Original Articles/นิพนธ์ต้นฉบับ

Disease-free Probability and Triple-negative Breast Cancer.

Chirappapha P, MD., Sukarayothin T, MD., Wasuthit Y, MD., Suvikapakornkul R, MD., Lertsithichai P, MD., Kongdan Y, MD.

Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400 Thailand

Abstract

Background: To compare the probabilities of local recurrence and distant metastasis between women with triple-negative and non-triple negative breast cancers.

Methods: Medical and pathological records of breast cancer patients treated between the years 2002 and 2006 were reviewed.

Results: There were 256 patients with complete data on estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) expression determinations. There were 54 patients (21%) with triple-negative (ER - , PR - , HER2 -) cancers. Triple-negative patients were more likely to have larger tumors with higher histologic grade. The median follow-up time was 4 years. The probabilities of local and distant recurrence were similar between the two groups of patients. Only two factors were independently and significantly associated with overall recurrence: tumor stage and tumor size.

Conclusion: Triple-negative breast cancer did not have a higher risk for both local recurrence and distant metastasis when compared with non-triple negative cancer.

Keywords: Triple-negative breast cancer, local recurrence, distant metastasis, disease-free probability

Corresponding Author: Kongdan Y, MD.
Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400 Thailand Telephone. 02 2011315 Fax: 02 2011316
Email: breastrama@gmail.com

Introduction

Triple-negative breast cancers, despite being chemo-responsive, are believed to have a poor prognosis relative to breast cancers with other receptor phenotypes.[1-4] Triple-negative cancers have an absence of ("negative") hormonal receptor (estrogen and progesterone receptors, ER and PR, respectively) and human epidermal growth factor receptor-2 (HER2) expressions. Most of these tumors have "basal-like" gene expression, although some also have "normal breast-like" gene expression, and are associated with BRCA1 gene mutations.[1-4]

Many previous studies documented a worse overall prognosis in terms of survival and disease recurrence for triple-negative breast cancers,[1-7] but a few did not find a significantly worse prognosis.[1,7-10] The objective of the present study was to determine whether triple-negative breast cancers have an increased risk of recurrent disease relative to non-triple negative breast cancers.

Patients and Methods

We reviewed the medical and pathological records of women with operable breast cancer who underwent modified radical mastectomy or breast conserving surgery between the years 2002 and 2006 at Ramathibodi Hospital. The Hospital's Research Ethics Committee approved the study. The follow-up cut-off date for the present study was June 2008. Collected patient information included age at diagnosis, method of cancer detection, mammographic Breast Image Reporting and Data System (BIRADS) category, pathologic tumor size, tumor grade, presence of lymphovascular invasion, axillary lymph node status, local recurrence, distant metastasis, and time to recurrence. In the present study, triple-negative breast cancers were defined as ER negative, PR negative, and HER2 negative cancers. Breast cancers that were positive for any of these markers were defined as non-triple negative.

Pathological lymph node classification and TNM (tumor, nodes, metastasis) breast cancer staging were according to the American Joint Committee on Cancer (AJCC) criteria.[11] Histologic grading was according to the criteria of Bloom and Richardson. Lympho-vascular invasion was defined as the presence of tumor emboli in peritumoral lymphatic spaces, capillaries or postcapillary venules. The expressions of ER, PR, and HER2 were determined by standard immunohistochemical techniques. Positive ER or PR status was defined as the staining more than 10% of tumor cells. An immunohistochemical score of 3+ defined HER2 positivity.

Disease recurrence, whether local or distant, was defined as the detection of previously undetected disease at least 90 days following initial treatment. Disease detected within 90 days of initial treatment was considered a part of the initial lesion complex. Deaths and loss to follow-up were considered censored events.

Clinicopathological variables were compared between the triple-negative and non-triple negative groups, using unpaired t-test for continuous variables and chi-square test for categorical variables. The Kaplan-Meier method was used to estimate disease-free probability curves, for both local recurrence and distant metastasis. The log-rank test was used to test for significant differences between these estimates. Multivariable Cox proportional hazards regression analysis was used to determine significant risk factors associated with disease recurrence. Statistical significance was defined as a two-sided p-value of 0.05 or less. All analyses were performed using Stata version 9 (Stata Corp, College Station, TX, USA).

Results

Overall, records of 590 women who underwent surgery for breast cancer during the period under study were available for review. Of these, 256 had

complete data on ER, PR and HER2 expression assessments. There were 54 patients (21%) with triple-negative breast cancers, 202 (79%) had positive expression for at least one receptor. For the 200 patients younger than 60 years, 46 (23%) were triple-negative. Of the 56 patients older than 60 years, 8 (14%) had triple-negative cancer. The median follow-time for these patients was 4 years. The clinicopathological characteristics of the two groups of patients in the present study are presented in Table 1.

According to Table 1, an overwhelming proportion of patients were able to detect their cancers by themselves. Patients with triple-negative breast cancer tended to have larger tumors (not statistically significant), higher histologic grade (57% were grade 3 tumors), and earlier recurrent disease (marginally significant). No clear differences between groups were seen in terms of mammographic findings, the proportion of patients with axillary lymph node metastasis and overall TNM staging. Patients with triple-negative tumors were followed for a relatively shorter period of time, mainly due to earlier and more numerous losses to follow-up.

Tumor size had no clear relationship with axillary lymph node positivity for patients with triple-negative breast cancer (mean size for the lymph node positive group, 3.5 cm; for the lymph node negative group, 3.4 cm; t-test p-value, 0.848). In contrast, for patients with non-triple negative cancer, there was a significant relationship (mean sizes for the lymph node positive and negative groups were 3.5 cm and 2.6 cm, respectively; t-test p-value < 0.001). There was a non-significant trend for triple negative patients to have fewer positive axillary nodes per patient (Table 1).

The overall recurrence- or disease-free probability curves for both groups of patients were not clearly different; the log-rank test p-value was 0.490. The local recurrence-free probability curves for both groups are shown in Figure 1. The difference between the two groups was not significant (log-rank test p-value, 0.780). Similarly, in Figure 2, the difference in the distant metstasis-free probability was not statistically significant (log-rank test p-value, 0.473).

On multivariable Cox proportional hazards regression analysis, the triple-negative phenotype was not significantly associated with any type of recurrent disease. The only independent risk factors associated with overall disease recurrence were TNM stage and tumor size (Table 2).

Discussion

Triple-negative breast cancers are of considerable current interest due to a number of reasons.[1-4] These cancers are thought to have poor prognoses. The only standard systemic adjuvant treatment for these cancers is chemotherapy. They may form a substantial portion of all breast cancers, especially in young or premenopausal patients and patients of certain racial ancestry, such as African Americans.[3,4,12]

In the present study, 21% of all operable breast cancers were triple-negative. This is a higher proportion of all breast cancers than those previously seen in Asian women,[10,13] but similar to or lower than those seen in Caucasians and African Americans.[3,12] Therefore, a substantial portion of breast cancer patients in the present institution was triple-negative. However, the relatively high proportion of triple-negative cancers could be due to selection bias, as many patients in the present series had more advanced cancers, or due to our method of assessing and defining ER, PR and HER2 expressions.

The characteristics of triple-negative breast cancer in the present study were similar to those reported in previous studies.[1,3-6,12] Triple-negative tumors were more likely to be histologic grade III (57% in the present series), and tended to be larger. However, axillary lymph node involvement and TNM stage were not significantly different between triple and non-triple negative tumors.[1,5,12] In fact, fewer positive axillary lymph nodes per patient were seen

Table 1 Comparison of clinicopathological characteristics between patients with triple and non-triple negative breast cancer (N = 256).

Characteristics	Non-triple negative cancer (N = 202)	Triple-negative cancer (N = 54)	p-value[a]
Age (years): mean (SD)	51.9 (10.9)	49.1 (11.0)	0.093
Cancer detection: no. (%)			
By patient	188 (93)	51 (94)	0.718
By clinician/radiologist	14 (7)	3 (6)	
Mammographic BIRADS categoryb			
3	1/167 (1)	1/39 (3)	0.311
4	44/167 (26)	7/39 (18)	
5	122/167 (73)	8/39 (80)	
Tumor size (cm.): mean (SD)	3.1 (1.7)	3.5 (1.8)	0.123
Tumor grade: no. (%)			
1	23/201 (12)	1/51 (2)	< 0.001
2	125/201 (62)	21/51 (41)	
3	53/201 (26)	29/51 (57)	
Lymphovascular invasion: no. (%)	72 (36)	20 (37)	0.850
Axillary node positive: no. (%)	110 (55)	25 (46)	0.286
Number of positive axillary nodes per pt.			
Median (range)	1 (0 to 37)	0 (0 to 23)	0.116
Mean (SD)	3.4 (6.2)	2.0 (4.4)	0.118
Total no. axillary nodes removed			
Mean (SD)	17.1 (7.1)	16.5 (7.6)	0.484
pTNM staging (AJCC, 7th ed.)			
I	29 (14)	6 (11)	0.553
II	126 (63)	38 (70)	
III	47 (23)	10 (19)	
Follow-up time (months)			
Median (range)	48 (17 to 75)	40.5 (3 to 62)	< 0.001
Time to all recurrence (months)			
Median (range)	43 (4 to 74)	36 (3 to 62)	0.056
All recurrence: no. (%)	36 (18)	8 (15)	NA
Local recurrence: no. (%)	14 (7)	4 (7)	NA
Distant metastasis: no. (%)	31 (15)	7 (13)	NA

a. p-value by t-test, rank test and chi-square test as appropriate; b. excluding patients with BIRADS category 6 (known cancer) mammograms; pTNM: pathological tumor, nodes, metastasis; AJCC: American Joint Committee on Cancer; BIRADS: breast imaging reporting and data system; no.: number; SD: standard deviation; pt.: patient; NA: not applicable.

Table 2 Independent risk factors associated with overall disease recurrence (multivariable Cox proportional hazard regression).

Risk factor	Hazard ratio (95% CI)	p-value
TNM stage	2.13 per stage increase (1.15 to 3.96)	0.017
Tumor size	1.25 per cm. increase in size (1.08 to 1.44)	0.003

TNM: tumor, nodes, metastasis; 95% CI: 95% confidence interval.

in the triple-negative group. Also, there was no clear association between tumor size and axillary lymph node positivity for patients with triple-negative cancer, consistent with the results of some studies.[1]

The present study focused on the prognosis of triple-negative breast cancer. Specifically, we looked at disease recurrence, local as well as distant. Differences in local, distant, and overall recurrence probabilities between triple and non-triple negative breast cancers were not statistically significant. Although many previous studies found decreased survival and increased disease recurrence for triple-negative cancers,[1-7] some did not find such evidence.[1,7-10]

Possible reasons for the discrepancy among studies are several-fold. Some studies found significant differences because the triple-negative phenotype was compared with other, clearly more favorable phenotypes such as those associated with positive hormone receptors.6 Different series in which triple-negative patients were selected differently might or might not have triple-negative tumors with worse prognosis, depending on the response of these tumors to chemotherapy.[2-4] Triple-negative tumors not responding to chemotherapy might do worse than tumors with hormone-negative, HER2-positive phenotypes.[5,14] But with a high proportion of response, triple-negative tumors might do better than hormone-negative, HER2-positive tumors.[1,7,9,12,15]

The similar prognoses between triple and non-triple negative breast cancers in the present study was probably due to a high proportion of chemo-responsive triple-negative tumors and the fortuitous mixture of good prognosis (hormone-positive) and bad prognosis (HER2-positive) tumors in the non-triple negative group.

Triple-negative breast cancers are therefore apparently heterogeneous tumors, associated with different types of gene expression at the transcriptional level.[1-4,8] They are not identical to basal-like tumors. They are associated with several genetic and histochemical markers which can differentiate among cancers with different prognoses.[8,10,14-16] Their usefulness as a class may be limited to conveying the need to find new targeted treatments specifically for this group of patients.[1-4,6] Nevertheless, they are not homogeneous, and "triple-negative" as a descriptive term will most likely be replaced, in the future, by the category of basal-like tumors, to be subclassified according to other tissue or genetic markers more useful and accurate for prognostication and predicting treatment response.[1,2,4,17]

The limitations of the present study included a small sample size and small number of recurrences, although the follow-up time extended to over 6 years. Selection bias was most likely important as well, since patients who had both hormonal receptor and HER2 expression assessments were probably at a higher risk for recurrence, thus explaining the relatively high proportion of triple-negative breast cancers in the present study.

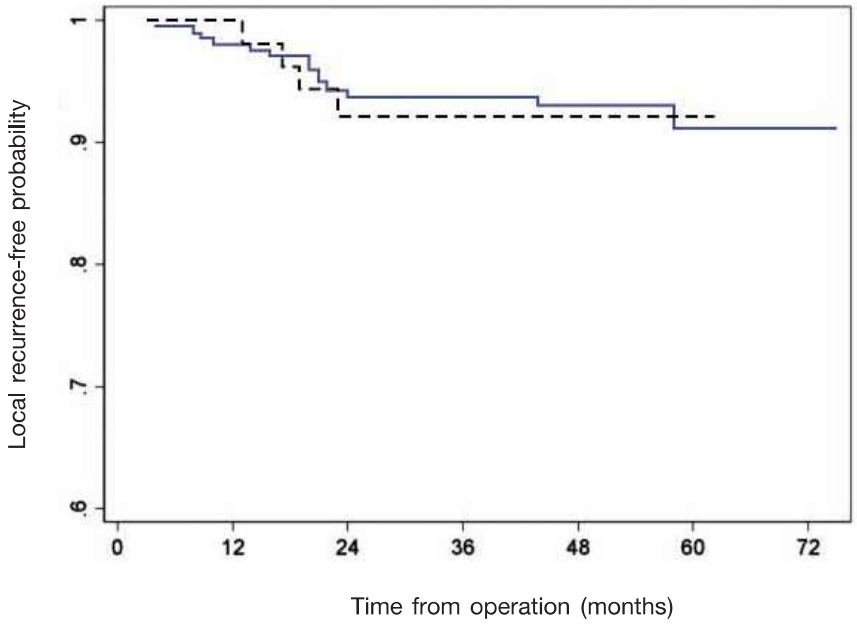


Figure 1 *Local recurrence-free probability for triple-negative cancer (dashed line) and non-triple negative cancer (solid line).*

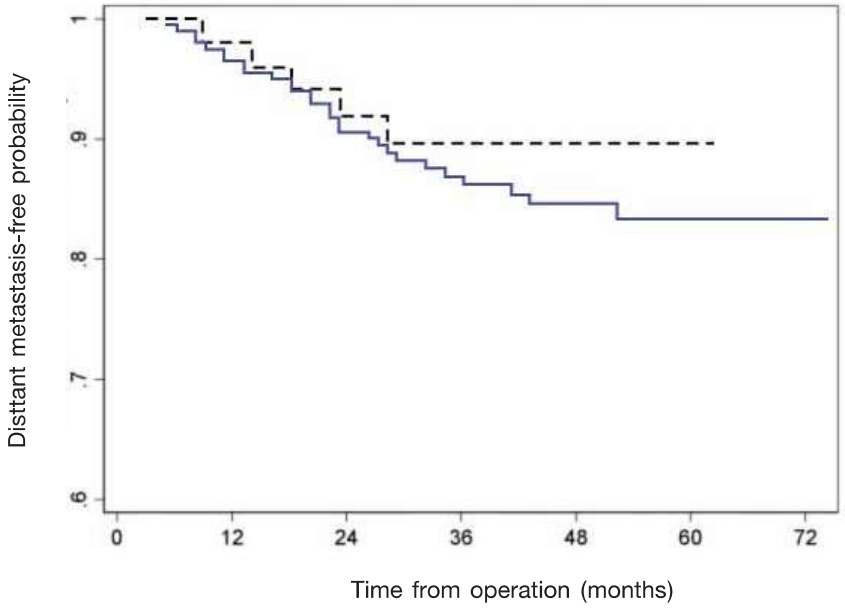


Figure 2 *Distant metastasis-free probability for triple-negative cancer (dashed line) and non-triple negative cancer (solid line).*

Conclusions

Triple-negative breast cancer did not have a higher risk for both local recurrence and distant metastasis when compared with non-triple negative cancer in the present study. The prognosis of triple-negative breast cancer relative to other breast cancers probably depended on the response of each of these tumors to various adjuvant systemic therapies as well.

References

1. Reis-Filho JS, Tutt ANJ. Triple negative tumors: a critical review. Histopathology 2008;52:108-18.
2. Cleator S, Heller W, Coombs RC. Triple-negative breast cancer: therapeutic options. Lancet Oncol 2007;8: 235-44.
3. Ray M, Polite BN. Triple-negative breast cancers. A view from 10,000 feet. Cancer J 2010;16:17-22.
4. Irvin WJ, Carey LA. What is triple-negative breast cancer? Eur J Cancer 2008;44:2799-805.
5. Nishimura R, Arima N. Is triple negative a prognostic factor in breast cancer? Breast Cancer 2008;15: 303-8.
6. Kaplan HG, Malmgren JA, Atwood M. T1N0 triple negative breast cancer: risk of recurrence and adjuvant chemotherapy. Breast J 2009;15:454-60.
7. Kaplan HG, Malmgren JA. Impact of triple negative phenotype on breast cancer prognosis. Breast J 2008;14:456-63.
8. Jumppanen M, Gruvberger-Saal S, Kauraniemi P, Tanner M, Bendahl PO, Lundin M, et al. Basal-like phenotype is not associated with patient survival in estrogen-receptor-negative breast cancers. Breast Cancer Res 2007;9:R16 doi:10.1186/bcr1649.
9. Gonzalez-Angulo AM, Litton JK, Broglio KR, Meric-Bernstam F, Rakkhit R, Cardoso F, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node negative tumors 1 cm or smaller. J Clin Oncol 2009;34:5700-6.
10. Yin WJ, Lu JS, Di GH, Lin YP, Zhou LH, Liu GY, et al. Clinicopathological features of triple-negative tumors in Chinese breast cancer patients. Breast Cancer Res Treat 2009;115:325-33.
11. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC Cancer Staging Handbook. 7th ed. New York:Springer;2010:347-76.
12. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006;295:2492-502.
13. Kurebayashi J, Moriya T, Ishida T, Hirakawa H, Kurosumi M, Akiyama F, et al. The prevalence of intrinsic subtypes and prognosis in breast cancer patients of different races. Breast 2007;16:S72-7.
14. Fulford LG, Reis-Filho JS, Ryder K, Jones C, Gillet CE, Hanby A, et al. Basal-like grade III invasive ductal carcinoma of the breast: patterns of metastasis and long-term survival. Breast Cancer Res 2007;9:R4 doi:10.1186/bcr1636.
15. Liu H, Fan Q, Zhang Z, Li X, Yu H, Meng F. Basal-HER2 phenotype shows poorer survival than basal-like phenotype in hormone receptor-negative invasive breast cancers. Hum Pathol 2008;39:167-74.

16. Fernandes SC, Bevilacqua JLB, Soares IC, Siqueira SAC, Pires L, Hegg R, Carvalho FM. Coordinated expression of ER, PR and HER2 define different prognostic subtypes among poorly differentiated breast carcinomas. Histopathology 2009;55:346-52.

17. Gong Y, Yan K, Lin F, Anderson K, Sotiriou C, Andre F, Holmes FA, et al. Determination of oestrogen-receptor status and ERBB2 status of breast carcinoma: a gene-expression profiling study. Lancet Oncol 2007;8:203-11.

Original Articles/นิพนธ์ต้นฉบับ

การอยู่รอดโดยปราศจากโรคในโรคมะเร็งเต้านมประเภท triple negative

ประกาศิต จิรัปปภา, พบ., ธงชัย ศุกรโยธิน, พบ., ยอดยิ่ง วาสุถิตย์, พบ., รณรัฐ สุวิกะปกรณ์กุล, พบ., ภาณุวัฒน์ เลศสิทธิชัย, พบ., เยาวนุช คงด่าน, พบ.

ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล กรุงเทพฯ 10400

บทคัดย่อ

วัตถุประสงค์: เพื่อเปรียบเทียบโอกาสเกิดมะเร็งปรากฏซ้ำเฉพาะที่ และในอวัยวะอื่นๆ ทั่วร่างกาย ระหว่างผู้ป่วยมะเร็งเต้านมหญิงประเภท triple negative และประเภทไม่เป็น triple negative

วิธีการ: ได้ทบทวนเวชระเบียนของผู้ป่วยมะเร็งเต้านมที่ได้รับการรักษาระหว่างปี พ.ศ. 2545 ถึงปี พ.ศ. 2549 ข้อมูลที่เก็บบันทึกประกอบด้วย อายุ ผลตรวจทางคลินิก ผลตรวจทางรังสีวิทยา และพยาธิวิทยา การจัดระยะมะเร็ง ผลตรวจตัวจับฮอร์โมนและ human epidermal growth factor receptor 2 (HER2) ในเนื้อเยื่อ การเกิดมะเร็งปรากฏซ้ำที่อวัยวะต่างๆ และระยะเวลาติดตามผู้ป่วยจนเกิดโรคปรากฏซ้ำ

ผลการศึกษา: พบผู้ป่วย 256 รายที่มีข้อมูลผลตัวจับฮอร์โมนเอสโตรเจน (ER), ตัวจับโปรเจสเตอโรน (PR) และ HER2 ครบทุกราย มีผู้ป่วย 54 ราย (ร้อยละ 21) ที่เป็นมะเร็งเต้านใประเภท triple negative (ER -, PR -, HER2 -) พบว่าผู้ป่วยมะเร็ง triple negative มีแนวโน้มจะมีมะเร็งขนาดใหญ่กว่า และมีเกรด (grade) ของมะเร็งที่สูงกว่า ผู้ป่วยมะเร็งที่ไม่ใช่ triple negative โดยโอกาสมีมะเร็งกระจายไปต่อมน้ำเหลืองที่รักแร้เทียบเท่ากันในผู้ป่วยทั้ง 2 กลุ่ม มีค่ามัธยฐานของระยะเวลาติดตามผู้ป่วย คือ 4 ปี พบโอกาสเกิดมะเร็งปรากฏซ้ำที่อวัยวะต่างๆ ไม่แตกต่างอย่างมีนัยสำคัญระหว่างผู้ป่วยทั้ง 2 กลุ่ม มีปัจจัยเสี่ยงที่สัมพันธ์กับการเกิดมะเร็งปรากฏซ้ำ 2 ปัจจัย อันได้แก่ การจัดระยะมะเร็งและขนาดของมะเร็ง

สรุป: มะเร็งเต้านมประเภท triple negative ไม่แตกต่างชัดเจนจากมะเร็งประเภทที่ไม่เป็น triple negative ในแง่ของการเกิดมะเร็งปรากฏซ้ำทั้งที่เกิดเฉพาะที่และที่เกิดในอวัยวะอื่นๆ ในร่างกาย

Corresponding Author: เยาวนุช คงด่าน พบ.
ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล กรุงเทพฯ 10400
โทร. 02 2011315 โทรสาร 02 2011316
Email: breastrama@gmail.com