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Correlation Factors Analysis of Breast Cancer Tumor Volume Doubling Time Measured by 3D-Ultrasound

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Statistical Analysis C
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Manuscript Preparation E
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Background: Tumor volume doubling time (TVDT) is relatively important for breast cancer diagnosis and prognosis evaluation. This study aimed to analyze the related factors that may affect the TVDT of breast cancer by three-dimensional ultrasound (3D-US).

Material/Methods: A total of 69 breast cancer patients were selected. 3D-US was applied to measure the volume of breast lumps diagnosed as BI-RADS-US 4A by conventional ultrasound. TVDT was calculated according to the formula $TVDT=\Delta T\times\log 2/\log(V2/V1)$. Multiple linear regression analysis was performed to analyze the factors influencing breast cancer TVDT.

Results: The mean and median TVDT were 185±126 (range 66–521) and 164 days, respectively. TVDT showed no statistical significance according to regular shape, coarse margin, spicule sign, peripheral hyperechoic halo, microcalcification, and different posterior echo characteristics ($P>0.05$). Patients grouped by age, axillary lymphatic metastasis, histological differentiation, and Nottingham prognostic index (NPI) score exhibited significantly different TVDT ($P<0.05$). On the contrary, patients with different menstrual conditions, breast cancer family history, or pathological types presented similar TVDT ($P>0.05$). TVDT was obviously different in breast cancer with different ER, PR, Ki-67, and molecular subtyping but not HER2 expression. Multivariate analysis revealed that NPI score, axillary lymphatic metastasis, Ki-67, and molecular subtyping were risk factors of TVDT in breast cancer ($P<0.05$).

Conclusions: Breast cancer TVDT was significantly correlated with NPI score, axillary lymphatic metastasis, Ki-67, and molecular subtyping. Triple-negative breast cancer exhibited the most rapid growth.

MeSH Keywords: Imaging, Three-Dimensional • Multivariate Analysis • Tumor Burden

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Background

Breast cancer is a malignant tumor characterized by various clinicopathological features, recurrence, and survival [1–3]. In addition to traditional pathological indicators, it can be classified by immunohistochemistry detection of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expressions [4]. The molecular subtyping shows good effect in predicting prognosis and treatment response [5]. Early diagnosis and treatment exhibit significant impacts on breast cancer patients. Tumors detected through screening are more likely to be ER-positive type instead triple-negative type. Moreover, triple-negative tumors usually present benign or indeterminate characteristics on ultrasound and mammography [6–8].

Tumor volume doubling time (TVDT) reflects the natural growth rate and the biology of malignancy. It not only determines the follow-up interval but also drives decisions about therapeutic schedule [9,10]. Breast lumps in breast imaging reporting and data system for ultrasonography (BI-RADS-US) 4A grade need biopsy [11,12]. However, its application is limited by various adverse impacts, such as unnecessary fear, anxiety, discomfort, and pain [13]. Patients who refuse biopsy are recommended to come in for review after 2~6 months [11], which provides the possibility for breast cancer TVDT study. In recent years, three-dimensional ultrasound (3D-US) has been widely applied in the evaluation of various diseases [14,15]. The present study used 3D-US technology to continuously measure the breast lump volume, calculate TVDT, and analyze the factors influencing breast cancer TVDT through multiple linear regression analysis. We believe this is the first report on breast cancer TVDT using 3D-US.

Material and Methods

Object of study

The patients received breast ultrasound examination in Wuxi People's Hospital were enrolled between Feb 2012 and May 2016. 3D-US technology was used to measure breast lump volume judged as BI-RADS 4A by conventional ultrasound. Exclusion criteria: (1) diameter >3 cm on any side of the lump; (2) capsule solid mass; (3) high echo neoplasm; and (4) cystic mass. Inclusion criteria: (1) volume data measured 2 times by consecutive 3D-US; (2) time interval >2 months; and (3) no biopsy puncture or clinical treatment in the time interval. This research was approved by the Ethics Committee of Wuxi People's Hospital and all subjects provided signed informed consent.

Ultrasound scanning

The patients were first scanned by conventional ultrasound examination using a Philips iU-Elite diasonograph with L12-5 probe and frequency at 5~12 MHz or VL13-5 probe and frequency at 5~13 MHz. BI-RADS-US descriptor was applied to evaluate the acquired image, including shape, coarse margin, spicule sign, peripheral hyperechoic halo, microcalcification, and different posterior echo characteristics. 3D-US scan was performed on breast lumps using the VL-13-5 probe. The patients held their breath for about 20 s during scanning.

TVDT measurement

The obtained image was analyzed by Qlab software according to the manual. The tumor was equally divided into multiple levels, and the tumor boundary on each section was depicted on sagittal view. After the boundary was depicted on all the layers, the tumor volume was assumed to grow exponentially and was automatically calculated by the system and stored on a hard disk. Each tumor image was collected 3 times to calculate the average value (Figure 1). Breast cancer TVDT=$\Delta T \times \log 2/\log(V2/V1)$. ΔT, time interval. V1, the volume detected in the first time. V2, the tumor volume detected in the second time [10].

Pathological examination

Pathological examination contained traditional indicators and prognostic molecular indicators. The former included the pathological type, tumor size, histological grade, and lymph node status from patients who accepted biopsy later. Nottingham prognostic index (NPI) was calculated according to the formula NPI=size (cm)×0.2 + lymph node staging (1~3) + histologic classification (1~3) [16]. The prognostic molecular indictors were ER, PR, HER2, and Ki-67. Judgment criteria for immunohistochemistry were [17]: ER and PR positively expressed in nucleus as brown granules, and positive cell number ≥10% was considered as positive. Ki-67 positively located in nucleus and positive cell number ≥14% was judged as positive. HER2 was positively expressed on the cell membrane as clear brown staining. The cases with "1+" or "–" were considered as negative. The patients with "++" received fluorescence in situ hybridization (FISH) technique to test HER-2 gene amplification, and those without amplification were defined as negative.

Molecular subtyping

Breast cancer was classified based on immunohistochemistry indicators. Luminal subtype A: ER and/or PR positive, HER2 negative, Ki-67 <14%; Luminal type B: ER and/or PR positive, HER2 positive and/or Ki-67 ≥14%; (3) HER2 overexpression

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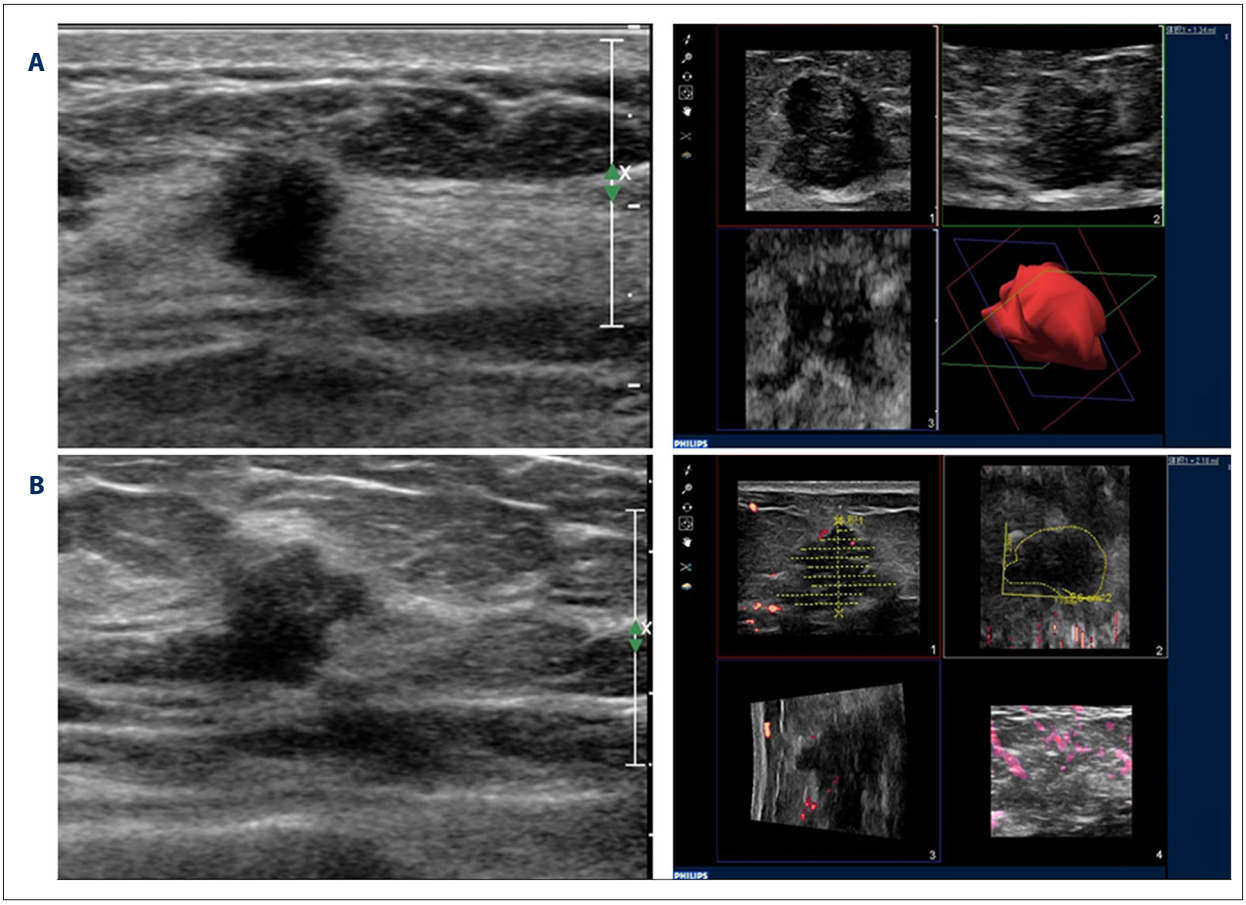

Figure 1. (**A**) Triple-negative type breast cancer patient with TVDT of 133 days. (**A**) First examination, volume=1.34 ml. (**B**) Second examination after 93 days, volume=2.18 ml. **Left**, primary ultrasound image. **Right**, TVDT calculation module.

type: ER negative, PR negative, and HER2 positive; and triple-negative type: ER negative, PR negative, and HER2 negative.

Statistical analysis

All data analysis was performed on SPSS 13.0 software. Measurement data are depicted as mean ± standard deviation and compared by *t* test or analysis of variance. The influence factors of breast cancer TVDT was analyzed by multiple linear regression analysis. A statistical significance was presented as P<0.05.

Results

A total of 69 female breast cancer patients were enrolled, with a median age of 52 (26~71) years. The mean initial tumor volume was 0.91 ± 0.33 ml and the mean time interval was 182±81.9 days. The mean and median TVDT were 185±126 (range 66~521) and 164 days, respectively. There were 29 cases of luminal subtype A, 12 cases of luminal subtype B, 10 cases of HER2 overexpression type, and 18 cases of triple-negative type.

TVDT showed no statistical significance according to regular shape, coarse margin, spicule sign, peripheral hyperechoic halo, microcalcification, and different posterior echo characteristics (P>0.05) (Table 1).

Patients grouped by age, axillary lymphatic metastasis, histological differentiation, and NPI score exhibited significantly different TVDTs (P<0.05). On the contrary, patients with different menstrual conditions, breast cancer family history, or pathological types presented similar TVDTs (P>0.05) (Table 2).

TVDT was obviously different in breast cancer with different ER, PR, Ki-67, and molecular subtyping but not HER2 expression (P<0.05). In addition, no significant difference in TVDT was observed in patients with different HER2 expression (P>0.05) (Table 3).

Factors that may affect breast cancer TVDT were imported to a multiple linear regression model. Multivariate analysis revealed that NPI score, axillary lymphatic metastasis, Ki-67, and molecular subtyping were the risk factor of TVDT in breast cancer (P<0.05) (Table 4).

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Table 1. The relationship between breast cancer TVDT and first time ultrasonographic features (χ±s, d, *n*=69).

Item	Cases	TVDT	*t* value/*F* value	*P* value
Shape				
Circular or elliptical	39	202±121	2.179	0.206
Irregular	30	187±158		
Coarse margin				
No	58	200±165	1.084	0.784
Yes	11	184±124		
Spicule sign				
No	62	208±136	0.351	0.109
Yes	7	175±88		
Peripheral hyperechoic halo				
No	59	197±122	–2.826	0.061
Yes	10	246±109		
Microcalcification				
No	62	197±115	–2.243	0.218
Yes	7	248±221		
Posterior echo characteristics				
No change	54	204±149	1.026*	0.090
Attenuation	7	230±176		
Enhancement	8	189±124		

* *F* value.

Discussion

High-frequency ultrasound technology greatly increased the detection rate of breast cancer, but its sensitivity and specificity are not high. BI-RADS-US 4A grade presented malignant possibility in 20~40% of breast lumps. Therefore, regular radiographic follow-up is extremely important to observe the dynamic changes of the lesions when the patients refuses biopsy. The degree of lesion enlargement is an important index, of which TVDT is widely used in the observation of tumor growth. As an index of lesion enlargement, TVDT allowed us to separate the poor outcomes associated with screening women [10]. Förnvik calculated the mean TVDT of breast cancer as 282 (46~749) days through mammography [16]. Eun Bi Ryu reported the average TVDT of breast cancer was 141 (46~825) days by two-dimensional ultrasound [17]. All of these studies used the elliptic sphere empirical formula to estimate the tumor volume, which has a variety of deficiencies. Firstly, since the tumor shape is irregular, the estimated volume is inaccurate and the repeatability of measurement is poor. Secondly, limited by unapparent resolution and poor repeatability, the short-term maximum diameter measured has difficulty in objectively and accurately evaluating subtle changes in the nodule. The volume may be twice as large when the measured diameter value was larger than 26% [10]. Thus, inaccurate measurement greatly restricts breast cancer TVDT investigation. Inconvenience of use and radioactivity of MRI or mammography also limited their application for tumor volume calculation and follow-up [18]. This study used 3D-US to measure the breast lump volume; it can delineate the mass boundary at each level, resulting in more accurate TVDT compared with the ellipsoid empirical formula. The present study calculated the mean breast cancer TVDT as 184 (66–521) days by 3D-US.

In-depth breast cancer research shows that breast cancer is a kind of molecular disease with high heterogeneity. Breast cancer patients with similar clinical pathological features often present different outcomes and prognoses, and they also exhibit divergent response to the same therapeutic schedule. Thus, this study investigated the correlation of breast cancer TVDT with multiple factors, including ultrasonographic characteristics, traditional pathological indexes, and prognostic molecular indicators.

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Table 2. The relationship between breast cancer TVDT and traditional pathological indicators ($\chi \pm s$, d, n=69).

Item	Cases	TVDT	*t* value/*F* value	*P* value
Age				
<52	37	167±89	–3.959	0.042
≥52	32	225±109		
Menstruation				
Premenopause	36	185±136	–2.543	0.204
Postmenopause	33	209±121		
Breast cancer family history				
Yes	16	175±64	–2.426	0.147
No	53	214±102		
Pathological type				
Invasive carcinoma	38	174±87	–2.819	0.103
Ductal carcinoma in situ	31	199±54		
Axillary lymph node				
Metastasis	10	131±63	–4.641	0.033
Non-metastasis	59	226±134		
Histological grade				
I	15	225±143	2.595*	0.116
II	42	201±156		
III	12	169±90		
NPI score				
<3.4	16	257±121	10.157*	0.019
3.4~5.4	39	198±108		
>5.4	14	135±72		

* *F* value.

We found no statistically significant difference in TVDT according to ultrasonographic image, menstruation, breast cancer family history, histological type, and HER2 expression. On the contrary, TVDT was obviously different among patients with different age, axillary lymphatic metastasis, histological grade, and NPI score. Our findings agree with previous studies reporting that breast cancer patients with younger age, axillary lymphatic metastasis, high histological grade, and NPI score exhibited faster breast cancer cell growth [16,17]. Moreover, TVDT revealed significant differences in breast cancer with different ER, PR, Ki-67, and molecular subtyping. ER (–), PR (–), and Ki-67 (+) breast cancer grows faster than that with ER (+), PR (+), and Ki-67 (–) expression. The tumor growth rate is closely correlated with cell proliferation. It was reported that about 70% of ER (–) breast cancer patients overexpressed phosphate dehydrogenase (PHGDH) [19]. It was confirmed that cancer cells may change the metabolism to maintain rapid growth, while a high level of PHGDH may promote such changes. It was found that suppression of PHGDH protein production in a breast cancer cell line stopped cancer cell proliferation [20]. PR expression was positively correlated with ER and negatively correlated with epidermal growth factor receptor (EGFR) [21]. EGFR-overexpressed cancer cells exhibited worse differentiation and stronger division. Moreover, EGFR overexpression may suppress cell apoptosis and promote neovascularization in tumors. Ki-67 is a type of cell proliferation-related protein that is considered as a marker to evaluate the proliferative activity of cancer cells. Ki-67 expression is related to tumor differentiation, invasion, and metastasis. It was confirmed that Ki-67 overexpression is a risk factor for breast cancer, and 58% of patients with local recurrence showed Ki-67-positive expression [22].

Multivariate analysis showed that TVDT was negatively correlated with NPI score, axillary lymphatic metastasis, Ki-67

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Table 3. Comparison of breast cancer TVDT with prognostic molecular indicators and molecular subtyping ($\chi \pm s$, d, n=69).

Item	Cases	TVDT	*t* value/*F* value	*P* value
ER				
Positive	41	221±156	8.513	0.031
Negative	28	160±86		
PR				
Positive	40	231±143	5.351	0.048
Negative	29	165±96		
HER2				
Positive	14	184±71	–0.628	0.739
Negative	55	195±112		
Ki-67				
Negative (<14%)	33	224±136	11.317	0.018
Positive (≥14%)	36	145±87		
Molecular subtyping				
Luminal subtype A	29	257±185	13.751*	0.013
Luminal subtype B	12	211±116[a]		
HER2 overexpression	10	184±71[ab]		
Triple negative	18	127±48[abc]		

* *F* value. [a] *P*<0.01, *vs.* luminal subtype A; [b] *P*<0.01, *vs.* luminal subtype B; [c] *P*<0.01, *vs.* HER2 overexpression type.

Table 4. Multiple linear regression analysis of the relevant factors on breast cancer TVDT (n=69).

Factors	Regression coefficient	Standard error	*t* value	*P* value
Constant	3.514	2.574	1.216	0.221
NPI	–0.468	0.234	6.238	0.021
Axillary lymphatic metastasis	–0.132	0.059	4.543	0.034
Ki-67	–0.171	0.087	6.327	0.019
Molecular subtyping	–0.189	0.129	8.502	0.002

expression, and molecular subtyping. NPI score is classic and objective, as the information is mainly from pathological grading and tumor stage. Ki-67 is considered to be the most powerful univariate factor to predict the growth rate [23]. Breast cancer TVDT in luminal subtype A was 257±185 days, in luminal subtype B it was 211±116 days, in HER2 expression type it was 184±71 days, and in triple-negative type it was 127±48 days. Previous studies only investigated the relationship between molecular subtyping and prognosis. The present study reveals that breast cancer is correlated with growth speed, and the triple-negative group exhibited the fastest speed. Previous breast cancer growth models demonstrated that the peak time of recurrence in ER-positive patients was 36 months, while it was 12~24 months in HER2 overexpression type and triple-negative type [24,25]. However, these models did not consider the breast cancer TVDT changes among different molecular classifications. Our study provides data for establishing a breast cancer growth model.

There are many limitations in this research. (1) It had a small sample size. (2) Clinical and experimental observation show that malignant tumor growth follows an S-shaped or linear Gompertzian curve [26]. Gompertzian model assumes that TVDT varies according to tumor size. Many lumps with rapid growth but no second 3D-US examination data were excluded during the process of the initial false-negative breast cancer follow-up, which may affect the whole and partial TVDT data. (3) The distribution of molecular subtyping in this study was

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different from the other reports, which may have led to selection bias. (4) As the span of TVDT is large, there were few patients with rapidly-developing tumors enrolled in this study. Therefore, it is necessary to carry out further multicenter prospective study in the future.

Conclusions

Breast cancer TVDT was significantly correlated with NPI score, axillary lymphatic metastasis, Ki-67, and molecular subtyping. Triple-negative breast cancer exhibited the most rapid growth.

Conflict of interest

None.

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