BJM Vol.5 No.2 July-December 2018

นิพนธ์ต้นฉบับ (Original article)

ปัจจัยเสี่ยงในการกลับเป็นซ้ำของมะเร็งเต้านมชนิด Triple-Negative Breast Cancer (TNBC)

ปองทิพย์ อุ่นประเสริฐ (พ.บ.)[1], ภาคภูมิ บำรุงราชภักดี (พ.บ.)[1], พุฒิศักดิ์ พุทธวิบูลย์ (พ.บ.)[2] และรัศมี สังข์ทอง (พ.บ.)[3]

[1]สาขาวิชาศัลยศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยบูรพา
[2]สาขาวิชาศัลยศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์
[3]หน่วยระบาดวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์

บทคัดย่อ

วัตถุประสงค์ เพื่อศึกษาปัจจัยเสี่ยงที่มีผลในการกลับเป็นซ้ำ และศึกษาลักษณะทางคลินิกในผู้ป่วย โรคมะเร็งเต้านมชนิด Triple-Negative Breast Cancer (TNBC)

วิธีการศึกษา เก็บรวบรวมข้อมูลจากเวชระเบียนผู้ป่วยของโรงพยาบาลสงขลานครินทร์ที่ได้รับการวินิจฉัยเป็น TNBC ตั้งแต่ 1 กันยายน พ.ศ. 2549 ถึง 31 สิงหาคม พ.ศ. 2552 นำมาแบ่งกลุ่มย่อยตามอายุ ประวัติครอบครัว อาการนำ วิธีการตรวจพบ ขนาดของก้อนมะเร็ง ระดับของมะเร็ง (cancer grade) การแพร่กระจายไปยังต่อมน้ำเหลือง การแพร่กระจายผ่านทางเดินน้ำเหลือง ขอบเขตของเนื้อเยื่อที่ตัด การรักษาด้วยวิธีการทางยา เพื่อศึกษาหาปัจจัยที่มีผลในการพยากรณ์โรค และการกลับเป็นซ้ำของผู้ป่วยโรคมะเร็งเต้านมชนิด TNBC

ผลการศึกษา มีผู้ป่วยทั้งสิ้น 80 รายที่ได้รับการวินิจฉัย TNBC อายุเฉลี่ย 50.9 ปี (พิสัย 28-79 ปี) เกือบทั้งหมดมาด้วยก้อนที่เต้านม (ร้อยละ 98.75) ส่วนใหญ่เป็นเนื้องอกระดับ (เกรด) 3 (ร้อยละ 64) และเนื้องอกมีขนาดมากกว่า 2 เซนติเมตร (ร้อยละ 73.7) ร้อยละ 30 มีส่วนประกอบของมะเร็งชนิด invasive intraductal ร้อยละ 56.25 พบการแพร่กระจายไปต่อมน้ำเหลือง ร้อยละ 38.75 พบว่ามีการแพร่กระจายผ่านทางเดินน้ำเหลือง โดยพบว่าการแพร่กระจายผ่านทางเดินน้ำเหลืองเป็นตัวแปรที่มีนัยสำคัญทางสถิติในการกลับเป็นซ้ำ (odds ratio 4.17, 95% CI : 1.5183 - 11.4343, p = 0.0056)

สรุป งานวิจัยนี้แสดงว่าการแพร่กระจายผ่านทางเดินน้ำเหลืองเป็นปัจจัยที่สำคัญทางสถิติในการกลับเป็นซ้ำในผู้ป่วยโรคมะเร็งเต้านมชนิด TNBC

คำสำคัญ มะเร็งเต้านม มะเร็งเต้านมชนิด triple-negative กลับเป็นซ้ำ

ผู้นิพนธ์ที่รับผิดชอบ ปองทิพย์ อุ่นประเสริฐ
สาขาศัลยศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยบูรพา ชลบุรี ประเทศไทย
E-mail: pupat054@gmail.com

Risk factors for recurrence in Triple-Negative Breast Cancer (TNBC)

Pongtip Unprasert (M.D.)[1], Pakpume Bumrungrachpukdee (M.D.)[1],
Puttisak Puttawibul (M.D.)[2] and Rassamee Sangthong (M.D. Ph.D.)[3]

[1]Department of Surgery, Faculty of Medicine, Burapha University, Chonburi, Thailand
[2]Department of Surgery, Faculty of Medicine, Prince of Songkla University, Songkla, Thailand
[3]Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Chonburi, Thailand

Abstract

Background Triple-negative breast cancer (TNBC) (estrogen receptor-negative, progesterone receptor-negative, and HER2-negative) is a high risk breast cancer due to its aggressive behavior and nature of high recurrence.

Objective To determine the risk factor for recurrence and to determine the clinical features in patients with TNBC.

Material and Methods The retrospective data from Songklanagarind Hospital was conducted between September 1st, 2006, and August 31st, 2009, and identified patients with TNBC. The study then characterized this specific subgroup of breast cancer according to risk factors: age, family history, clinical manifestations, detection methods, tumor size, tumor grading, lymph node status, extensive intraductal component (EIC), lymphovascular invasion (LVI), resection margin and systemic therapy, to estimate the recurrence of TNBC.

Results 98.75% of our eighty (80) patients diagnosed with TNBC (mean age 50.9 years with an age range between 28-79 years old), presented breast masses – of which 64% had grade 3 tumors. Of those grade 3 tumors, 73.7% were more than 2 centimeters in size. Further, 30% had an invasive intraductal component, 56.25% were nodal status positive and 38.75% had lymphovascular invasion. The presence of lymphovascular invasion showed a significant statistical factor in the recurrence of TNBC patients (an odds ratio of 4.17, 95% CI : 1.5183 - 11.4343, p = 0.0056).

Conclusions The present study shows the status of lymphovascular invasion as the significant risk factor for recurrence of TNBC in patients.

Keywords Breast carcinoma, Triple-negative breast cancer, Recurrence disease

Corresponding author Pongtip Unprasert
Department of Surgery, Faculty of Medicine,
Burapha University, Chonburi, Thailand
E-mail: pupat054@gmail.com

Introduction

Breast carcinomas represent a heterogeneous group of tumors that are diverse in behavior, outcome and response to therapy. To reduce mortality from breast cancer, there is a desire to examine and characterize tumors of poor prognosis, to predict their biology, to ensure adequate therapy and to improve outcome. There is also a need to develop additional forms of effectiveness systemic treatment in those tumors that fail to express known targets, such as estrogen receptors, progesterone receptors or C-erbB-2 (HER2)[1]. In this way, Triple-negative breast cancer (TNBC) (estrogen receptor-negative, progesterone receptor-negative, and HER2-negative), is considered to be a high risk breast cancer due to its aggressive behavior and highly recurrent nature, according to previous studies [2-4]. The objective was to determine the risk factor for recurrence of TNBC as well as to determine the clinical features of TNBC patients.

Material and methods

Patient medical records who underwent treatment at Songklanagarind Hospital from September 1st, 2005, to August 31st, 2009, for TNBC (with confirmed diagnosis by pathological report) were analysed. The systematic data was studied with a focus on the patient's age (in years) at diagnosis, family history of breast cancer, clinical manifestations, detection methods, pathologic tumor size in centimeters, tumor grade, lymph node status, extensive intraductal component, lymphovascular invasion, resection margin as well as systemic treatment (e.g., chemotherapy, tamoxifen therapy and radiation treatment). For this study, triple-negative breast cancers were defined as those were estrogen receptor (ER) negative, progesterone receptor (PR) negative and HER2 negative. While the primary objective was to discover the risk factor for recurrence, a secondary objective was to determine the clinical features of TNBC patients.

Clinical follow-up

The database coordinator maintained patient follow-up by reviewing their clinical charts and then contacting them by telephone. Local-regional relapses and subsequent surgeries during the 30-day post-surgery period were considered part of the primary management, while distant recurrence during this period disqualified the patient from study. Relapses after 30 days were considered "events." Relapses were dated and reviewed by the staff surgeons responsible for their respective cases. Patients were to be followed-up with for a minimum of 6 months after surgery.

Statistical methods

Baseline demographic data and tumor characteristics were compared between recurrent cases and non-recurrent cases, using a t-test statistic for means, and M2 statistic for frequencies. Pearson's chi-square test/Fisher exact test and odds ratios (OR) were used to examine the statistical significance of the

differences observed between the groups (with probability values of $p < 0.05$). All analyses were carried out with EpiData applications (the statistical program R epical, version 2.9.1).

Results

Eighty female patients were defined as having TNBC. The mean age at diagnosis was 50.9 years old (from a total range of 28 to 79 years old). Most of them did not have a family history of breast cancer (97.5%). Every patient was followed up with for at least a minimum of 6 months (the longest being up to 3 years), with a mean follow up time of 14.1 months. Breast mass was presented in 98.75% of patients. Patients with TNBC were also more likely to have grade III tumors (64%), with 73.7% of cases reporting tumor sizes greater than 2 centimeters. More than half (56.25%) of TNBC patients first presented with nodal status positive, while 38.75% of the patients showed lymphovascular invasion. Two cases were found to have distant metastasis (bone = 1 and liver = 1). After surgical treatment, the patients were given one adjuvant systemic therapy such as chemotherapy alone (76.25%), chemotherapy and tamoxifen (15%), tamoxifen only (1.25%), aromatase inhibitor only (1.25%), and finally no systemic therapy (6.25%).

Twenty four out of 80 patients (30%) developed overall recurrences, while 10 of those 24 patients (41.67%) developed local events within the first follow up (30 days). Only the presence of lymphovascular invasion was significantly higher in recurrence rate (48.39%) when compared with the group with no lymphovascular invasion (22.5%, $p = 0.004$, odds ratio = 4.17 95% CI: 1.5183 - 11.4343, $p = 0.0056$). There was no significant difference between the non-recurrent and recurrent groups in terms of the age at presentation, clinical manifestation, tumor detection, tumor size, tumor grading, nodal status, extensive intraductal component, resection margin and type of systemic treatment. Moreover, all 24 patients in this recurrent group did not have any family history of breast cancer (Tables 1).

Three patients having positive margins from the first operation (breast conserving) underwent a second operation at the free margin resection. However, two of these three patients developed local recurrence, although the case of these recurrences is not significant in statistical relevance.

Table 1 Baseline and clinical characteristics of the TNBC patients, comparing non-recurrent (n=56) and recurrent groups (n = 24)

	Total n=80 (%)	**Non-Recurrent** n=56 (%)	**Recurrent** n=24 (%)	*p* - value
Age				0.573
≤ 40 years	20 (25)	15 (26.79)	5 (20.83)	
> 40 years	60 (75)	41 (73.21)	19 (79.17)	
Family history				1
Yes	2 (2.5)	2 (3.57)	0	
No	78 (97.5)	54 (96.43)	24 (100)	
Manifestation				0.3
Breast mass	79 (98.75)	56 (100)	23 (95.83)	
Nipple discharge	1 (1.25)	0	1 (4.17)	
Detection				0.246
Physical examination	53 (66.25)	34 (60.72)	19 (79.17)	
Mammography	2 (2.5)	2 (3.57)	0	
Both	25 (31.25)	20 (35.71)	5 (20.83)	
Tumor size				0.103
T1 (<2 cm.)	21 (26.25)	17 (30.36)	4 (16.66)	
T2 (2-5 cm.)	38 (47.5)	28 (50)	10 (41.67)	
T3 (>5 cm.)	21 (26.25)	11 (19.64)	10 (41.67)	
Tumor grade				0.398
Grade I	2 (2.5)	1 (1.79)	1 (4.17)	
Grade II	14 (17.5)	8 (14.29)	6 (25)	
Grade III	64 (80)	47 (83.92)	17 (70.83)	
Lymph node status				0.555
N0	35 (43.75)	27 (48.21)	8 (33.33)	
N1	25 (31.25)	15 (26.79)	10 (41.67)	
N2	14 (17.5)	10 (17.86)	4 (16.67)	
N3	6 (7.5)	4 (7.14)	2 (8.33)	
Extensive intraductal component				0.338
Yes	24 (30)	15 (26.79)	9 (37.5)	
No	56 (70)	41 (73.21)	15 (62.5)	

Table 1 Baseline and clinical characteristics of the TNBC patients, comparing non-recurrent (n=56) and recurrent groups (n=24) (continued)

	Total n=80 (%)	**Non-Recurrent n=56 (%)**	**Recurrent n=24 (%)**	***p* - value**
Lymphovascular invasion				0.004
Yes	31 (38.75)	16 (28.57)	15 (62.5)	
No	49 (61.25)	40 (71.43)	9 (37.5)	
Resection margin				0.359
Positive margin	3 (3.75)	1 (1.79)	2 (8.33)	
Negative margin	69 (86.25)	49 (87.5)	20 (83.34)	
Close margin	8 (10)	6 (10.71)	2 (8.33)	
Distant metastasis				0.532
Lung	0	0	0	
Liver	1 (1.25)	0	1 (4.17)	
Bone	1 (1.25)	1 (1.79)	0	
Brain	0	0	0	
None	78 (97.5)	55 (98.21)	23 (95.83)	
Systemic therapy				0.614
Chemotherapy	61 (76.25)	44 (78.57)	17 (70.83)	
Tamoxifen	1 (1.25)	1 (1.79)	0	
Aromatase inhibitor	1 (1.25)	1 (1.79)	0	
Chemotherapy + Tamoxifen	12 (15)	6 (10.71)	6 (25)	
Chemotherapy + Aromatase Inhibitor	0	0	0	
None	5 (6.25)	4 (7.14)	1 (4.17)	

Discussion

TNBC was considered a surrogate to represent the basal-like category of breast cancer because the immunostaining data was available[5]. Currently, there is no consensus about how best to define a basal-like breast cancer.

The present study showed that demographic and clinical data in TNBC patients was similar to previous studies: mean age at diagnosis (50.9 years compared with 49-55 years[6-9]), the wide range of ages (28-79 years compared to 22-88.5 years[6, 7, 9]), tumor sizes at presentation ranging between 2-5 centimeters (47.5% compared with 46.8-68.4%[6, 8]), positive lymph nodes (56.25% compared to 46.1-55%[6, 8, 9]), the presence of grade III tumors (64% compared against 66-

84%[6, 8, 9]) and cases of lymphovascular invasion (38.75% compared with 24.7-39.6%[6, 8, 9]). Though most of the TNBC patients presented breast mass (like other types of breast cancer which do commonly present breast mass, and can be detected via mammography), detection is less likely by mammography. Collett et al. evaluated interval cancers diagnosed in a screening program between 1996 and 2001, and found that, compared with other breast cancers, TNBC was more likely to appear during the intervals between regular mammograms[10]. Hence, detecting the disease with mammography in younger ages in the future may help to detect early forms of TNBC and, consequently, earlier treatment and a lower rate of recurrence. The family history of breast cancer is not seen to be helpful in understanding TNBC. The only risk factor in the present study's demographic and clinical data was the lymphovascular invasion status. If the patient's pathology report includes lymphovascular invasion, crucial attention must be paid by the physician to consider a more intense regimen of chemotherapy in these specific patients, due to the more aggressive and higher risk of recurrence.

Ten of the 24 patients with recurrence (41.67%) developed local events within 30 days, but not associated with the resection margin, maybe from tumors with aggressive natures. Thus, despite having a high risk of early recurrence, it seems patients who were diagnosed with TNBC could be treated more aggressively and prescribed more intensive chemotherapy. Two of the three patients who underwent a second operation for free margin resection developed local recurrence (although not of a significant statistical relevance), which might later turn out to be a crucial risk factor.

The risk factor for recurrence in TNBC patients in the present study was lymphovascular invasion, with clinical features of TNBC patients quite similar to previous studies[6-9, 11].

Limitation

The present study is a retrospective, small sample size, single-institute study. The authors did not evaluate the main effects of treatment on survival. The longest follow up period was 3 years due to the higher recurrence rates of TNBC in the first 3 years, in previous studies[9, 11]. About half of the patients received chemotherapy, while 7 patients received only tamoxifen or together with chemotherapy. However, only one of the patients was treated with aromatase inhibitors due to old age.

Conclusions

There is a consistent trend across all studies confirming the relatively poor prognosis of TNBC, or basal-like breast cancer subgroups, and response to systemic treatment. Novel therapeutic options are needed to target this aggressive type of breast cancer. The authors hope to alert all physicians to become aware of how important it is to give more intense therapies against this aggressive form of breast cancer.

What is already known on this topic?

TNBC is an aggressive type of breast cancer with a high recurrence rate within the first 3 years after treatment. Age (over 65 years old) and nodal status could be the important risk factors for recurrence.

What this study adds?

The present study added that the lymphovascular invasion status was the significant risk factor for recurrence in TNBC patients.

Potential conflicts of interest

None.

References

1. Rakha EA, Ellis IO. Triple-negative/basal-like breast cancer: review. Pathology. 2009; 41: 40-7.
2. Dawood S, Broglio K, Kau SW, Green MC, Giordano SH, Meric-Bernstam F, et al. Triple receptor-negative breast cancer: the effect of race on response to primary systemic treatment and survival outcomes. J Clin Oncol. 2009; 27: 220-6.
3. Rakha EA, El-Sayed ME, Green AR, Lee AH, Robertson JF, Ellis IO. Prognostic markers in triple-negative breast cancer. Cancer. 2007; 109: 25-32.
4. Tan DS, Marchió C, Jones RL, Savage K, Smith IE, Dowsett M, et al. Triple negative breast cancer: molecular profiling and prognostic impact in adjuvant anthracycline-treated patients. Breast Cancer Res Treat. 2008; 111: 27-44.
5. Matkovic B, Juretic A, Separovic V, Novosel I, Separovic R, Gamulin M, et al. Immunohistochemical analysis of ER, PR, HER-2, CK 5/6, p63 and EGFR antigen expression in medullary breast cancer. Tumori. 2008; 94: 838-44.
6. Nofech-Mozes S, Trudeau M, Kahn HK, Dent R, Rawlinson E, Sun P, et al. Patterns, of recurrence in the basal and non-basal subtypes of triple-negative breast cancers. Breast Cancer Res Treat. 2009; 118: 131-7.
7. Carey LA, Rugo HS, Marcom PK, Mayer EL, Esteva FJ, Ma CX, et al. TBCRC 001: EGFR inhibition with cetuximab added to carboplatin in metastatic triple-negative (basal-like) breast cancer. J Clin Oncol. 2008; 8: 178-86.
8. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-negative breast cancer: Clinical features and patterns of recurrence. Clin Cancer Res. 2007; 13: 4429-34.
9. Ovcaricek T, Frkovic SG, Matos E, Mozina B, Borstnar S. Triple negative breast cancer – prognostic factors and survival. Radiol Oncol. 2011; 45: 46-52.
10. Collett K, Stefansson IM, Eide J, Braaten A, Wang H, Eide GE, et al. A basal epithelial phenotype is more frequent in interval breast cancers compared with screen detected tumors. Cancer Epidemiol Biomarkers Prev. 2005; 14: 1108-12.

11. Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol. 2008; 26: 1275-81.

12. Banerjee S, Reis-Filho JS, Ashley S, Steele D, Ashworth A, Lakhani SR, et al. Basal-like breast carcinomas: clinical outcome and response to chemotherapy. J Clin Pathol. 2006; 59: 729-35.