a reasonably satisfactory 5-year disease-free survival rate of approximately 71% in patients with localized disease, despite many resource limitations. However, > 30% of patients presented with stage III and IV disease, and just 3% of patients were treated with breast-conserving surgery.

Relevance

More effective screening and early detection programs along with improved access to better quality radiotherapy and establishment of multidisciplinary breast cancer teams are an urgent need to improve breast cancer outcomes in Sri Lanka.

In this study, we report clinical, pathologic, and therapeutic data as well as survival outcomes of a cohort of > 2,000 patients with breast cancer treated at the National Cancer Institute of Sri Lanka from 1994 to 2006. To our knowledge, this study represents the largest analysis of breast cancer survival in Sri Lanka.

PATIENTS AND METHODS

Study Population

All female patients with histologically confirmed breast cancer treated at a single unit at the National Cancer Institute of Sri Lanka between 1994 and 2006 were included in the study. Clinical records were reviewed and data obtained on the following clinical and pathologic factors: age, histology, stage at presentation, grade, and immunohistochemistry profile. Treatment details such as type of surgery and use of systemic chemotherapy, hormonal therapy, trastuzumab, and radiation therapy were also collected. Patients with incomplete staging and treatment data were excluded from the study.

Diagnosis and Staging

Patients underwent triple assessment with clinical examination, breast ultrasound, and fine-needle aspiration cytology at diagnosis. Core biopsy was not performed in most patients because it was not standard practice during the period in which the study population was treated. Although mammography was available, access was often limited, even in the diagnostic setting, and as a result, many patients could not undergo this investigation. Staging was performed by chest radiography and ultrasonography of the abdomen for all patients. Bone scintigraphy and computed tomography scanning were performed in patients with stage III tumors and those with symptoms suggestive of metastatic disease. Immunohistochemistry for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)/neu overexpression was performed in patients treated from the year 2000. Confirmation with fluorescent in situ hybridization

testing for gene amplification in patients with equivocal HER2/neu overexpression was done in some patients, with access being limited because of funding restrictions.

Surgical Treatment

Patients with localized disease were treated with modified radical mastectomy, or less commonly with a breast-conserving strategy of wide local excision of the primary tumor and axillary nodal clearance, followed by adjuvant radiotherapy. Sentinel lymph node biopsy was not standard practice during this period, and all patients underwent either axillary nodal sampling or level 1 and 2 axillary clearance.

Adjuvant Systemic Therapy

Adjuvant chemotherapy was offered to all patients with localized disease and good performance status with high-risk features, such as node positivity, high tumor grade, triple-negative or HER2/neu overexpression on immunohistochemistry, and tumor size > 5 cm. Standard regimens that comprised an anthracycline (doxorubicin or epirubicin) and/or taxanes (docetaxel or paclitaxel) were used.

All premenopausal patients with hormone-sensitive disease received adjuvant tamoxifen for 5 years. Because aromatase inhibitors were available only since 2005, most postmenopausal patients were also treated with tamoxifen for 5 years.

Adjuvant trastuzumab was offered to patients with HER2/neu overexpression from 2004. Trastuzumab was accessible through a special fund, but its high cost meant that restrictions applied. Even in the instances when it was available, long delays meant that it could only be delivered upon completion of adjuvant chemotherapy. Therefore, most patients received 3 weekly trastuzumab after adjuvant chemotherapy for 1 year as in the Herceptin Adjuvant (HERA) trial.[8]

Neoadjuvant Chemotherapy

Patients with locally advanced inoperable disease with tumor spread to skin (ulceration, peau d'orange, or satellite nodules) or chest wall were treated with neoadjuvant

chemotherapy, with regimens similar to what was used in the adjuvant setting. Neoadjuvant chemotherapy for operable breast cancer was not practiced in our setting during the study period.

Adjuvant Radiotherapy

All patients treated with breast-conserving surgery received whole-breast radiotherapy to a dose of 50 Gy in 25 fractions over 5 weeks. Postmastectomy radiotherapy to a dose of 44 Gy in 22 fractions over 4.5 weeks was delivered to patients with one or more of the following high-risk features: tumor size > 5 cm, tumor extension to skin or chest wall, lymph node positivity, positive deep margin, and treatment

TABLE 1. Clinical and Pathologic Characteristics of the Study Cohort

Characteristic	No. (%)
Mean age, years (range)	52 (18-89)
Histology	
Ductal	1,999 (95)
Lobular	61 (3)
Others	44(2)
Stage at presentation	
I	440 (24)[a]
II	812 (44)[a]
III	336 (18)[a]
IV	270 (14)[a]
Not available	246 (12)
Grade	
1	639 (30)
2	1,174 (56)
3	291 (14)
Immunohistochemistry	
ER+/PR+ HER2–	506 (53)[a]
ER+/PR+ HER2+	36 (4)[a]
ER–/PR– HER2+	95 (10)[a]
ER–/PR– HER2–	319 (33)[a]
Not available	1,148 (55)
Surgical treatment	
Mastectomy	1,761 (84)
Wide local excision	71 (3)
Unknown/biopsy only	272 (13)
Other treatment	
Chemotherapy	1,331 (63)
Hormonal therapy	1,637 (78)
Trastuzumab	51 (2)
Radiation therapy	1,649 (78)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2/neu overexpression or gene amplification; PR, progesterone receptor.

[a]Given as a proportion of patients with available data.

with neoadjuvant chemotherapy for locally advanced disease. All patients were treated with two-dimensional conventional planning in the cobalt teletherapy units because the first linear accelerator in Sri Lanka was commissioned only in 2007.

Treatment of Metastatic Disease

Patients with metastatic disease were treated with palliative intent. Hormonal therapy with tamoxifen (or rarely aromatase inhibitors in postmenopausal patients) was initiated in patients with hormone-sensitive disease, while others received systemic chemotherapy. As mentioned previously, trastuzumab became available for use in patients with HER2/neu overexpression in 2004. Palliative radiotherapy was delivered for relief of pain or pressure symptoms. In this setting, 30 Gy in 10 fractions over 2 weeks was the most common regimen. Treatment of the primary tumor with either palliative radiotherapy or mastectomy was undertaken for local symptom relief.

Analysis of Survival

Because metastatic breast cancer is incurable, these patients were analyzed separately from those with localized disease who were treated with curative intent. In patients with localized disease, disease-free survival (DFS), defined as time to either death or disease recurrence (local recurrence and/or systemic metastases) from diagnosis, was the primary end point, and survival was censored at 5 years. Progression-free survival (PFS), defined as the time to death or clinical and/or radiologic disease progression from diagnosis, was the primary end point in patients who presented with de novo metastatic disease.

In localized disease, univariable survival analysis was performed using Cox proportional hazards regression for the following variables: age, histology type, grade, stage, immunohistochemical group, and type of surgery. Variables with $P > .1$ were included in a multivariable analysis. In patients with metastatic disease, a similar analysis was performed for the following variables: age, histology type, grade, and immunohistochemical group.

Because trastuzumab was not freely available as a result of its high cost, some patients with HER2/neu-positive breast cancer did not receive the drug both in the adjuvant and in the metastatic setting. Therefore, a separate analysis was performed to determine the outcome with use of trastuzumab in patients with HER2/neu overexpression or amplification.

RESULTS

Clinicopathologic Data

Table 1 lists the clinical and pathologic characteristics of the study population. Most patients presented with stage II disease, while 14% of patients had de novo metastases at presentation. Because routine immunohistochemistry commenced in 2000, data were available only in 956 of 2,104 patients. Fifty-seven percent of patients had

hormone-sensitive disease, and 14% were found to have HER2/neu overexpression.

Modified radical mastectomy was the most common curative surgical treatment. Breast-conserving surgery was performed only in 3% of patients. Endocrine therapy was the most common systemic treatment option used, but this was because before 2000, patients received adjuvant tamoxifen on an empirical basis because immunohistochemistry was not available. Radiotherapy was used in 78% of patients, and only 51 (39%) of 131 patients with HER2/neu overexpression went on to receive trastuzumab.

The χ^2 test revealed a significant association between immunohistochemistry profile and stage at presentation ($P = .01$). As evident in Appendix Table A1, patients with stage I and II breast cancer had a higher proportion of hormone-sensitive disease. There was an increase in the proportion of patients with triple-negative disease in stage III and IV, while HER2/neu overexpression was also higher in patients with metastatic disease.

The association between tumor grade and stage at presentation showed a clear association between higher grade and advanced stage (χ^2 test $P < .001$; Appendix Table A2). Finally, hormone receptor expression was associated with lower tumor grade, while HER2/neu-positive and triple-negative tumors had a higher proportion of high-grade tumors (χ^2 test $P < .001$; Appendix Table A3).

DFS in Patients With Localized Disease

The 5-year DFS rate was 71.6% (95% CI, 69.2% to 74.0%) in patients with localized disease. The Kaplan-Meier survival curve for DFS in the whole population is shown in Appendix Figure A1. Figure 1 shows the DFS curves by immunohistochemical group, while Appendix Figure A2 illustrates DFS by stage. The results of univariable and multivariable analyses for DFS are listed in Table 2. Stage at presentation and immunohistochemical group were the only two significant prognostic variables on multivariable analysis, even though age and tumor grade were significant on univariable analysis. There was no difference in outcome between type of surgery (mastectomy v breast conservation) or histology type.

PFS in Patients With Metastatic Disease

The median PFS in patients with metastatic disease was 20 months (95% CI, 18 to 22 months), while the median overall survival was 30 months (95% CI, 32 to 35 months). Appendix Figure A3 shows the PFS survival curve for the whole population, while Figure 2 depicts PFS by immunohistochemical group. Table 3 lists the results of the univariable and multivariable survival analysis in which high tumor grade and triple-negative disease emerged as significant prognostic variables. We performed additional analysis with overall survival as the end point, and the outcome was the same.

Trastuzumab

In patients with HER2/neu overexpression or amplification, trastuzumab was used in 10 (43%) of 24 patients with metastatic disease and 39 (36%) of 107 patients with localized disease. In 2 patients who received trastuzumab, full staging data were not available. The respective survival plots in localized and metastatic disease are depicted in Appendix Figures A4 and A5, respectively. In patients with localized disease, use of trastuzumab resulted in a trend toward improved DFS (hazard ratio, 0.51; 95% CI, 0.24 to

FIG 1. Disease-free survival (DFS) by immunohistochemical group in patients with localized disease. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.
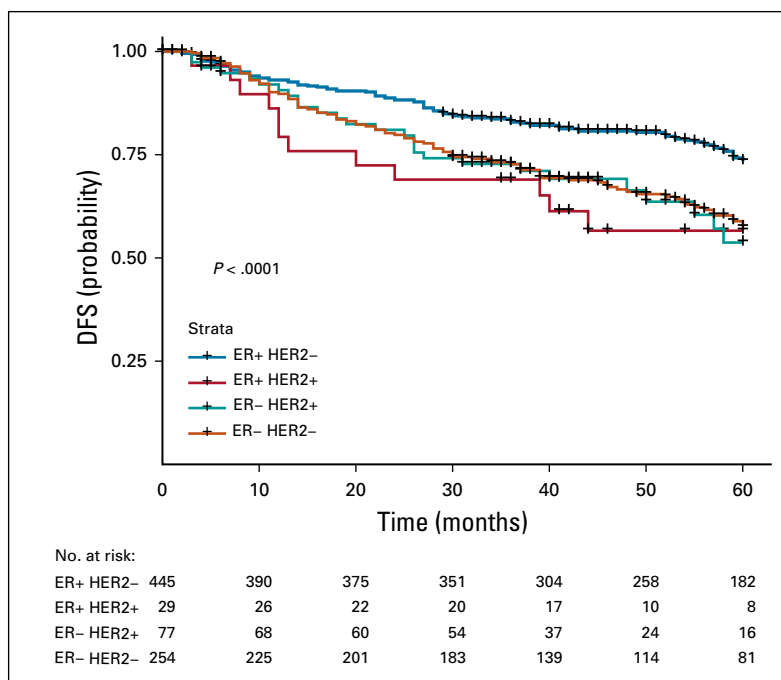
No. at risk:

ER+ HER2−	445	390	375	351	304	258	182
ER+ HER2+	29	26	22	20	17	10	8
ER− HER2+	77	68	60	54	37	24	16
ER− HER2−	254	225	201	183	139	114	81

TABLE 2. Disease-Free Survival Analysis of Patients With Localized Disease

Variable	Univariable Analysis		Multivariable Analysis	
	P	HR (95% CI)	*P*	HR (95% CI)
Age	< .001	1.03 (1.02 to 1.03)	.280	—
Stage	< .001	1.6 (1.4 to 1.6)	< .001	1.4 (1.2 to 1.7)
Grade	< .001	1.6 (1.2 to 2.0)	.29	—
Histology	.320	—	—	—
Type of surgery	.550	—	—	—
Immunohistochemical group	< .001	—	< .001	—
ER+/PR+ HER2–		1.0		1.0
ER+/PR+ HER2+		2.2 (1.2 to 3.9)		2.1 (1.1 to 3.8)
ER–/PR– HER2+		1.9 (1.2 to 2.9)		1.8 (1.2 to 2.8)
ER–/PR– HER2–		1.8 (1.3 to 2.4)		1.6 (1.2 to 2.2)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2/neu overexpression or gene amplification; HR, hazard ratio; PR, progesterone receptor.

1.08; *P* = .07), while there was no difference in PFS in patients with metastatic disease (*P* = .76).

DISCUSSION

In this article, we report survival outcome of the largest cohort of patients with breast cancer in Sri Lanka to our knowledge along with other clinical and pathologic data. Significantly, 14% of our patients presented with de novo metastases, while 18% presented with locally advanced (stage III) disease, and just 24% presented with stage I cancer. While our data are superior to that in some sub-Saharan African countries, where nearly 77% of patients present with stage III or IV disease, the proportion of patients who presented with de novo metastatic and locally advanced disease is more than twice the proportion in more developed countries, which highlights the urgent need for more robust and effective programs for screening and early detection of breast cancer in Sri Lanka.[9,10]

Another area of concern is the very low rate of breast conservation, with just 3% of patients being treated with this strategy, even though 24% of patients presented with stage I disease. Restricted access to diagnostic mammography was a major contributing factor because only three centers in the country had this facility during the study period. The government has now expanded mammography facilities to the provincial hospitals, which hopefully will lead to higher rates of breast conservation in the future. However, increasing awareness of both surgeons and patients

FIG 2. Progression-free survival (PFS) by immunohistochemical group in patients with metastatic disease at presentation. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.
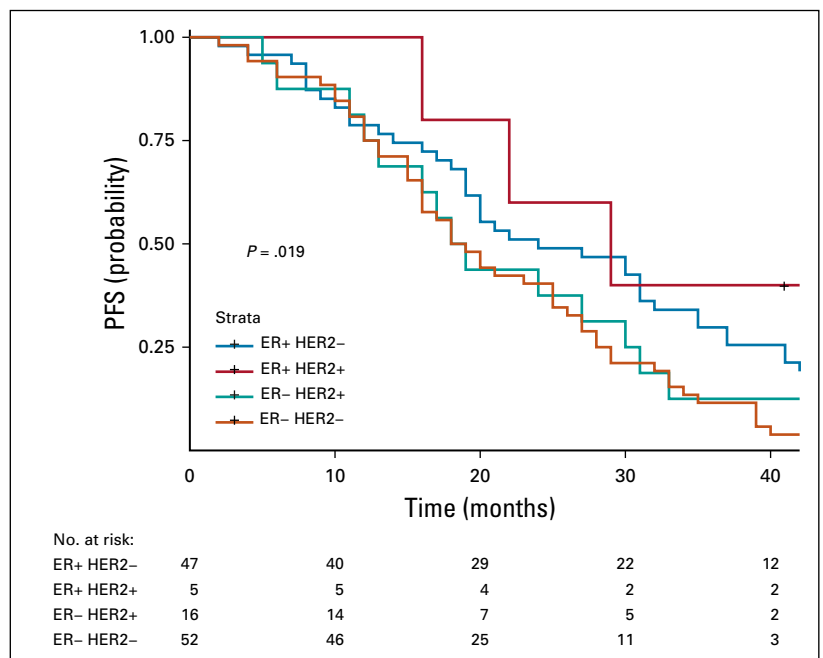
TABLE 3. Progression-Free Survival Analysis of Patients With Metastatic Disease

	Univariable Analysis		Multivariable Analysis	
Variable	P	HR (95% CI)	P	HR (95% CI)
Age	.110	—	.20	—
Grade	.020	1.40 (1.05 to 1.95)	.03	1.60 (1.05 to 2.50)
Histology	.450	—	—	—
Immunohistochemical group	< .001	—	—	—
ER+/PR+ HER2–	—	1.00	—	1.00
ER+/PR+ HER2+	.450	—	.23	—
ER–/PR– HER2+	.150	—	.33	—
ER–/PR– HER2–	.005	1.80 (1.20 to 2.80)	.04	1.60 (1.01 to 2.40)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2/neu overexpression or gene amplification; HR, hazard ratio; PR, progesterone receptor.

on the merits of breast-conserving surgery followed by adjuvant whole-breast radiotherapy as a treatment option that is in clinical equipoise with mastectomy is of pivotal importance.

Approximately 70% of our patients were treated with radiation therapy either in the adjuvant or in the palliative setting, which emphasizes the importance of this modality in the management of breast cancer. At the time the study population was treated, there were no linear accelerators in the country, and radiotherapy was only available in five centers.[1] At present, there are four commissioned linear accelerators in the country, five more machines have been procured by the government, and a program is under way to establish a radiation oncology center in each province. Availability of linear accelerators; easier access for radiotherapy; and establishment of multidisciplinary breast cancer teams comprising surgeons, oncologists, pathologists, and radiologists along with specialized nursing staff will be key to improving quality of care.

In terms of immunohistochemical profile, our results conform with previous studies and regional data, which show a slightly higher proportion of patients with triple-negative disease.[4-7] As expected, patients with hormone-sensitive breast cancer presented at an earlier stage at diagnosis and had a lower tumor grade. Immunohistochemical profile and stage at diagnosis were the only two prognostic factors on multivariable analysis in localized disease, while tumor grade in addition to

immunohistochemistry profile were significant in patients who presented with de novo metastases. While patients with hormone-sensitive disease had a better outcome, there was no difference between triple-negative and HER2/neu-positive tumors because only 36% of patients with HER2/neu-positive disease received trastuzumab as a result of funding restrictions. Even with small numbers, a nonrandomized comparison of patients with localized cancer revealed a trend toward superior DFS with the use of trastuzumab with a hazard ratio (0.51) very similar to what was observed in landmark clinical trials.[8] The advent of biosimilars has significantly reduced the cost of trastuzumab, and it is hoped that improved access will translate to better outcomes in the future.[11] The absence of benefit of trastuzumab in metastatic disease could be attributed to small numbers as well as to the drug being used after many lines of systemic therapy.

Being retrospective in design, our study was limited by incomplete and missing data, especially in relation to treatment toxicities, patient-related outcomes, and quality-of-life data. Nevertheless, we report a reasonably satisfactory 5-year DFS rate of approximately 71% in patients with localized disease, despite many resource limitations. In conclusion, more effective screening and early detection programs along with improved access to better quality radiotherapy and the establishment of multidisciplinary breast cancer teams are urgently needed to improve breast cancer outcomes in Sri Lanka.

AFFILIATIONS
[1]General Sir John Kotelawela Defence University, Kandawala, Sri Lanka
[2]National Cancer Institute, Ministry of Health, Maharagama, Sri Lanka
[3]Sri Lanka Cancer Research Group
[4]District General Hospital, Ministry of Health, Chilaw, Sri Lanka

CORRESPONDING AUTHOR
Nuradh Joseph, MBBS, MD, District General Hospital, Chilaw, Sri Lanka; Twitter: @nuradh, @slconcology, @slcancer; e-mail: m23355@pgim.cmb.ac.lk.

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AUTHOR CONTRIBUTIONS

Conception and design: All authors
Financial support: Wasantha Rathnayake
Administrative support: All authors
Provision of study material or patients: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: Jayantha Balawardena, Thurairajah Skandarajah, Nuradh Joseph
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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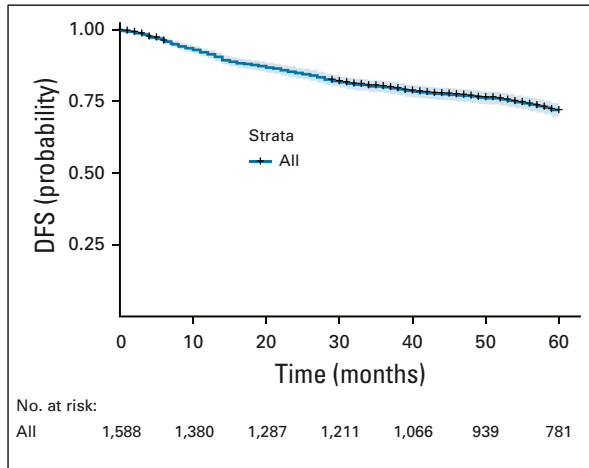
APPENDIX

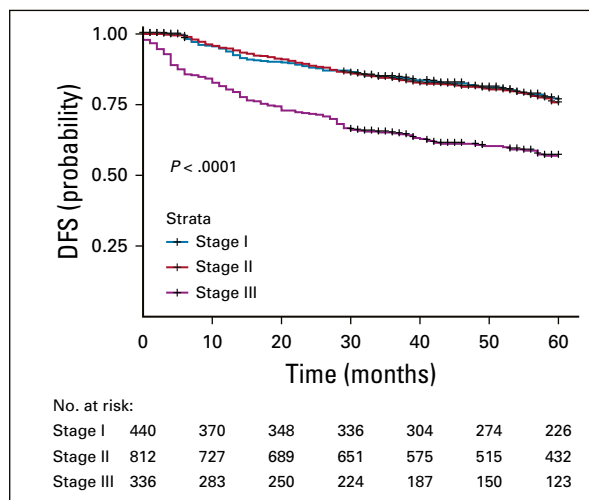**FIG A1.** Disease-free survival (DFS) in patients with localized disease.

No. at risk:

All	1,588	1,380	1,287	1,211	1,066	939	781

FIG A2. Disease-free survival (DFS) in patients with localized disease by stage at presentation.

No. at risk:

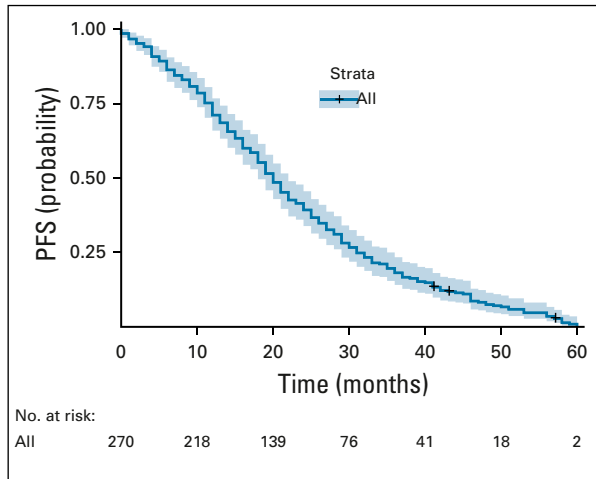|							
Stage I	440	370	348	336	304	274	226
Stage II	812	727	689	651	575	515	432
Stage III	336	283	250	224	187	150	123

FIG A3. Progression-free survival (PFS) in patients with metastatic disease at presentation.
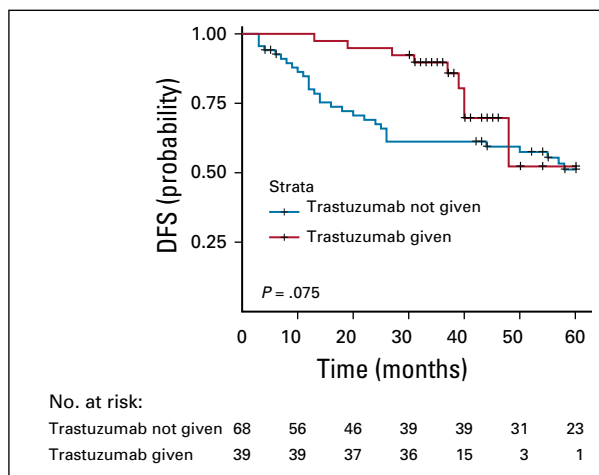

FIG A4. Disease-free survival (DFS) in patients with human epidermal growth factor receptor 2–positive tumors and localized disease by use of trastuzumab.
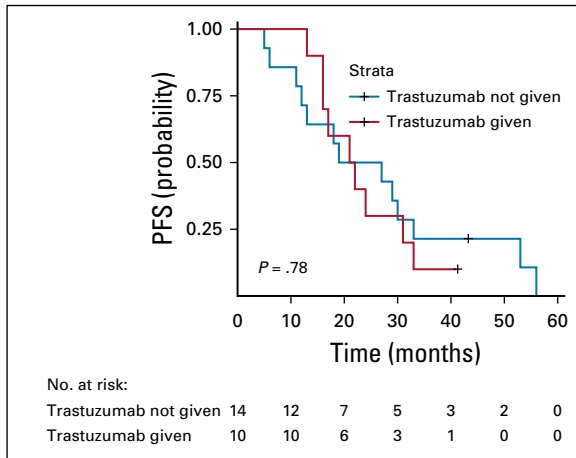
FIG A5. Progression-free survival (PFS) in patients with human epidermal growth factor receptor 2–positive tumors and metastatic disease by use of trastuzumab.

TABLE A1. Immunohistochemistry Profile and Stage at Presentation

	Immunohistochemistry Profile, No. (%)			
Stage	ER Positive, PR Positive, HER2 Negative	ER Positive, PR Positive, HER2 Positive	ER Negative, PR Negative, HER2 Positive	ER Negative, PR Negative, HER2 Negative
I	120 (61)	6 (3)	18 (9)	51 (26)
II	242 (54)	17 (4)	46 (10)	136 (30)
III	83 (48)	6 (3)	13 (8)	6 (39)
IV	47 (37)	5 (4)	16 (13)	52 (42)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2/neu overexpression or gene amplification; PR, progesterone receptor.

TABLE A2. Tumor Grade and Stage and Presentation

Stage	Grade, No. (%)		
	1	2	3
I	274 (62)	134 (30)	32 (7)
II	218 (26)	460 (57)	134 (17)
III	108 (32)	181 (54)	47 (14)
IV	32 (11)	183 (68)	55 (20)

TABLE A3. Tumor Grade and Immunohistochemistry Profile

Immunohistochemistry Profile	Grade, No. (%)		
	1	2	3
ER+/PR+ HER2–	205 (41)	250 (49)	51 (10)
ER+/PR+ HER2+	12 (33)	16 (44)	8 (22)
ER–/PR– HER2+	17 (18)	45 (47)	33 (35)
ER–/PR– HER2–	72 (23)	152 (48)	95 (30)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2/neu overexpression or gene amplification; PR, progesterone receptor.