

To evaluate correlation of hormone receptors, Ki67 and human epidermal growth factor with other prognostic factors in invasive ductal carcinoma of breast

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Summary

Objective: The objective of this study was to determine the expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor (HER2), Ki67 and their correlation with other prognostic factors in invasive ductal carcinoma of breast. **Subject and method:** A retrospective and prospective descriptive study on 175 patients with invasive ductal carcinoma of breast at the 108 Military Central Hospital from May 2019 to September 2021. The status of ER, PR, HER2 and Ki67 expression was examined by immunochemistry. **Result:** The mean age of the patients was 53.3 ± 12.5 years. The common rate of 2 - 5cm tumor was (95/175) 54.3%. The percentage of cases with tumor grade 2 was the highest at (90/175) 51.4%. The expression of ER, PR, HER2, Ki67 ($\geq 14\%$) were found positive in 53.7%, 51.4%, 33.1%, and 57.7%, respectively. We observed significant correlation between age and ER, PR, HER2 expression ($p < 0.05$). **Conclusion:** None of these markers showed association with location of tumor ($p > 0.05$). A significant correlation was observed between tumor size and ER, PR expression ($p < 0.05$). Histological grade was related to ER, Ki67 expression ($p < 0.05$).

Keywords: Invasive ductal carcinoma of breast, immunohistochemistry, ER, PR, HER2, Ki67.

1. Background

Female breast carcinoma is the most common malignancy and the leading cause of cancer related death among women all around the world, with over two million cases diagnosed in 2018 [1], [9]. Breast cancer patient survival is linked to early detection, timely appropriate treatment and genetic predisposition. Factors that are known to be important in the prognosis of breast malignancies in individual patients include tumor size, stage of the disease at diagnosis, histological type, tumor grade, lymph node metastasis and hormonal receptor status [2], [8]. Currently, the determination of ER, PR,

HER2, Ki67 are routine in the diagnosis of breast cancer [1]. ER, PR, HER2, Ki67 have an increasing importance influenced the management of the breast cancer [2]. The most common histological type of breast cancer is invasive ductal carcinoma [5]. In Vietnam, there have been some studies on histopathological and immunohistochemical characteristics of breast carcinoma [6], [7], [10], but studies on invasive ductal carcinoma aimed of evaluating the correlation between the expression of immunohistochemical markers and histopathological features have still been limited. This study performed to determine the expression of ER, PR, HER2, Ki67 and their possible correlation with other prognostic factors in infiltrating ductal carcinoma of breast.

2. Subject and method

2.1. Subject

Received: 12 October 2021, Accepted: 24 November 2021

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175 patients were enrolled in our study. All of them were diagnosed with invasive ductal carcinoma of breast at the 108 Military Central Hospital from May 2019 to September 2021.

2.2. Method

A cross-sectional, retrospective and prospective study.

Specimens are routinely processed and fixed overnight in 10% neutral buffered formalin, paraffin embedded. Four to five micrometer thick tumor sections were stained with Haematoxylin-Eosin.

Immunohistochemical staining: Immunohistochemical staining slides using BenchMark ULTRA machine of Ventana (USA) with ER, PR, HER2, Ki67 markers (Dako Company, Denmark).

2.3. Research content

3. Result

3.1. Clinicopathological and immunohistochemical characteristics of the invasive ductal carcinoma of breast

Table 1. Clinicopathological and immunohistochemical characteristics of the infiltrating ductal carcinoma of breast

Features		n	%
Total cases		175	100
Age (years)	< 40	26	14.9
	40 - 49	41	23.4
	50 - 59	52	29.7
	≥ 60	56	32
Location	Right	76	43.4
	Left	99	56.6
Tumor size (cm)	< 2	66	37.7
	2 - 5	95	54.3
	> 5	14	8
Histological grade	1	14	8
	2	90	51.4
	3	71	40.6
ER, PR	ER-	81	46.3
	ER+	94	53.7
	PR-	85	48.6
	PR+	90	51.4
HER2	HER2-	117	66.9
	HER2+	58	33.1
Ki67	< 14%	74	42.3
	≥ 14%	101	57.7

Age, location, tumor size.

Histological grade was assessed according to Nottingham modification of the Bloom-Richardson system.

To evaluate the expression of immunohistochemical markers: Evaluating ER, PR results according to the standards of Allred and the manufacturer Dako; evaluating HER2 results according to ASCO/CAP standards. Ki67 is positive when any nuclei of tumor cells are stained. The Ki67 index is divided into 2 levels: Low (< 14%) and high (≥ 14%).

2.4. Statistical analysis

Using IBM SPSS 22.0 software for analyzing data. Differences at $p < 0.05$ were regarded as statistically significant.

The mean age of the patients was 53.3 ± 12.5 (23 - 82 years). Most of the patients were ≥ 60 years at diagnosis. The left breast was more commonly (56.6%). The common rate of 2-5cm tumor was 54.3%. The percentage of cases with histologic grade 2 was highest at 51.4%. ER, PR, HER2, Ki67 ($\geq 14\%$) were positive in 94 (53.7%), 90 (51.4%), 58 (33.1%), and 101 (57.7%) cases, respectively.

3.2. Correlation of ER, PR, HER2, Ki67 with others prognostic factors

Table 2. Correlation of ER, PR, HER2, Ki67 with others prognostic factors

Features	ER			PR			HER2			Ki67		
	+	-	p	+	-	p	+	-	p	≥ 14%	< 14%	p
Age (years)												
< 40	11	15	0.002	13	13	0.002	10	16	0.026	18	8	0.272
40 - 49	19	22		28	13		7	34		19	22	
50 - 59	22	30		16	36		24	28		32	20	
≥ 60	42	14		33	23		17	39		32	24	
Location												
Left	40	36	0.801	35	41	0.212	31	45	0.06	43	33	0.79
Right	54	45		55	44		27	72		58	41	
Tumor size (cm)												
≤ 2	53	31	0.017	50	34	0.04	26	58	0.554	47	37	0.65
> 2	41	50		40	51		32	59		54	37	
Histological grade												
1	4	10	0.015	7	7	0.516	5	9	0.162	5	9	0.001
2	57	33		50	40		24	66		43	47	
3	33	38		33	38		29	42		53	18	

There was correlation between age and ER, PR, HER2 expression ($p < 0.05$).

None of these markers showed significant correlation with location of tumor.

The statistically significant correlation was observed between tumor size and ER, PR expression ($p < 0.05$).

The significant positive correlation was observed between histological grade and ER, Ki67 expression ($p < 0.05$).

4. Discussion

4.1. Clinicopathological and immunohistochemical characteristics of the invasive ductal breast carcinoma

This study was conducted on 175 patients with invasive ductal breast carcinoma. Most of the

patients (61.7%) were more than 50 years at diagnosis, and the mean age of the study participants was 53.3 years. This corresponds to what was reported by Dodiya H et al [4] with the data was 63.2%. On the contrary, some studies reported the rate was higher in patients under 50 years of age [1], [9]. The left breast was more commonly (56.6%). This was consistent with the study conducted by Van Chu Nguyen (2016) [7].

Tumor size: More than half of the tumors were 2 - 5cm (54.3%). Other authors also published similar results such as Cong Thuan Dang (2011) [3], Azizun-Nisa et al (2008) [2], Usman Malami Aliyu et al (2020) [1] with the corresponding rate of 57.4%, 52.7% and 50.6%. When the tumor size is from 2 to 5cm, patients can easily detect it by themselves, so the percentage of tumors in this size range accounted for the highest rate.

Histological grade: Tumor grade 2 had the highest rate of 51.4%, followed by tumor grade 3 accounting for 40.6%, tumor grade 1 had the lowest

rate with 8%, consistent with the results of some local studies and international studies.

Table 3. Comparison of histological grades between studies

Authors	Histological grade (%)		
	1	2	3
Van To Ta (2004) [10]	12.2	71.4	16.4
Cong Thuan Dang (2011) [3]	5.7	44.3	50
Azizun-Nisa (2008) [2]	6.7	55.3	38
Usman Malami Aliyu (2020) [1]	23.9	50.6	25.5
Our study	8	51.4	40.6

Histological grade was related not only to recurrence rate, mortality rate, but also to disease-free survival and overall survival of patients with breast carcinoma after surgery. The 5-year survival rate gradually decreased by grade 1, grade 2, grade 3 with a statistically significant difference [10].

Expression of some immunohistochemical markers in invasive ductal breast carcinoma

The positive rates for ER, PR, HER2 in our study were 53.7%, 51.4% and 33.1%, respectively. Comparing with the results of some studies conducted by Vietnamese authors and foreign authors presented in the following table:

Table 4. Positive ER, PR, HER2 staining results across studies

Authors	ER (+) (%)	PR (+) (%)	HER2 (+) (%)
Cong Thuan Dang (2011) [3]	53.3	46.7	61.3
Van Chu Nguyen (2016) [7]	52.7	50.3	26.7
Van To Ta (2004) [10]	59.1	51.4	35.1
Usman Malami Aliyu (2020) [1]	68.5	77.7	57.5
Edlira Pajenga (2016) [8]	69.1	66.4	41
Hardik Dodiya (2012) [4]	60.8	54.9	46.6
Our study	53.7	51.4	33.1

Ki67 expression: Ki67 ($\geq 14\%$) was positive in 57.7%. This data is similar to the result of the study conducted by Van Chu Nguyen (58.4%) [7].

4.2. Correlation of ER, PR, HER2, Ki67 with other prognostic factors

In this study, the majority of ER, PR, and HER2 positives were in the age group over 50 years old, with rates of 68%, 54.4% and 70.7%, respectively. The expression of ER, PR, HER2 between age groups was statistically significant ($p < 0.05$). This is in line with studies by Siadati S et al (2015) [9], Dodiya H et

al (2013) [4]. The results showed that the expression of ER, PR were significant relationship with age, but it was not seen in HER2 expression. None of these markers showed significant correlation with the location of tumor.

In our study, the statistically significant correlation was observed between tumor size and ER, PR expression ($p < 0.05$). In contrary to the study of Siadati S et al (2015) [9], they found no correlation between tumor size and these makers. The explanation for these variable results is not obviously

known, eventhough tumor size was considered as one of the substantially prognostic factors.

This study also found that a significant positive correlation was observed between histological grade and ER, Ki67 expression ($p < 0.05$). A study conducted by Pajenga E et al (2016) also reported the same result [8].

In his work, Cong Thuan Dang studied on 150 patients with breast carcinoma showed that the expression of ER, PR, and HER2 did not correlate with age groups ($p > 0.05$) but the correlation was observed in the tumor grade ($p < 0.05$) [3].

The difference could due to evaluating histological and immunohistochemical apperance depended on the personal opinions of pathologists. In addition, it is also possible that the biological characteristics of the research groups in geographical areas are different.

5. Conclusion

This study was conducted on 175 patients with invasive ductal breast carcinoma. We obtained the following results:

The percentage of cases with tumor grade 2 was highest at (90/175) 51.4%.

The expression of ER, PR, HER2, Ki67 ($\geq 14\%$) were found positive in 53.7%, 51.4%, 33.1%, and 57.7%, respectively.

There was significant correlation between age and ER, PR, HER2 expression. None of these markers showed a significant asscociation with location of tumor. The statistically significant correlation was observed between tumor size and ER, PR expression. The positive relation between histological grade and ER, Ki67 expression was noticed.

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