

ภาวะตัวรับฮอร์โมนในผู้ป่วยมะเร็งเต้านมของหญิงไทยในภาคตะวันออกเฉียงเหนือ : ผลวิเคราะห์จากผู้ป่วย 241 ราย ที่โรงพยาบาลศรีนครินทร์

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Hormonal Receptors Status of Breast Cancer in Northeastern Thai Women : An Analysis of 241 cases at Srinagarind Hospital

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หลักการและเหตุผล: การรักษาผู้ป่วยมะเร็งเต้านมขึ้นอยู่กับความผิดปกติของยีนและปัจจัยที่เกี่ยวข้องกับการพยากรณ์โรคขึ้นกับภาวะตัวรับฮอร์โมน ลักษณะทางจุลพยาธิวิทยาของเซลล์มะเร็ง ขนาดของก้อนมะเร็งและการแพร่กระจายไปต่อมน้ำเหลือง

วัตถุประสงค์: เพื่อศึกษาปัจจัยที่เกี่ยวข้องกับการพยากรณ์โรค ได้แก่ ภาวะตัวรับฮอร์โมนเอสโตรเจน ภาวะตัวรับฮอร์โมนโปรเจสเตอโรน และ HER2 ของผู้ป่วยหญิงไทยในภาคตะวันออกเฉียงเหนือ

วัสดุและวิธีการ: การศึกษาย้อนหลังในผู้ป่วย 294 รายที่ได้รับการวินิจฉัยว่าเป็นมะเร็งเต้านมที่ส่งมาเพื่อศึกษาภาวะตัวรับฮอร์โมน ที่ภาควิชาพยาธิวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น โรงพยาบาลศรีนครินทร์ ระหว่างเดือนมกราคม 2547 ถึงเดือนมิถุนายน 2549

ผลการศึกษา: อายุเฉลี่ยและอายุมัธยฐานของผู้ป่วยกลุ่มนี้เท่ากับ 52.21 ปีและ 53 ปี ตามลำดับ พยาธิวิทยาของผู้ป่วยพบ 89.83% เป็นมะเร็งเต้านมชนิด invasive ductal carcinoma และเป็น grade II เท่ากับ 50.93 % พบภาวะตัวรับฮอร์โมนเอสโตรเจนเท่ากับ 53.1 % ภาวะตัวรับฮอร์โมนโปรเจสเตอโรนเท่ากับ 42.26 % และ HER2 เท่ากับ 27.15 % โดยที่มีความสัมพันธ์ร่วม ER+PR+, ER+PR-, ER-PR+, ER-PR- กับ HER2 เป็น 4.7 % 20.5 % 29.4% และ 44.2 % ตามลำดับ

สรุป: จากการศึกษาพบว่าโอกาสที่ HER2 เป็นบวกจะสูงขึ้นเมื่อทั้งภาวะตัวรับฮอร์โมนเอสโตรเจนและภาวะตัวรับฮอร์โมนโปรเจสเตอโรนเป็นลบ

Background: The most effective treatment for breast cancer cases is based on an abnormal oncogene of the cancer cell and the finding of protein expression. The prognostic factor depends on hormonal receptors status and biological characteristics such as histological grading, tumor size or nodal metastasis.

Objective: To study prognostic factors including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status in Northeastern Thai female breast cancer.

Materials and Methods: A retrospective review was performed on 294 patients who have been diagnosed with breast cancer by hormonal study at department of Pathology, Khon Kaen University (Srinagarind hospital) during January 2004 - June 2006.

Result: The mean and median ages were 52.21 year and 53 year, respectively. The 89.83 % of the patients were invasive ductal carcinoma and 50.93 % in histological grading II. The ER+, PR+ and HER2 positive were 53.1%, 42.26% and 27.15%, respectively. The proportion of ER+PR+, ER+PR-, ER-PR+, ER-PR- and HER2 were 4.7, 20.5, 29.4 and 44.2 % , respectively.

Conclusion: The present study showed that the highest chance to get HER2 positive was when both ER and PR were negative.

Keywords: Breast Cancer, Estrogen Receptor, Progesterone Receptor, Human Epidermal Growth Factor Receptor 2

Introduction

Breast cancer is an increasingly important cause of illness and death among women. It is the most common malignancy affecting women in North America and Europe. In 2000 approximately 184,200 new cases of invasive breast carcinoma were diagnosed in the United States¹. In Thailand, it is the second most common cancer among women which comprises 16.3 % of all female malignancies².

It has been proven that chemotherapy and hormonal therapy improves the prognosis of post operation breast cancer. Recently, the selection of the most effective treatment for breast cancer cases is based on an abnormal oncogene of the cancer cell and the finding of expression of the protein. Estrogen receptor (ER) and progesterone receptor (PR) are used as prognostic factors. For instance, ER positive (ER+) tumors are more responsive to hormonal therapies than ER negative (ER-)⁴⁻⁷. The significance of PR status has been studied to determine its predictive role in breast cancer treatment⁶ and its role as a prognostic factor^{5,7}. There are some evidences to suggest that the joint classification of ER and PR status enhances the predictative power compared with either one separately⁷⁻⁹. The evaluation of high levels of human epidermal growth factor receptor 2 (HER2) overexpressed in breast cancer patients is another prognostic factor^{3,18}, which might benefit from trastuzumab treatment¹⁶.

Clinical data have shown differences in the status of hormonal receptors according to age and other biological characteristics such as histological grading, tumor size, nodal status or race and ethnicity¹⁰⁻¹³.

To study prognostic factors including ER, PR and HER2 in Northeastern Thai female breast cancer, the authors examined data of ER, PR and HER2 status in female breast cancer at Srinagarind hospital between January 2004 to June 2006.

This study reports the characteristics of the ER/PR/HER 2 status and correlation by age, histologic grading, tumor size and nodal status.

Material and Methods

All breast cancer specimens at Srinagarind hospital between January 2004 and June 2006 were reviewed. There were 294 cases, including 98 cases of paraffin blocks referred from other hospitals requesting for

hormonal study. These cases were confirmed by microscopic examination. There were 241 cases included in the study because of the availability of ER and/or PR, and HER2 results. Four cases of carcinoma in situ with microinvasive carcinoma were excluded, finally, 241 specimens were analyzed (241 cases for ER, 240 cases for PR and 221 cases for HER2).

The ER, PR and HER2 status was coded by Pathologists using immunohistochemical analysis. The ER and PR reports as negative and positive 1+, 2+, 3+ and 4+ as shown in table 1. The HER2 reported as negative (0, 1+) and positive (2+ or 3+) as shown in table 2.

The frequency of tumors for age groups was subdivided into <35 years, 35-39 years, 40-49 years, 50-59 years, 60-69 years and >_70 years.

The histologic grade codes were determined based on histologic type data of the World Health Organization (WHO)¹⁷. Grade I tumors were well differentiated. Grade II tumors were moderately differentiated. Grade III tumors were poorly differentiated. Unknown grade indicated that the grade type was not applicable.

Statistical Analyses

The frequency of ER/PR and HER2 groups with correlation to age group, histological grading, tumor size and nodal status were determined using frequency count and percentage.

Result

Studying of 294 cases of female invasive breast cancer patients whose the youngest one was 23 years old and the oldest one was 83 years old. The mean age was 52.21 years and the median age was 53 years. Sixty - one point two - two of all patients were in two age groups divided by 31.97 % for 40-49- year age group and 29.25 % for 50-59- year age group. The less number of patients was in <35-year age group which was 3.40 % (table 3).

Majority of histological grading was in grade II which was 50.93 % of 216 cases, discounted 78 unknown cases. Only 1.85 % of patients were in grade 0 (ductal carcinoma in situ and microinvasive carcinoma) which distributed only to 40-49-year age group and 50-59-year group (table 4). The tumor size also revealed the same finding which was 50.95 % in size >2-5 centimeters in diameter and only 0.95 % in size 0(no mass) (table 5). Most of cancers were in no axillary lymph node metastasis

Table 1 Reporting system

Expression of Estrogen receptor (ER)	Expression of Progesterone receptor (PR)	Score
0-10	0-10	0
11-25	11-25	1+
26-50	26-50	2+
51-75	51-75	3+
76-100	76-100	4+

Table 2 Reporting system of HER2

Staining of cell membrane border in 10% of invasive malignant cells	Classified as
Non staining	0
Few staining	1+
Whole cellular border staining	2+
Marked staining in whole cellular border	3+

Table 3 Number of female invasive breast cancer patients

Age, year	Number of case	%
< 35	10	3.40%
35-39	28	9.52%
40-49	94	31.97%
50-59	86	29.25%
60-69	50	17.01%
>=70	26	8.84%
Total	294	100.00%

Table 4 Relation of Age and Histological Grading

Age	Histological Grading					
	0	I	II	III	Others*	Unknown
< 35	0	0	2	2	4	2
35-39	0	1	12	4	0	11
40-49	1	9	35	15	8	26
50-59	3	6	34	14	6	23
60-69	0	6	16	12	6	10
>=70	0	2	11	3	4	6
Total	4	24	110	50	28	78

*NB. Other tumors were twelve mucinous, nine medullary and seven lobular carcinoma

Table 5 Relation of Age and Tumor Size

Age	Tumor Size(cms)				
	0	≤2	>2-5	>5	Unknown
< 35	0	2	3	0	5
35-39	0	6	12	2	8
40-49	1	19	35	9	30
50-59	1	23	25	11	26
60-69	0	11	15	10	14
≥70	0	4	17	4	1
Total	2	65	107	36	84

Table 6 Relation of Age and Tumor Size

Age	Positivity of axillary lymph node				
	0	1-3	4-9	≥10	Unknown
< 35	4	0	0	0	6
35-39	13	4	1	2	8
40-49	46	11	4	3	30
50-59	37	9	5	6	29
60-69	18	9	5	6	12
≥70	16	3	5	1	1
Total	134	36	20	18	86

Table 7 Relation of Age and ER

Age	ER					Total
	0	1+	2+	3+	4+	
< 35	4	0	2	2	2	10
35-39	6	3	5	1	3	18
40-49	36	8	9	10	16	79
50-59	42	4	11	8	7	72
60-69	19	8	5	3	5	40
≥70	6	2	4	1	9	22
Total	113	25	36	25	42	241

Table 8 Relation of Age and PR

Age	PR					Total
	0	1+	2+	3+	4+	
< 35	7	0	2	1	0	10
35-39	10	1	1	2	4	18
40-49	40	7	7	10	14	78
50-59	49	8	8	5	2	72
60-69	25	4	6	3	2	40
>=70	8	2	5	1	6	22
Total	138	22	29	22	28	240

Table 9 Relation of Age and HER2

Age	HER2				Total
	0	1+	2+	3+	
< 35	3	4	2	0	9
35-39	7	5	2	3	17
40-49	38	17	15	3	73
50-59	31	13	20	4	68
60-69	25	3	5	2	35
>=70	12	3	4	0	19
Total	116	44	48	12	221

Table 10 Relation of ER, PR and HER2

ER	PR	HER2			Total
		2+	3+	Negative	
+	+	3	1	68	72
+	-	7	2	35	44
-	+	4	1	9	14
-	-	34	8	49	91

which was 64.42 % out of 208 cases. The patients, age below 35 years old were not found axillary lymph node metastasis (table 6).

In analysis (tables 7 - 9), ER negative was 40 % in <35-year age group, 33.33 % in 35-39-year age group, 45.57 % in 40-49-year age group, 58.33 % in 50-59-year age group, 47.50 % in 60-69-year age group, 27.27 % in >=70-year age group. PR negative was 66.67 % in <35-year age group, 55.56 % in 35-39-year age group, 51.28 % in 40-49-year age group, 68.06 % in 50-59-year age group, 62.50 % in 60-69-year age group, 36.36 % in

>=70-year age group. HER2 negative was 75 % in <35-year age group, 70.59 % in 35-39-year age group, 75.34 % in 40-49-year age group, 64.71 % in 50-59-year age group, 80 % in 60-69-year age group, 78.95 % in >=70-year age group. The authors found that in 50-59-year age group showed highest ER negative and PR negative which were 58.33 % and 68.06 %, respectively, but HER2 was the highest number at 35.29 %. ER negative and PR negative were the least in >=70-year age group, which were 27.27 % and 36.36 %, respectively.

Table 11 Relation of ER, PR, HER2 and Grading

		Grading					Total
		0	I	II	III	Others	
ER	0	1	5	45	31	6	88
	1+	0	3	15	4	1	23
	2+	2	2	12	4	2	22
	3+	1	5	10	2	6	24
	4+	0	6	0	2	9	17
	Total	4	21	82	43	24	174
PR	0	2	7	54	35	10	108
	1+	0	2	15	1	3	21
	2+	1	5	9	4	3	22
	3+	1	4	10	1	5	21
	4+	0	3	18	2	3	26
	Total	4	21	106	43	24	198
HER2	0	1	14	48	27	11	101
	1+	0	2	25	5	7	39
	2+	1	1	24	6	4	36
	3+	0	2	4	1	0	7
	Total	2	19	101	39	22	183

Table 12 Relation of ER, PR, HER2 and Tumor size

		Tumor Size(cms)				Total
		0	=<2	>2-5	>5	
ER	0	1	23	34	18	76
	1	0	10	9	2	21
	2	0	6	17	3	26
	3	0	4	10	2	16
	4	0	12	19	1	32
	Total	1	55	89	26	171
PR	0	1	32	40	18	91
	1	0	4	10	2	16
	2	0	6	11	3	20
	3	0	3	10	1	14
	4	0	4	16	2	22
	Total	0	17	47	8	163
HER2	0	0	34	36	12	82
	1	0	12	13	4	29
	2	1	4	21	6	32
	3	0	3	6	1	10
	Total	1	53	76	23	153

Table 13 Relation of ER, PR, HER2 and Node

		Positivity of axillary lymph node				Total
		0	1-3	4-9	>=10	
ER	0	47	13	9	6	75
	1	13	2	2	3	20
	2	16	3	6	1	26
	3	11	3	0	1	15
	4	22	7	1	2	32
	Total	109	28	18	13	168
PR	0	61	17	10	10	98
	1	11	2	3	0	16
	2	14	3	2	1	20
	3	8	3	1	1	13
	4	15	3	2	1	21
	Total	109	28	18	13	168
HER2	0	54	12	12	5	83
	1	20	2	1	3	27
	2	14	11	3	3	33
	3	7	1	1	1	13
	Total	95	26	17	12	150

Table 10 showed most of patients (41.18 %) was both ER & PR negative. Next was both ER and PR positive at 32.58 %. The patient at the amount of 19.91 % was ER positive and PR negative. The smallest number of patients, 6.33% was ER negative and PR positive. The relation of ER, PR and HER2 showed when ER and PR were both positive then HER2 was 5.56 % positive. HER2 showed highest positive figure (46.15 %), when both ER and PR were negative. When ER positive and PR negative, HER2 was 20.45 %. HER2 was 35.71 % when ER negative and PR positive.

It could indicate from table 11 that the higher the number of grading, the higher chance to get ER negative (Grading I = 23.81 %, Grading II = 54.88 % and Grading III = 72.09 %). The correlation could be found in PR (Grading I = 33.33 %, Grading II = 50.94 % and Grading III = 81.40 %). If grading is 0, then HER2 has 50% chance to be positive. Grading II portrayed higher possibility to get HER2 positive comparing to grading I and III.

Among three tumor sizes, the tumor size >2-5 centimeters gave the smallest chance of ER negative and PR negative which were 38.2 % and 45.98 %, respectively, on the other hand, it gave the highest chance of HER2 positive, 35.53 % (table 12). The tumor size of >5

centimeters increased chances of ER negative and PR negative which showed the same figure of 69.23 %.

The results from table 13 could be categorized that the chance to get ER negative at 43.12 % for tumor with no axillary lymph node metastasis was 46.43 % with 1-3 nodes metastasis, 50 % with 4-9 nodes metastasis, and 46.15 % with >=10 nodes metastasis. The chance of PR negative was 55.96 % with no axillary lymph node metastasis, 60.71 % with 1-3 nodes metastasis, 55.56 % with 4-9 nodes metastasis, and 76.92 % with >=10 nodes metastasis. The chance of HER2 positive was 22.11 % with no axillary lymph node metastasis, 46.15 % with 1-3 nodes metastasis, 23.53 % with 4-9 axillary lymph nodes metastasis, and 33.33 % with >=10 nodes metastasis.

Discussion

ER and PR status have been established as a predictive factor for breast cancer treatment (ER+, PR+ tumors are more responsive to hormonal therapies than ER-, PR- tumors)^{4,15} and a prognostic factor for survival⁴⁻⁶.

From the above result it was found that both ER and PR positive responded very well to patients at the age above 70 years who were post-menopause. The chance to get ER positive was 72.72 % and PR positive was

64.64%. In contrast, the chance to get HER2 positive was only 22.05 %.The PR positive did not respond so well (34.33 %), comparing to ER positive (60 %), in patients at the age below 35 years.

The authors found that it seems to get the same responsive result of ER and PR. In this study the chance to get ER positive/PR positive or ER negative/PR negative was 73.76 %. Where as that of HER2 positive was much less (27.15 %) comparing to ER and PR (53.1 % and 42.26 % respectively). The authors found patients in this study had less ER positive and/or PR positive compared to others studies^{10,11}. The study by Rayter showed that 70% of breast cancer has ER positive and 50% has PR positive. However, the study by Lertsanguansinchai, et al in Thai female study¹⁴ showed 53.4% has ER positive and 42.1% has PR positive similar to our study.

The authors also found the highest chance to get HER2 positive was when both ER and PR were negative. The chance to get HER2 positive was less when ER and PR were the opposite. The smallest chance to get HER2 positive was when both ER and PR were positive.

In this study of relation among ER/PR/HER2 against grading/tumor size/node metastasis, we found that the lesser the number of grading, the higher the chance to get ER and/or PR positive. We could not see the same trend for HER2. We could not conclude the correlation between ER/PR/HER2 and tumor size/node metastasis, but it might be able to mention that the tumor size of >5 centimeters might give the smallest chance to get ER positive and same for PR positive. On the other hand, the smallest size of tumor might give the smallest chance to get HER2 positive. It could be observed also when the axillary lymph node metastasis was >=10 nodes, while the chance to get PR positive was much less, only 23.08 % in this study.

Summary

The present study showed the highest chance to get HER2 positive was when both ER and PR were negative. The highest chance to get HER2 negative was when both ER and PR were positive. The higher chance to get ER and/or PR positive was when lower number of histological grading.

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