The Clinical Significance of Triple-negative Phenotype on Prognosis of Young Age(\leq 35) Breast Cancer Patients

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The Clinical Significance of Triple-negative Phenotype on Prognosis of Young Age(≤35) Breast Cancer Patients

Directed by Professor Seung Il Kim

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<TABLE OF CONTENTS>

ABSTRACT ................................................................. 1

I. INTRODUCTION ....................................................... 3
II. MATERIALS AND METHODS ........................................ 4
   1. Patients .............................................................. 4
   2. Statistical analysis .............................................. 4
III. RESULTS ............................................................... 6
   1. Patients characteristics ........................................ 6
   2. Survival analysis ................................................ 9
IV. DISCUSSION .......................................................... 12
V. CONCLUSION .......................................................... 13

REFERENCES ............................................................ 15
ABSTRACT(IN KOREAN) .................................................. 18
LIST OF FIGURES

Figure 1. Survival curves ............................................. 11

LIST OF TABLES

Table 1. Patients characteristics.................................. 7
Table 2. Details in treatment patterns ........................... 8
ABSTRACT

The Clinical Significance of Triple-negative Phenotype on Prognosis of Young Age (≤35) Breast Cancer Patients

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(Directed by Professor Seung Il Kim)

Young age and triple-negative phenotype have been well-known as a poor prognostic factor in breast cancer. On the basis of hypothesis that differing distributions of molecular subtypes in young women may be a contributor to their poor prognosis, we designed this study to identify clinical significance of triple-negative phenotype in young age breast cancer patients. Between January 1985 and December 2007, 277 patients who had final results of status of hormone receptors and HER2 (human epidermal growth factor receptor 2)/neu expression were selected as study cohort. Selected patients were divided into four groups.: Group I, ER (estrogen receptor) or PR (progesterone receptor)-positive and HER2/neu-negative group; Group II, ER or PR-negative and HER2/neu-positive group; Group III, ER, PR and HER2/neu-positive group; Group IV, ER, PR and HER2/neu-negative group. We compared clinicopathological features and analyzed disease-free survival (DFS), locoregional relapse-free survival (LRRFS), distant relapse-free survival (DRFS), and overall survival (OS). In patients characteristics, there was no significant difference among four groups. The median
follow-up of all patients was 70.6 months. Survival analysis was performed by comparing group IV with other three groups. There was no significant difference in five-year DFS (p=0.544), LRRFS (p=0.464), DRFS (p=0.872) and OS (p=0.452) between group IV and control group (group I+II+III). In this study, in young age breast cancer patients, triple-negative phenotype did not show worse prognosis compared with other phenotypes.

Key words: Young age; breast cancer; triple-negative phenotype; prognosis
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I. INTRODUCTION

In Korea, breast cancer is the second leading cancer in women. And also distinctively, patients under 35 years old comprise larger proportion than those in western countries.\textsuperscript{1,2} Since younger women with breast cancer generally have been regarded to have worse prognosis, especially in hormone receptor-positive cases, patients under 35 years at diagnosis have been considered as an important risk category.\textsuperscript{3,4}

Triple-negative breast cancer is a subtype which is in absence of estrogen receptor(ER), progesterone receptor(PR) and human epidermal growth factor receptor type 2(HER\textsubscript{2}/neu).\textsuperscript{5,6} This phenotype is well-known as a poor prognostic factor in breast cancer. Nevertheless, only combined chemotherapy is expected to be effective in this type due to lack of targeted therapy.

On the basis of hypothesis that differing distributions of molecular subtypes in young women may be a contributor to their poorer prognosis\textsuperscript{7}, we designed this
study to identify clinical significance of triple-negative phenotype in young age breast cancer patients.

II. MATERIALS AND METHODS

1. Patients

Between January 1985 and December 2007, total 513 patients whose age was 35 years old or less were diagnosed as breast cancer and treated at Severance Hospital, Yonsei University Health System, in Seoul, Korea. Among these patients, 277 patients who had final results of status of hormone receptors and HER2 expression were selected as study cohort. Individual medical records including clinicopathologic features and treatment patterns were reviewed retrospectively. The patients with recurrent or metastatic disease, non-epithelial origin tumor such as phyllodes tumor, lymphoma or sarcoma were excluded.

Selected patients were divided into four groups according to the status of hormone receptor and HER2/neu expression.: Group I, ER or PR-positive and HER2/neu-negative group; Group II, ER or PR-negative and HER2/neu-positive group; Group III, ER, PR and HER2/neu-positive group; Group IV, ER, PR and HER2/neu-negative group. Tumors with 10% nuclear-stained cells were considered as ER and PR positivity. HER2/neu immunohistochemical staining was scored from 0 to 3+ based on the guidelines
from HercepTest™ (Dako, Glostrup, Denmark). HER2/neu positivity was defined when strong (3+) staining was observed.

We compared clinicopathologic features including histologic type, TNM staging, tumor grade, ER/PR/HER2/neu status, treatment patterns such as neoadjuvant chemotherapy, radiotherapy or adjuvant chemotherapy and endocrine therapy.

Survival analysis was performed as described previously in our data. Tumor recurrence in the ipsilateral breast, chest wall, and regional lymph node was considered as locoregional recurrence. Any recurrence at a distant site including the contralateral axillary or supraclavicular lymph nodes was considered as a distant metastasis. Disease-free survival (DFS) was defined from the date of curative surgery to the date of locoregional or systemic recurrence or death before relapse. Locoregional relapse-free survival (LRRFS) was calculated from the date of the first operation to the date of the first locoregional relapse or death without any type of recurrence. Distant relapse-free survival (DRFS) was measured from the date of the first operation to the date of the first distant metastasis or death without any type of recurrence. Overall survival (OS) was defined from the date of the first curative surgery to the date of the last follow-up or death from any other cause.

2. Statistical analysis
Categorical variables were compared by using Pearson’s chi-square test or Fisher’s exact test. Survival curves were constructed by Kaplan-Meier method. Statistical analysis was performed by SPSS 18.0 (SPSS Inc, Chicago, Ill, USA). Intergroup differences in the survival time were analyzed by the log-rank test and statistical significance was accepted for $p$ values of $< 0.05$.

III. RESULTS

Patients characteristics

Among a total 277 patients eligible for this study, 124 patients were included into Group I, 28 were into group II, 45 were into group III and 80 patients were categorized into Group IV. The mean age at diagnosis was 31.8 and follow-up duration was 70.6 months. There was no significant difference in patients characteristics among four groups (Table 1). When compared with other groups, group IV showed statistically significant differences in details of treatment patterns. Breast-conserving surgery was more frequently performed in group IV and as a result, patients in group IV underwent radiotherapy more often. Also due to lack of targeted therapy, adjuvant chemotherapy was administered in 93.8% of patients in group IV. On the contrary to this, endocrine therapy was nearly not done, which comprised only 3.8% of all patients in group IV (Table 2).
Table 1. Patients characteristics

<table>
<thead>
<tr>
<th>Factors</th>
<th>Group I (HR+/HER2- (n=124)(%)</th>
<th>Group II (HR-/HER2+ (n=28)(%)</th>
<th>Group III (HR+/HER2+ (n=45)(%)</th>
<th>Group IV (HR-/HER2- (n=80)(%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.333</td>
</tr>
<tr>
<td>Ductal</td>
<td>112(90.3)</td>
<td>27(96.4)</td>
<td>43(95.6)</td>
<td>70(87.5)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>12(9.7)</td>
<td>1(3.6)</td>
<td>2(4.4)</td>
<td>10(12.5)</td>
<td></td>
</tr>
<tr>
<td>T stage (n=276)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.369</td>
</tr>
<tr>
<td>T0/Tis</td>
<td>16(12.9)</td>
<td>5(17.9)</td>
<td>7(15.6)</td>
<td>2(2.5)</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>53(42.7)</td>
<td>11(39.3)</td>
<td>19(42.2)</td>
<td>31(39.2)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>49(39.5)</td>
<td>10(35.7)</td>
<td>17(37.8)</td>
<td>42(53.2)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>5(4.0)</td>
<td>1(3.6)</td>
<td>2(4.4)</td>
<td>3(3.8)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>1(0.8)</td>
<td>1(3.6)</td>
<td>0(0.0)</td>
<td>1(1.3)</td>
<td></td>
</tr>
<tr>
<td>N stage (n=275)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.458</td>
</tr>
<tr>
<td>N0</td>
<td>70(56.5)</td>
<td>14(51.9)</td>
<td>27(60.0)</td>
<td>52(65.8)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>28(22.6)</td>
<td>9(33.3)</td>
<td>11(24.4)</td>
<td>18(22.8)</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>13(10.5)</td>
<td>2(7.4)</td>
<td>1(2.2)</td>
<td>6(7.6)</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>13(10.5)</td>
<td>2(7.4)</td>
<td>6(13.3)</td>
<td>3(3.8)</td>
<td></td>
</tr>
<tr>
<td>ER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>14(11.3)</td>
<td>28(100.0)</td>
<td>42(6.7)</td>
<td>80(100.0)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>110(88.7)</td>
<td>0(0.0)</td>
<td>3(93.3)</td>
<td>0(0.0)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>21(16.9)</td>
<td>28(100.0)</td>
<td>9(20.0)</td>
<td>80(100.0)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>103(83.1)</td>
<td>0(0.0)</td>
<td>36(80.0)</td>
<td>0(0.0)</td>
<td></td>
</tr>
<tr>
<td>HER2/neu</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>124(100.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>80(100.0)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0(0.0)</td>
<td>28(100.0)</td>
<td>45(100.0)</td>
<td>0(0.0)</td>
<td></td>
</tr>
</tbody>
</table>

T=Tumor; N=Node; HR=hormone receptor; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2
n=number of patients

Table 2. Details in treatment patterns

<table>
<thead>
<tr>
<th>Factors</th>
<th>Group I+II+III</th>
<th>Group IV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+ or HER2+</td>
<td></td>
<td>(N=197)(%)</td>
<td>(N=80)(%)</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not done</td>
<td>178(90.4)</td>
<td>66(82.5)</td>
<td></td>
</tr>
<tr>
<td>Done</td>
<td>19(9.6)</td>
<td>14(17.5)</td>
<td></td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breast-conservins</td>
<td>53(26.9)</td>
<td>43(53.8)</td>
<td></td>
</tr>
<tr>
<td>Total mastectomy</td>
<td>144(73.1)</td>
<td>37(46.3)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy(N=272)</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Not done</td>
<td>101(52.3)</td>
<td>24(30.4)</td>
<td></td>
</tr>
<tr>
<td>Done</td>
<td>92(47.7)</td>
<td>55(69.6)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Not done</td>
<td>39(19.8)</td>
<td>5(6.3)</td>
<td></td>
</tr>
<tr>
<td>Done</td>
<td>158(80.2)</td>
<td>75(93.8)</td>
<td></td>
</tr>
<tr>
<td>Endocrine therapy(N=272)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Not done</td>
<td>56(28.9)</td>
<td>75(96.2)</td>
<td></td>
</tr>
<tr>
<td>Done</td>
<td>138(71.1)</td>
<td>3(3.8)</td>
<td></td>
</tr>
</tbody>
</table>

N=Number of patients; HR=hormone receptor; HER2=human epidermal growth factor receptor 2.
**Survival analysis**

The median follow-up of all patients was 70.6 months. Survival analysis was performed by comparing group IV with other three groups. The Kaplan-Meier survival curves according to were demonstrated in Figure 1. There was no significant difference in five-year DFS ($p = 0.544$), LRRFS ($p = 0.464$), DRFS ($p = 0.872$), and OS ($p = 0.452$) between two groups. Group IV has comparable prognosis with that of other groups.

(A)
(B)

![Graph showing local relapse-free survival with p = 0.464](image)

(C)

![Graph showing distant relapse-free survival with p = 0.872](image)
Figure 1. (A) Disease-free survival (DFS), (B) Locoregional relapse-free survival (LRRFS), (C) Distant relapse-free survival (DRFS), (D) Overall survival (OS) curves. The green line represents Group IV and the blue line represents control group (Group I+II+III).
IV. DISCUSSION

The findings of present study suggest that in young age breast cancer patients, triple-negative phenotype does not show worse prognosis compared with other phenotypes. There was no significant difference in five-year DFS, LRRFS, DRFS, and OS compared with other three groups.

The definition of “young age” has been different among previous studies. In this study, according to our previous data which demonstrated an age of 35 years was a rational cut-off value to determine prognosis at the time of diagnosis, we defined “young age” as those aged younger than 35 years old. Generally, young age breast cancer patients tend to have worse prognosis compared with elder women, and are more likely to be hormone receptor-negative, to have higher grade and higher proliferation fraction, to have lymphovascular invasion. Especially, unlike elder women, young age breast cancer with hormone receptor-positive tumor shows poorer outcome, mainly due to tamoxifen-resistance.

Triple-negative breast cancer is an interesting target of research area as well as young age breast cancer. This phenotype plays a leading role as a poor prognostic factor without any specific available targeted therapy. Liedtke et al reported that triple-negative breast cancer was associated with higher risk of visceral metastases and shorter post-recurrence survival. Also, they found that
triple-negative breast cancer patients with residual tumor after neoadjuvant chemotherapy have significantly poorer survival compared with those with other phenotypes.

This result remains same in earlier-stage of triple-negative breast cancer. Even in early stage, triple-negative breast cancer shows early relapse. In 2007, researchers from the Swedish Cancer Institute also suggested that patients with T1N0, but triple-negative phenotype have twice higher risk of recurrence, even with more aggressive treatment.13-15

This study was designed to identify clinical significance of triple-negative phenotype in young age breast cancer. From current study, we found that triple-negative phenotype does not contribute to poor prognosis of young age breast cancer. However, this study has several limitations, especially with many missing HER2 results and no FISH test. Our analysis needs further investigation, including genetic differences according to age and each phenotype.

V. CONCLUSION

Current study demonstrated that in young age breast cancer patients, triple-negative phenotype did not show worse prognosis compared with other
phenotypes. Prognostic significance of young age breast cancer was not dependent on molecular subtypes.
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analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer 2007;109:1721-8.


11. Ahn SH, Son BH, Kim SW, Kim SI, Jeong J, Ko SS, et al. Poor outcome of


ABSTRACT

35세 이하의 젊은 여성 유방암 환자에서 Triple-negative 유형이 가지는 임상적 의의

<지도교수 김 승 일>

연세대학교 대학원 의학과

김 임 경

젊은 나이와 triple-negative 유형은 유방암에 있어서 나쁜 예후인자로써 잘 알려져 있다. 젊은 유방암 환자에서 보이는 분자적 유형의 분포의 차이가 나쁜 예후에 영향을 미칠 것이라는 가정 하에, 본 연구자는 젊은 유방암 환자에서 triple-negative 유형이 가지는 임상적 의의를 확인하고자 이 연구를 계획하였다. 1985년 1월부터 2007년 12월 사이에 호르몬 수용체 및 HER2/neu 발현 상태가 확인된 277명의 유방암 환자를 연구 대상으로 선정하였다. 호르몬 수용체 및 HER2/neu 발현 상태에 따라 4그룹으로 분류하였다: 그룹 I, ER 또는 PR 양성이면서 HER2/neu 음성인 그룹; 그룹 II, ER 또는 PR 음성이면서 HER2/neu 양성인 그룹; 그룹 III, ER, PR 및 HER2/neu 모두 양성인 그룹; 그룹 IV, ER, PR 및 HER2/neu 모두 음성인 그룹으로 구분하였다. 본 연구에서는 각 그룹의 임상병리학적 특징을 비교하였고, 무병생존률, 국소지역적 무재발 생존률, 전신적 무재발 생존률 및 전체 생존률을 분석하였다. 환자군의 임상학적 특징상에서는 4그룹간의 유의미한 차이는 없었다. 평균 추적 기간은 70.6개월이었고, 생존률 분석은 그룹 IV와 나머지 그룹(I+II+III)을 비교하였다. 5년 무병생존률, 국소지역 및 전신적 무재발 생존률, 전체 생존률은 두 그룹간의 차이가 없었다. 본 연구에서는, 젊은 유방암 환자에서, triple-negative 유형이 다른 유형과 비교하였을 때 더 나쁜 예후를 보이지는
않았다.

핵심되는 말: 젊은 나이; 유방암; triple-negative 유형; 예후