Int J Clin Exp Pathol 2015;8(7):8500-8505
www.ijcep.com /ISSN:1936-2625/IJCEP0009815

Original Article

Clinicopathological classification and traditional prognostic indicators of breast cancer

Jiehua Li, Zhibai Chen, Ka Su, Jian Zeng

Department of Gastrointestinal and Gland Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Province, China

Received May 2, 2015; Accepted June 22, 2015; Epub July 1, 2015; Published July 15, 2015

Abstract: Breast cancer is a heterogeneous disease with molecular subtypes that have biological distinctness and different behavior. The objective of this study is to evaluate the value of molecular subtypes in breast cancer management according to a retrospective analysis of breast carcinoma molecular subtypes, histopathological grade, and TNM stage. A retrospective study of 475 paraffin-embedded tissues of breast cancer samples from the First Affiliated Hospital of Guangxi Medical University was performed. Expression of ER, PR, Her-2 and Ki-67 was analyzed to classify molecular subtypes of breast cancer by immunohistochemistry. The differences of molecular subtypes of breast cancers in regard to TNM staging and pathological grade were analyzed using χ^2 tests. Values of $P<0.05$ were considered statistically significant. The frequency of luminal A, luminal B, HER2-positive luminal B, triple negative and non-luminal HER2-positive subtypes were: 35.5%, 22.5%, 13.1%, 15.2% and 13.7%, respectively. Among the five subtypes of breast cancer, the distribution of pathological grades showed a significant difference ($P<0.001$). There were significant differences in the distribution of TNM staging among the five subtypes of breast cancer ($P<0.001$). In addition to traditional prognostic indicators such as TNM staging and pathological grade, molecular subtype may aid clinical practice and research into breast cancer. Different molecular subtypes will lead to different prognosis and therapeutic option. Molecular subtyping is essential for breast cancer management.

Keywords: Clinicopathological classification, histopathological grade, tumor-nodal-metastatic staging, breast cancer

Introduction

Breast carcinoma is a heterogeneous disease, including five clinicopathological subtypes with different biological behavior, clinical risk factor, natural histories, response to individualized therapy and prognosis [1]. Breast cancer is classified into 5 subtypes using the expression of four markers (estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2 and Ki-67): luminal A (ER-and/or PR-positive/HER2-negative /low Ki-67), luminal B (ER- and/or PR-positive/HER2-negative/high Ki-67), HER2-positive luminal B (ER- and/or PR-positive/HER2 overexpression/any Ki-67), non-luminal HER2-positive (ER and PR absent/HER2 overexpression), and triple negative (ER and PR absent/HER2-negative) [1]. TNM staging and pathological grade are traditional prognostic indicators and basis of individualized treatment. The discovery of several clinicopathological subtypes of breast carcinoma has led to a better understanding of molecular biology and has produced an effect on the risk assessment of recurrence and clinical treatment of breast cancer. The significance of this study is to uncover the associations between breast cancer molecular subtypes and traditional prognostic indicators (TNM staging and pathological grade).

Materials and methods

Patients

523 patients were diagnosed with breast cancer between January 2013 and May 2014 at the First Affiliated Hospital of Guangxi Medical University. All patients underwent surgical resection or ultrasound-guided core needle biopsy and the final diagnosis was obtained from the analysis of clinicopathological find-

Table 1. Distribution of histopathological grade and TNM stage among the various breast cancer subtype

	Total cases	Luminal A	Luminal B	HER2+ luminal B	Triple negative	non-luminal HER2+	*P* vaules
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total (n (%))	475 (100)	169 (35.6)	107 (22.5)	62 (13.1)	72 (15.2)	65 (13.7)	
Histologic grade							
I	166 (34.9)	122 (72.7)	25 (23.4)	13 (21.0)	4 (5.6)	2 (3.1)	<0.001
II	188 (39.6)	47 (27.8)	62 (57.9)	34 (54.8)	18 (25.0)	27 (41.5)	
III	121 (25.5)	0 (0)	20 (18.7)	15 (24.2)	50 (69.4)	36 (55.4)	
Tumor stage							
0	61 (12.8)	30 (17.8)	6 (5.6%)	11 (17.7%)	2 (2.8%)	12 (18.5%)	<0.001
I A	109 (22.9)	48 (28.4%)	21 (19.6%)	12 (19.4%)	16 (22.2%)	12 (18.5%)	
I B	77 (16.2)	30 (17.8%)	20 (18.7%)	8 (12.9%)	12 (16.7%)	7 (10.8%)	
II A	120 (25.3)	33 (19.5%)	31 (29.0%)	16 (25.8%)	27 (37.5%)	13 (20.0%)	
II B	52 (10.9)	10 (5.9%)	19 (17.8%)	9 (14.5%)	7 (9.7%)	7 (10.8%)	
III A	24 (5.1)	7 (4.1%)	5 (4.7%)	3 (4.8%)	4 (5.6%)	5 (7.7%)	
III B	17 (3.6)	6 (3.6%)	2 (1.9%)	2 (3.2%)	2 (2.8%)	5 (7.7%)	
III C	12 (2.5)	3 (1.8%)	2 (1.9%)	1 (1.6%)	2 (2.8%)	4 (6.2%)	
IV	3 (0.6)	2 (1.2%)	1 (0.9%)	0 (0)	0 (0)	0 (0)	

ings. Patients who did not undergo breast surgery for metastatic disease (n=6) or who underwent surgery at another hospital (n=22) were excluded from the analysis. 20 patients with HER2 (2+) were excluded for rejecting the FISH test. The remaining 475 patients, including 5 patients with bilateral tumor, constituted the study. Before inclusion, all patients signed informed consent .The samples were otherwise anonymous and without any identifying personal information. Our study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University.

Cancer staging

All patients were evaluated by complete physical examinations, chest X-ray, bilateral mammography, and ultrasonography of the breasts, axilla, cervical region, and abdomen before surgical resection, core needle biopsy, and neoadjuvant therapy. TNM stage was assessed according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging manual.

Pathology analysis

475 embedded paraffin blocks of breast carcinoma taken from the First Affiliated Hospital of Guangxi Medical University. Samples were stained histologically to determine histological grade, which was classified into low, moderate and poor grade according to criteria modified by Elston and Ellis [2]. The status of ER, PR and HER2 were detected by methods of immunohistochemical (IHC). ER/PR expression is defined positive if it is stained in >1% of nuclei of the total tumor cells [3]. As to HER2: + negative, ++ uncertain, and +++ positive. Cancers with Her-2 scored 2+ should be additionally evaluated by fluorescent in situ hybridization (FISH). In this study, breast cancer is classified into five groups as follows: luminal A (ER-and/or PR-positive/HER2-negative /low Ki-67), luminal B (ER- and/or PR-positive/HER2-negative/high Ki-67), HER2-positive luminal B (ER- and/or PR-positive/HER2 overexpression/any Ki-67), non-luminal HER2-positive (ER and PR absent/HER2 overexpression), and triple negative (ER and PR absent/HER2-negative) (Goldhirsch et al., 2011).

Statistical analysis

The differences of molecular subtypes of breast cancers in regard to TNM staging and pathological grade were analyzed using χ^2 tests. Values of $P<0.05$ were considered statistically significant. The SPSS 17.0 software package (SPSS, Chicago, IL, USA) was used for statistical analysis.

Table 2. Difference of histopathological grade according to breast cancer subtype

Landmark of subtype	Compared subtype	χ^2 values	*P* values
Luminal A			
	Luminal B	75.977	<0.001
	HER2+ luminal B	70.700	<0.001
	Triple negative	160.387	<0.001
	Non-luminal HER2+	138.712	<0.001
Luminal B			
	Luminal A	75.977	<0.001
	HER2+ luminal B	0.741	0.690
	Triple negative	47.226	<0.001
	Non-luminal HER2+	29.427	<0.001
HER2+ luminal B			
	Luminal A	70.700	<0.001
	Luminal B	0.741	0.690
	Triple negative	27.943	<0.001
	Non-luminal HER2+	17.456	<0.001
Triple negative			
	Luminal A	160.387	<0.001
	Luminal B	47.226	<0.001
	HER2+ luminal B	27.943	<0.001
	Non-luminal HER2+	4.400	0.111
Non-luminal HER2+			
	Luminal A	138.712	<0.001
	Luminal B	29.427	<0.001
	HER2+ luminal B	17.456	<0.001
	Triple negative	4.400	0.111

Results

Clinicopathologic subtypes

In the study, luminal A tumors showed the highest percentage (35.6%, 169 of 475), followed by luminal B (22.5%, 107 of 475), HER2-positive luminal B (13.1%, 62 of 475), triple negative (15.2%, 72 of 475), and non-luminal HER2-positive (13.7%, 65 of 475) tumors (**Table 1**).

Pathological grade and clinicopathologic subtypes

Based on histological grade in breast cancer, Grade II is the most common grade (39.6%, 188/475), in comparison with Grade I (34.9%, 166/475) and Grade III (25.5%, 121/475). In term of pathological grading, the 169 luminal A subtype tumors were of Grade I in 122 (72.2%), Grade II in 47 (27.8%), and Grade III in 0. The 107 luminal B subtype diseases consisted of 25 (23.4%) of Grade I, 62 (57.9%) of Grade II, and 20 (18.7%) of Grade III. Among 62 HER2-positive luminal B tumors, 13 (21.0%) were of Grade I, 34 (54.8%) of Grade II, and 15 (24.2%) of Grade III. The histological grade in 72 patients with the triple negative subtype was Grade I in 4 patients (5.6%), Grade II in 18 (25.0%), and Grade III in 50 (69.4%). The 65 non-luminal HER2-positive tumors included 2 (3.1%) of Grade I, 27 (41.5%) of Grade II, and 36 (55.4%) of Grade III. The proportion of tumors histopathologically classified as Grade I in the patients with luminal A tumors was the highest compared with the other subtypes. Among all subtypes, the proportion of tumors histopathologically classified as Grade III in the patients with triple negative subtype was the highest (**Table 1**).

Among the five subtypes of breast cancer, the distribution of pathological grades showed a significant difference (*P*<0.001) (**Table 1**). The distribution of pathological grades in patients with the luminal A tumor exhibited statistically significant differences from the other subtypes: luminal B (*P*<0.001), HER2-positive luminal B (*P*<0.001), triple negative (*P*<0.001) and non-luminal HER2-positive (*P*<0.001). The distribution of pathological grades in patients with the luminal B tumor showed statistically significant differences from that in patients with the triple-negative or non-luminal HER2-positive subtype (*P*<0.001), whereas there was not a statistically significant difference between that in patients with luminal B and HER2-positive luminal B subtype (*P*=0.690). The distribution of pathological grades in patients with the HER2-positive luminal B tumor was also significantly different from that in patients with the triple-negative or non-luminal HER2-positive subtype (*P*<0.001). There was not a statistically significant difference between the distribution of pathological grades in patients with the triple-negative and non-luminal HER2-positive subtype (*P*=0.111) (**Table 2**).

TNM stage and clinicopathologic subtypes

The majority of the patients was Stage II A (25.3%, 120 of 475), followed by Stage I A (22.9%, 109 of 475), Stage I B (16.2%, 77 of

Table 3. Difference of TNM stage according to breast cancer subtype

Landmark of subtype	Compared subtype	χ^2 values	*P* values
Luminal A			
	Luminal B	21.442	0.006
	HER2+ luminal B	7.439	0.468
	Triple negative	19.418	0.007
	Non-luminal HER2+	11.146	0.168
Luminal B			
	Luminal A	21.442	0.006
	HER2+ luminal B	7.816	0.437
	Triple negative	5.160	0.779
	Non-luminal HER2+	16.674	0.023
HER2+ luminal B			
	Luminal A	7.439	0.468
	Luminal B	7.816	0.437
	Triple negative	10.736	0.132
	Non-luminal HER2+	4.072	0.794
Triple negative			
	Luminal A	19.418	0.007
	Luminal B	5.160	0.779
	HER2+ luminal B	10.736	0.132
	Non-luminal HER2+	15.771	0.023
Non-luminal HER2+			
	Luminal A	11.146	0.168
	Luminal B	16.674	0.023
	HER2+ luminal B	4.072	0.794
	Triple negative	15.771	0.023

475), Stage 0 (12.8%, 61 of 475), Stage II B (10.9%, 52 of 475), Stage III A (5.1%, 24 of 475), Stage III B (3.6%, 17 of 475), Stage III C (2.5%, 12 of 475), and Stage IV (0.6%, 3 of 475). The 169 luminal A subtype tumors were of Stage 0 in 30 (17.8%), Stage I A in 48 (28.4%), Stage I B in 30 (17.8%), Stage II A in 33 (19.5%), Stage II B in 10 (5.9%), Stage III A in 7 (4.1%), Stage III B in 6 (3.6%), Stage III C in 3 (1.8%), and Stage IV in 2 (1.2%). The 107 luminal B subtype diseases consisted of Stage 0 in 6 (5.6%), Stage I A in 21 (19.6%), Stage I B in 20 (18.7%), Stage II A in 31 (29.0%), Stage II B in 19 (17.8%), Stage III A in 5 (4.7%), Stage III B in 2 (1.9%), Stage III C in 2 (1.9%), and Stage IV in 1 (0.9%) . The 62 HER2-positive luminal B tumors consisted of Stage 0 in 11 (17.7%), Stage I A in 12 (19.4%), Stage I B in 8 (12.9%), Stage II A in 16 (25.8%), Stage II B in 9 (14.5%), Stage III A in 3 (4.8%), Stage III B in 2 (3.2%), Stage III C in 1 (1.6%), and none had Stage IV. The TNM stage in 72 patients with the triple negative subtype was Stage 0 in 2 (2.8%), Stage I A in 16 (22.2%), Stage I B in 12 (16.7%), Stage II A in 27 (37.5%), Stage II B in 7 (9.7%), Stage III A in 4 (5.6%), Stage III B in 2 (2.8%), Stage III C in 2 (2.8%), and none had Stage IV. The 65 non-luminal HER2-positive tumors consisted of Stage 0 in 12 (18.5%), Stage I A in 12 (18.5%), Stage I B in 7 (10.8%), Stage II A in 13 (20.0%), Stage II B in 7 (10.8%), Stage III A in 5 (7.7%), Stage III B in 5 (7.7%), Stage III C in 4 (6.2%), and none had Stage IV (**Table 1**).

Among the five subtypes of breast cancer, the distribution of TNM staging showed a significant difference ($P<0.001$) (**Table 1**). The distribution of TNM staging in patients with the luminal A tumor exhibited statistically significant differences from the distributions in the luminal B ($P<0.001$) and triple negative subtypes ($P=0.007$), but not the HER2-positive luminal B ($P=0.468$) and non-luminal HER2-positive ($P=0.168$). The distribution of TNM staging in patients with the luminal B tumor showed statistically significant differences from that in patients with non-luminal HER2-positive subtype ($P=0.023$), but not the HER2-positive luminal B ($P=0.437$) and triple negative subtypes ($P=0.779$). The distribution of TNM staging in patients with the HER2-positive luminal B tumor was not significantly different from that in patients with the triple-negative ($P=0.132$) or non-luminal HER2-positive subtype ($P=0.794$). There was a statistically significant difference between the distribution of TNM staging in patients with the triple-negative and non-luminal HER2-positive subtype ($P=0.023$) (**Table 3**).

Discussion

Breast cancer is a heterogeneous disease with different biological behavior, epidemiological character, natural histories, response to treatment and prognosis. In the past, the management of breast cancer was essentially based on histopathological grade and TNM stage, which had achieved some consensus [4]. Breast cancer including five molecular subtypes has different biological behavior, natural histories, response to individualized therapy and prognosis [1]. Our study showed that frequency

of luminal A, luminal B, HER2-positive luminal B, triple negative and non-luminal HER2-positive subtypes were: 35.6%, 22.5%, 13.1%, 15.2% and 13.7%, respectively. This result is concordant with other studies [5]. In the study, we observed that 72.2% of patients with luminal A tumors belonged to histopathological grade I. The luminal A subtype is significantly associated with low grade cancers [6]. The indicator of Ki67, a nuclear antigen expressed in proliferating cells, reflects the proliferation rate of malignant tumors. Low Ki67 index is the main reason, which luminal A cancers have low grade tumors and the best prognosis. In our study, the distribution of pathological grades in patients with the luminal A tumor exhibited statistically significant differences from the luminal B (HER2-negative) subtypes. The Ki-67 labeling index is main indicator used to differentiate between the luminal A and luminal B (HER2-negative) subtypes, which require different treatment options and also have different prognosis [7]. However, 18 luminal A subtype tumors with histopathological grade Ior v II, had TNM staging III disease, or worse. This may be due to delay from patients. Luminal A patients are less responsive to chemotherapy. Luminal A breast cancer with high-grade tumor differentiation and a low degree of malignancy, in most cases, can be successfully treated with endocrine therapy alone, in addition to high bulk disease (e.g., multiple positive nodes) where chemotherapy may be used as supplementary treatment. Another research in China found that luminal A cancers have the best prognosis, whereas Her-2+ cancers have the poorest [8]. The study showed that the patients with *HER2* gene amplification tumors, including non-luminal HER2-positive and HER2-positive luminal B subtypes, were classified as Grade II (48.0%, 61/127) and Grade III (40.2%, 51/127). The HER family of receptors and their associated signal-transduction pathways play a dominant role in cell growth and survival. *HER2* amplification was found to be correlated with a poor prognosis in breast cancer [9]. HER2-positive tumors tend to be larger than HER2-negative tumors, present more commonly with lymph node involvement, and are more likely to be associated with a short disease free survival. Adjuvant trastuzumab reduces the risk of recurrent HER2-positive disease by roughly 50% [10]. HER2-positive disease appears to be particularly sensitive to anthracyclines. In the study, we observed that 94.4% of patients with triple negative breast cancers (TNBC) were classified as histopathological Grade II, or worse. 11.2% patients with TNBC were classified as Stage III. This result is in agreement with recent observations that triple negative tumors are aggressive [11, 12]. TNBC is a heterogeneous breast cancer modality, and has only partial overlapping features with basal-like (BL) breast cancer [13, 14]. The BL subtype was the most frequently observed (about 75%) in TNBC [15]. TNBC with a particularly aggressive biological course, is strongly associated with distant recurrence, visceral metastases, and death in comparison with the other subtypes [16]. Our study showed that the distribution of the histopathological grades in patients with the triple negative subtype was significantly different from those in patients with the luminal A, luminal B, or HER2-positive luminal B subtypes. Anders et al [16] observed that TNBC recurrence often appears within 3 years of initial diagnosis, and 5-year death rates appear to be increased after diagnosis. The median survival of advanced TNBC is at most 12 months, much less than that of other advanced breast cancer subtypes [17]. At present a lot of new targeted therapies are actually under study, but the efforts are not reaching the hoped results.

This clinicopathological subtypes study of Chinese breast cancer confirmed that the luminal subtype of breast cancer tend to have a better prognosis in comparison with the non-luminal subtype because the luminal subtype is a hormone receptor-positive. Therefore, it is more sensitive to hormone therapy. The Her-2 positive and triple negative subtypes of breast cancer have a poorer prognosis and are more apt to early and frequent recurrence and metastasize. Her-2 positive subtype has a better prognosis than triple negative subtype, because it can benefit from trastuzumab. In addition to traditional prognostic indicators such as TNM staging and pathological grade, molecular subtype may aid clinical practice and research into breast cancer. Different molecular subtypes will lead to different prognosis and therapeutic option. Thus, molecular subtyping is essential for breast cancer management.

Acknowledgements

This study was supported by Guanxi University Research Foundation (Grant No. KY2015-ZD031).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jian Zeng, Department of Gastrointestinal and Gland Surgery, The First Affiliated Hospital of Guangxi Medical University, 6 Shuang-Yong Road, Nanning 530021, China. Tel: +86-771-5350100; Fax: +86-771-535-6701; E-mail: 137601101@qq.com

References

[1] Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B and Senn HJ. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 2011; 22: 1736-1747.

[2] Cuzick J, Dowsett M, Pineda S, Wale C, Salter J, Quinn E, Zabaglo L, Mallon E, Green AR, Ellis IO, Howell A, Buzdar AU and Forbes JF. Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. J Clin Oncol 2011; 29: 4273-4278.

[3] Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes A, Sasano H, Schwartz JN, Sweep FC, Taube S, Torlakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL and Wolff AC. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010; 28: 2784-2795.

[4] Liu YH and Xu L. [The current status in diagnosis and treatment of breast cancer]. Zhonghua Wai Ke Za Zhi 2010; 48: 1841-1846.

[5] Salhia B, Tapia C, Ishak EA, Gaber S, Berghuis B, Hussain KH, DuQuette RA, Resau J and Carpten J. Molecular subtype analysis determines the association of advanced breast cancer in Egypt with favorable biology. BMC Womens Health 2011; 11: 44.

[6] El-Hawary AK, Abbas AS, Elsayed AA and Zalata KR. Molecular subtypes of breast carcinoma in Egyptian women: clinicopathological features. Pathol Res Pract 2012; 208: 382-386.

[7] Elston CW and Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 1991; 19: 403-410.

[8] Jia WJ, Jia HX, Feng HY, Yang YP, Chen K and Su FX. HER2-enriched tumors have the highest risk of local recurrence in Chinese patients treated with breast conservation therapy. Asian Pac J Cancer Prev 2014; 15: 315-320.

[9] Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A and McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987; 235: 177-182.

[10] Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN and Wolmark N. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005; 353: 1673-1684.

[11] Malone KE, Begg CB, Haile RW, Borg A, Concannon P, Tellhed L, Xue S, Teraoka S, Bernstein L, Capanu M, Reiner AS, Riedel ER, Thomas DC, Mellemkjaer L, Lynch CF, Boice JD Jr, Anton-Culver H and Bernstein JL. Population-based study of the risk of second primary contralateral breast cancer associated with carrying a mutation in BRCA1 or BRCA2. J Clin Oncol 2010; 28: 2404-2410.

[12] Tun NM, Villani G, Ong K, Yoe L and Bo ZM. Risk of having BRCA1 mutation in high-risk women with triple-negative breast cancer: a meta-analysis. Clin Genet 2014; 85: 43-48.

[13] Dawood S, Broglio K, Esteva FJ, Yang W, Kau SW, Islam R, Albarracin C, Yu TK, Green M, Hortobagyi GN and Gonzalez-Angulo AM. Survival among women with triple receptor-negative breast cancer and brain metastases. Ann Oncol 2009; 20: 621-627.

[14] Weigelt B, Baehner FL and Reis-Filho JS. The contribution of gene expression profiling to breast cancer classification, prognostication and prediction: a retrospective of the last decade. J Pathol 2010; 220: 263-280.

[15] Prat A, Adamo B, Cheang MC, Anders CK, Carey LA and Perou CM. Molecular characterization of basal-like and non-basal-like triple-negative breast cancer. Oncologist 2013; 18: 123-133.

[16] Anders CK and Carey LA. Biology, metastatic patterns, and treatment of patients with triple-negative breast cancer. Clin Breast Cancer 2009; 9 Suppl 2: S73-81.

[17] Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P and Narod SA. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007; 13: 4429-4434.