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Article

Pathologic Complete Response (pCR) and Survival of Women with Inflammatory Breast Cancer (IBC): An Analysis Based on Biologic Subtypes and Demographic Characteristics

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Abstract: The aim of this study was to examine pathologic complete response (pCR) and overall survival (OS) of patients diagnosed with non-metastatic inflammatory breast cancer (IBC). A total of N=8,550 cases undergoing surgery were identified between 2004-2013, using the National Cancer Database (NCDB). Patients were grouped into 4 biologic subtypes ($HR^+/HER2^-$, $HR^+/HER2^+$, $HR^-/HER2^+$, $HR^-/HER2^-$). The median age at diagnosis was 56 years. On average, women were followed for 3.7 years [interquartile range=3.0]. The majority were white (80%), had private health insurance (50%), and presented with poorly differentiated tumors (57%). Approximately 46% of the cancers were >5cm. Most patients underwent mastectomy (94%) and received radiotherapy (71%). Differences by biologic subtypes were observed for grade, lymph node invasion, race, and tumor size (p<.0001). Compared with non-pCR (54%), patients experiencing pCR had superior 5-year survival (77%) (p<.0001). Survival was poor for triple-negative (TN) tumors (37%) vs. other biologic subtypes (60%) (p<.0001). On multivariable analysis, TN-IBC, positive margins, and not receiving either chemotherapy, hormonal therapy or radiotherapy were independently associated with poor 5-year survival (p<.0001). In this large multicentric analysis of IBC, categorized by biologic subtypes, we observed significant differential tumor, patient and treatment characteristics, and OS.

Keywords: Biologic subtypes; diagnosis; inflammatory breast cancer; pCR; survival

1. Introduction

Inflammatory breast cancer (IBC) is an aggressive breast cancer with rapid onset and poor outcomes.[1] In the United States (US), its incidence ranges between 1-6%.[2] Originally described by Sir Charles Bell in 1814, IBC has been recognized by its distinct clinical characteristics. This includes rapid onset of breast skin erythema with edema (known as peau d'orange).[3] The classic appearance of IBC is attributed to tumor emboli invasion of the dermal lymphatic vessels which may or may not be seen on skin biopsy. The diagnosis of IBC is by its clinical appearance and/or pathologic features, with the latter not being required to confirm the diagnosis.[4,5] Overall, the 5-year survival for IBC remains poor (55% among patients receiving triple-modality therapy).[6]

Analogous to non-IBC, IBC has 5 molecular subtypes based on their gene expression profile: luminal A, luminal B, human epidermal growth factor receptor 2 ($HER2$) over-expression, basal, and normal-breast like.[7,8] Furthermore, IBC can be characterized according to phenotypic expression of

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hormone receptors (HR) and HER_2 and is often grouped into 4 distinct biologic subtypes (HR^+/HER_2^-, HR^+/HER_2^+, HR^-/HER_2^+, HR^-/HER_2^-).[9]

Given its rarity, IBC has not been well characterized according to biologic subtypes and associated treatment outcomes. This is especially true in the modern era with the introduction of HER_2 directed therapies and the more frequent use of anthracyclin+taxanes based chemotherapy.[10]

We undertook this study to analyse the incidence, pattern of care and survival outcome of IBC based on different biologic subtypes.

2. Results

The median age of women at diagnosis was 56 years (N=8,550; IQR=18) (Table 1). On average, they were followed for 3.7 years [IQR=3.0]. Over half of the patients had private health insurance and lived more than 9 miles from their treatment facility, which in most cases was a comprehensive community cancer center (47%). White race was the predominant group within each biologic subtype (≥80%). Less than 4% of patients were classified as "other race".

A total of 7,087 (82%) of patients presented with HER_2^+ tumors. HR^+/HER_2^- (49%) and HR^+/HER_2^+ (36%) were the most common biologic subtypes, followed by HR^-/HER_2^- (10%) and HR^-/HER_2^+ (7%). Triple negative-IBC (TN-IBC) (25%) was the most frequently occurring subtype among black patients, with HR^+/HER_2^- having the lowest representation (14%).

The majority of patients presented with clinical stage IIIB disease (82%) and had poorly differentiated tumors (57%) (Table 2). TN-IBC had the highest percentage of grade III tumors (75%). Nearly 46% of tumors exceeded 5cm in size. The lowest risk of lymph node involvement was for HR^-/HER_2^+ (86%) compared with other biologic subtypes.

Approximately 71% of patients received radiotherapy, with a median dose of 5040 cGy (IQR=40) (Table 3). Systemic chemotherapy was administered to over 90% of patients while ~50%-60% of patients with HR^+ IBC received endocrine therapy. NACT was more commonly administered to patients with HR^-/HER_2^+ and TN subtypes than those having positive hormone receptor status. Neoadjuvant endocrine therapy was used in 15% patients (not shown in tables). The greatest pathologic complete response (pCR) rate was observed for women with HR^-/HER_2^+ tumors (27%) (p<.0001).

Mastectomy was the primary modality of surgery with partial mastectomy being used in only 5%-6% of patients. Less than 25% of women underwent contralateral mastectomy.

On univariable analysis, chemotherapy (HR=.41), hormone therapy (HR=.46), and radiotherapy (HR=.47) were associated with improved survival (p<.0001), while TN-IBC (HR=2.2) and positive margins (HR=2.0) conferred poorer survival (p<.0001).

Overall survival (OS) for patients with IBC at 5 years was 58% (95%CI=57%-59%). TN-IBC had the lowest survival rate, with only 37% (95%CI=33%-41%) surviving 5 years, compared with other subtypes (p<.0001) (Figure 1). Survival was consistently better for women who achieved pCR (77%, 95%CI=70%-83%) vs. non-pCR (54%, 95%CI=51%-56%) (HR=.40, 95%CI=.29-.53) (Figure 2 and 3). The greatest improvement in 5-year survival following pCR was for TN-IBC.

On multivariable analysis, TN-IBC subtype, positive margins and grade III/IV tumors were significant predictors of poor 5-year OS (p<.0001) (Table 4). Any systemic therapy and radiotherapy were associated with improved OS (p<.0001). Pairwise adjustment for age, clinical stage, comorbidities, facility type, grade, great circle distance, Hispanic ethnicity, immunotherapy, income, insurance status, lymph node invasion, lumpectomy, NACT, race, and tumor size did not substantively impact the model.

3. Discussion

3.1. Pathophysiology and classification of IBC

IBC is a distinct form of breast cancer noted for its higher tumor grade, -ve hormonal status, rapid progression, node +ve disease, metastasis at the time of diagnosis, and poor survival. [4,11-15] Upon physical examination, IBC typically presents as redness of skin (erythema), warm to touch, with edema

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(swelling) affecting over half of the breast.[16] Other features may include inverted nipple, lymphatic invasion of the skin, pain or itching, and/or no palpable tumor mass. [17] IBC is characterized by either diffused or localized radiographic density. [18] In most cases, the sign and symptoms of IBC will appear within a 6-month period. [19]

The expression of different cell growth and apoptosis related markers on the surface of IBC cells play an important role in disease prognosis and management. To aid in decision-making, IBC is increasingly being classified into biologic subtypes based on their phenotypic expression of HR and HER_2 receptors.[20,21] While phenotypic subtypes are important for predicting outcomes among women with non-IBC stage groups, this is not well established for IBC.

3.2. pCR and survival outcomes

Overall, clinical and radiologic findings do not correspond well with residual disease after therapy, necessitating the need for pathologic evaluation of tumor response. [22] Achieving pCR following NACT is an important surrogate endpoint of breast cancer survival, especially for high grade and aggressive cancers like HER_2^+ or TNBC. It also facilitates tumor shrinkage prior to surgery.[23-26] Increasingly, pCR is being used as a short-term endpoint in neoadjuvant clinical trials, given its prognostic association with longer-term outcomes.[27] Similar to the overall literature for breast cancer, we observed that pCR varies significantly among different biologic subtypes of IBC, with HR^-/HER_2^+ having the highest rate of pCR.[27-30] This supports the general belief that HR status is an important mechanism of underlying chemoresistance in this biologic subtype.[31,32] Additionally, patients achieving pCR in our study had superior 5-year survival compared with non-pCR and this was most significant for the TN-IBC subtype.

3.3. Comparison with published studies

Overall, clinical and radiologic findings do not correspond well with residual disease after therapy. Our results differ from a recent analysis of patients with IBC in the SEER database, which reported the best survival outcome for HR^+/HER_2^+.[20] Approximately 20% of patients in the SEER analysis had HR^+/HER_2^+ tumors compared with 36% in our study. This may be explained by different inclusion criteria and disease definition in the latter study. For example, we only included non-metastatic patients and also were able to identify IBC patients based on both clinical and pathologic characteristics. Additionally, patients with unknown biologic subtype were excluded in the SEER analysis. Nonetheless, both studies reported poor survival for patients with TN-IBC, which is consistent with our report and other studies in the literature.[33,34]

In a small single center study (n=316) of newly diagnosed IBC between 1989-2008, HR^-/HER_2^+ had inferior survival to HR^+/HER_2^+ and HR^+/HER_2^-.[34] Again, this differs from our results which found similar survival outcomes for the above biologic subtypes. Likely, this reflects the use of HER_2^+ targeted therapies in our study population, whereas many of the patients in the former study preceded the introduction of this treatment option. Furthermore, 99% of patients with IBC in this tertiary cancer care center received NACT, compared with ~37% in the current analysis.

Among patients in our study who did not achieve pCR, survival was better for those with HR^-/HER_2^+ tumors, than other biologic subtypes. This would suggest that HER_2^+ targeted therapies provide systemic benefit independently of achieving pCR, targeting microscopic residual tumor.

3.4. Use of triple-modality therapy in IBC

In the past, using single modality surgery or radiation, the survival of IBC was extremely poor (~5%). Although the use of triple-modality therapy for IBC has increased in recent times, OS remains low in comparison with non-IBC.[6,35] For example, in a population-based analysis of the SEER database, the 5-year OS of patients with estrogen receptor positive (ER^+) IBC was 49% and 25% for ER^- IBC. This is in comparison with 91% for women presenting with non-IBC ER^+ tumors and 77% for those with ER^- tumors, respectively.[35] The peak hazard rate (53%) among women with ER^- tumors occurred in the 12^{th} month following their diagnosis, compared with 8% in the 17^{th} month for non-IBC

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cases. However, beyond 7-years, there were no significant differences in hazard rates between ER^- and ER^+ tumors, for either IBC or non-IBC.

In an earlier study using NCDB, the use of triple-modality therapy increased from 58% in 1998 to the highest level of 73% in 2004.[6] On average (across biologic subtypes), RT was used in 71% of patients in the current analysis, conveying a significant survival advantage (HR=.63, p<.0001). This is similar to a recent study of 7,304 women with non-metastatic IBC, wherein radiotherapy was associated with improved 5-year survival (adjusted HR=.64, 95%CI=.61-.69).[36]

3.5. Strengths and limitations

Little is known about IBC especially in the context of biologic subtypes. By using NCDB, a multi-centric sample, we were able to analyze the data by these groups, while adjusting for outcome related covariates. To our knowledge, this is the first large-scale study of IBC, as defined by clinical, pathologic, histologic, and immunohistochemical characteristics.

While NCDB is the most comprehensive collection of IBC in the US, it may underrepresent certain priority populations and those lacking comprehensive health insurance.[37] Significant variability also exists in how data was reported across NCBD sites, limiting the generalizability of our results. Furthermore, information on specific systemic therapy, genomic profiling, functional imaging, tumor markers (e.g., EZH2 expression) and disease-specific survival was not available in NCDB.

The definition of pCR varies in the literature. [22] In our study, pCR was coded as a unique site-specific field (CSF-21), based on clinician documentation. While this may have introduce some inconsistencies, our outcomes among patients achieving pCR were congruent with other published results.[28-30]

Future studies will benefit by using a uniform criteria to identify IBC and incorporating information on loco-regional control. Obtaining functional phosphoproteomics data (e.g., hyperactive kinases such as (PRKCE, P70S6K, PNKP, ERK1/2, c-KIT, CDK6) also may be important when developing new prognostic models and treatment strategies for TN-IBC.[38,39]

4. Materials and Methods

4.1. Data Source

The NCDB database has been previously described.[40] In brief, over 1,500 Commission on Cancer (CoC) accredited cancer programs report data to the NCDB, encompassing approximately 70% of incident cancer cases in the US. [41] The database is the largest cancer registry in the world and contains nearly 10 million cases. In comparison, only 25% of new cancer cases are identified through the Surveillance, Epidemiology, and End Results (SEER) program. [42] Participant hospitals must satisfy 35 standards pertaining to the delivery of cancer care in order to be accredited by CoC. Every three years, hospitals are re-evaluated for their compliance with these standards. Records in NCDB are de-identified. NCDB has been collecting information on biologic subtypes for breast cancer since 2004. This study was considered exempt by the institutional review board (IRB) at the recipient NCDB member facility (Code of Federal Regulations 45 part 46.101(b)).

4.2. Eligibility

Patients with primary histologic diagnosis of invasive ductal, lobular or other primary breast histology subtypes undergoing any surgical resection from 2004-2013 were included in the analysis dataset. Patients were excluded if their RT dose was not within the range of 4000-6000 cGy or the primary target was outside the breast, chest wall or lymph nodes. Sarcomas, lymphomas, and leukaemias of the breast also were excluded in the analyses.

4.3. Definitions

Clinical and pathological stage were coded and assessed by each CoC facility based upon the American Joint Committee on Cancer (AJCC) TNM (**T**umor, **N**odes and **M**etastasis) system.[43] The

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majority of patients were staged according to the sixth and seventh editions of this coding system. Data was not converted from the lower TNM editions. Instead, a sensitivity analysis was performed by stratifying the data by year of diagnosis, with the cut-off value based on the year that the seventh edition was introduced (i.e., 2010).

IBC was defined as clinical stage IIIB/C tumours that were either: 1) clinical/pathology stage T4D, 2) histology code 8530, or 3) had a site specific extension code indicative of IBC (518, 519, 520, 575, 600, 613, 615, 620, 710, 720, 715, 725, 730, 750, 780).

Response to neoadjuvant chemotherapy (NACT) was recorded in the NCDB database as collaborative stage site-specific factor 21 (CSF-21), based on clinician documentation.

4.4. Treatment

Surgery remains the optimal treatment strategy for IBC, as part of a trimodal approach including chemotherapy and radiotherapy. NACT typically consisted of anthracycline based poly-chemotherapy and Trastuzumab (in the case of HER_2^+ tumors). Neoadjuvant or adjuvant hormone therapy when applicable was administered to patients with HR^+ tumors.

4.5. Statistical Analysis

Categorical variables were denoted as frequency and percentage, while continuous variables were reported as median and interquartile range (IQR). Statistical significance for categorical variables was tested using the chi-square (χ^2) procedure and the Kruskal-Wallis H test for continuous variables. A proportional hazard model was used to analyse 5-year survival, with corresponding probabilities computed using the Kaplan-Meier (product-limit) method. Follow-up time was measured from the date of surgery (baseline) to death (or censoring at 5 years). Variables with HR≥2.0 and p<.0001 in univariable analysis were included in the multivariable Cox regression survival model. The method of Grambsch and Therneau was used to test the proportional-hazards assumption of our survival models.[44]

Unless indicated otherwise, the reference group for binary coded variables was the complement of the indicated category. Other variables were categorized according to NCDB definitions. A multistage expectation-maximization (EM) algorithm was used to handle missing values.[45] Statistical significance was defined as p≤.05. SAS statistical software (version 9.4, SAS Institute Inc, Cary, NC) was used for all analyses.

5. Conclusions

This study demonstrates that the achieving pCR confers a survival benefit for all biologic subtypes of IBC. However, patients with TN-IBC were observed to have the worst survival outcome overall and when stratified by pCR status.

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Conflicts of Interest: None.

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Table 1: Patient demographic characteristics for IBC (N=8,550, 2004-2013)§

Characteristic	Biologic Subtype				P value
	$HR^+/HER2^-$ n (%) Median [IQR]	$HR^+/HER2^+$ n (%) Median [IQR]	$HR^-/HER2^+$ n (%) Median [IQR]	$HR^-/HER2^-$ n (%) Median [IQR]	
Overall (n)	4005	3082	610	853	
Age (years)	57 [19]	56 [19]	56 [17]	56 [19]	.011¶
<45	664 (17)	561 (18)	1112 (18)	157 (18)	
45-65	2248 (56)	1729 (56)	358 (59)	467 (55)	.17†
>65	1093 (27)	792 (26)	140 (23)	229 (27)	
Facility type					
Academic/research	1235 (31)	946 (31)	200 (33)	285 (33)	
Community	512 (13)	345 (11)	83 (14)	91 (11)	.14†
Comprehensive community	1872 (47)	1473 (48)	282 (46)	395 (46)	
Integrated network	387 (10)	318 (10)	45 (7)	82 (10)	
Great circle distance (miles)	9 [16]	9 [16]	10 [15]	9 [15]	.73¶
Health insurance					
Medicaid	555 (14)	438 (14)	106 (17)	142 (17)	
Medicare	1181 (29)	822 (27)	160 (26)	233 (27)	.0037†
Other government	38 (1)	27 (1)	3 (<1)	8 (1)	
Private	2056 (51)	1642 (53)	308 (50)	410 (48)	
None	175 (4)	153 (5)	33 (5)	60 (7)	
Hispanic	324 (8)	252 (8)	54 (9)	89 (9)	.14†
Income					
<$38,000	713 (18)	564 (18)	116 (19)	202 (24)	
$38,000-$47,999	943 (24)	768 (25)	151 (25)	200 (23)	.0065†
$48,000-$62,999	1169 (29)	863 (28)	184 (30)	238 (28)	
$63,000 +	1180 (29)	887 (29)	159 (26)	213 (25)	
Black race	578 (14)	492 (16)	103 (17)	212 (25)	<.0001†

§Non-metastatic, pathologically confirmed, primary tumours. †Chi-square test. ¶Kruskal-Wallis H test. AJCC: American Joint Committee on Cancer. HER=Human epidermal growth factor receptor. HR=Hormone receptor. IBC=Inflammatory breast cancer. IQR=Interquartile range.

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Table 2: Patient clinical characteristics for IBC (N=8,550, 2004-2013)[§]

Characteristic	Biologic Subtype				P value
	$HR^+/HER2^-$ n (%) Median [IQR]	$HR^+/HER2^+$ n (%) Median [IQR]	$HR^-/HER2^+$ n (%) Median [IQR]	$HR^-/HER2^-$ n (%) Median [IQR]	
Overall (n)	4005	3082	610	853	
Clinical stage (AJCC)					
IIIb	3315 (83)	2522 (82)	498 (82)	676 (79)	.12[†]
IIIc	690 (17)	560 (18)	112 (18)	177 (21)	
Charlson/Deyo score					
0	3367 (84)	2573 (83)	516 (85)	700 (82)	.67[†]
1	519 (13)	420 (14)	78 (13)	120 (14)	
2	119 (3)	89 (3)	16 (3)	33 (4)	
Differentiation (Grade)					
Well (I)	161 (4)	107 (3)	5 (1)	4 (<1)	
Moderately (II)	1676 (42)	1249 (41)	168 (28)	192 (23)	<.0001[†]
Poorly (III)	2122 (53)	1676 (54)	420 (69)	637 (75)	
Undifferentiated (IV)	46 (1)	50 (2)	17 (3)	20 (2)	
Lymph node invasion	3658 (91)	2845 (92)	523 (86)	763 (89)	<.0001[†]
Margins (positive)	558 (14)	370 (12)	56 (9)	108 (13)	.0036[†]
Tumour size (cm)					
≤2	455 (11)	373 (12)	80 (13)	88 (10)	<.0001[†]
>2-5	1763 (44)	1339 (43)	248 (41)	293 (34)	
>5	1787 (45)	1370 (44)	282 (46)	472 (55)	

[§]Non-metastatic, pathologically confirmed, primary tumours. [†]Chi-square test. [¶]Kruskal-Wallis H test. AJCC: American Joint Committee on Cancer. HER=Human epidermal growth factor receptor. HR=Hormone receptor. IBC=Inflammatory breast cancer. IQR=Interquartile range.

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Table 3: Treatment variables for IBC (N=8,550, 2004-2013)§

Treatment	Biologic Subtype				P value
	$HR^+/HER2^-$ n (%) Median [IQR]	$HR^+/HER2^+$ n (%) Median [IQR]	$HR^-/HER2^+$ n (%) Median [IQR]	$HR^-/HER2^-$ n (%) Median [IQR]	
Chemotherapy	3576 (89)	2801 (91)	570 (93)	807 (95)	<.0001†
Endocrine therapy	2423 (61)	1591 (52)	76 (12)	45 (5)	<.0001†
Immunotherapy ($HER2^+$)	NA	155 (5)	92 (15)	NA	<.0001†
Neoadjuvant therapy	1102 (28)	605 (20)	281 (46)	464 (54)	<.0001†
Response					
NR	488 (44)	286 (47)	75 (27)	128 (28)	<.0001†
pCR	71 (6)	76 (13)	77 (27)	59 (13)	
PR	543 (49)	243 (40)	129 (46)	277 (60)	
Radiotherapy	2888 (72)	2176 (71)	436 (71)	611 (72)	.58†
Dose (cGy)	5040 [40]	5040 [40]	5040 [40]	5040 [40]	.99¶
4000-5000	1106 (38)	824 (38)	163 (37)	241 (93)	.89†
>5000-6000	1782 (62)	1352 (62)	273 (63)	370 (61)	.24†
Lymph nodes treated	2002 (69)	1534 (71)	302 (69)	448 (73)	
Surgery					
BCS/Partial mastectomy	233 (6)	182 (6)	28 (6)	44 (5)	.53†
Mastectomy	3772 (94)	2900 (94)	582 (95)	809 (95)	.041†
Contralateral	782 (21)	575 (20)	143 (25)	183 (23)	

§Non-metastatic, pathologically confirmed, primary tumours. †Chi-square test. ¶Kruskal-Wallis H test. cGy=centigray NR=No response. HER=Human epidermal growth factor receptor. HR=Hormone receptor. IBC=Inflammatory breast cancer. IQR=Interquartile range. pCR=Pathologic complete response. PR=partial response.

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Table 4. Multivariable Cox regression survival model (5-years) for IBC (N=8,550, 2004-2013)[†]

Characteristic[§]	HR (95% CI)
Chemotherapy (-)	2.0 (1.8-2.2)
Hormone therapy (-)	1.9 (1.8-2.1)
Margins (+)	1.8 (1.7-2.0)
Triple negative	1.8 (1.6-2.0)
Radiotherapy (-)	1.6 (1.5-1.7)

[†]Variables with HR≥2.0 and p<.0001 in univariable analysis were included in the multivariable Cox regression survival model. [§]Pairwise adjustment for age, clinical stage, comorbidities, facility type, grade, great circle distance, Hispanic ethnicity, immunotherapy, income, insurance status, lymph node invasion, lumpectomy, neoadjuvant therapy, race, and tumor size did not substantively impact the model. CI=Confidence interval. HR=Hazard ratio. IBC=Inflammatory breast cancer.

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Figure 1. All patients (5-year survival)

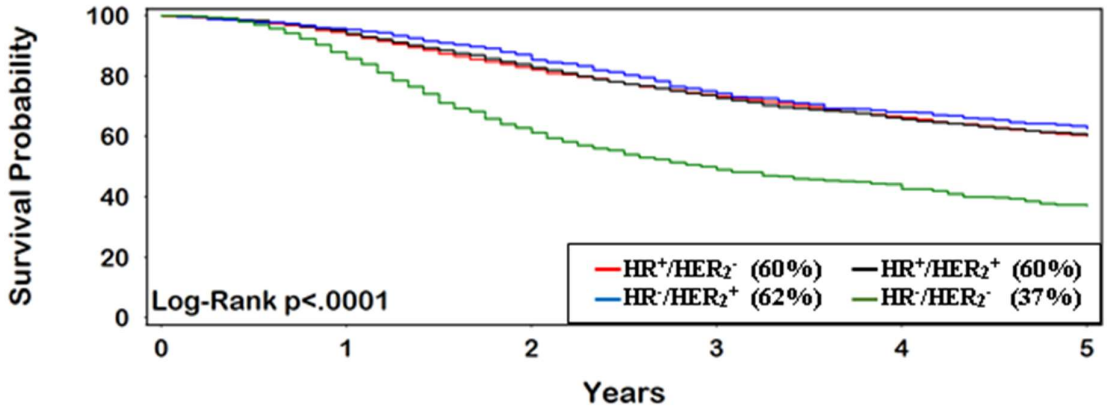

Figure 2. Patients with pCR following neoadjuvant therapy (5-year survival)

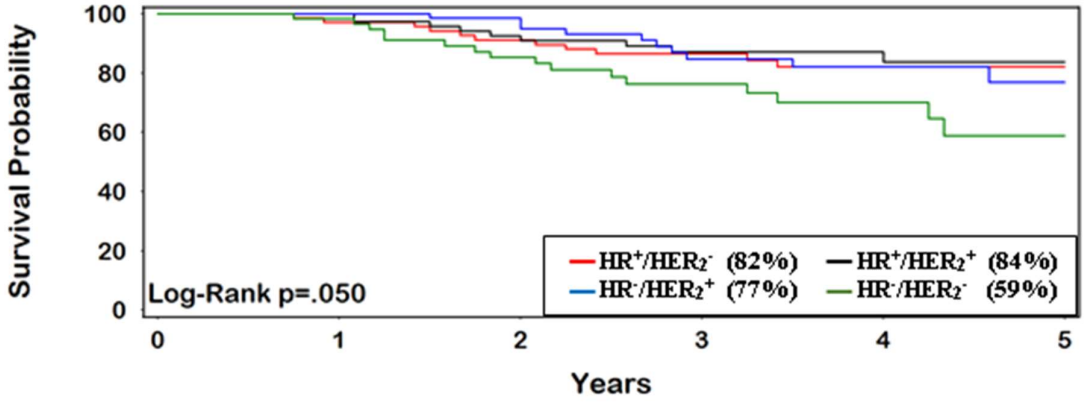

Figure 3. Patients without pCR following neoadjuvant therapy (5-year survival)