Are there the specific prognostic factors for triple-negative subtype of early breast cancers (pT1-2N0M0)?

T1-2 림프절 음성 삼중음성유방암의 예후인자

Department of General Surgery, Anam Hospital, Korea University, College of Medicine, 126-, Anam-dong 5-ga, Seongbuk-gu, Seoul, Korea[1], Department of General Surgery, Guro Hospital, Korea University, College of Medicine, 97 Gurodong-Gil Guro-Ku, Seoul, Korea[2], Division of Medical Oncology, Department of Internal Medicine, Anam Hospital, Korea University, College of Medicine, 126-, Anam-dong 5-ga, Seongbuk-gu, Seoul, Korea[3]

Ji-Young You[1], Hye-yoon Lee[1], Sang-uk Woo[2], Kyong-hwa Park[3], Eun-sook Lee[1], Jeoung-won Bae[1]

고려대학교 안암병원 외과 **유지영, 이혜윤, 이은숙, 배정원,** 고려대학교 구로병원 외과 **우상욱,** 고려대학교 안암병원 내과 **박경화**

초 록

배경 : 삼중음성유방암은 비삼중음성유방암군에 비해 조기라 해도 더 나쁜 예후를 보이는 걸로 알려져 있다. 따라서 삼중음성유방암의 초기 치료를 위해서 정확한 예후인자를 찾는 것이 중요하다. 본 연구에서는, T1-2 림프절 음성인 삼중음성유방암의 나쁜 예후와 관련된 예후인자를 찾아 보고자 하였다.

방법 : 1995년부터 2006년까지 고려대학교 의료원 안암병원에서 유방암으로 근치절제술을 시행받은 환자 중 림프절 전이나 원격전이가 없는 환자를 대상으로 하였다. 이 중에서 호르몬 수용체 및 HER2 수용체 여부에 대한 기록이 있는 환자들만을 포함시켰다. 의무기록의 후향적 분석을 통해 삼중음성유방암 및 비삼중음성유방암 환자들의 임상병리적 특징이 분석되었다.

결과 : 79명 (22.9%) 의 환자들이 삼중음성유방암군으로 분류되었다. 삼중음성유방암군에서 p53 양성 환자군에서 p53 음성 환자군보다 더 낮은 무병생존율을 보였다 (p=0.028). 다변량 회귀분석에서는 35세 이하의 낮은 연령이 삼중음성유방암과 관련된 독립적인 예후인자로 나타났으며, Ki-67은 단변량 회귀분석에서 삼중음성유방암과 통계적으로 유의하게 관련성을 보였다.

결론 : 본 연구에서, T1-2 림프절 음성인 삼중음성유방암에서 연령은 독립적인 예후인자이고 어릴수록 나쁜 예후와 연관됨을 알 수 있었고, Ki-67 은 통계적으로 증명되지는 않았지만, 삼중음성유방암의 예후인자가 될 수 있을 것으로 생각된다.

중심단어 : triple negative breast cancer, lymph node negative, p53, Ki-67, young age

책임저자 : 배정원
136-705, 서울시 성북구 안암동 5가 고려대학교 안암병원 외과
Tel: 02-920-5978 Fax: 02-928-1631 E-mail: kujwbae@korea.ac.kr
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Background

Breast cancer is a heterogeneous disease, encompassing a number of distinct biological entities that are associated with specific morphological and immunohistochemical features and clinical behavior.

Triple-negative breast cancer (TNBC) accounts for 10-20% of all breast carcinomas1. Patients with TNBC typically have inferior prognoses compared to patients with other subtypes of breast cancer. The poor prognosis of TNBC is associated with the aggressive course of the tumor, increased risk of distant metastasis, and the lack of specific treatment[2-4]. TNBC has a pattern of rapid recurrence following diagnosis, and the peak risk of recurrence is within three years[3]. However, after the peak risk period, the risk of recurrence declines rapidly and recurrence becomes rare[3, 5]. The initial management of TNBC patients is therefore very important, even in early stages of the disease. There was unmet clinical need for the development of biologic markers for TNBC in order to identify patients with poor prognoses, thus, more significant efforts has been made to improve clinical outcome of TNBC patients so far. As part of these efforts, various immunohistochemical molecules have been studied, and p53 and Ki-67 markers are being actively investigated.

p53 functions in maintenance of genomic stability, cell cycle regulation, and the induction of apoptosis[6]. Disruption of these functions appears to play an important role in carcinogenesis. Since non-functional mutated p53 accumulates in the nuclei of tumor cells, immunohistochemical

(IHC) staining for p53 has been used as a popular surrogate marker for its mutational status. p53 mutations are present in 18-25% of primary breast cancers and are well known to reduce patients' survival, although the exact mechanism has not been determined [7-12]. Because mutated p53 helps to predict good response to anthracycline based chemotherapy, it is expected as promising prognostic factor.

The proliferation marker Ki-67 has repeatedly been confirmed as an independent predictive and prognostic factor for early breast cancer [13]. Breast cancer with high Ki-67 expression responds better to chemotherapy, but is associated with poor prognoses. This phenomenon is similar to the triple-negative paradox, in which TNBC shows poorer survival, despite a higher response rate to neoadjuvant chemotherapy. TNBC is associated with higher expression of Ki-67 than non-TNBC[14, 15].

Our aim was to study the relationships between early TNBC prognoses and markers p53 and Ki-67, in order to identify the predictive or prognostic value of p53 and Ki-67 among patients with early TNBC, and therefore enable better assessment of the need for close follow-up.

Patients and Methods

1) Patients

Patients with available reports on hormone receptor and human epidermal growth factor receptor-2 (HER2) status were selected among 1200 breast cancer patients who were female and underwent surgical resection at the Korea University Anam Hospital (Seoul, Korea) between August 1995 and December 2006. Patients were excluded if they had lymph node metastasis, distant metastasis, or T3 (size 〉 5 cm) tumors. All of the subjects underwent surgical treatment and standard adjuvant chemotherapy and/or radiotherapy. All included patients were clinically followed up by the end of year 2010. The median follow-up period was 78.12 (±38.45) months. Clinico-pathological data were collected from medical records and analyzed retrospectively. These data included age at surgery, tumor stage and histologic grade, surgical procedure, adjuvant therapy, receptor status and clinical follow-up data. Tumors were staged according to the 7th edition of the American Joint Committee on Cancer tumor-node-metastasis (AJCC 7th TNM)[16]. Grades were grouped from 1 to 3 by pathologic reports of our hospital.

2) Immunohistochemical Staining

Tumor tissues from surgical specimen were immunohistochemically(IHC) stained using monoclonal antibodies (mouse anti-human estrogen receptor (ER) or progesterone receptor (PR) monoclonal antibody, DiNonA Inc. Seoul, Korea) after slicing and embedding in paraffin. The sliced, paraffin-embedded tissues were deparaffinized with xylene and sequentially hydrated with 100%, 90%, 80% and 70% ethanol solutions. The samples were incubated with an ethanol and H_2O_2 solution, cleaned with phosphate buffered saline (PBS), left at room temperature for 20 minutes and mixed with normal serum to block nonspecific intrinsic reactions. Tissues were then incubated with biotinylated secondary anti-rat antibody, cleaned three times with PBS for 20 minutes, reacted with a streptavidin biotinylated peroxidase complex and dyed with a diaminobenzidine solution and hematoxylin for contrast. HER2 positivity was defined as an intensity of 3+ by IHC or as gene ampilification ratio of ≥2.2 by fluorescence in situ hybridization (FISH) in the case of an intensity of 1+ or 2+ by IHC. The Ki-67 expression status (percentage) was considered positive when at least 20% of cells showed moderate to strong staining and a negative (≤20%) groups. The p53 expression status was interpreted as positive when at least 10% of the tumors showed moderate to strong nuclear staining and negative (≤10%) groups. ER and PR data were acquired from the pathologic report. TNBC was defined all negative to ER, PR & HER2 and the others were grouped to non-TNBC.

3) Fluorescence in situ Hybridization (FISH)

FISH was performed using 4 ㎛-thick serial sections according to the guidelines of the HER2 FISH kit

(PathVysion, Abott/Vysis, Downers Grove, USA), after deparaffinization and lysis with protease. After antigen restoration by heating at 95-99 °C, sections were incubated with the HER2/CEP17 probe at 45 °C for 16 hours. One or two green fluorescent signals were observed in resting phase cells indicating binding of the CEP17 DNA probe to the No.17 chromosome centromere, and one or two red fluorescent signals indicated the HER2 DNA probe localized to the HER2 gene.

4) Statistical Analysis

SPSS (ver13.0) for Windows was used to examine clinico-pathologic features. The frequency distribution was determined using the Pearson chi-square method. P-values < 0.05 were considered statistically significant. To obtain the overall survival (OS) and disease-free survival (DFS), survival curves were compared by the Kaplan-Meier method. A log-rank test was employed to examine the differences in survival rates. The Cox hazards ratio model was used for univariate and multivariate analysis of breast cancer survival, with corrections for interactions between prognostic factors.

Results

The patients were all women. There were 79 patients (22.9%) in the triple-negative breast cancer group and 266 patients (77.1%) in the non-TNBC group. The median age at diagnosis in the study population was 49 years(range: 26~86), 47 years for TNBC and 50 years for non-TNBC (p = 0.125). The mean tumor size was 1.3 cm(range: 0.1-2.0). Low T-stage, high histologic grade, p53 positivity, and high Ki-67 expression were significantly associated with the TNBC group (Table 1). Three patients (3.8%) in the TNBC group and 11 patients (3.8%) in the non-TNBC group died during the follow-up period. Local recurrence or distant metastasis was observed in 10 patients (8.9%) in the TNBC group and in 32 patients (8.8%) in the non-TNBC group. In addition, the pattern of recurrence between the two groups was not different (Table 2).

Table 1. Clinico-pathologic features of the TNBC and non-TNBC groups.

Factor	TNBC (n =79)		non-TNBC (n=266)		*p*-value
Age (median: 49)	(median: 47)		(median: 50)		0.078
<35	9	11.4%	15	5.6%	
≥35	70	88.6%	251	94.4%	
T stage					0.003
1	52	65.8%	125	47.0%	
2	27	34.2%	141	53.0%	
Histologic grade					< 0.001
1	4	5.1%	74	27.8%	
2	19	24.0%	116	43.6%	
3	47	59.5%	55	20.7%	
Unknown	9	11.4%	21	7.9%	
p53					< 0.001
Negative	26	32.9%	178	66.9%	
Positive	53	67.1%	88	33.1%	
Ki-67					< 0.001
Negative	16	20.3%	109	41.0%	
Positive	63	79.7%	141	53.0%	
Unknown	0	0.0%	16	6.0%	
Chemotherapy					< 0.001
Yes	72	91.2%	166	62.4%	
No	7	8.8%	100	37.6%	
Hormone therapy					< 0.001
Yes	0	0.0%	163	61.3%	
No	79	100.0%	103	38.7%	
Radiotherapy					0.106
Yes	45	57.0%	124	46.6%	
No	34	43.0%	142	53.4%	

TNBC = triple-negative breast cancer
T stage = tumor stage

Table 2. Prognostic events of the TNBC and non-TNBC groups.

Event	TNBC n =79 (22.9%)	non-TNBC n=266 (77.1%)	*p*-value
Median follow-up	87.84 (±38.97) months	75.96 (±38.12) months	
Disease-free	69 (87.3%)	231 (87.5%)	
Recurrence			0.754
Local	5 (6.3%)	16 (6.1%)	
Distant	2 (2.6%)	7 (2.7%)	
Death	3 (3.8%)	10 (3.8%)	0.631

TNBC = triple-negative breast cancer

In the TNBC group, young age less than 35 years patients show poorer prognosis than older group in the disease free survival ($p<0.001$) (Fig. 1-C). High Ki-67 expression had statistically significant negative impact on the disease-free

survival of both the TNBC group (p =0.035) (Fig. 2-C) and the non-TNBC group (p =0.016) (Fig. 2-D), but neither group showed statistical differences in overall survival according to Ki-67 expression (Fig. 2-A,B). The disease-free survival rate of p53-positive patients in TNBC was significantly lower than that of p53-negative patients (p =0.028) (Fig. 3-C). However, there was no such difference in the non-TNBC group (Fig. 3-D). For overall survival, p53

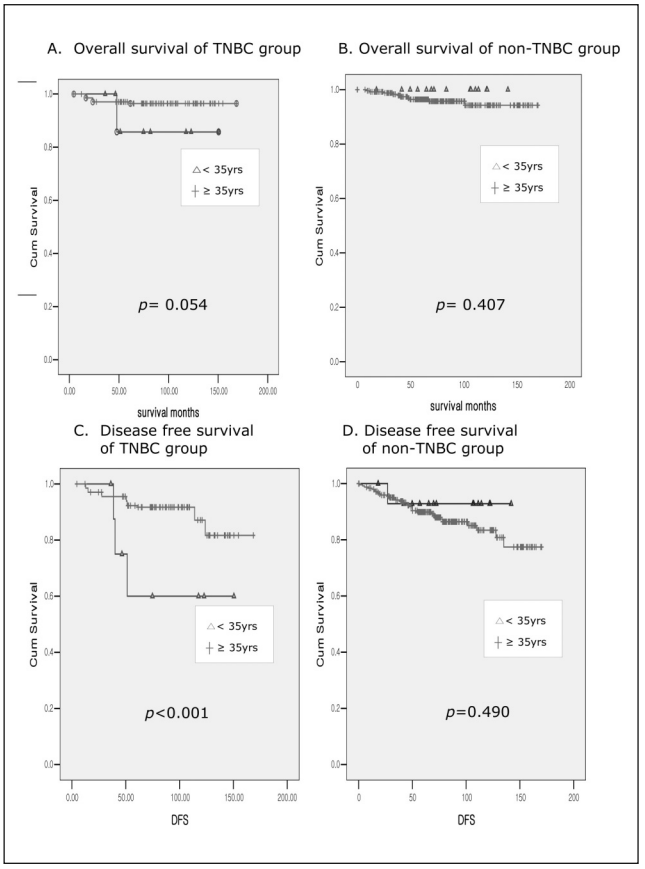

Fig. 1. Analysis of overall survival and disease free survival of TNBC and non-TNBC groups according to age by log-rank test

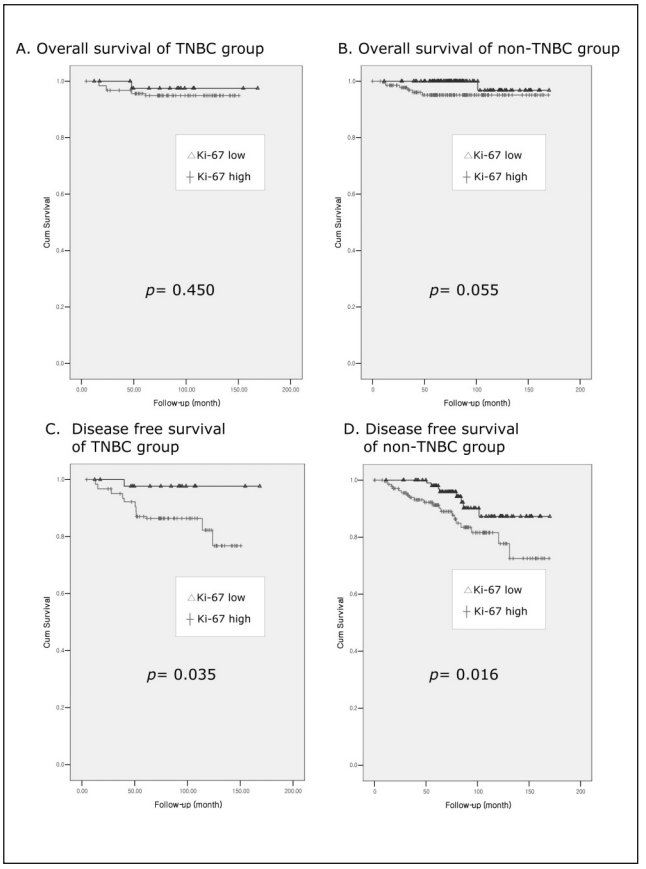

Fig. 2. Analysis of overall survival and disease free survival of TNBC and non-TNBC groups according to Ki-67 expression by log-rank test

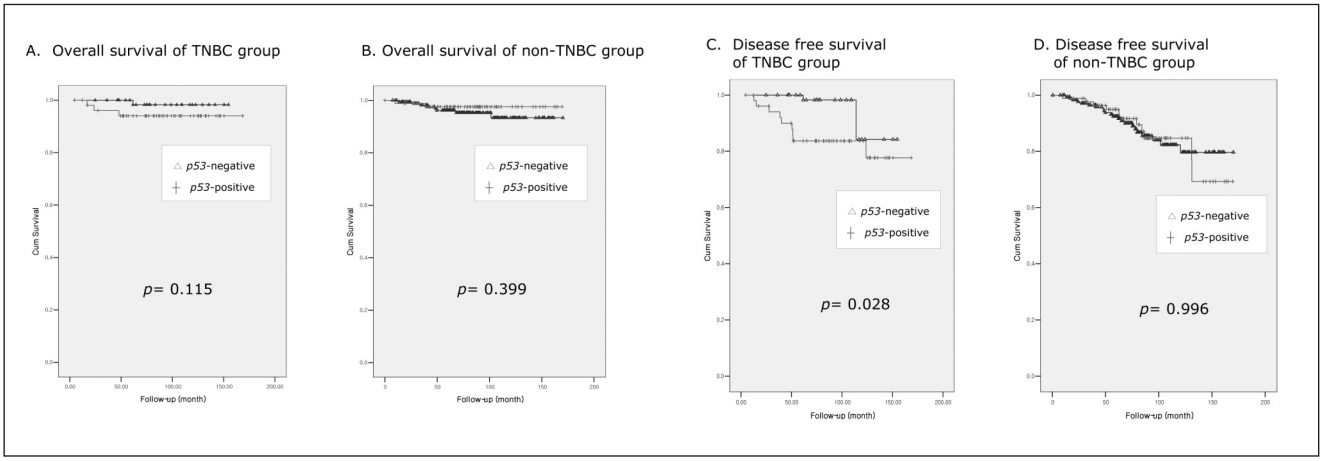

Fig. 3. Analysis of overall survival and disease free survival of triple negative breast cancer (TNBC) and non-TNBC groups according to p53 expression by log-rank test

status was not significant in both groups (Fig. 3-A,B).

Univariate analysis including all patients revealed that stage T2, high Ki-67 expression, and chemotherapy had prognostic value for overall survival. In multivariate analysis, T-stage (T2) was implicated as the only independent prognostic factor for overall survival (p=0.037, relative risk (RR) = 8.2 (1.1-59.3)). For disease-free survival, T-stage (T2) (p<0.001, RR = 7.5 (2.9-19.3)) and high histologic grade (p=0.006) were significant predictors in multivariate analysis (Table 3).

For the overall survival of the TNBC group, age, T-stage (T2) and high histologic grade were significant predictors by univariate analysis, but in multivariate analysis, age and T-stage (T2) were the independent prognostic factors. For the disease-free survival of TNBC, young age, T-stage (T2), high histologic grade and high Ki-67 expression were significant in univariate analysis. An age younger than 35 years (p=0.003, RR =4.1 (1.6-10.6)) and T-stage (T2) (p=0.005, RR =4.8 (1.6-14.4)) were independent prognostic factors in multivariate analysis (Table 4). For disease-free survival, high Ki-67 expression was significant only in univariate analysis (p=0.038) but it was not an independent prognostic factor in multivariate analysis (p=0.052).

There were no variables correlated with overall survival in the non-TNBC group. For the disease-free survival of non-TNBC patients, T-stage (T2) (p=0.005, RR =3.72 (1.48-9.35))

Table 3. Cox proportional hazards model results for overall survival and disease-free survival for all breast cancer patients.

Factor	Overall survival			Disease-free survival		
	uni	multi	RR (95% CI)	uni	multi	RR (95% CI)
Age (<35 vs ≥35)	0.089			0.718		
T stage (1 vs 2)	0.015*	0.037*	8.2 (1.1-59.3)	<0.001*	<0.001*	7.5 (2.9-19.3)
Grade	0.611			0.006*	0.036*	
Grade 1/2				0.004*	0.013*	4.8 (1.4-16.7)
Grade 2/3				0.759		
ER	0.908			0,175		
PR	0.323			0.519		
HER2	0.156			0.043		
Triple negative	0.426			0.339		
p53(N vs P)	0.843			0.543		
Ki-67(N vs P)	0.129	0.073		0.074		
Chemotherapy (yes vs no)	0.046*	0.052		0.167		
Hormone therapy (yes vs no)	0.409			0.224		

* : p<0.05
ER = estrogen receptor; PR = progesterone receptor
HER2 = Human Epidermal Growth Factor Receptor 2
N = negative ; P = positive

Table 4. Cox proportional hazards model results for overall survival and disease-free survival for the TNBC group.

Factor	Overall survival			Disease-free survival		
	uni	multi	RR (95% CI)	uni	multi	RR (95% CI)
Age (<35 vs ≥35)	0.003*	0.483		0.001*	0.003*	4.1 (1.6-10.6)
T stage (1 vs 2)	0.001*	0.293		0.006*	0.005*	4.8 (1.6-14.4)
Grade	0.002*			0.049*		
Grade 1/2	<0.001*			0.035		
Grade 2/3	0.002*			0.458		
p53(N vs P)	0.711			0.235		
Ki-67(N vs P)	0.346			0.038*	0.052	
Chemotherapy (yes vs no)	0.569			0.109		

* : p<0.05
TNBC = triple-negative breast cancer T stage = tumor stage
N = negative ; P = positive

Table 5. Cox proportional hazards model results for overall survival and disease-free survival for the non-TNBC group.

Factor	Overall survival			Disease-free survival		
	uni	multi	RR (95% CI)	uni	multi	RR (95% CI)
Age (<35 vs ≥35)	0.524			0.778		
T stage (1 vs 2)	0.052			0.003*	0.005*	3.72 (1.48-9.35)
Grade	0.350			0.023*	0.061	
Grade 1/2	0.993			0.017*	0.019*	4.39 (1.27-15.14)
Grade 2/3	0.199			0.900	0.173	
p53(N vs P)	0.843			0.511		
Ki-67(N vs P)	0.098			0.105		
Chemotherapy (yes vs no)	0.064			0.738		

* : p<0.05
T stage = tumor stage N = negative ; P = positive

and high histologic grade (p=0.019, RR=0.39 (1.27-15.14)) were independent prognostic factors in the multivariate analysis (Table 5). T-stage showed a similar result in univariate analysis of both the TNBC and the non-TNBC groups.

Discussion

Breast cancer was the most common cancer in Korean women between 2001 and 2007, and has been the second most common cancer since then[17]. While the incidence of breast cancer appears to be leveling off in Western countries after decades of increasing, it is still high and continues to increase in certain countries where it initially had a low incidence. Early detection of breast cancer and the use of aggressive multimodal treatment have been successful in decreasing the mortality rate.

Currently, TNBC that is associated with the lack of expression of the estrogen receptor, progesterone receptor and HER2 receptor, continues to pose a major problem because of its more aggressive clinical behavior and poorer prognosis compared to other subtypes.

Hudis et al.[18] and many other investigators have reported that the period until recurrence or metastasis in TNBC patients is shorter than in any other subtype. This has been attributed to the low efficacy of hormone therapy due to the negative hormone receptor status, and the lack of response to new medications that target the HER2 gene, such as trastuzumab[19]. As a result, TNBC patients have high recurrence and low survival rates[20]. In addition, the briefness of the disease-free period after surgery means that there are few treatment options. Park et al.[21] insisted that these subtypes including hormone receptor status need to be considered with existing TNM stages when designing a treatment plan. For patients with early breast cancer without lymph node metastasis, chemotherapy is limited and treatment options are restricted. A novel standard treatment strategy to achieve better prognosis in TNBC patients will require more studies of prognostic factors and feasible screening tools.

This subject is being explored by many researchers, but there are only a few studies involving early breast cancer without lymph node metastasis. Rhee et al. investigated triple negativity in node-negative breast cancer. TNBC is associated with younger age, higher histologic and nuclear grade, negative staining for bcl-2, positive staining for epidermal growth factor receptor (EGFR), and high levels of p53 and Ki-67 expression15. These findings are similar to our results, except that we did not investigate bcl-2 or EGFR. Rhee et al. investigated T3 node-negative breast cancers, but there have also been several attempts to evaluate prognostic factors associated with TNBC of only small size tumors (T1) in node-negative breast cancer. Garassino et al.[22] recently evaluated 214 patients with T1N0M0 breast cancer and reported that there are no significant differences in the relapse free survival and overall survival among the risk categories (high/intermediate/low) defined by the St. Gallen 1998 recommendations. Kim et al.[23] investigated the prognostic significance of molecular subtype in T1N0M0 breast cancer and reported that the triple-negative subtype is an independent predictor for recurrence, especially for early recurrence.

There have been relatively few studies of T2 tumors, and we specifically included T2 in our study. Less is known about TNBC in early breast cancer without lymph node metastasis, and specific predictive or prognostic factors have not been elucidated. We therefore sought to identify the predictive or prognostic values of candidate factors such as age, histological grade and molecules like p53 or Ki-67 among patients with TNBC and T1-2 node-negative tumors, and to ascertain the need for close follow-up of a high risk group based upon these factors . These considerations serve to underline the importance of our study and set it apart from others.

In our study, young age (less than 35 years old) was an independent prognostic factor for disease-free survival only for the TNBC group, and not for the non-TNBC group . High Ki-67 expression was a significant prognostic factor in

univariate analysis for TNBC, but it was not significant in multivariate analysis. High T-stage was an independent prognostic factor in both groups for disease-free survival.

We examined other studies concerning these individual prognostic factors, since our study showed that young age less than 35 years was the only independent poor prognostic factor in the disease-free survival of TNBC. Dobi et al.[24] reported higher systemic metastasis and axillary lymphadenectomy rates in TNBC patients younger than 40 years. Kwon et al.[25] similarly reported higher recurrence in TNBC patients younger than 35 years. Their study also showed that the triple-negative breast cancer group has a significantly lower survival rate than the other subtypes in the same younger age group (9.6% vs. 36.1%). We similarly found that the younger TNBC group had an unfavorable prognosis compared to the older non-TNBC group. Therefore, young age (less than 35 years) should be regarded as a poor prognostic factor when adjuvant therapy is considered. This is especially important in Asian contexts, because the proportion of young women in Asian countries is higher than in Western countries[26].

In contrast to age, we found that high expression of the proliferation marker Ki-67 was a statistically significant factor for disease-free survival of TNBC by univariate analysis, but not by multivariate analysis. A larger study may have resulted in statistical significance of Ki-67 by multivariate analysis. Other studies have repeatedly confirmed Ki-67 as an independent predictive and prognostic factor in early breast cancer[13]. TNBC is associated with higher expression of Ki-67 than non-TNBC[14, 15]. Keam et al.[14] found that TNBC with high Ki-67 expression is associated with poorer survival than TNBC with low Ki-67 expression, despite a higher rate of complete pathological remission. Furthermore, TNBC with high Ki-67 expression shows rapid recurrence within three years, whereas TNBC with low Ki-67 expression shows a near-constant recurrence rate. However, the role of Ki-67 is not yet conclusive because of the heterogeneous patient samples, small sample sizes, and different chemotherapeutic regimens found across studies.

Mutations in the tumor suppressor gene p53 are present in 18-25% of primary breast carcinomas[7, 8]. Chae et al.[27] compared the clinical outcomes of breast cancer patients according to p53 accumulation in TNBC and non-TNBC patients and suggested that p53 status could be a specific prognostic factor in TNBC patients treated by adjuvant anthracycline-based regimens. Their results indicated that overall survival and relapse-free survival rate of patients overexpressing p53 were worse than patients harboring TNBC cells. Jung et al.[28] showed that p53 accumulation assayed by immunohistochemical staining had prognostic impact in lymph node-negative breast cancer. In addition, p53 status contributed additional prognostic information for intrinsic subtypes, especially in luminal A subtype and triple-negative subtype, and in the St. Gallen consensus. Based upon these previous findings, we initially expected p53 to be a prognostic factor associated with TNBC, but we did not observe such an association in this study.

Our study is one of very few that have aimed to identify the prognostic factors associated with TNBC in T1-2 node-negative breast cancer patients. Node-negative triple-negative breast cancers have been studied before, but with limited outcomes, and investigations of prognostic factors are hard to come by.

We note that our study also had several limitations. First, it involved a retrospective cohort. In addition, some variables like HER2 receptor status or Ki-67 expression were not present in the older medical records before these tests became widely available. Thus, many patients had to be excluded from this study. Second, the sample population was from a single institution and was relatively small compared to the worldwide breast cancer collaboration database. Third, we concentrated on relatively early patients with lymph node-negative breast cancer. They lived long after surgery and seldom had events of local recurrences, distant metastasis or deaths. For this reason, several difficulties exsited in analyzing the survival rate, and especially disease-free survival, presenting a major

drawback of our study. Based on our findings and these limitations, a larger, randomized long-term study will be needed to achieve stability and consensus.

Conclusions

At last, overall survival of TNBC and non-TNBC had no significant difference between two groups. But, we found that young age of less than 35 years was an independent factor related to poor prognosis for the disease-free survival of patients with TNBC group. p53-positivity was not a significant prognostic factor in either univariate of multivariate analyses of patients with TNBC. High Ki-67 expression was a significant prognostic factor according to univariate analysis in the TNBC group, but it was not significant according to multivariate analysis. T-stage (T2) and higher histologic grade could be independent factors related to poor prognosis for disease-free survival in patients with or without TNBC.

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Are there the specific prognostic factors for triple-negative subtype of early breast cancers (pT1-2N0M0)?

Department of General Surgery, Anam Hospital, Korea University, College of Medicine, 126-, Anam-dong 5-ga, Seongbuk-gu, Seoul, Korea[1], Department of General Surgery, Guro Hospital, Korea University, College of Medicine, 97 Gurodong-Gil Guro-Ku, Seoul, Korea[2], Division of Medical Oncology, Department of Internal Medicine, Anam Hospital, Korea University, College of Medicine, 126-, Anam-dong 5-ga, Seongbuk-gu, Seoul, Korea[3]
Ji-Young You[1], Hye-yoon Lee[1], Sang-uk Woo[2], Kyong-hwa Park[3], Eun-sook Lee[1], Jeoung-won Bae[1]

Abstract

Purpose : Triple-negative breast cancer typically results in poorer prognoses compared to non-triple negative breast cancer, even in early stages. The initial management of triple negative breast cancer patients and detection of clear prognostic factors are therefore of great importance. We aimed to identify specific prognostic factors associated with unfavorable outcomes of triple negative breast cancer in T1-2 node-negative breast cancer.

Materials and Methods : We analyzed breast cancer patients without lymph node metastasis or distant metastasis who underwent curative surgery at the Anam Hospital of the Korea University Medical Center between 1995 and 2006. Among them, patients were eligible for analysis, only if the reports about hormone receptor and human epidermal growth factor receptor-2 status were available. Clinico-pathological features were reviewed by retrospective examination and comparison of medical records of triple negative breast cancer and non-triple negative breast cancer patients.

Results : Seventy-nine patients (22.9%) were categorized to the triple negative breast cancer group. The disease-free survival rate of TNBC p53-positive patients was significantly lower than that of p53-negative patients (p =0.028). In multivariate analysis, young age was an independent prognostic factor for disease-free survival of the triple negative breast cancer group. High Ki-67 expression was a significant prognostic factor in univariate analysis in triple negative breast cancer, but it was not significant in multivariate analysis.

Conclusion : We suggest that age is an independent prognostic factor of triple negative breast cancer in T1-2 and node-negative patients and that Ki-67 could also be a prognostic factor in these patients.

Key Words : triple negative breast cancer, lymph node negative, p53, Ki-67, young age

Correspondence : Jeoung-won Bae
Department of General Surgery, Anam Hospital, Korea University, College of Medicine, 126-, Anam-dong 5-ga, Seongbuk-gu, Seoul, Korea
Tel: 82-2-920-5978 Fax: 82-2-928-1631 E-mail: kujwbae@korea.ac.kr
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