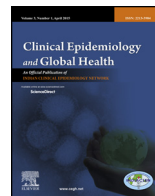




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Evidence summaries

Human epidermal growth factor receptor 2 borderline mortality in breast cancer patients: Evidence from surveillance, epidemiology, and end results program population-based study

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ABSTRACT

Background: Breast cancers with Human Epidermal Growth Factor Receptor 2 (HER2) borderline outcomes are very puzzling for patient management. To whether HER2 borderlines are having different prognostic status in comparison to HER2 positive/negative.

Methods: This is a study among women diagnosed with invasive breast cancer from 1973 to 2014 who were identified in the Surveillance, Epidemiology, and End Results (SEER) of 9 registries database and having diagnosed with HER2 status (N=102167), i.e. HER2 positive (N=14678), HER2 negative (N=85354) and HER2 borderline (N=2135).

Results: This Surveillance, Epidemiology, and End Results (SEER) study represents the largest report of prospective invasive breast cancer with HER2 status till five years from the date of registration. The five years survival rate among HER2 borderline was found completely separate with HER2 positive and HER2 negative patients. In several subtypes of analysis, it has been found that status of survival among HER2 borderline patients is significantly poor than HER2 positive and HER2 negative. The likelihood of death in HER2 borderline is found high (15.06%) in comparison to HER2 positive (14.24%) and HER2 negative (6.49%) at the end of five years. Different types of metastasis like Bone, Brain, Liver, and Lung are also observed with the higher rate in HER2 borderline in comparison to HER2 negative.

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Conclusion It can be concluded that HER2 borderline breast cancer patients are required to take specific treatment management, not in line with HER2 positive or HER2 negative.

1. Introduction

There is an existing variation on treatment success in breast cancer with different factors with Age, Race etc.^{1,2} Recently, organizations like are traced about the development of new research model to adopt in the clinical practice for the development of value-added cancer therapy.^{3,4} However, there is good success towards breast cancer particularly in the developed countries but breast cancer remains the leading cause among all types of female cancer deaths.⁵ The management of invasive breast cancer is decided through the evaluation of Human Epidermal

Growth Factor Receptor 2 (HER-2) status. There is a discrepancy on HER-2 status detection between manual Immuno Histo Chemistry (IHC) and Fluorescence In Situ Hybridization(FISH). The IHC is performed through a special staining process on frozen or fresh breast cancer tissue. It is performed to test the presence of HER2 receptors in cancer cell. The FISH test is performed on breast tissue to count the extra copies of HER2 gene. The outputs provide through FISH is considered as 'gold standard'.⁶ The gene amplification is considered to classify the status of the FISH as positive or negative. However, FISH and IHC both provides the HER-2 status with borderline status as well. Once it becomes difficult to classify the gene amplification as positive/negative then it is classified as "borderline". It is very important to test the hypothesis that whether the borderline HER-2 patients are clinically equivalent with presence or absences of HER-2 status or not. The Surveillance, Epidemiology, and End Results (SEER) Program was started in 1973 by the National Cancer Institute. It is a population-based cancer surveillance program. Nearly 30% of US populations are covered under this program and more than 98% incidence of

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cancer cases were covered.⁷ Information on demographics profile, site of the tumor, type of treatment and survival status of the patients is recorded. Patients treated with breast cancer and their HER-2 status was recorded in the SEER database.

The objective of this study is to check the performance of HER-2 borderlines in comparison to HER-2 positive/negative. In this study, we analyze the 'borderline' group of tumors identified by FISH. The median overall survivals (OS) of patients with HER-2 positive, negative are compared with HER-2 borderlines.

2. Methods

This study analyzed data on HER2 status in breast cancer patients from the SEER registries. The dataset are accessible from <https://seer.cancer.gov/data/citation.html> through signed Research Data Agreement Form. Data is based on the population-based cancer registries that participate in the SEER program under National Cancer Institute (NCI).⁵ The SEER program covers the data from states of Connecticut, Iowa, New Mexico, Utah, Hawaii, Louisiana, Kentucky, New Jersey, and California and from Alaska Natives in Alaska, in addition to the metropolitan areas of Detroit, Michigan; San Francisco-Oakland, San Jose-Monterey, and Los Angeles County, California, Atlanta, Georgia, and Seattle-Puget Sound, Washington. Around 30% of U.S. populations are covered under SEER program. Different types of patient's demographic information, diagnosis confirmation, and the first course of treatment, the extent of disease, morphology, and active patient follow-up for vital status including the cause of death are included in this program. The cause of death is derived from death certificate of a resident when cancer is listed as a cause of death. The reported incidence and death status data are available nearly two years after the end of the calendar year. Till now the incidence data till December 2014 is available. The HER2 status of all breast cancer patients is included in this study. The influence of HER2 status on survival outcomes is considered. The survival analysis is performed through the Cox Proportional Hazard (CPH) and Accelerated Failure Time (AFT) models.

3. Results

Total of 102167 patients in the participating SEER registries of invasive breast are included in this study (Table 1). The distribution pattern of age, race and tumor size of these patients are like: Age (<40 years, i.e. 3127 [9.95%]), Age(40–49 years i.e. 5401 [17.19%]),

Age(50–59 years i.e. 8256 [26.28%]), Age(60–69 years i.e. 7603 [24.2%]), Age(70–79 years i.e. 4436 [14.12%]) and Age(>80 years i.e. 2585 [8.23%]). The tumor sizes are classified as <5 mm, 5–10 mm, 10–15 mm, 15–20 mm, 20–40 mm and >40 mm. All histological grades are presented with grades 1, 2 and 3 respectively. The further demographic classification based on Grade1, Grade2 and Grade3 of the breast cancer are provided in Tables 4–6 (Supplementary File S1) respectively. The Progesterone Receptor (PR) and Estrogen Receptor (ER) status of the patients in all grades are given in Table 1 and Tables 4–6. Comparison of the occurrence of HER-2 positive, HER-2 negative and HER-2 borderline in different Age groups, tumor sizes and Race are given with p-value. It shows that there is not any difference about occurrence of HER-2 positive, HER-2 negative and HER-2 borderline in any subtypes of Age, Race and Tumor size except race for Grade 1. The analysis provides the comparison of the bone, liver, lung and brain metastasis in HER-2 positive, HER-2 negative and HER-2 borderline in Table 2. It provides that there is a significant occurrence of HER-2 status in different metastasis. It shows that occurrence of different metastasis is relatively higher in HER-2 borderline group in comparison to HER-2 positive, HER-2 negatives. Occurrence of different metastasis in ER and PR status also presented graphically. It shows that different types of metastasis are relatively higher in ER borderline in comparison to ER positive and ER negative. Same

Table 2
Different Types of Metastasis on HER2 Status, ER Status and PR Status for the treated patients from 2010+.

Types of Metastasis	HER2+	HER2-	HER2 B	P-value
Bone	634(4.25%)	2226(2.55%)	80(3.66%)	<2.2e-16
Brain	94(0.63%)	204(0.23%)	12(0.55%)	<2.2e-16
Liver	401(2.69%)	708(0.81%)	22(1.01%)	<2.2e-16
Lung	317(2.12%)	961(1.10%)	31(1.42%)	<2.2e-16
ER+ ER- ER B P-value				
Bone	2441(2.8%)	481(2.85%)	1(1.37%)	0.7046
Brain	189(0.22%)	118(0.7%)	0(0.0%)	<2.2e-16
Liver	743(0.85%)	378(2.24%)	1(1.37%)	<2.2e-16
Lung	901(1.03%)	401(2.38%)	1(1.37%)	<2.2e-16
PR+ PR- PR B P-value				
Bone	1964(2.59%)	945(3.35%)	7(4.76%)	2e-10
Brain	140(0.18%)	164(0.58%)	2(1.36%)	<2.2e-16
Liver	547(0.72%)	567(2.01%)	5(3.40%)	<2.2e-16
Lung	713(0.94%)	582(2.06%)	3(2.04%)	2.2e-16

Table 1
Patient Demographics by HER2, ER and PR status(N = 102167).

Category	All Grades									
	HER2+	HER2-	HER2B	ER+	ER-	ERB	PR+	PR-	PRB	P-value
Age	1532	4234	109	4312	1551	5	3752	2104	9	0.65
	2615	12239	296	12404	2698	15	11391	3694	16	0.07
	4215	20131	525	23012	4513	10	17356	7410	37	0.91
	3527	23911	569	23841	4112	15	20576	7336	36	0.22
	1839	16066	405	15967	2304	19	13796	4456	25	0.19
	950	8773	231	8618	1313	5	7304	2604	16	0.35
Race	1820	8777	255	7874	2956	7	6449	4376	7	0.02
	1867	9087	192	9344	1787	6	8149	2968	13	0.81
	42	230	4	241	35	0	213	62	1	0.07
	10949	67260	1684	67995	11713	56	59364	20198	118	0.2
	Tumor Size	1237	7380	211	7693	1108	8	6539	2230	13
1687		16529	340	16752	1775	5	14917	3579	22	0.2
4280		29768	711	30050	4649	17	26524	8130	45	0.27
4574		21505	554	20984	5595	22	17977	8571	29	0.34
2900		10172	319	9945	3364	17	8218	5094	30	0

*153 patients ER status and 249 patients ER and PR status were unknown in this cohort of 102167, A total of 4023 patients Grades were unknown.

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