Eur Radiol (2014) 24:2227–2235
DOI 10.1007/s00330-014-3256-0

BREAST

Tumour volume doubling time of molecular breast cancer subtypes assessed by serial breast ultrasound

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Received: 6 March 2014 / Revised: 14 May 2014 / Accepted: 19 May 2014 / Published online: 4 June 2014

Abstract
Objectives The aim of our study was to evaluate the tumour volume doubling time (TVDT) of molecular breast cancer subtypes by serial ultrasound (US).
Methods Sixty-six patients (mean age, 50 years; range, 29–78 years) with invasive breast cancer underwent initial and follow-up breast US examinations (at least three months apart) with no intervention. TVDT was determined using the tumours' greatest dimensions in two orthogonal planes. The results were compared with clinical, imaging, and tumour variables and molecular subtypes (oestrogen receptor [ER]-positive, human epidermal growth factor receptor 2 [HER2]-positive, and triple negative) using a multiple linear regression analysis.
Results TVDT exhibited a wide range (46–825 days; median, 141 days) with an overall mean of 193±141 days and mean values of 241±166 days for ER-positive tumours (n=37), 162±60 days for HER2-positive tumours (n=12), and 103±43 days for triple-negative tumours (n=17) (P<0.0001). In a multivariate regression analysis, compared to other features, only the different molecular breast cancer subtypes showed significant difference in TVDT (P<0.0001).
Conclusions TVDT differed significantly among the three molecular breast cancer subtypes, with the triple-negative tumours showing the fastest growth.
Key Points
• *Knowledge of tumour volume doubling time provides clues for improving screening.*
• *TVDT assessed by serial US differed significantly between breast cancer subtypes.*
• *Triple-negative tumours had 2.4-fold shorter TVDT compared to ER-positive tumours.*
• *Tumours classified as BI-RADS 3 had shorter TVDT than BI-RADS 4.*

Keywords Breast cancer · Molecular subtypes · Ultrasound · Tumour volume doubling time · Triple-negative breast cancer

Abbreviations and acronyms

TVDT	Tumour volume doubling time
ER	oestrogen receptor
PR	progesterone receptor
HER2	human epidermal growth factor receptor 2
IHC	immunohistochemistry
BI-RADS	Breast Imaging Reporting and Data System

Introduction

The characterisation of tumour volume doubling time (TVDT) is important not only for determination of the optimal interval for screening and follow-up but also for developing new strategies for treatment [1]. A few reports have evaluated breast cancer TVDT on mammography [2, 3]. However, mammography is not a reliable imaging modality for breast cancer size measurement and detection, particularly in dense breast tissue [4]. Sectional imaging modalities, such as breast magnetic resonance imaging (MRI) and ultrasound (US), are more accurate in the measurement of tumour size and volume, and they could be used to evaluate TVDT of breast cancers [5–7]. With the increasing use of US for both screening and

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diagnostic purposes, breast cancers initially assessed as benign or suspicious undergo serial breast US examinations without any intervention, thus providing TVDT assessment [8].

Breast cancer is a heterogeneous disease with different clinicopathological features, recurrence patterns, and survival [9–11]. Three major molecular breast cancer subtypes can be distinguished by immunohistochemistry (IHC): oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-positive, and triple-negative [10]. This classification has been widely used for predicting the prognosis and response to treatment in breast cancer patients [12]. Dawson et al. investigated the distribution of these subtypes in breast cancers detected at screening and those detected without screening [13]. Tumours detected at screening were more likely to belong to the ER-positive subtype and were less likely to belong to the triple-negative subtype. Imaging findings of the three molecular breast cancer subtypes have recently been published and triple-negative tumours frequently have benign or indeterminate features on mammography and US [14–16]. To our knowledge however, no data have been published on TVDT according to molecular breast cancer subtype.

The primary objective of this study was to determine the TVDT of molecular breast cancer subtypes on a serial US; secondary objectives were to identify clinical, imaging, and tumour variables linked to TVDT, and to assess the reproducibility and accuracy of the measurement.

Materials and methods

Patients

This retrospective study was approved by the institutional review board (Seoul National University Hospital) and informed consent was waived. A search of departmental preoperative US databases identified 2030 female patients with invasive breast cancer between January 2003 and May 2012, and a total of 305 patients underwent serial breast US with no intervention (i.e., needle biopsy or treatment). Cases were then excluded for the following reasons: no visible lesion on previous breast US (155 patients), an interval of less than three months between the first and last breast US examinations (52 patients), and no immunohistochemistry results (32 patients). These exclusions yielded a final cohort of 66 female patients (mean and median age, 50 and 52 years; range, 29–78 years) with 66 cases of invasive breast cancer. To minimize measurement bias related to varying US data acquisition, we restricted our analyses to patients who had undergone two US examinations that were at least three months apart. In three patients who had more than two breast US examinations, the initial and final follow-up breast US examinations were selected for TVDT analysis.

All patients were asymptomatic at the initial breast US examination. Of these patients, two neglected the biopsy recommendation for suspicious breast lesions on US, and the others were scheduled at six (n=8) or 12 (n=56) months follow-up for probably benign or benign lesions on US. The reason for prompt biopsy at the time of diagnosis was either the presence of a palpable mass (n=21) or an increase in tumour size on follow-up US (n=45). Mammograms were available in 56 women at the time of the initial US examination, and all 66 women had mammograms at the time of diagnosis.

US examinations and imaging review

All US images were obtained using an HDI 5000 system (Advanced Technology Laboratories, Bothell, Wash) with a 12-5 MHz linear transducer or an EUB-8500 system (Hitachi Medical, Tokyo, Japan) with a 14-6 MHz linear transducer. Twelve breast radiologists with 2–25 years of experience in breast US performed the breast US examination. The imaging protocol included transverse and longitudinal real-time imaging of the lesions. All images were sent and saved in a picture archiving and communications system (PACS). The 5,000-pixel monochrome liquid crystal display monitor (ME1i2-BC, Totoku, Electric Co., Tokyo, Japan) and PACS workstation were used to review the images.

For this study, initial breast US were retrospectively reviewed in consensus by two breast radiologists without clinical or pathologic information. Imaging findings were analysed according to BI-RADS US lexicon (shape, orientation, margin, echo pattern, lesion boundary, posterior acoustic features, and calcifications), and a final assessment category was provided to indicate the probability of malignancy [17]. A solid mass with ovoid shape, circumscribed margin, and parallel orientation was assessed as BI-RADS category 3, and masses with any suspicious findings were assessed as BI-RADS category 4 or 5. We performed this retrospective review because the BI-RADS US lexicon was not used until 2005 in our institution.

Calculation of TVDT

An investigator who was not involved in the reader study retrieved the representative transverse and longitudinal images of lesions at initial and follow-up breast US. A single transverse image and a single longitudinal image for each lesion were provided for the readers.

Table 1 Clinical, imaging, and tumour variables according to molecular breast cancer subtype

	Molecular breast cancer subtypes			
Variables	ER-positive (n=37)	HER2-positive (n=12)	Triple-negative (n=17)	P Value
Age at diagnosis (yrs)*	50±9	52±13	48±9	0.542
Menopausal status				0.074
Premenopausal	23 (62 %)	3 (25 %)	10 (59 %)	
Postmenopausal	14 (38 %)	9 (75 %)	7 (41 %)	
Previous history of breast cancer				0.095
No	35	7	10	
Yes	2	5	7	
Symptoms at diagnosis**				0.021
No	29 (78 %)	9 (75 %)	7 (41 %)	
Yes	8 (22 %)	3 (25 %)	10 (59 %)	
Mammographic density†				0.350
Fatty	6 (16 %)	2 (17 %)	4 (24 %)	
Dense	31 (84 %)	10 (83 %)	13 (76 %)	
BI-RADS category				0.094
Category 3	32 (86 %)	11 (92 %)	15 (88 %)	
Category 4	5 (14 %)	1 (8 %)	2 (12 %)	
Tumour size and volume on US				
Initial size (mm) ‡	7.6±3.3	10.3±7.3	8.9±5.1	0.456
Follow-up size (mm)	11.6±4.9	17.0±9.6	17.9±6.7	0.002
Initial volume (mm^3)	1255±2258	4914±13624	2054±4189	0.693
Follow-up volume (mm^3)	4130±5435	17393±29613	16060±17148	0.001
Interval of follow-up US (days)	391±214	393±239	316±105	0.790
Tumour volume doubling time (days)	241±166	162±60	103±43	<0.0001
Histologic type				0.306
Invasive ductal carcinoma	33 (90 %)	9 (75 %)	16 (94 %)	
Invasive ductal carcinoma with ductal carcinoma in situ	2 (5 %)	3 (25 %)	1 (6 %)	
Invasive lobular carcinoma	2 (5 %)	0 (0)	0 (0)	
Invasive tumour size (cm)	1.1±0.6	1.7±0.8	1.8±0.9	0.010
Histologic grade				< 0.0001
Grade I	13 (35 %)	0 (0)	0 (0)	
Grade II	19 (51 %)	1 (8 %)	5 (29 %)	
Grade III	5 (14 %)	11 (92 %)	12 (71 %)	
Lymph node metastases				0.297
No	35	10	14	
Yes	2	2	3	

Note. —

* Data are the means ± standard deviations

** Eighteen had palpable masses and three had both palpable masses and nipple discharges

† Fatty includes BI-RADS grade 1 and 2; Dense includes BI-RADS grade 3 and 4

‡ Greatest dimension at initial US

The longest dimension and maximal perpendicular dimension of each lesion were measured by four radiologists, who did not perform the US examinations and who were blinded to the image acquisition technique by using electronic callipers on the transverse images. Additionally, the longest dimension of each lesion on the longitudinal scans was measured. The volume of each tumour was estimated using the formula for oblate spheroids [5]: $V=4/3\pi \cdot a/2 \cdot b/2 \cdot c/2$, where a, b, and c denote the means of the four observers' measurements.

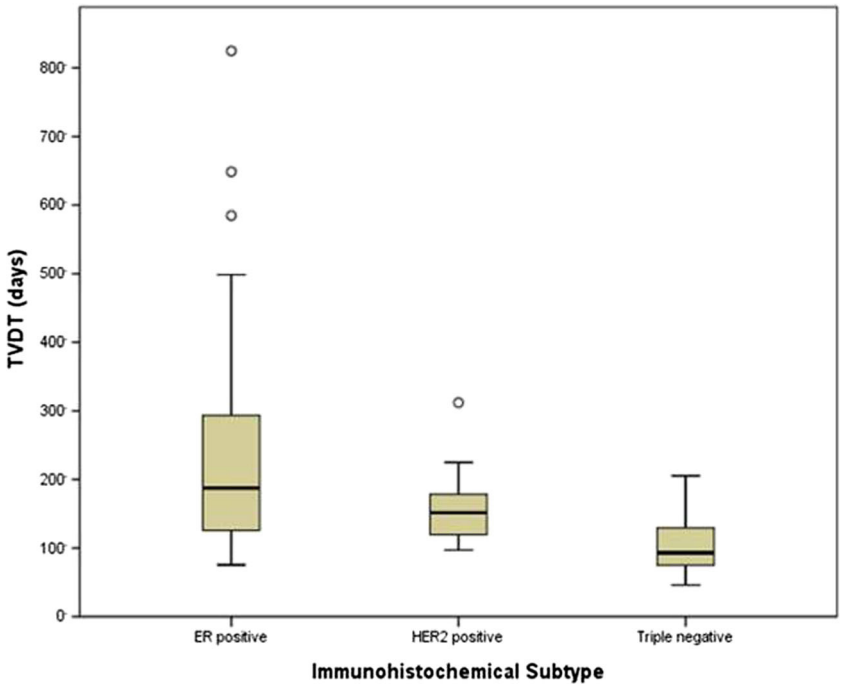

Fig. 1 TVDT according to molecular subtype, using box-and-whisker plots (open circles for more than 1.5 times the upper quartile)

By using the volumes from the initial and follow-up examinations, TVDT was calculated in days by using the equation: TVDT=t • log 2/(log V2– log V1), where t represents the interval in days between the two examinations and V1 and V2 represent lesion volume on the initial and follow-up studies, respectively [2, 18]. Tumours were assumed to have exponential growth, as this is usually the best approximation for the range of tumour sizes in our study [2].

Histological evaluation

Breast conserving surgery (n=45) or mastectomy (n=21) was performed for all breast cancers. The histological type, invasive tumour size, histological grade, and lymph node status were determined from the surgically excised specimens. The expression of ER, progesterone receptor (PR), HER2, and the Ki-67 index were evaluated in the surgically excised specimens by standard avidin–biotin complex IHC staining methods.

Based on the expression of ER, PR, and HER2 status, breast cancers were classified into three molecular subtypes: ER-positive, HER2-positive, and triple-negative. The ER subtype was defined by a finding of at least 1 % positive tumour cells on either or both of the ER and PR assays [19]. The HER2 status could be either negative or positive. The HER2 subtype was defined to include ER-negative cancers showing HER2 over-expression and/or HER2 gene amplification [20]. The triple-negative subtype was defined as cancers with ER-negative/PR-negative/HER2-negative results. For the Ki-67 index, a cutoff value of 14 % was used as a cellular marker for proliferation [21].

Data analysis

The documented information on clinical, imaging, and tumour variables included patient age at diagnosis, menopausal status, previous history of breast cancer, symptoms at diagnosis, mammographic density, BI-RADS category and tumour size (defined as maximal diameter) on initial US, histologic type, invasive tumour size, histologic grade, lymph node metastases, ER, PR, HER2, Ki-67, and molecular subtypes. Univariate analysis was performed to compare TVDT and variables of breast cancer. Analysis of variance (ANOVA) or Kruskal-Wallis analysis was used to compare continuous variables, and Fisher's exact test or the $\chi 2$ test was used for categorical variables. Multiple linear regression analysis was used to perform multivariate analyses to determine which variables were most influential on TVDT. A t-test or Wilcoxon's rank sum test was used to assess the differences of TVDT according to BI-RADS US features. The analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC). A P-value less than 0.05 was considered to indicate a significant difference.

Interobserver agreement in three-dimensional measurements, and between the greatest dimension on follow-up US and at pathologic examination, was assessed by using intraclass correlation coefficient (ICC) values. ICCs were defined as follows: an ICC of 0–0.20 indicated no agreement; an ICC of 0.21–0.40, poor agreement; an ICC of 0.41–0.60, moderate agreement; an ICC of 0.61–0.80, good agreement; and an ICC greater than 0.80, excellent agreement.

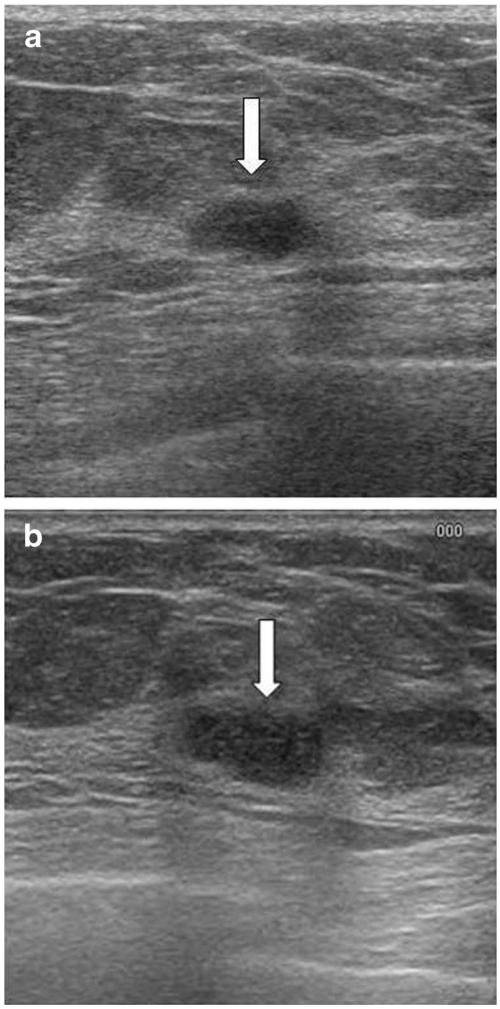

Fig. 2 Transverse US images in a 69-year-old woman with ER-positive, grade 1 invasive ductal carcinoma. *a* US image shows an 8x4-mm hypoechoic, oval-shaped mass (*arrow*). The mass was initially classified as probably benign and follow-up was chosen as a management. *b* US image obtained after 12 months shows a 10x6-mm hypoechoic mass (*arrow*). Initial and follow-up tumour volumes were 835 mm^3 and 2010 mm^3, respectively, and the tumour volume doubling time was 276 days

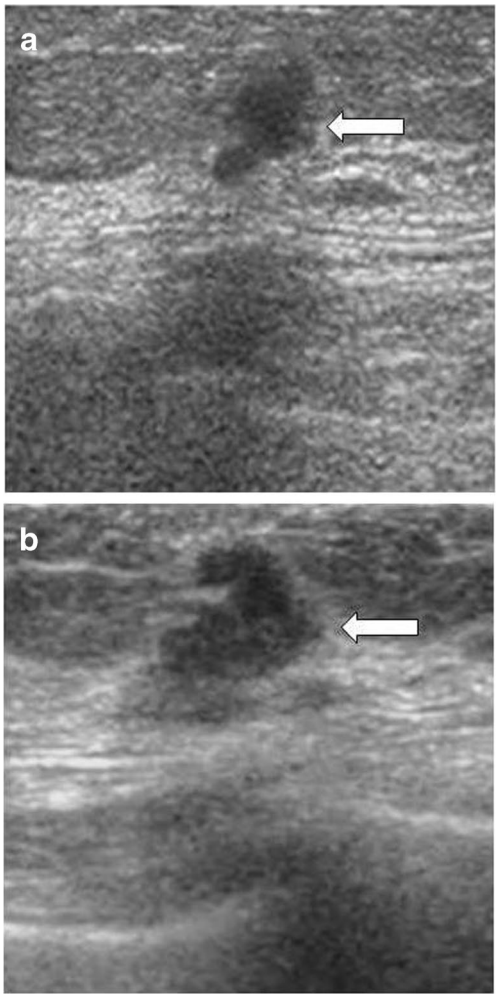

Fig. 3 Transverse US images in a 75-year-old woman with HER2-positive, grade 3 invasive ductal carcinoma. *a* US image shows a 6x4-mm hypoechoic, irregularly-shaped mass (*arrow*). The mass was initially classified as suspicious; however, the patient neglected a core biopsy. *b* US image obtained after 11 months (now palpable) shows a 9x8-mm hypoechoic mass. Initial and follow-up tumour volumes were 807 mm^3 and 2398 mm^3, respectively, and the tumour volume doubling time was 224 days

Results

Clinical, imaging, and tumour characteristics

There were 37 ER-positive (including one ER-positive and HER2-positive cancer), 12 HER2-positive, and 17 triple-negative tumours. Clinical, imaging, and tumour characteristics according to molecular breast cancer subtypes are summarised in Table 1. Women with triple-negative subtypes more often had symptoms at diagnosis, a larger tumour size and volume on follow-up US, larger invasive tumour size, and higher tumour grade compared to women with ER-positive subtypes. The three molecular breast cancer subtypes did not differ in terms of age at diagnosis, menopausal status, previous history of breast cancer, mammographic density, BI-RADS category, tumour size and volume on initial US, interval between initial and follow-up US examinations, histologic type, and lymph node metastases.

Tumour volume doubling time

All tumours increased in diameter and volume between initial and follow-up US examinations. A large variation in TVDT was observed from 46 days to 825 days (mean, 193±141 days; median, 141 days). There were significant differences in TVDT among molecular breast cancer subtypes ($P<0.0001$) (Fig. 1) with mean values of 241±166 days (range, 75-825 days; median, 194 days) for ER-positive tumours (Fig. 2), 162 ±60 days (range, 97-312 days; median, 154 days) for HER2-positive tumours (Fig. 3), and 103±43 days (range, 46-205

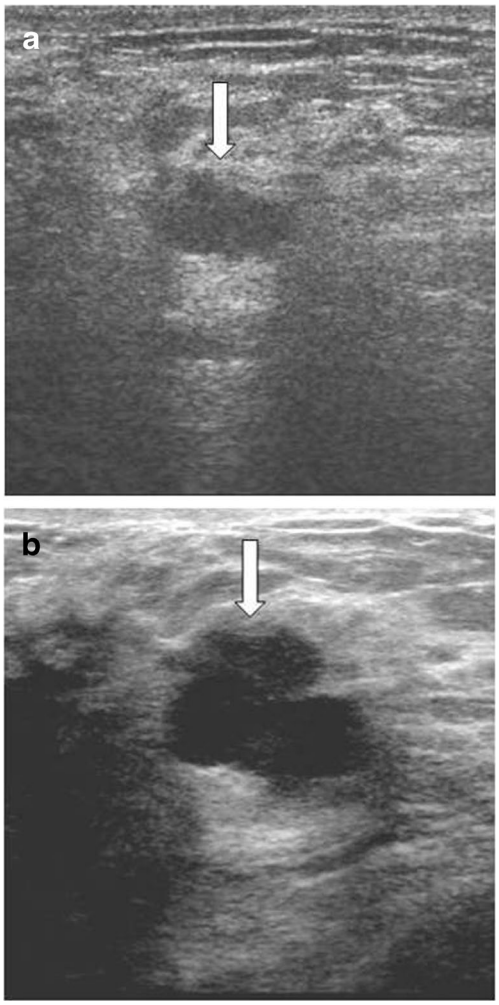

Fig. 4 Transverse US images in a 59-year-old woman with triple-negative, grade 3 invasive ductal carcinoma. *a* US image shows an 11x7-mm hypoechoic, oval-shaped mass (*arrow*) with posterior enhancement. The mass was initially classified as probably benign and follow-up was chosen as a management. *b* US image obtained after seven months (now palpable) shows a 20x19-mm hypoechoic mass (*arrow*). Initial and follow-up tumour volumes were 3,730 mm^3 and 23,864 mm^3, respectively, and the tumour volume doubling time was 81 days

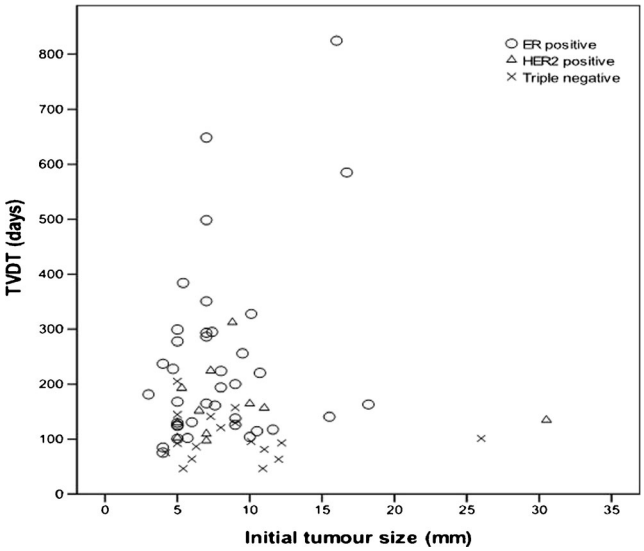

Fig. 5 TVDT and initial tumour size for each molecular subtype. In ER-positive tumours, TVDT increased with increasing tumour size, whereas TVDT remained constant in HER2-positive and triple-negative tumours

days; median, 93 days) for triple-negative tumours (Fig. 4). In ER-positive tumours, TVDT increased with increasing tumour size whereas TVDT remained constant in HER2-positive and triple-negative tumours (Fig. 5).

According to the retrospective review, 58 tumours were classified as BI-RADS category 3 and eight tumours were classified as category 4, with TVDT values of 176±111 days and 302±264 days, respectively (P=0.001) (Table 2). However, there were no significant US features related to shorter TVDT (Table 3).

In univariate analysis, significant differences in TVDT were found with respect to symptoms at diagnosis (P=0.005), BI-RADS category (P=0.001) on initial US, ER status (P=0.001), PR status (P=0.002), Ki-67 index (P=0.004), and molecular subtypes (P<0.0001). However, age at diagnosis, menopausal status, previous history of breast cancer, mammographic density, histologic grade, HER2 status, and lymph node metastases did not affect TVDT (Table 2). By multivariate regression analysis, only the molecular breast cancer subtype was significantly associated with TVDT (P<0.0001).

Interobserver agreement

There was excellent ICC between the dimensions measured by four readers: the longest dimension on transverse scan (ICC=0.95, 95 % CI: 0.92 – 0.97), maximal perpendicular dimension on transverse scan (ICC=0.91, 95 % CI: 0.83 – 0.98), and longest dimension on longitudinal scan (ICC=0.87, 95 % CI: 0.79 – 0.90) (Table 4). TVDT measured by four readers also showed excellent ICC (ICC=0.91, 95 % CI: 0.80 – 0.96).

The greatest dimension measured on US and at pathologic examination showed good ICC (ICC=0.77, 95 % CI: 0.64 – 0.86). Differences in measurements of the greatest dimension by US and pathologic examination were found in six invasive ductal carcinomas with ductal carcinoma in situ. After exclusion of these six cases, an excellent ICC for the greatest dimension measured by US and pathologic examination was observed (ICC=0.91, 95 % CI: 0.83 – 0.95).

Discussion

Although, there were several clinical, imaging, and tumour variables that exhibited association with TVDT by univariate analysis, only the molecular breast cancer subtype was

Table 2 Tumour volume doubling times according to clinical, imaging, and tumour variables

Variables	No. of patients (n=66)	TVDT * (days)	*P* Value
Age at diagnosis			0.463
<40	8	173±76	
40-50	26	190±183	
>50	32	195±115	
Menopausal status			0.206
Premenopausal	36	186±158	
Postmenopausal	30	201±121	
Previous history of breast cancer	52	206±153	0.051
No	14	134±61	
Yes			
Symptoms at diagnosis			0.005
No	45	212±146	
Yes	21	146±122	
Mammographic density	12	204±161	0.530
Fatty	54	188±138	
Dense			
BI-RADS category			0.001
Category 3	58	176±111	
Category 4	8	302±264	
Histologic grade			0.090
Grade I	13	204±149	
Grade II	25	230±179	
Grade III	28	154±0.80	
ER status			0.001
Negative	28	133±66	
Positive	38	234±166	
PR status			0.002
Negative	34	144±74	
Positive	32	241±177	
HER2 status			0.848
Negative	54	197±154	
Positive	12	162±60	
Ki-67 index			0.004
<14 %	56	205±146	
≥14 %	10	114±78	
Molecular breast cancer subtypes			< 0.0001
ER-positive	37	241±166	
HER2-positive	12	162±60	
Triple-negative	17	103±43	
Lymph node metastases			0.101
No	59	199±146	
Yes	7	122±58	

* Data are the means±standard deviations

significantly associated with TVDT according to multiple linear regression analysis. We measured TVDT using the greatest dimensions of the tumour in two orthogonal planes at serial breast US, and the measurement showed high

Table 3 Tumour volume doubling times according to US features

Features	No. of patients (n=66)	TVDT * (days)	*P* Value
Shape			0.891
Oval or round	58	197±152	
Irregular	8	158±62	
Orientation			0.644
Parallel	58	196±148	
Not parallel	8	154±74	
Margin			0.784
Circumscribed	59	184±124	
Not circumscribed†	7	200±165	
Echo pattern			0.619
Isoechoic	23	195±134	
Hypoechoic	43	184±158	
Lesion boundary			NA
Echogenic halo	0	NA	
Abrupt interface	66	234±166	
Posterior acoustic features			0.388
No posterior acoustic features	63	194±144	
Enhancement	3	130±66	
Calcifications			0.208
None	61	177±110	
Microcalcification in mass	5	365±322	

* Data are the means ± standard deviations. NA=not applicable

†Not circumscribed margin contains indistinct (n=5), angular (n=1), and microlobulated (n=1)

reproducibility among four observers, as well as a good correlation with pathology. Breast US with its sectional imaging capability is more accurate in the measurement of tumour size and volume compared to mammography, and could be used as a nonionizing method to evaluate TVDT of breast cancers. The TVDT values (mean, 193 days; median, 141 days; range, 46–825 days) of the breast cancers in our study were within the range of previously measured or estimated TVDTs using mammography or MRI [2–6]. Most mammography studies, however, were conducted before the molecular breast cancer subtype was published [22]. This study is, to our knowledge, the first to investigate TVDT according to molecular breast cancer subtypes.

Our results showed significantly different TVDT values among the three molecular breast cancer subtypes. Triple-negative tumours, the most aggressive form of breast cancer, had 2.4-fold and 1.6-fold shorter TVDT (103±43 days) compared to ER-positive (241±166 days) and HER2-positive (162±60 days) tumours, respectively. Because we are now able to identify the type of breast cancer for which women are at risk, this information will provide important clues for designing demonstration projects to associate risk-based screening and tumour molecular subtype [10, 11, 23, 24]. Our

Table 4 Agreement on the measurements of tumour dimension, tumour volume, and tumour volume doubling time

Measurements	Observer 1	Observer 2	Observer 3	Observer 4	Mean
a	0.91	0.96	0.95	0.98	0.95 (0.92–0.97)
b	0.89	0.85	0.94	0.96	0.91 (0.83–0.98)
c	0.85	0.87	0.84	0.92	0.87 (0.79–0.90)
V1	0.90	0.96	0.97	0.91	0.91 (0.78-0.98)
V2	0.86	0.94	0.93	0.95	0.92 (0.82-0.98)
TVDT	0.91	0.89	0.90	0.96	0.91 (0.80-0.96)

a Longest dimension on transverse scan

b Maximal perpendicular dimension on transverse scan

c Longest dimension on longitudinal scan

V1 Initial volume

V2 Follow-up volume

TVDT Tumour volume doubling time

findings on TVDT also support that molecular breast cancer subtype should be considered when planning ongoing management and surveillance for breast cancer patients [25]. In previous studies, the peak recurrence for ER-positive tumours was after 36 months post-operation, while the recurrence of HER2-positive and triple-negative tumours peaked at 12-24 months [26, 27].

Clinical and experimental observations show that cancer growth follows an S-shaped or Gompertzian curve between linear and exponential kinetics [28, 29]. The Gompertzian model predicts that TVDT does not remain constant over time but is related to tumour size, such that TVDT increases with increasing tumour size. Our results showed that there was, however, a significant difference in tumour growth patterns according to the molecular breast cancer subtype. In ER-positive tumours, TVDT increased with increasing tumour size whereas TVDT remained constant in HER2-positive and triple-negative tumours. This finding, to the best of our knowledge, has not been previously reported and will be helpful to develop mathematical modelling of tumour growth and metastases according to molecular breast cancer subtypes. In contrast to previous studies [2, 6], no significant difference in TVDT was found between young and old women in our study.

Notably, breast cancer classified as BI-RADS category 3, probably benign, on initial US has a significantly shorter TVDT than category 4, suspicious (176±111 days and 302± 264 days, P=0.001). This finding is concordant with previous reports that triple-negative and high-grade tumours have a tendency to exhibit benign US features such as round or oval shape, circumscribed margins, and posterior enhancement due to necrosis and lack of a host desmoplastic reaction [14, 30]. In our study, however, no US features within the BI-RADS lexicon were significantly related to shorter TVDT. Additional studies such as colour Doppler and elastography will be helpful to avoid misclassifying triple-negative and high-grade tumours as probably benign on US [31, 32]. Triple-negative tumours more often presented as interval cancer compared to other subtypes in our study (59 % in triple negative vs. 22 % in ER positive and 25 % in HER2 positive, P=0.021).

This study has several limitations. First, this is a retrospective study with a small sample size, and only one case of ER-positive and HER2-positive cancer was included. Selection bias was inevitable because only cancers visible on both initial and follow-up breast US were included. Many of the fast-growing tumours could be excluded and our results on TVDT may differ from those obtained from population-based screening [33]. Second, we did not evaluate the interobserver variability for data acquisition. Variability within data acquisition and tumour volume measurement could occur as a result of minor changes in position or degree of compression. An automated 3D US scanner has been developed and could be used to monitor changes in tumour volume during follow-up [34]. Third, we did not provide treatment response or prognosis according to TVDT. Previous studies have shown that patients with shorter TVDT tend to have a poorer prognosis, particularly when multiple nodal metastases are combined [35].

In conclusion, the TVDT of breast cancer differed significantly among the three molecular subtypes, with the triple-negative tumours showing the fastest growth. This information will provide important clues for improving screening and surveillance of breast cancer patients.

Acknowledgments The scientific guarantor of this publication is Woo Kyung Moon. The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article. This study has received funding by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (No. 2012R1A2A1A01010846). No complex statistical methods were necessary for this paper. Institutional Review Board approval was obtained. Written informed consent was waived by the

Institutional Review Board. Methodology: retrospective, observational, performed at one institution.

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