Evaluation of the new prognostic staging system for breast cancer of the American Joint Committee on Cancer (AJCC), 8th edition, in a Latin American cohort

Journal:	*Annals of Surgical Oncology*
Manuscript ID	ASO-2021-02-0434
Manuscript Type:	Original Article
Date Submitted by the Author:	16-Feb-2021
Complete List of Authors:	CERVERA BONILLA, SERGIO; Instituto Nacional de Cancerología, Bogotá, Breast Cancer Unit Rodríguez-Ossa, Paola; Instituto Nacional de Cancerología, Bogotá, Breast Cancer Unit Vallejo-Ortega, María; Instituto Nacional de Cancerología, Bogotá, Clinical and Epidemiological Cancer Research Group Osorio-Ruiz, Ana; Instituto Nacional de Cancerología, Bogotá, Breast Cancer Unit Mendoza, Sara; Instituto Nacional de Cancerologia, Breast Cancer Unit Orozco-Ospino, Martha; Instituto Nacional de Cancerología, Bogotá, Breast Cancer Unit Lehmann-Mosquera, Carlos; Instituto Nacional de Cancerología, Bogotá, Breast Cancer Unit DUARTE, CARLOS; Instituto Nacional de Cancerologia, Breast Cancer Unit Ángel-Aristizábal, Javier; Instituto Nacional de Cancerología, Bogotá, Breast Cancer Unit Guzmán-Abisaab, Luis; Instituto Nacional de Cancerologia, Breast Cancer Unit García, Mauricio; Instituto Nacional de Cancerologia, Breast Cancer Unit Diaz, Sandra; Instituto Nacional de Cancerologia, Breast Cancer Unit

Evaluation of the 8th edition of the American Joint Committee on Cancer's prognostic staging system for breast cancer in a Latin American cohort

Evaluation of the 8th AJCC prognostic staging system for breast cancer in a Latin American cohort

Sergio Cervera-Bonilla[1], Paola Rodríguez-Ossa[1], María Vallejo-Ortega[2], Ana Osorio-Ruiz[1], Sara Mendoza-Diaz[1], Martha Orozco-Ospino[1], Carlos Lehmann-Mosquera[1], Carlos Duarte-Torres[1], Javier Ángel-Aristizábal[1], Luis Guzmán-Abisaab[1], Mauricio Garcia-Mora[1], Sandra Diaz-Casas[1].

1. Functional Breast Unit, National Cancer Institute of Colombia, Bogotá, Colombia

2. Clinical and Epidemiological Cancer Research Group, National Cancer Institute of Colombia, Bogotá, Colombia

Corresponding author: Sergio Cervera-Bonilla, Calle 1A #9-85, Clínica de Mama y Tejidos Blandos, Instituto Nacional de Cancerología, Bogotá, D.C., Colombia

Telephone: (+57) (310) 8193898

E-mail: scervera@cancer.gov.co

Synopsis: Although the implementation of the new AJCC 8th edition staging system for breast cancer began in 2018, Latin American countries have just recently started using it. We evaluated the restaging of 912 patients using the AJCC 8th edition classification, of which 54·82% presented changes in staging, with downstaging in 40·3% and upstaging in 14·47%.

Abstract

Background. The staging of breast cancer has been based on tumor size, lymph node involvement, and the presence or absence of distant metastases. The American Joint Committee on Cancer (AJCC) staging system in its eighth edition incorporates hormone receptors, HER2 (Human epidermal growth factor receptor 2), and histological grade, due to their prognostic importance; in Latin America, however, the impact of the new edition is unknown. This article evaluates the performance of the 8th edition AJCC staging system in a cohort of patients with breast cancer at a reference center in Colombia.

Materials and methods. It is a descriptive cohort of 912 patients with non-metastatic invasive breast cancer, with information on the anatomic stage and biological factors, who received complete treatment. All patients were restaged using the 8th edition AJCC classification; changes in clinical stages and differences between the two classifications were compared.

Results. 912 patients were included, of which 54·82% presented changes in staging, with downstaging in 40·3% and upstaging in 14·47%. For recurrence-free survival, the C-Index of the 8th AJCC was 0.726, and the AIC was 1323.7; while the C-Index of the 7th AJCC was 0.731, and the AIC was 1314.3 (p= 0.99).

Conclusions. The 7th and 8th AJCC staging systems have similar predictive values in our population for recurrence-free survival. It is necessary to develop future studies to evaluate the performance of the 8th AJCC to predict overall survival.

Keywords: Neoplasm staging, prognosis, breast neoplasms, survival.

Introduction

Breast cancer has the second highest incidence in the world (11·6%) and the fifth in mortality (6·6%), according to data published by GLOBOCAN in 2018; in Colombia, it is the first in incidence (44·1 per 100,000) and in mortality (15·9% of all cancers).[1]

The American Joint Committee on Cancer (AJCC) used to classify breast cancer into clinical stages according to anatomic factors like tumor size, lymph node involvement, and the presence or absence of distant metastases. The primary goals of breast cancer staging are to establish a prognosis, as well as to determine a treatment plan. Perou et al. classified breast cancer based on variations in gene expression patterns in luminal, triple-negative, and pure HER2 (Human epidermal growth factor receptor 2) tumors.[2] Subsequent studies showed a significant impact on overall survival according to the molecular subtype.[3] Hortobagyi et al. evaluated whether the inclusion of biological factors in the triple-negative subtype would modify the prognostic accuracy of breast cancer staging, showing that overall survival curves for patients with triple-negative breast cancer coincided with those of patients with luminal or HER2 subtypes, who had a higher stage based on anatomic staging.[4] This is why in 2018 the AJCC 8th edition manual incorporated biological factors (histological grade, estrogen receptor, progestin receptor, and HER2 receptor statuses), and additional analyses were performed to assess the prognostic importance of these factors. In order to define a new prognostic staging system, a study of 238,265 patients was carried out that included anatomic stage and biological factors; subgroups were defined based on the possible combinations of stage and biological variables.[5]

Following the publication of the 8th AJCC manual, a validation study was conducted with a cohort from the MD Anderson Cancer Center (MDACC) and the California Cancer Registry (CCR) databases. In the MDACC cohort, 29·5% of the cases were upstaged, and 28·1% downstaged, compared to the anatomic stage. In the CRR cohort, 31% of the cases were upstaged, and 20·6% were downstaged. In both cohorts, the prognostic stage was more accurate than the anatomic stage in terms of disease-specific survival.[6] Since the implementation of the AJCC 8th edition staging system, several studies have been published about its validation, with data revealing significant changes in stages, with increases in 26% to 41% of the cases, and decreases in 19% to 33%.[7,8] In terms of overall survival in different populations, prognostic staging is more accurate than anatomic staging;[7,9] it is important, however, to acknowledge that the AJCC staging system depends on appropriate treatments that

are administered according to the biology of each tumor. Anatomic staging could be preserved for developing countries that may not have adequate tests or treatments.

Although the implementation of the 8th AJCC staging system for breast cancer started in 2018, it has not been widely implemented in developing countries. The Functional Breast Unit of the National Cancer Institute (INC), the most important referral center for cancer in Colombia, maintains a database with detailed records of histopathological factors, treatment, and clinical outcomes of patients with breast cancer. Based on the clinical records of this cohort, all patients with breast cancer were restaged using the 8th edition AJCC staging system, evaluating cases of upstaging and downstaging, as well as comparing the results with anatomic staging.

Materials and methods

An analysis was performed based on the cohort of 1600 patients with breast cancer, who were admitted to the Functional Breast Unit of the INC for primary treatment between 2013 and 2018. For the analysis, all patients with non-metastatic invasive breast cancer admitted for initial treatment were considered eligible, with a complete record of the anatomic stage based on the 7th edition TNM system and who received complete treatment at the institution. We excluded patients with in situ breast cancer; those with no information on histological grade, HER2 and hormone receptor status; patients who received treatment in a different institution; those who died before completing clinical staging or before starting treatment; and patients who were lost to follow-up. Stage IV patients, due to no changes in staging, were also excluded from the present analysis (Figure 1).

Data collection

The eligibility criteria of patients in the cohort were reviewed. An electronic database was created using the *REDCap™* platform, where data related to demographic, clinical, pathological, biological, and treatment aspects were collected, based on information extracted from the database and from the INC's medical records system (SAP®), registering the restaging of patients based on the 8th AJCC criteria.

Anatomic staging was performed according to the 7th edition TNM classification (tumor size, lymph node involvement and distant metastasis); the 8th edition AJCC clinical prognostic staging was performed using the *Integrated Cancer Research* (CanXer) app, available for Android® mobile devices and freely accessible. To

verify the quality of information, data collection was carried out by two study investigators; next, an assistant assigned by the sub-directorate of research of the INC verified the information. In order to explore possible changes in overall survival, all patients in the cohort were contacted by phone or had face-to-face consultation during 2019 and 2020, aiming to confirm their current vital status.

Based on the prognostic restaging, the proportion of change in clinical stages (upstaging or downstaging) with respect to the anatomic staging was calculated. In addition, overall survival was estimated as the time from disease diagnosis (date of the pathology review report at the INC) to the date of the last control recorded in the medical history or death of the patient. The study was approved by the INC Research and Ethics Committee. Peer reviewers disclose no conflicts of interest.

Statistical analysis

A descriptive analysis of data was performed to estimate the proportions of the qualitative variables, as well as the mean and median values and the ranges of the quantitative variables; the Shapiro-Wilk test was used to assess whether quantitative variables presented a normal distribution. Similarly, the Kaplan-Meier method was used to calculate the cumulative probability of the overall survival of the cohort. Regarding the survival of patients who had the same stage according to the anatomic and prognostic classifications, the log rank test was used to assess whether the survival curves were similar between degrees of change in the cohort according to anatomic staging, or there were differences in the survival of patients with no changes and patients who had some type of change (upstaging or downstaging) based on the anatomic and pathologic classifications; these were also stratified according to the type of stage. Patients who did not die were censored at the time of the last recorded follow-up, and the time to the event was determined between the date of disease confirmation and death or last contact. Additionally, the presence of difference regarding risk of death according to the type of reclassification was also explored using the Chi-square test.

To evaluate the predictive performance of the AJCC staging systems, a multivariate Cox proportional hazards regression model was used for each classification, adjusted by age and treatment (chemotherapy, radiotherapy, hormonotherapy, and anti-HER2 therapy). Then, the Harrell's concordance index (C-index) and the Akaike information criterion (AIC) were calculated for each model. A Somers' D test was performed to compare the C-index between models, which measures the association between two predicted variables and the significance of the difference between them.[10] Analyses were run using the Stata® software.

Results

Of the 1600 patients registered in the INC database during the study period, 688 patients were excluded because they did not meet the study inclusion criteria. The final analysis was performed with 912 patients, with a median follow-up of 39·1 months (range: 1·32 to 181·41 months) (Figure 1). Of the included patients, 99·5% were women. The mean age was 58·2 years (+/- 12.2). Invasive ductal carcinoma was the most frequent histological type (85·3%; n=778), and patients were mostly in locally advanced states (IIB, IIIA, IIIB, IIIC) (56·5%; n=516); specifically, stage IIIB (28·9%). 41% of the tumors (n=374) were luminal A, and 13·2% were triple-negative tumors. 86·7% (n=791) of the patients had histological grades II or III. The overall mortality of the cohort was 5·3%, while disease recurrence was 11·97% (108/902). The other clinical and histopathological factors are described in Table 1.

Based on anatomic staging, 14·6% of the patients (n=134) were in stage I; with prognostic staging, this stage corresponded to 38·2% (n=349). In contrast, 14·6% (n=134) had stage IIB tumors by anatomic staging, while this stage corresponded to 6·1% of patients (n=56) in prognostic staging. Stages IIA, IIIA, and IIIB had the lowest and stage IIIC had the highest frequency in prognostic staging (Table 2).

A comparison of changes in the distribution of patients after using the 8th AJCC classification system showed that 54·82% (n=500) presented changes in their staging. Of the 500 patients who were reclassified, 368 were downstaged (73·6%), while 132 patients were upstaged (26·4%), which represents a percentage of 40·3% for downstaging and 14·47% for upstaging, compared to the total cohort. Regarding the magnitude of change, 62·2% presented a one-stage decrease, 20% a one-stage increase, 11·4% a two-stage decrease, and 6·4% a two-stage increase. As for the dynamics of change compared to the anatomic stage, stage IIA had the highest proportion of changes (229/262, 87·4%), followed by stage IIB (111/134, 82·84%) and IIIA (69/90, 76·67%). When observing the stages that presented greater downstaging, stage IIIA had the most cases with two-stage decrease (39/57 68·42%), while stage IIA had the largest number of one-stage decrease (202/311, 64·95%). On the other hand, regarding upstaging, stage IIIB had the highest percentage of one-stage increase (60/100, 60%), while stages IIB and IIIA were the only ones with two-stage increases (16/32, 50% each). Of the cases that did not present any changes, the highest proportion of patients were in stage IIIB (193/412, 46·84%). Table 3 presents the distribution of staging based on the two systems, as well as the dynamics of change in the cohort.

During the follow-up time, 49 deaths occurred, 37 of which were documented as "death with disease" (75·51%); within the group of people who were still alive, 782 were classified as "alive without disease" (90·61%). As part of the exploratory analysis, statistically significant differences were found between the risk of death and the degree of classification (p=0·00), the risk being higher in patients who presented upstaging (19/132). When evaluating the recurrence-free survival curves regarding the dynamics of change in anatomic staging, statistically significant differences were found among them (log rank=0·00) (Supplementary material). The analysis of behavior in the anatomic stage showed differences between the recurrence-free survival curves related to the degree of change in stages IIA (log rank: 0·0002) and IIIA (log rank: 0·0055), but there were no differences in the other stages (Figure 2). The supplementary material also shows survival curves for overall survival.

For recurrence-free survival, the C-index was 0·726 for prognostic staging, while the AIC was 1323·7. For anatomic staging, the C-index was 0·731 and the AIC was 1314·3. There were no differences between the two C-index models (p=0·99). Table 4 summarizes the hazard ratios for both staging systems. Due to a lower mortality rate in our cohort, we could not perform comparison between the two models to evaluate their prediction value in overall survival.

Discussion

The biological classification of breast cancer has allowed a better understanding of the prognostic and predictive behavior of the disease, being historically important tumor size, lymph node involvement and histological grade. Current evidence shows the relevance and impact of hormone receptors and HER2 on survival.[4,11] The AJCC has recognized the impact of biological factors on the treatment and prognosis of patients with breast cancer; consequently, it designed a staging system in the 8th edition with prognostic and pathological clinical stages, incorporating biological factors in the standard anatomic categories.[2]

This is the first approach carried out in Latin America using the new AJCC 8th edition staging system and comparing it with anatomic staging, with a focus on the Latin population, which is rarely included in predictive studies. One of the most relevant findings of our study is the significant percentage of cases that presented downstaging, which was higher compared to the results of other series: 40·3% vs. 19·4% reported by Kim et al.;[7] and 28·1 % and 20·6% in the MDACC and CCR validation cohorts, respectively.[6] Regarding upstaging,

our cohort presented the lowest reported percentage in the literature to date: 14·47 % vs. 41% reported by Wang et al.;[8] 26% in Kim et al.;[7] and 29·5% and 31% in the MDACC and CCR validation cohorts, respectively.[6] These data can be attributed to the high percentage of locally advanced tumors in our cohort, suggesting that the new AJCC 8th edition staging provides a more accurate prognosis compared to the anatomic classification in our patients. A similar example is found in what was reported by Wang et al.,[8] who conducted a prospective study to assess the prognostic stage in locally advanced breast cancer based on the Surveillance, Epidemiology and End Results (SEER) database (33%). Our finding could also be because our patients are detected in advanced stages. Nevertheless, we found that despite their large tumors, they have a good clinical response, which can be explained by their favorable tumoral biology.

When observing the dynamics of change according to anatomic stages, our data suggests that the highest proportion of cases with no change were patients in stage IIIB (84%). The stage with the highest number of downstaging was stage IIA (95%), which differs from the study by Kim et al.,[7] where the stage with the highest percentage of patients that remained unchanged was stage IA (82·4%). Finally, stage IIIB had the highest frequency of downstages. These data possibly correspond to the ethnic differences and heterogeneity of our Latin population, with higher presentation of locally advanced breast tumors. On the other hand, when exploring the survival behavior of patients based on the dynamics of change, the differences found in the dynamics of patients from anatomic stage to prognostic stage evidenced the important role of adding biological factors to the classification system for patient survival.

As for the predictive performance of the anatomic and prognostic staging systems in terms of relapse-free survival, what calls the attention is that our study did not find statistically significant differences in the C-index values of the two models, which were lower than those reported in other studies for both systems with similar covariates. This phenomenon is possibly due to the fact that our population is admitted to first treatment with an important tumoral burden, which is a critical factor for overall survival. These results should be evaluated carefully, taking into account that the main purpose of the AJCC staging systems is to predict overall survival, an outcome that we could not assess due to limitations in sample size and the number of deaths.

This is the first study of a Latin American cohort of patients with breast cancer, which was conducted in a Latin American reference center, with very few losses to follow-up in the study cohort. The main limitations of the study include: a) low number of death events, b) our cohort has not yet completed the 5 years of follow-up;

consequently, we were not able to evaluate the predictive performance of the 8th AJCC staging system in overall survival, and c) it was not possible to include all the patients who appear in the database due to obstacles posed by the Colombian health system, which does not allow treatment continuity with transfers to other institutions through fractionated therapies. We expect to assess in the close future the performance of the 8th AJCC in predicting overall survival.

In our population, the changes generated by the new AJCC 8th edition staging system were previously unknown, thus the present study offers relevant information to help decision-making for clinicians and patients. It is still uncertain what clinical impact the restaging may pose in terms of long-term overall survival, and a longer follow-up of the cohort is needed to compare changes in each staging.

In conclusion, our data suggest that the AJCC 8th edition staging system has a similar predictive value for recurrence-free survival as the anatomic staging system in patients with breast cancer in a Latin American cohort. It is necessary to develop, though, future studies to assess the predictive value of these staging systems for overall survival.

- **Authors and contributors**

Authors' contributions to the manuscript:

*Sergio Cervera-Bonilla: conception of the research idea, literature search, data collection, data analysis, creation of figures and tables, data interpretation, manuscript writing and correction

E-mail: scerverab@gmail.com

*Paola Rodríguez-Ossa: conception of the research idea, literature search, data collection, data analysis, creation of figures and tables, data interpretation, manuscript writing and correction

E-mail: docossa1985@gmail.com

*María Vallejo-Ortega: study design, data analysis, creation of figures and tables, data interpretation, manuscript writing and correction

E-mail: mvallejo@cancer.gov.co

*Ana Osorio-Ruiz: literature search, data collection

E-mail: anamariaosorior@gmail.com

*Sara Mendoza-Díaz: literature search, data collection

E-mail: mendozadiaz.sara@gmail.com

*Martha Orozco-Ospino: literature search, data collection

E-mail: marthacecilia.orozco@gmail.com

*Carlos Lehmann-Mosquera: data analysis, data interpretation, manuscript writing and correction

E-mail: lehmannmd@gmail.com

*Carlos Duarte-Torres: data analysis, data interpretation, manuscript writing and correction

E-mail: duarte10.carlos@gmail.com

*Javier Ángel-Aristizábal: study design, data analysis, data interpretation, manuscript writing and correction

E-mail: javieraad@hotmail.com

*Luis Guzmán-Abisaab: data analysis, data interpretation, manuscript writing and correction

E-mail: guzmanlucho@hotmail.com

*Mauricio Garcia-Mora: data analysis, data interpretation, manuscript writing and correction

E-mail: maurogmora@hotmail.com

*Sandra Díaz-Casas: data analysis, data interpretation, manuscript writing and correction

E-mail: sdiazcasas@yahoo.com

Declaration of interests

The authors declare that they have no financial relationships or interests to disclose.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424.

2. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature.* 2000;406:747-52.

3. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A.* 2001;98(19):10869-74.

4. Bagaria SP, Ray PS, Sim MS, et al. Personalizing breast cancer staging by the inclusion of ER, PR, and HER2. *JAMA Surg.* 2014;149(2):125-9.

5. Hortobagyi GN, Edge SB, Giuliano A. New and Important Changes in the TNM Staging System for Breast Cancer. *Am Soc Clin Oncol Educ Book.* 2018;38:457-67.

6. Weiss A, Chavez-MacGregor M, Lichtensztajn DY, et al. Validation Study of the American Joint Committee on Cancer Eighth Edition Prognostic Stage Compared With the Anatomic Stage in Breast Cancer. *JAMA Oncol.* 2018;4(2):203-9.

7. Kim I, Choi HJ, Ryu JM, et al. Prognostic Validation of the American Joint Committee on Cancer 8th Staging System in 24,014 Korean Patients with Breast Cancer. *J Breast Cancer.* 2018;21(2):173-81.

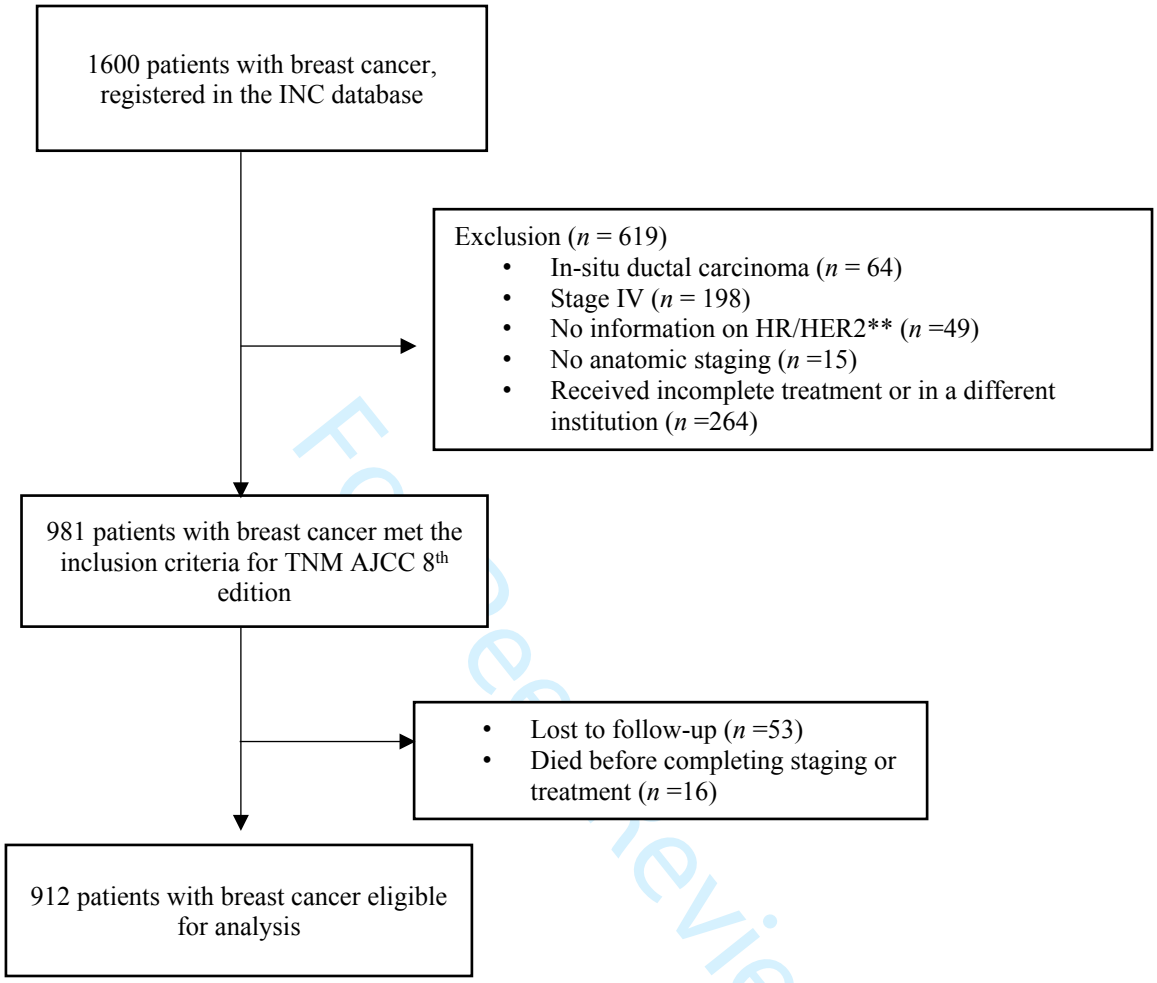
8. Wang M, Chen H, Wu K, Ding A, Zhang M, Zhang P. Evaluation of the prognostic stage in the 8th edition of the American Joint Committee on Cancer in locally advanced breast cancer: An analysis based on SEER 18 database. *Breast.* 2018;37:56-63.

9. Li X, Zhang Y, Meisel J, Jiang R, Behera M, Peng L. Validation of the newly proposed American Joint Committee on Cancer (AJCC) breast cancer prognostic staging group and proposing a new staging system using the National Cancer Database. *Breast Cancer Res Treat.* 2018;171(2):303-13.

10. Newson R. Confidence intervals for rank statistics: Somers' D and extensions. *The Stata Journal.* 2006;6(3):309-34.

11. Yi M, Mittendorf EA, Cormier JN, et al. Novel staging system for predicting disease-specific survival in patients with breast cancer treated with surgery as the first intervention: time to modify the current American Joint Committee on Cancer staging system. *J Clin Oncol.* 2011;29(35):4654-61.

Figure 1. Flow chart of patient inclusion in the AJCC 8th edition prognostic staging cohort



** HR: hormone receptor; HER2: Human epidermal growth factor receptor 2

Table 1. Baseline characteristics of patients included in the cohort for assessing the 8th AJCC prognostic staging system for breast cancer

Baseline characteristics	n. (%)
Sex	
Female	908 (99·5%)
Male	4 (0·4%)
Age (years)	
<40	48 (5·2 %)
40 a 50	210 (23%)
51 a 69	488 (53·5%)
>70	166(18·2%)
Histological type	
Invasive ductal carcinoma	778 (85·3%)
Invasive lobular carcinoma	41 (4·4%)
Tubular carcinoma	19 (2 %)
Medullary carcinoma	2 (0·2%)
Others	72 (7·8%)
Tumor size	
T0	1 (0·10%)
T1	152 (16·6%)
T2	393 (43 %)
T3	79 (8·6%)
T4	287 (31·4%)
T4a	3 (0·3%)
T4b	283 (31%)
T4c	1 (0·1%)
Lymph node involvement	
N0	433 (47·4%)
N1	280 (30·7%)
N2	171 (18·7%)
N2a	170 (18·6%)
N2b	1 (0·1%)
N3	28 (3%)
N3a	11 (1·2%)
N3b	3 (0·3%)
N3c	14 (1·5%)
Histological grade	
1	121 (13·2%)
2	543 (59·5%)
3	248 (27·1%)
Estrogen receptors	
Positive	733 (80·3%)
Negative	179 (19·6%)
Progestin receptors	
Positive	683 (74·8%)
Negative	229 (25·1%)
HER 2* (FISH/DISH)	
Positive	144 (15·7%)
Negative	768 (84·2%)
Molecular subtype	
Luminal A**	374 (41%)
Luminal B HER2-negative	273 (29·9%)
Luminal B HER2-positive	103 (11·2%)
Pure HER2	41 (4·4%)

Baseline characteristics	n. (%)
Triple-Negative	121 (13·2%)
Type of therapy	
Surgery	891 (97·7%)
Chemotherapy	677 (74·2%)
Radiotherapy	808 (88·6%)
Hormonotherapy	735 (80·6%)
Anti-HER2 therapy	155 (17%)
Intraoperative radiotherapy	14 (1·5%)

** Luminal A (hormone receptor-positive, HER2-negative, cell proliferation marker (KI67) <20%), Luminal B HER2-negative (hormone receptor-positive, HER2-negative, KI67> 20%), Luminal B HER2-positive (hormone receptor-positive, HER2-positive), pure HER2 (hormone receptor-negative, HER2-positive), triple-negative (hormone receptor-negative, HER2-negative). Abbreviations: HER 2: Human epidermal growth factor receptor 2. FISH: fluorescence in situ hybridization; DISH, dual-ISH.

Table 2. Distribution of the anatomic and prognostic stages of patients included in the cohort for the evaluation of the 8th AJCC prognostic staging system for breast cancer

Clinical staging	Anatomic n. (%)	Prognostic n. (%)
I	134 (14·6%)	349 (38·2 %)
IIA	262 (28·7%)	149 (16·3%)
IIB	134 (14·6 %)	56 (6·1 %)
IIIA	90 (9·8%)	42 (4·6 %)
IIIB	264 (28·9%)	232 (25·4%)
IIIC	28 (3 %)	84 (9·2%)

Table 3. Distribution of the AJCC 8th edition prognostic stage, according to the anatomic stage of patients included in the cohort

Clinical or anatomic staging	n. (%)	Prognostic staging	n. (%)	Upstaging	Downstaging	No change
I	134 (14·6)	I	134 (100)	-	-	134
				-	-	-
IIA	262 (28·7)	I	202 (77·1)	-	202	-
		IIA	33 (12·6)	-	-	33
		IIB	27 (10·3)	27	-	-
IIB	134 (14·6)	I	13 (9·7)	-	13	-
		IIA	77 (57·4)	-	77	-
		IIB	23 (17·1)	-	-	23
		IIIA	5 (3·7)	5	-	-
		IIIB	16 (11·9)	16	-	-
IIIA	90 (9·8)	IIA	39 (43·3)	-	39	-
		IIB	6 (6·6)	-	6	-
		IIIA	21 (23·3)	-	-	21
		IIIB	8 (8·8)	8	-	-
		IIIC	16 (17·7)	16	-	-
IIIB	264 (28·9)	IIIA	11 (4·1)	-	11	-
		IIIB	193 (73·1)	-	-	193
		IIIC	60 (22·7)	60	-	-

IIIC	28 (3·7)	IIIA IIIB IIIC	5 (17·8) 15 (53·5) 8 (28·5)	- - -	5 15 -	- - 8
Total	912 (100)			132 (14.47)	368 (40·35)	412 (45·18)

Figure 2. Recurrence-free survival according to changes in staging, comparing the 7th and 8th edition AJCC systems

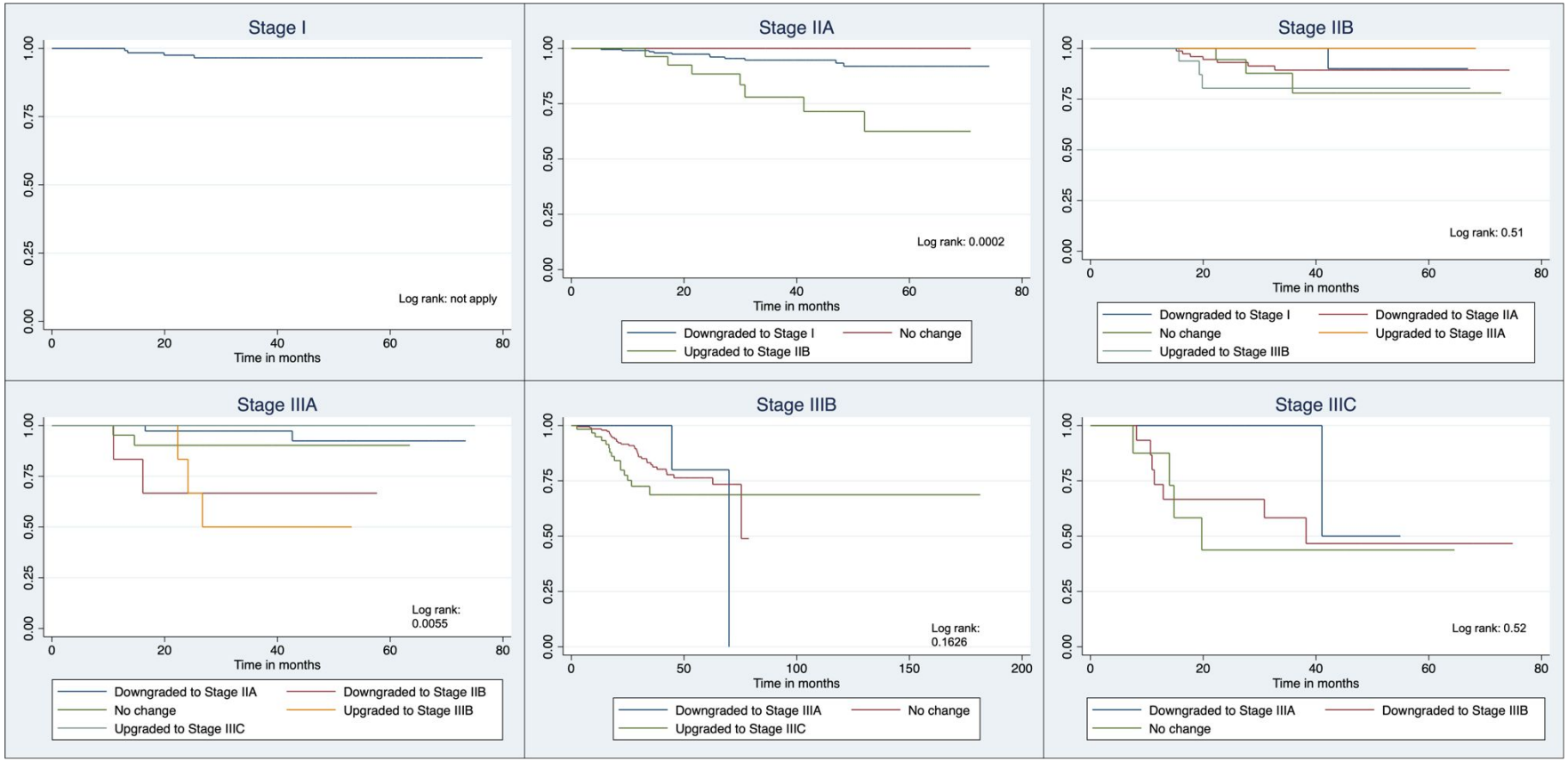
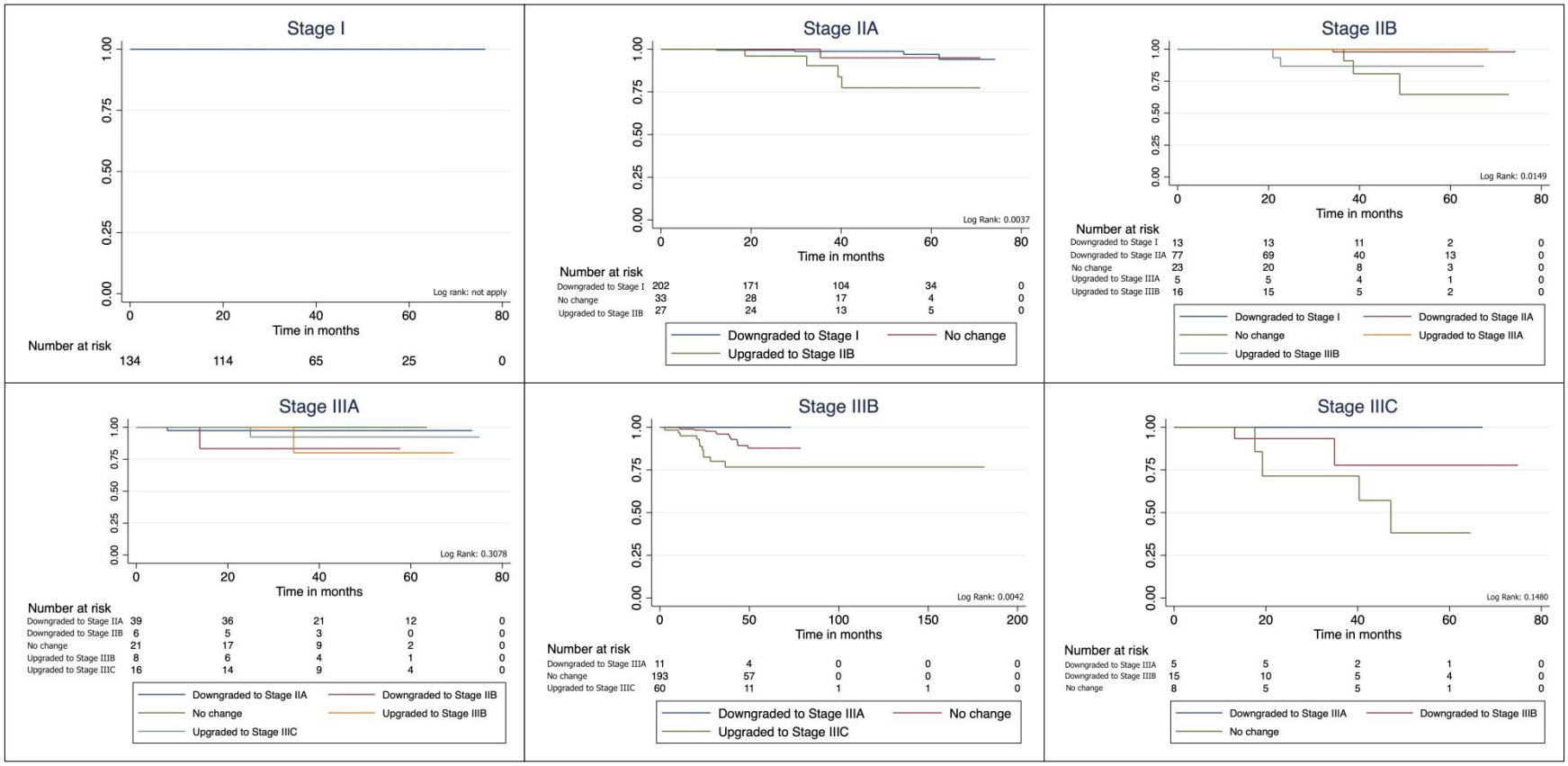


Table 4. Hazard ratio for recurrence-free survival by stage

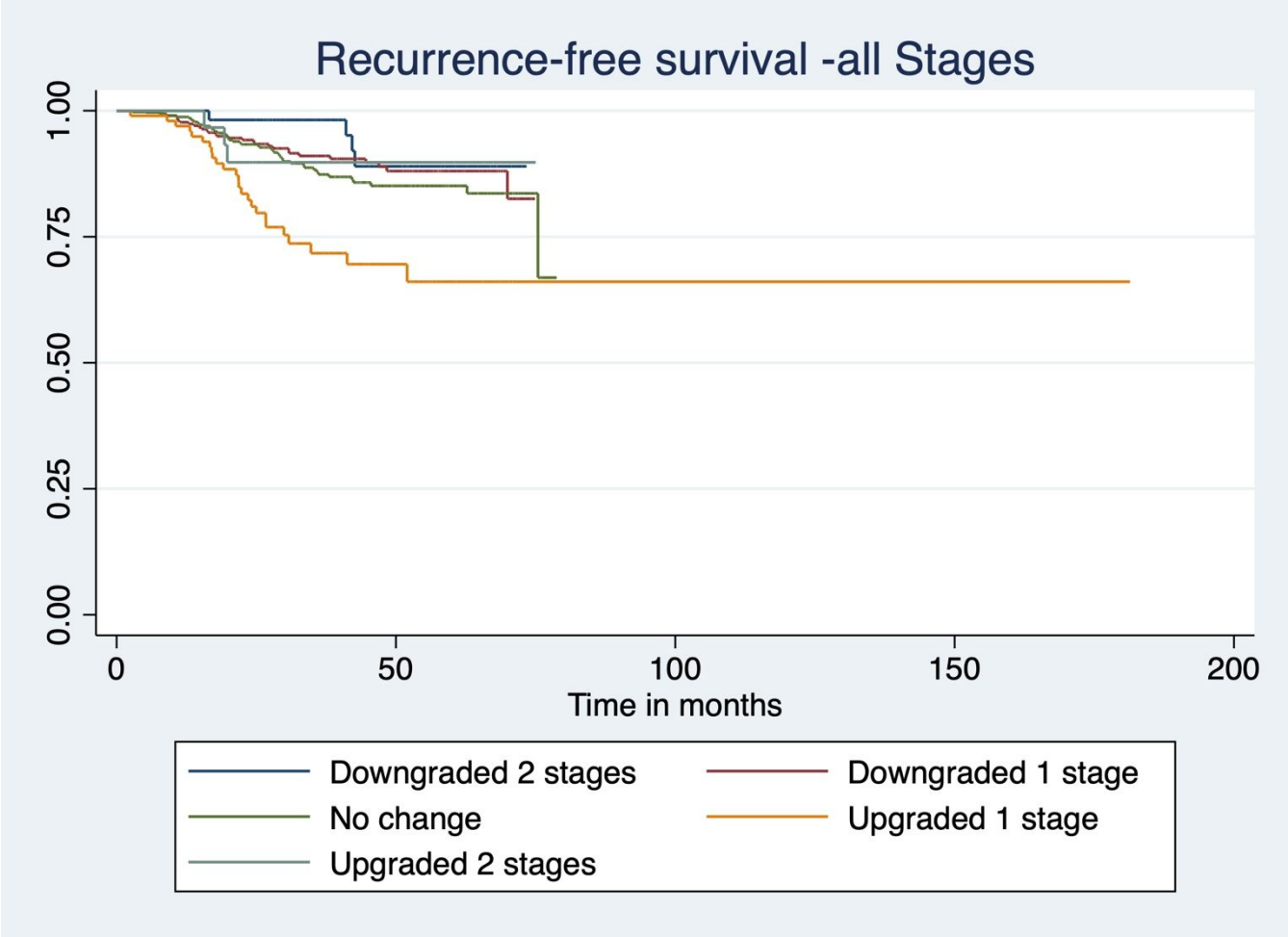
Stage	Recurrence-free survival, Hazard ratio (IC95%)	
	Clinical or anatomic staging	Prognostic staging
I	1 (Reference)	1 (Reference)
IIA	2·29 (0·77 – 6·85)	1·19 (0·51 – 2·79)
IIB	3·41 (1·07 – 10·83)	3·18 (1·36 – 7·43)
IIIA	2·79 (0·81 – 9·59)	2·71 (0·92 – 8)
IIIB	6·49 (2·22 – 19)	4·3 (2·27 – 8·15)
IIIC	14·9 (4·53 – 49·02)	3·93 (1·66 – 9·31)

SUPPLEMENTARY MATERIAL

Supplementary material 1. Overall survival according to changes in staging, comparing the 7th and 8th edition AJCC systems



Supplementary material 2. Recurrence-free survival according to changes in staging



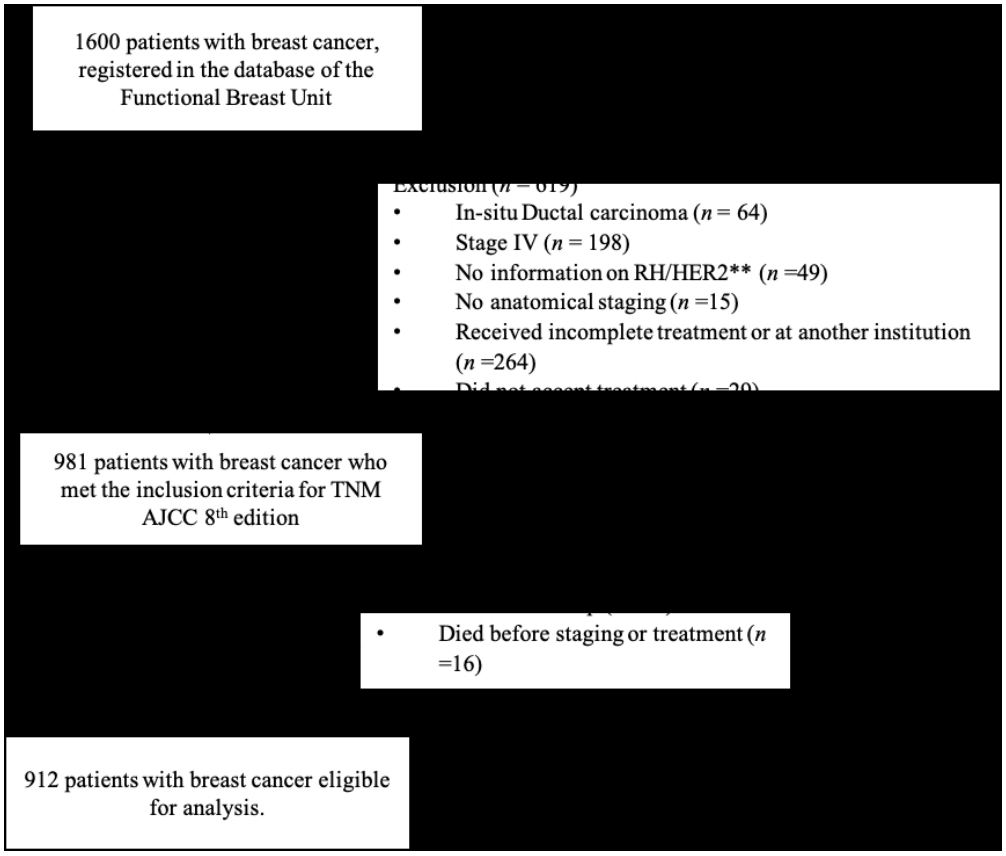
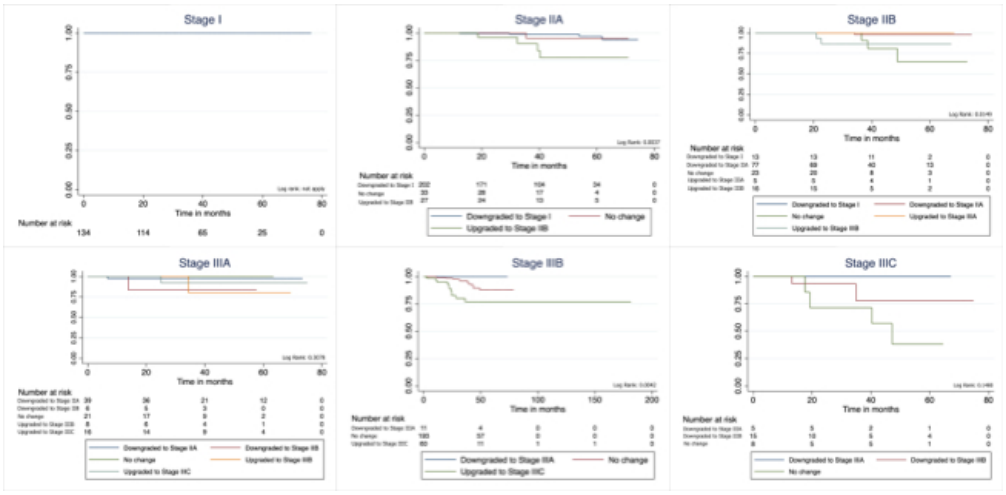
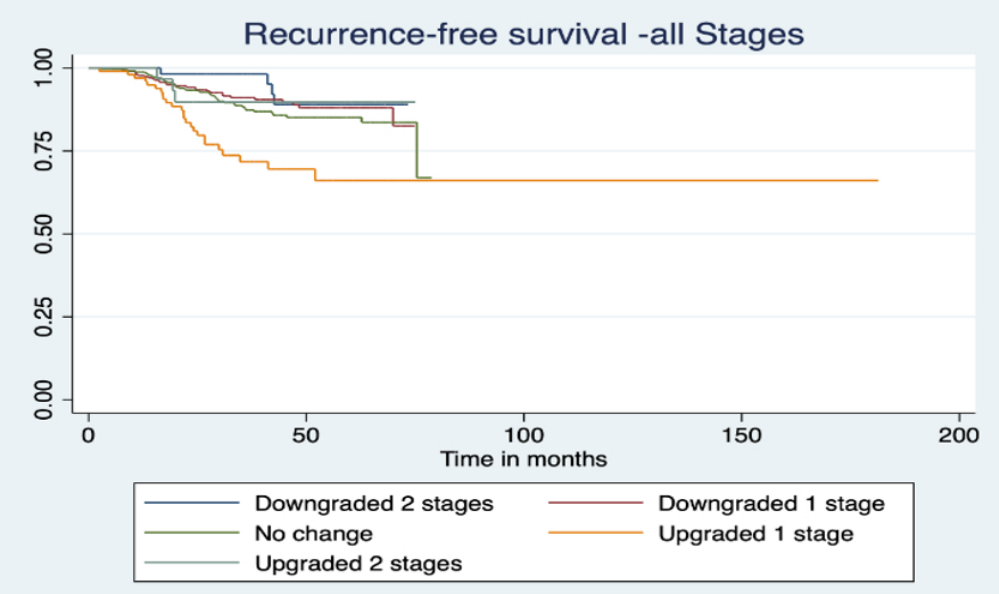


Figure 1.Flow chart of patient inclusion in the AJCC 8th edition prognostic staging cohort.


Stage I
Stage IIA
Stage IIB
Stage IIIA
Stage IIIB
Stage IIIC
Time in months
Number at risk


Recurrence-free survival -all Stages
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
Time in months
Downgraded 2 stages
Downgraded 1 stage
No change
Upgraded 1 stage
Upgraded 2 stages