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면역조직학적 염색에 의해 분류한 유방암 기저형과 내강형의 생존율 분석

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The Prognostic Importance of Triple negative breast carcinoma

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Abstract

목 적 : 유방암은 이질적인 병으로 같은 병기의 환자들 중에서도 예후는 다양하게 나타난다. 그래서 유방암을 유전자의 형태에 따라서 4가지로 흔히 분류하여서 예후를 추정하는데 도움을 받고 있다. 이 4가지 유형중 에서 기저형은 ER(-), PR(-), HER(-)의 표현형을 보이며 예후가 좋지 않은 것으로 알려져 있다. 이에 본 조사는 본원에서도 기저형의 세포유형이 예후에 영향을 미치는지를 알아보고자 본 연구를 시작하였다

방 법 : 2001년 1월부터 2006년 12월 까지 본원에서 유방암으로 수술을 한 561명의 환자를 대상으로 하였다. 의학적인 기록을 후향적으로 조사하였다. 기저형의 환자군을 GroupA로 그 외 유형의 환자군을 Group B로 하여서 양군을 비교 분석 하였다. 임상 병리학적 인자를 중심으로 무병생존율에 미친 영향과 전체생존율에 영향을 미친 인자를 분석하였다

결 과 : 103명의(16.9%) 환자가 기저형 이였다. 양 그룹간의 임상병리학적 인자의 분포는 통계학적으로 유의한 차이는 없었다. 무병 생존률에 영향을 미치는 임상병리학적 인자는 종양의 크기(p=0.0297), 임파절의 전이유무(p=0.0262), PR양성율(p=0.0541) 이였다. 기저형의 세포유형은 무병생존률에는 영향을 미치지 않았다.

결 론 : 본원의 조사에서는 기저형의 세포유형이 무병생존율에는 영향을 미치지 않았다. 그러나 전체 생존율에는 영향을 미치는 것으로 나왔다. 환자에 대한 추적기간을 계속해가면서 대상 환자의 수가 증가하게 되면 유방암의 세포유형에 따른 분류법은 유방암환자의 예후를 추정하는데 도움이 될 것으로 생각된다

Key words : Breast carcinoma; Triplenegative;HER2;ER;PR

Introduction

Breast cancer is a heterogeneous disease with different clinical courses, outcomes and responses to therapies.[1] Recent DNA microarray profiling studies have identified a number of biological subtypes of breast carcinomas that are associated with different clinical outcomes.[2] and [3]Among these types, "basal-like" group is a distinct category of breast carcinomas, and accounts for 15% of all breast carcinomas, but comprises nearly 85% of triple negative breast carcinomas that are negative for the estrogen receptor (ER), progesterone receptor (PR) and HER2.[4,5] The presence of ER and/or PR usually predicts a more indolent and slower growing tumor with longer times to disease recurrence than ER-negative and PR-negative tumors, while HER2 overexpression is associated with increased tumor aggressiveness, increased rates of recurrence, and increased mortality in both node-positive and node-negative patients.[6] On the other hand, ER and PR are inversely related to HER2 overexpression, and the patients with ER-negative/ PR-negative/HER2-positive tumor have a more aggressive clinical outcome.[7] Interestingly, the recent data suggested that triple negative breast carcinomas also exhibited high proliferative capacity

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and poor prognosis.[8,9] However, information on the triple negative subtype is based on limited and confusing data in the literature.

The aim of this study was to determine the prognostic significance of triple negative tumors with respect to disease-free survival (DFS) and overall survival(OS) in a group of homogeneously treated breast carcinoma patients.

Materials and methods

The medical records and the final pathological reports of female patients who underwent modified radical mastectomy from 2001 to 2006 at Kosin University Gospel Hospital for primary invasive breast carcinoma within clinically operable stages were reviewed retrospectively. The follow-up cut-off date of this study was January 2008. Patient inclusion criteria forthis study were as follows: no clinical features of locally advanced stage, no serious concomitant diseases, age less than 70 years, no prior specific treatment, having complete axillary dissection, having at least 10 lymph nodes on dissection material, having information on estrogen receptor status, progesterone receptor status and HER2 status, and having available adjuvant treatment if necessary, according to the current guidelines.[10,11] Five hundreds sixty one patients met the eligibility criteria for the study.

Pathological lymph node classification and tumor staging were performedaccording to the American Joint Committee on Cancer criteria.[12] Histologic grading was performed using the criteria of Bloom and Richardson.[13] Lymphatic vascular invasion (LVI) was defined as the presence of tumor emboli in peritumoral lymphatic spaces, capillaries or postcapillary venules. ER status, PR status, p53 and HER2 status were determined by immunohistochemical means on paraffin-embedded tissue. ER status and PR status were taken as positive if more than 10% of tumor cells showed staining. Immunohistochemical score of 3+ for HER2 was accepted as HER2 positivity.

The primary outcome examined was DFS, and secondary endpoint of the study was overall survival (OS). For the estimations of DFS and OS as endpoint by the end of follow-up, the standardized definitions proposed recently by Hudis etwere used.[14] The first event approach was used for DFS estimates. DFS was estimated from the date of biopsy diagnosis before treatment to all types of first event as locoregional or distant metastasis, or all deaths due to breast carcinoma, new breast carcinoma or non-breast carcinoma as endpoint by the end of follow-up. Estimates of OS were evaluated from the date of biopsy diagnosis before treatment to the date of death due to breast carcinoma, new breast carcinoma or non-breast carcinoma related reasons by the end of follow-up.

Statistical tests were performed using the SPSS 12.0 statistical software package for Windows (SPSS Inc, Chicago, IL). Survival estimates and curves were established using the Kaplan–Meier method and differences in observed survival distribution among patient subgroupswere tested with two-sided log-rank test. All survival rates were presented with their standard errors.

We used Pearson's correlation to determine the association of pairs of explanatory variables and differences in qualitative variables were evaluated by Chi-squared test, where necessary. All p-values were two-sided and a p-value of less than 0.05 was considered to indicate a statistically significant difference.

Results

The median age was 49 (range 26~70)years, median tumor size was 2.83 (range 2.6~9.4) cm, and the median number of lymph nodes in dissection materials was 22 (range 10–53). Patients' characteristics were given in Table 1. 103 patients(16.9%) were classified a triple negative and Remaining 458 patients(75.3%) were defined as nontriple negative group. There is no distributional difference of adverse prognostic factors between two groups.

The median observation time was 49 (range 26~94) months for patients still alive at the follow-up cut-off date. Whereas 17 patients (2.8%) had a locoregional recurrence, 48 patients (8%) experienced a distant metastasis. 9 patients(1.5%) died because of cancer-related reasons in their follow-up periods.

103 patients (16.9%) who had tumors with negative status for all ER, PR and HER2 were classified as triple negative group (Group-A) and the remaining 458 patients (75.3%) were defined as non-triple negative group (Group-B). There was no distributional difference of adverse prognostic factors between two groups (Table 1). Among Group-2 patients, 111 (18.3%) had a histology of ER-positive and/or PR-positive and HER2-negative; 196(32.2%) had a histology of ER-positive and/or PR-positive and HER2-positive; and 151 (24.8%) had a histology of ER-negative, PR-negative and HER2-positive (HER2-positive). Nine patients in Group-1 and 33patients in Group-2 died due to breast carcinoma (p663). The estimated rates of 5-year overall survival were 97.5% in Group-1 and 99.4% in Group-2 . There was a first event in 9patients of Group-1 and 33 patients of Group-2. Therefore, the rates of DFS were 90.5%(±0.06) in Group-1 and 92.2% (±0.03) in Group-2 (p=0.663).

The univariate analysis for prognostic factors associated with DFS revealed that the tumor group as triple negative or non-triple negative was not statistically significant in addition to some known clinicopathological features (Table 2).

But The univariate analysis for prognostic factors associated with OS revealed that the tumor group as triple negative or non-triple negative was statistically significant in addition to some known clinicopathological features (Table 3).

Whereas a first event was observed in 9 patients with triple negative cancer; 33 patients with non triple negative cancer. Estimated 5-year DFS rate was 90.5% for triple negative cancer, this rate was 92.2% in non triple negative cancer. And Estimated overall survival was 97.5% for triple negative cancer, this rate was 99.4% for non triple negative breast cancer(Fig.1).

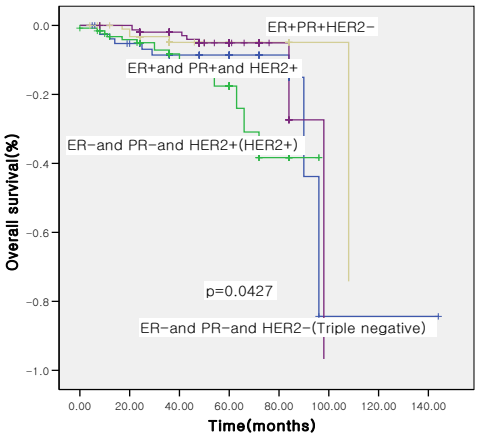

Fig. 1. Overall-survival curves according to the patient's groups

Table 1. Patients characteristics according to the tumor subgroups

Features		Total (n)	Group A Triple-negative	Group B Non triple-negative	p-value
Age	>35yrs	45	11	34	0.182
	<35yrs	516	92	424	
Histologic type	Ductal	545	101	444	0.413
	Lobular	16	2	14	
Tumor-size	<2cm	221	46	175	0.392
	>2cm	340	62	278	
Pathologic axillary status	Negative	313	57	256	0.385
	Positive	248	49	199	
Number of positive nodes	<3	428	83	345	0.568
	>3	133	26	107	
Histologic grade	G1	106	35	71	0.129
	G2	199	48	151	
	G3	256	74	182	
Extracapsular involvement	No	417	99	318	0.969
	Yes	144	48	96	
P53 mutation	No	322	54	268	0.078
	Yes	239	58	181	
Adjuvant RTx	No	448	104	344	0.342
	Yes	113	47	81	

Table 2. Prognostic factors for disease-free survival in univariate Cox regression analysis

Features	p-value	HRa	95% CIb
Age groups(<35 vs >35)	0.5881	0.443	0.072~2.717
Tumor size(<2cm vs >2cm)	0.0297	0.031	0.003~0.354
Histologic type(ductal vs lobular)	0.9566	0.461	0.036~5.961
Lymph node status(positive vs negative)	0.0262	0.473	0.147~1.516
Number of metastatic lymph nodes(>4 vs <4)	0.0214	0.610	0.202~1.840
Estrogen receptor status(negative vs positive)	0.3524	0.0	0.0~7.0
Progesteron receptor status(negative vs positive)	0.0372	1.2	0.5~3.2
Tumor subgroup(Group A vs Group B)c	0.8283	0.748	0.235~2.384
Tumor subgroup according to DNA profilingd	0.0541	1.9	0.8~4.3
Ki67 status(positive vs negative)	0.316	0.486	0.119~1.990

[a] Hazards ratio.
[b] 95% Confidence interval
[c] Group-A, triple negative and Group-B, non-triple negative
[d] Luminal A type, ER(+) PR(+) HER-2(-) and Luminal B type, ER(+) PR(+) HER-2(+)and HER-2 type, ER(-) PR(-) HER-2(+) and Basal type, ER(-) PR(-) HER-2(-)

Table 3. Prognostic factors for overall survival in univariate Cox regression analysis

Features	p-value	HRa	95% CIb
Age groups(<35 vs >35)	0.3908	0	0.072~2.717
Tumor size(<2cm vs >2cm)	0.8187	0	0.003~0.354
Histologic type(ductal vs lobular)	0.2004	0.12	0.036~5.961
Lymph node status(positive vs negative)	0.2005	0	0.147~1.516
Number of metastatic lymph nodes(>4 vs <4)	0.1524	0.9	0.1~7.1
Estrogen receptor status(negative vs positive)	0.6726	0.0	0.0~7.0
Progesteron receptor status(negative vs positive)	0.3402	1.2	0.5~3.2
Tumor subgroup(Group1 vs Group2)c	0.4028	0	0.235~2.384
Tumor subgroup according to DNA profilingd	0.049	2.4	0.1~3.1
Ki67 status(positive vs negative)	0.316	2.4	0.1~3.1

[a] Hazards ratio.
[b] 95% Confidence interval
[c] Group-1, triple negative and Group-2, non-triple negative
[d] Luminal A type, ER(+) PR(+) HER-2(-) and Luminal B type, ER(+) PR(+) HER-2(+)and HER-2 type, ER(-) PR(-) HER-2(+) and Basal type, ER(-) PR(-) HER-2(-)

Discussion

Breast carcinomas have been traditionally classified as hormone receptor (ER and/or PR)-positive or negative.[14]In the recent years, newer approaches to breast carcinomas using gene-expression profiles and immunohistochemical (IHC) biomarkers have identified at least four subtypes of these tumors.[15] These subtypes are basal-like (ER-negative, PR-negative, HER2-negative), HER2-positive (ER-negative, PR-negative, HER2-positive), luminal A (ER-positive and/or PR-positive and HER2-negative), and luminal B (ER-positive and/or PR-positive and HER2-positive).[8] Several studies demonstrated that HER2-positive subtypes are correlated with reduced survival, and there is a considerable evidence at the molecular level that HER2 overexpression/amplification leads to up-regulation of multiple secondary target molecules which affect the malignant phenotype.[16,17] The present study showed that HER2-positive tumors as apart from ER or PR status had a higher incidence of event and, therefore, these patients showed the poor survival rates, and HER2 status was an independent prognostic factor in the multivariate analysis, as similar to other studies.[18,19] HER2 is amplified and/or overexpressed in approximately 30% of breast carcinomas, 6as in our study. Currently, HER2 overexpression/amplification predicts response to endocrine therapy, and to a humanized antibody (trastuzumab) in the metastatic setting, in addition to prognosis. HER2-negative tumors lack the benefit of specific therapy that targets this protein.[19]

The presence of ER and PR in breast carcinoma is both prognostic for good outcome and predictive for hormone therapy. 6ER- and/or PR-negative tumors present a heterogeneous group of breast carcinomas that are generally thought to be aggressive with poor prognosis and fewer treatment strategies compared with tumors expressing hormone receptor. 18Our multivariate analysis in step three demonstrated that ER and PR status were the prognostic factors for DFS and, whereas ER-positive and/or PR-positive and HER2-negative patients had the best clinical outcome with a5-year DFS of 87%; ER-negative, PR-negative and HER2-positive patients (HER2-positive subtype) showed the worst outcome with a 5-year DFS of 39%. These findings were consistent with previous studies.[20,21,22]

On the other hand, the recent studies indicated that, although HER2-negative disease had a more favourable prognosis than HER2-positive disease, ER-negative, PR-negative, and HER2-negative (so-called “triple negative”) subtype, interestingly, was associated with a poorer clinical outcome.[23,24]Ninety percent of breast carcinomas in women with germline BRCA1 mutations are triple negative, and 80–90% of triple negative breast carcinomas are basal-like by DNA microarray and IHC analysis with staining of cytokeratin such as CK5/6 and/or CK14.[24] Since triple negative breast carcinoma does not respond to any endocrine manipulation or HER2-targeted therapy, treatment in these groups of patients is still a challenge. One of the reasons of unfavourable prognosis of triple negative breast carcinoma may be the limited number of treatment approaches available. Although treatment is limited to chemotherapy, adjuvant antracyclin-based chemotherapy seems to be less effective for these patients.[25] Some recent studies suggested that the majority of triple negative patients express EGFR and it is tempting to speculate that these patients represent the subgroup of breast carcinoma patients who may derive optimal benefit from EGFR-targeted therapies.[22]

In our series including patients treated homogeneously and adjuvant treatments, the rate of triple negative patients was

16.9%, which is similar to some reports21 but higher than others.[9,10] Triple negative and non-triple negative patients displayed similar distribution of clinicopathological characteristics such as tumor size, histologic grade, and lymphatic vascular invasion, in contrast to other studies.[18] These previous reports indicated that triple negative tumors were associated with larger size and high grade,and therefore had a poorer outcome in terms of overall survival and disease-free interval. In our study, although more deaths were observed in triple negative patients than non-triple negative patients, overall survival rates in these groups were not statistically different. This result may be related with the relatively short follow-up period. On the other hand, more number of events was observed in the triple negative patients, and therefore, DFS in this group of patients was worse, in accordance with other studies.[19,20]In spite of this finding, the DFS for triple negative subtype was not statistically different from those for HER2-positive subtype in contrast to earlier studies reported that triple negative subtype was the most aggressive type of breast carcinoma,[2,3]although HER2-positive subtype had poorer DFS in the present study, as indicated above. A recent study demonstrated that the distant metastases in triple negative breast carcinoma tend to occur with a specific pattern with a high frequency of spinal cord and meninges, brain, liver and lung metastases.18In the current study, no specific pattern of metastases could be observed. On the other hand, since there was no distributional difference of known adverse prognostic factors between triple negative and non-triple negative patients, it is probable that some intrinsic differences at molecular level, which is not the subject of our study, may have a role in the poor outcome of triple negative breast carcinoma patients.

In conclusion, our study indicates that triple negative breast carcinoma is not uncommon and it tends to display a more aggressive clinical course, as HER2-positive breast carcinoma, and the tumor subtype as triple negative or non-triple negative is an independent predictor of OS. New treatment strategies should be investigated for patients with triple negative tumors, as in HER2-positive tumors. Further studies will be appropriate to confirm the validity of our results.

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