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Tumor growth rate of invasive breast cancers during wait times for surgery assessed by ultrasonography

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Abstract

Several studies suggest that delay in the surgical treatment of breast cancer is significantly associated with lower survival. This study evaluated the tumor growth rate (TGR) of invasive breast cancers during wait times for surgery quantitatively using ultrasonography (US) and identified clinicopathologic factors associated with TGR.

This retrospective study was approved by our institutional review board and the requirement for written informed consent was waived. Between August 2013 and September 2014, a total of 323 unifocal invasive breast cancers in 323 women with serial US images at the time of diagnosis and surgery were included. Tumor diameters and volumes were measured using 2-orthogonal US images. TGR during wait times for surgery was quantified as specific growth rates (SGR; %/day) and was compared with clinicopathologic variables using univariate and multivariate analyses.

Median time from diagnosis to surgery was 31 days (range, 8–78 days). Maximum tumor diameters and volumes at the time of surgery (mean, 15.6 mm and 1.6 cm^3) were significantly larger than at diagnosis (14.7 mm and 1.3 cm^3) ($P < 0.001$). On multivariate analysis, surrogate molecular subtype was a significant independent factor of SGR ($P = 0.001$); triple negative cancers showed the highest SGR (1.003%/day) followed by HER2-positive (0.859 %/day) and luminal cancers (luminal B, 0.208 %/day; luminal A, 0.175%/day) ($P < 0.001$). Clinical T stage was more frequently upgraded in nonluminal (triple negative, 18% [12/67]; HER2-positive, 14% [3/22]) than luminal cancers (luminal B, 3% [1/30]; luminal A, 2% [4/204]) ($P < 0.001$).

Invasive breast cancers with aggressive molecular subtypes showed faster TGR and more frequent upgrading of clinical T stage during wait times for surgery.

Abbreviations: BI-RADS = Breast Imaging Reporting and Data System, DICOM = digital imaging and communications in medicine, FISH = fluorescence in situ hybridisation, HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, ICC = intraclass correlation coefficient, IHC = immunohistochemistry, PACS = picture archiving and communication system, SGR = specific growth rate, TGR = tumor growth rate, TVDT = tumor volume doubling time, US = ultrasonography.

Keywords: breast cancer, surrogate molecular subtype, tumor growth rate, ultrasonography, wait-times for surgery

1. Introduction

Breast cancer patients typically wait weeks before surgery for preoperative work-up, consideration of options such as reconstruction, and referral to tertiary care centers.[1–3] Wait times for breast cancer surgery have increased over the past decade.[1,4] Delay between diagnosis and surgery can cause anxiety in women with breast cancer over concerns of interim tumor progression. Indeed, several studies have reported that a delay in the surgical treatment of breast cancer is significantly associated with lower survival.[5,6] Accordingly, the wait time for surgery has recently been proposed as a quality indicator in breast cancer care as it is an important contributor to patient satisfaction and cancer outcomes.[7–9] At present, there is no established benchmark for the wait time before breast cancer surgery, although a period of $\leq$30 days is considered to be a modest delay with better prognosis compared to wait times of longer intervals.[6,7,10] In addition, Wagner et al[2] has reported that a modest time interval between diagnosis and surgery is not significantly associated with tumor size progression.

However, breast cancer is a highly heterogeneous disease with variable biological features and clinical outcomes.[11] Therefore, it is natural for breast cancers to have varying growth rates according to the characteristics of patients and tumors.[12] A

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previous study evaluated the tumor growth rate of breast cancers before diagnosis and demonstrated that intrinsic tumor growth rates were different according to the molecular subtype with triple-negative tumors showing the fastest growth.[13] Therefore, we hypothesized that different molecular subtypes of breast cancers may also affect tumor progression, defined as an increase in size, during wait times for surgery after diagnosis and that the fast-growing tumors may show a considerable change in size over a short time interval. Ultrasonography (US) is an accurate method for measuring tumor size and repetitive evaluation is feasible because of its nonionizing technique. By comparing tumor sizes on serial follow-up US images, quantitative parameters of tumor growth rates can be derived including the tumor volume doubling time (TVDT) and specific growth rate (SGR).[13,14] SGR has been proposed as a more suitable parameter than TVDT for shorter time intervals, for all tumor volume changes including both increases and decreases, and for statistical testing.[15,16]

The purpose of our study, therefore, was to quantitatively evaluate the tumor growth rate of invasive breast cancers during wait times for surgery using US and to identify clinicopathologic factors associated with tumor growth rates.

2. Materials and methods

2.1. Patients and Lesions

This retrospective study was approved by our institutional review board and the requirement for written informed consent was waived. A search of our database identified 1328 consecutive women diagnosed with invasive breast cancers who had undergone primary surgical treatment at Seoul National University Hospital between August 2013 and September 2014. Among them, 1118 women had available serial breast US images at the time of diagnosis and surgery. From this population, we excluded women who were not eligible for tumor growth rate assessment with US for the following reasons: multifocal or diffuse cancers on pathologic examination[17] owing to the difficulty in correlating tumor sizes on US and pathology (n = 402), vacuum-assisted core needle biopsy or surgical excisions performed before definitive surgery ($n = 214$), unavailability of 2-orthogonal image sets with the same probe direction on serial US examinations (n = 135), and poor visibility of lesions on US (n = 44). Finally, 323 unifocal invasive breast cancers in 323 women with serial 2-orthogonal US image sets constituted our study population.

2.2. US examinations

All women underwent breast US examinations at both diagnosis and surgery. Initial US examinations were performed as a first diagnostic imaging either at our institution (n = 123) or outside referring facilities (n = 200). The second US images were acquired 1 day before surgery in all women according to the routine protocol of our institution. All breast US examinations at our institution were performed by 1 of 5 radiologists with 2 to 8 years of experience using the Aixplorer system (Supersonic Imagine, Aix en Provence, France) with a 15- to 4 MHz linear-array transducer or HI VISION Preirus (Hitachi Medical Systems, Tokyo, Japan) with a 13- to 5 MHz linear-array transducer. For the US examinations performed at outside referring facilities, various scanners equipped with a high-resolution linear array transducer with a center frequency of at least 10 MHz were used fulfilling the American College of Radiology practice parameters[18] and all examinations were performed by physicians board certified in radiology with varying degrees of experience. At least 2-orthogonal images were acquired in either the transverse/longitudinal or radial/anti-radial planes for each breast mass and the same probe directions were applied for the serial US examinations. All images were sent and saved to a picture archiving and communication system (PACS) in digital imaging and communications in medicine (DICOM) file format.

2.3. Tumor diameter measurement and calculation of tumor growth rates

Three breast radiologists (YK, SHL, WKM) independently measured the tumor diameters using serial US images on PACS workstations. All readers were fellowship trained in breast imaging and had an average of 8.7 years of experience (range, 1–20 years) in breast US examinations. A set of 2-orthogonal images of each tumor were provided for the readers in random order regardless of the time sequence. Three perpendicular tumor diameters (referred to as a, b, and c) were measured using electronic calipers and then were used to estimate the tumor volume using the formula for oblate spheroids[19]: $V = 4/3\pi \bullet a/2 \bullet b/2 \bullet c/2$, where a, b, and c denote the longest diameter of a lesion, the maximum perpendicular diameter in the same plane, and the longest vertical diameter in the orthogonal plane, respectively.[20] The tumor growth rate between diagnosis and surgery was quantified using the parameter of specific growth rate (SGR, %/day) calculated using the following equation:[15] $SGR = \ln (V_2/V_1)/(t_2 - t_1)$, where V_1 and V_2 are the tumor volumes at the time of diagnosis (t_1) and surgery (t_2), respectively.

2.4. Data collection

All clinicopathologic data were obtained from our prospectively maintained web-based database. The clinical data collected included the patients' age at diagnosis, menopausal status, presence or absence of palpable symptoms, a personal or first-degree family history of breast cancer, mammographic breast density and findings according to the Breast Imaging Reporting and Data System (BI-RADS),[21] initial tumor size on US, biopsy needle gauge, number of acquired samples on US-guided core needle biopsy, length of time between diagnosis and surgery, and type of breast surgery. Pathologic data collected included the histologic type of breast cancer, invasive tumor size, histologic grade according to the Nottingham Grading System,[22] presence or absence of carcinoma in situ components, lymphovascular invasion, and axillary lymph node metastasis. Tumor stage was classified according to the American Joint Committee on Cancer 7th edition.[23] Immunohistochemical (IHC) staining was performed for hormone receptor (HR) (estrogen receptor and progesterone receptor), human epidermal growth factor receptor 2 (HER2), and Ki-67 using standard methods as previously described.[24–26] Fluorescence in situ hybridization for HER2 DNA amplification assessment was performed in all equivocal cases with HER2 IHC 2+ cases. Surrogate molecular subtypes were classified on the basis of their HR, HER2, and Ki-67 status: luminal A (HR-positive, Ki-67 low, and HER2-negative), luminal B (HR-positive, Ki-67 high, and HER2-negative or HR-positive, any Ki-67, HER2-positive), HER2-positive (HR-negative and HER2-positive), and triple negative (HR-negative and HER2-negative).[27]

Table 1

Interobserver agreements between the three readers regarding the measurement of tumor diameters, tumor volumes, and specific growth rates.

	Reader 1	Reader 2	Reader 3	Median*	Agreement
Variable measured	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	ICC (95% CI)
Initial US at diagnosis (t_1)					
a_1 (mm)	14.7 ± 6.0	13.4 ± 5.9	15.2 ± 6.3	14.7 ± 6.1	0.949 (0.855–0.975)
b_1 (mm)	9.7 ± 3.8	9.3 ± 3.9	10.0 ± 3.9	9.7 ± 3.7	0.952 (0.928–0.966)
c_1 (mm)	12.2 ± 5.0	11.3 ± 5.0	12.8 ± 5.3	12.4 ± 5.0	0.892 (0.780–0.938)
V_1 (cm^3)	1.3 ± 1.5	1.1 ± 1.3	1.5 ± 1.8	1.3 ± 1.5	0.927 (0.891–0.949)
Second US at surgery (t_2)					
a_2 (mm)	15.5 ± 6.6	14.2 ± 6.6	15.6 ± 6.7	15.6 ± 6.6	0.955 (0.907–0.974)
b_2 (mm)	10.1 ± 4.1	9.6 ± 4.2	10.2 ± 4.4	10.0 ± 4.1	0.955 (0.938–0.967)
c_2 (mm)	12.8 ± 5.6	11.9 ± 5.7	13.4 ± 5.9	13.0 ± 5.5	0.942 (0.889–0.965)
V_2 (cm^3)	1.6 ± 2.0	1.4 ± 2.0	1.7 ± 2.2	1.6 ± 2.0	0.964 (0.947–0.975)
Wait times for surgery (t_2-t_1)					
SGR (%/day)	0.356 ± 1.097	0.348 ± 1.062	0.243 ± 1.294	0.337 ± 1.067	0.862 (0.834–0.887)

a = longest diameter of a lesion, b = maximum perpendicular diameter in the same plane, c = longest vertical diameter in the orthogonal plane, CI = confidence interval , ICC = intraclass correlation coefficient, SD = standard deviation, SGR = specific growth rate, US = ultrasound, V = tumor volume.

* Median of measurements by the 3 readers.

2.5. Statistical analysis

Interobserver agreement among the three readers regarding the measurement of tumor diameters, tumor volumes, and SGR was evaluated using intraclass correlation coefficient (ICC) values. An ICC of 0.00–0.20 indicates slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement.[28] Median tumor diameters measured by the three readers were determined for each lesion and were used to calculate the tumor volumes and SGR. Tumor diameters and volumes acquired at the two time points of diagnosis and surgery were compared using the paired samples *t*-test. The association between clinicopathologic variables and SGR was evaluated using the independent samples t-test or analysis of variance with a post-hoc Tukey test. Multiple linear regression analysis was performed to determine the variables independently associated with SGR. Changes in tumor diameters and clinical T stages determined on serial breast US examinations were compared according to the clinicopathologic variable using analysis of variance or Fisher exact test, as appropriate. Correlation and agreements between the tumor diameters on breast US and pathology were evaluated using Pearson correlation coefficient and Bland–Altman analysis. Two-tailed *P* values of <0.05 were considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS software (PASW Statistics, version 20; SPSS Inc, Chicago, IL).

3. Results

3.1. Measurement of tumor diameters, tumor volumes, and the specific growth rate

The 3 readers showed almost perfect agreement for the measurement of tumor diameters (range of ICCs, 0.892–0.955), tumor volumes (0.927–0.964), and SGR (0.862) (Table 1). The median tumor diameters and volumes at the time of surgery (a_2, 15.6 ± 6.6 mm [mean ± standard deviation]; b_2, 10.0 ± 4.1 mm; c_2, 13.0 ± 5.5 mm; V_2, 1.6 ± 2.0 cm^3) were significantly larger than those at the time of diagnosis (a_1, 14.7 ± 6.1 mm; b_1, 9.7 ± 3.7 mm; c_1, 12.4 ± 5.0 mm; V_1, 1.3 ± 1.5 cm^3) ($P < 0.001$, all). SGR calculated using median tumor diameters and volumes at the time of diagnosis and surgery was a mean of 0.337 ± 1.067 %/day (range, −3.954 to 4.678 %/day).

3.2. Clinical, imaging, and pathologic characteristics

The median age of women was 53 years (range, 27–82 years). Among the 323 women with 323 invasive breast cancers, 162 (50%) presented with palpable symptoms and the other 161 (50%) were detected by screening examinations. A personal history and family history of breast cancer were present in 3% (10/323) and 7% (24/323) of women, respectively. Mammography was performed in all women and showed a breast tissue composition of dense (BI-RADS grade c–d) in 72% (234/323) and non-dense (BI-RADS grade a–b) in 28% (89/323) of women. Mass or asymmetry without microcalcification was the most common mammographic finding (65% [210/323]). Percutaneous needle biopsy was performed using a 14-gauge core needle with a mean number of core samples of 5 (range, 3–8). The median time from initial imaging to surgery was 31 days (range, 8–78 days). Breast-conserving surgery was performed in 81% (262/323) of women and the other 19% (61/323) underwent total mastectomy. The majority of breast cancers were invasive ductal carcinomas, not otherwise specified type (88% [283/323]), 73% (237/323) were pathologic T stage 1, and 81% (261 of 323) did not have involved axillary lymph nodes. The histologic grade was low to intermediate in 60% (194/323) and high in 40% (129/323) of cases. The most common surrogate molecular subtype was luminal A (63% [204/323]), followed by triple negative (21% [67/323]), luminal B (9% [30/323]), and HER2-positive (7% [22/323]) (Table 2).

3.3. Clinicopathologic factors associated with specific growth rate

Among the clinicopathologic factors, a palpable symptom at diagnosis, pathologic T stage, histologic grade, HR status, Ki-67 expression, and surrogate molecular subtype were significant factors associated with SGR on univariate analysis ($P < 0.05$) (Table 2). Palpable cancers showed higher SGR than nonpalpable cancers ($P = 0.005$). Higher pathologic T stage and histologic

Table 2

Specific growth rates of 323 invasive breast cancers according to clinicopathologic factors.

Variable	No. of patients	Specific growth rate	
		Mean ± SD	*P*
Age, y			0.310
<40	27 (8)	0.726 ± 1.042	
40–49	90 (28)	0.381 ± 1.231	
50–59	121 (38)	0.414 ± 1.036	
≥60	85 (26)	0.282 ± 0.919	
Menopausal status			0.754
Premenopause	144 (45)	0.375 ± 1.152	
Postmenopause	179 (55)	0.413 ± 0.997	
Palpable symptom at diagnosis			0.005
Absent	161 (50)	0.229 ± 1.018	
Present	162 (50)	0.562 ± 1.093	
Personal history of breast cancer			0.493
Absent	313 (97)	0.389 ± 1.079	
Present	10 (3)	0.625 ± 0.563	
Family history of breast cancer			0.979
Absent	299 (93)	0.397 ± 1.033	
Present	24 (7)	0.391 ± 1.460	
Mammographic density			0.175
Non-dense (a-b)	89 (28)	0.527 ± 0.918	
Dense (c-d)	234 (72)	0.347 ± 1.117	
Mammographic finding			0.093
Mass or asymmetry without microcalcification	210 (65)	0.438 ± 1.088	
Mass or asymmetry with microcalcification	66 (20)	0.484 ± 0.997	
Occult	47 (15)	0.086 ± 1.037	
Tumor size on initial US (mm)			0.448
≤10	74 (23)	0.299 ± 1.125	
>10 to ≤20	188 (58)	0.390 ± 1.065	
>20	61 (19)	0.533 ± 1.004	
Method of core needle biopsy			0.743
14-gauge, 5 cores or less	84 (26)	0.466 ± 0.978	
14-gauge, 6 cores or more	39 (12)	0.321 ± 1.207	
14-guage, Unknown	200 (62)	0.382 ± 1.078	
Time between diagnosis and surgery, days)			0.767
≤30	154 (48)	0.378 ± 1.212	
>30	169 (52)	0.413 ± 0.920	
Type of breast surgery			0.182
Breast conserving surgery	262 (81)	0.358 ± 1.094	
Mastectomy	61 (19)	0.561 ± 0.936	
Histologic type of breast cancer			0.221
Invasive ductal carcinoma, NOS	283 (88)	0.368 ± 1.107	
Invasive lobular carcinoma	17 (5)	0.356 ± 0.808	
Other types	23 (7)	0.769 ± 0.594	
Mucinous carcinoma	11	0.679 ± 0.609	
Metaplastic carcinoma	5	1.384 ± 0.307	
Adenoid cystic carcinoma	3	0.378 ± 0.473	
Secretory carcinoma	2	0.448 ± 0.511	
Invasive papillary carcinoma	1	1.017	
Invasive apocrine carcinoma	1	0.256	
pT stage			<0.001
1	237 (73)	0.270 ± 1.073	
2	86 (27)	0.744 ± 0.978	
Histologic grade			<0.001
Low	39 (12)	0.118 ± 1.009	
Intermediate	155 (48)	0.183 ± 0.979	
High	129 (40)	0.736 ± 1.103	
Carcinoma in situ component			0.970
Absent	86 (27)	0.393 ± 1.011	
Present	237 (73)	0.398 ± 1.089	
Lymphovascular invasion			0.090
Absent	269 (83)	0.351 ± 1.020	
Present	54 (17)	0.621 ± 1.265	
pN stage			0.822
0	261 (81)	0.403 ± 1.099	

(*continued*)

Table 2

(continued).

Variable	No. of patients	Specific growth rate	
		Mean ± SD	*P*
≥1	62 (19)	0.369 ± 0.933	
Hormone receptor			<0.001
Negative	89 (28)	0.967 ± 1.084	
Positive	234 (72)	0.179 ± 0.979	
HER2			0.351
Negative	287 (89)	0.377 ± 1.053	
Positive	36 (11)	0.553 ± 1.180	
Ki-67			<0.001
Low (<14%)	250 (77)	0.251 ± 1.012	
High (≥14%)	73 (23)	0.892 ± 1.110	
Surrogate molecular subtype			<0.001
Luminal A	204 (63)	0.175 ± 0.979	
Luminal B	30 (9)	0.208 ± 0.996	
HER2-positive	22 (7)	0.859 ± 0.978	
Triple negative	67 (21)	1.003 ± 1.121	

Data in parentheses are percentages of the column total. Mammographic density; a = almost entirely fatty, b = scattered fibroglandular, c = heterogeneously dense, d = extremely dense, HER2 = human epidermal growth factor receptor 2, NOS = not otherwise specified.

grade were significantly associated with higher SGR ($P < 0.001$, both). Among the IHC factors, negative HR status and high Ki-67 level were associated with higher SGR ($P < 0.001$, both). Whereas, HER2 status was not significantly associated with SGR. Triple negative breast cancers showed the highest SGR followed by HER2-positive and luminal (luminal B and luminal A) breast cancers ($P < 0.001$). The difference in SGR between triple negative and HER2-positive breast cancers was not statistically significant ($P = 0.939$). Luminal A breast cancers showed significantly lower SGR than triple negative ($P < 0.001$) and HER2-positive breast cancers ($P = 0.015$). Luminal B breast cancers showed significantly lower SGR than triple negative cancers ($P = 0.002$) and showed a trend toward lower SGR than HER2-positive breast cancers ($P = 0.101$).

Parameters showing statistical significance on univariate analysis were used as input variables for multiple linear regression analysis. Among the 6 variables, collinearity was observed between 2 predictor variables of HR status and surrogate molecular subtype ($r = -0.955$, $P < 0.001$), as expected, because the surrogate molecular subtype is mainly determined by HR status. Therefore, 2 different models were used to evaluate the association between clinicopathologic factors and SGR. HR status and surrogate molecular subtype showed an independently significant relationship with SGR in each model (Table 3).

3.4. Tumor diameter changes on serial breast US and comparison with pathology

Changes in maximum tumor diameters between initial and second US images were significantly different among the molecular subtypes ($P < 0.001$) (Table 4). Breast cancers with more aggressive molecular subtypes showed larger diameter changes (triple negative, 2.1 ± 2.6 mm; HER2-positive, 1.9 ± 2.0 mm) than luminal breast cancers (luminal B, 0.6 ± 2.4 mm; luminal A, 0.4 ± 1.6 mm) ($P < 0.005$ for triple negative vs. luminal subtypes; $P = 0.005$ for HER2-positive vs. luminal A; $P = 0.110$ for HER2-positive vs. luminal B). The clinical T stage determined by breast US was more frequently upgraded from T1 to T2 during wait times for surgery in nonluminal breast cancers (14% [3/22] for HER2-positive and 18% [12/67] for triple negative cancers) than in luminal cancers (luminal B, 3% [1/30]; luminal A, 2% [4/204]) ($P < 0.001$) (Figs. 1 and 2).

Correlations and agreements between maximum tumor diameters measured on breast US and pathology are shown in

Table 3

Multiple linear regression analysis to evaluate the association between clinicopathologic factors and specific growth rates of invasive breast cancers.

Variable	β coefficient	Standard error	*P*	VIF
Model 1				
Palpable symptom at diagnosis	0.105	0.121	0.390	1.189
Pathologic T stage	0.250	0.136	0.067	1.167
Histologic grade	0.100	0.101	0.321	1.451
Ki-67	0.115	0.168	0.495	1.592
Hormone receptor	−0.595	0.154	<0.001	1.536
Model 2				
Palpable symptom at diagnosis	0.102	0.122	0.405	1.189
Pathologic T stage	0.238	0.137	0.083	1.168
Histologic grade	0.104	0.102	0.308	1.472
Ki-67	0.079	0.179	0.660	1.790
Surrogate molecular subtype	0.207	0.062	0.001	1.833

Adjusted R^2 was 0.12 and 0.11 for Models 1 and 2, respectively. VIF = variation inflation factor.

Table 4

Changes in maximum tumor diameters and clinical T stage during wait times for surgery according to surrogate molecular subtype.

	Luminal A (n = 204)	Luminal B (n = 30)	HER2-positive (n = 22)	Triple negative (n = 67)	*P*
Time between diagnosis and surgery, days	32.3 ± 11.7	34.5 ± 10.3	32.3 ± 13.0	31.2 ± 11.8	0.647
Changes in maximum tumor diameters, mm	0.4 ± 1.6	0.6 ± 2.4	1.9 ± 2.0	2.1 ± 2.6	<0.001
Clinical T stage*					<0.001
Unchanged	200 (98)	29 (97)	19 (86)	55 (82)	
Upgraded†	4 (2)	1 (3)	3 (14)	12 (18)	

Data are mean ± standard deviation.

* Data are number of lesions with percentages in parentheses. Luminal denotes both luminal A and luminal B subtypes.

† Clinical T stage was upgraded from T1 to T2 during wait times for surgery.

Figure 3. There was a trend toward slightly better correlation and agreement in tumor diameter between the second US and pathology than between the initial US and pathology. The mean difference in tumor diameter between initial US and pathology (initial US diameter – pathologic diameter) was −2.9 ± 4.7 mm, and between second US and pathology (second US diameter – pathologic diameter) was −2.0 ± 4.6 mm. The diameter difference between initial US and pathology was not different according to surrogate molecular subtype (triple negative, −3.9 ± 5.5 mm; HER2-positive, −1.5 ± 3.6 mm; luminal B, −3.6 ± 5.3 mm; and luminal A, −2.6 ± 4.4 mm) ($P = 0.117$).

4. Discussion

In our study, the tumor growth rate of invasive breast cancers during wait times for surgery quantified as SGR was significantly associated with surrogate molecular subtypes ($P = 0.001$). Triple negative breast cancers showed the fastest growth rates followed by HER2-positive breast cancers. Those nonluminal breast cancers, which are more aggressive forms of breast cancer, showed greater changes in maximum tumor diameters between diagnosis and surgery than luminal breast cancers causing more frequent upgrading of the clinical T stage as determined by US. The results of our study are consistent with a previous study, which reported the fastest growth rates in triple negative breast cancers with a shorter sojourn time.[13] To the contrary, a recent study by Yoo et al,[14] which calculated SGR using 2 time point tumor sizes on US before surgery, reported that SGR did not significantly differ according to the molecular tumor subtype. However, they used only 1 dimension of tumors based on the medical records for the calculation of SGR assuming that the tumor shape was a sphere. In our study, 3 perpendicular diameters of tumors on 2-orthogonal US images were independently measured by 3 radiologists and a meticulous comparison of serial US images in the same probe directions was performed. In addition, our study consistently compared the tumor diameters between the patients' initial diagnostic images, not the one performed at the initial visit to a tertiary care center and second images performed 1 day before surgery. Therefore, we were able to obtain information on how much the tumor diameters had

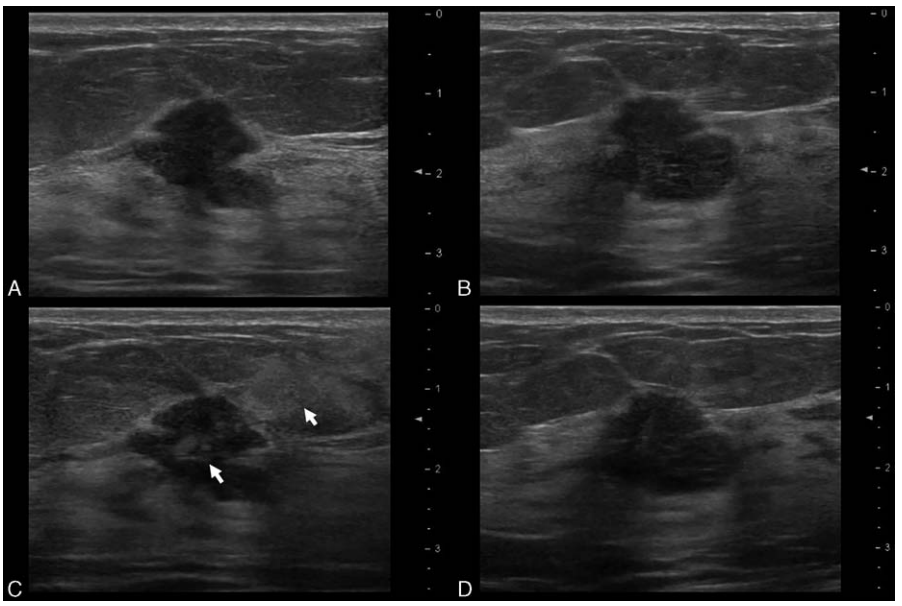

Figure 1. A 53-year-old woman with an invasive ductal carcinoma in the left breast 12 o'clock location detected on screening US examination. On initial US images (A, B) acquired on the same day of core needle biopsy, maximum tumor diameter and volume were 17.1 mm and 2.56 cm^3, respectively. On the second US images (C, D) acquired 1 day before surgery and 21 days after the initial US, the tumor size did not change significantly but only with biopsy changes in and around the tumor (arrows). Maximum tumor diameter and volume were measured as 18.5 mm and 2.58 cm^3, respectively. The calculated SGR was 0.045 %/day. On pathologic examination, the invasive tumor size was 18 mm (pT1) with a histologic grade 3, HR-positive, HER2-negative, low Ki-67 (1%), and luminal A subtype. HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, SGR = specific growth rate; US = ultrasound.

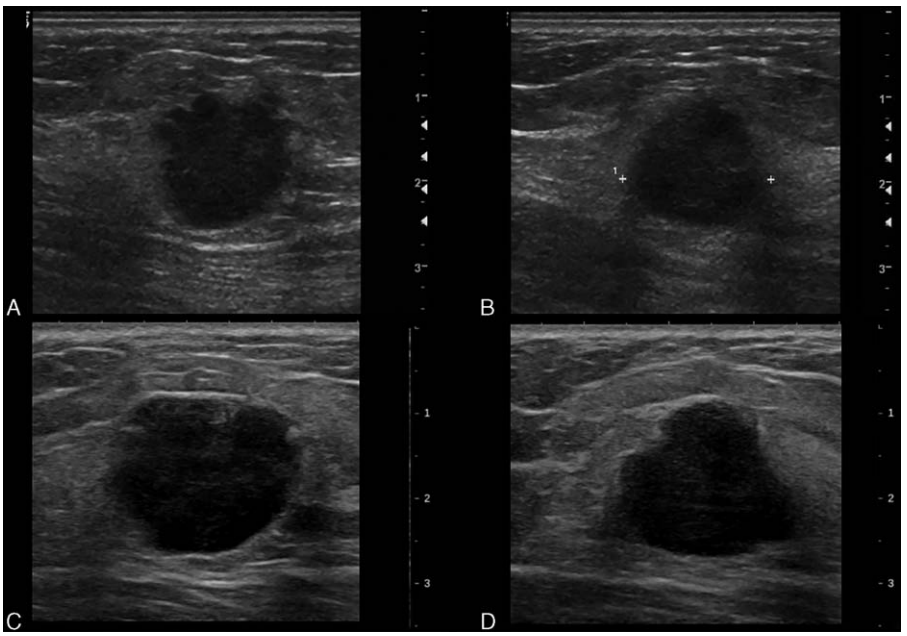

Figure 2. A 31-year-old woman with an invasive ductal carcinoma in the left breast 11 o'clock location presented with a palpable lump. On initial US images (A, B) acquired on the same day of core needle biopsy, maximum tumor diameter and volume were 17.8 mm and 2.53 cm^3, respectively. On the second US images (C, D) acquired 1 day before surgery and 40 days after the initial US, the tumor size increased considerably. Maximum tumor diameter and volume were measured as 23.3 mm and 4.70 cm^3, respectively. The calculated SGR was 1.552 %/day. On pathologic examination, the invasive tumor size was 25 mm (pT2) with a histologic grade 3, HR-negative, HER2-negative, high Ki-67 (15%), and triple negative subtype. HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, SGR = specific growth rate; US = ultrasound.

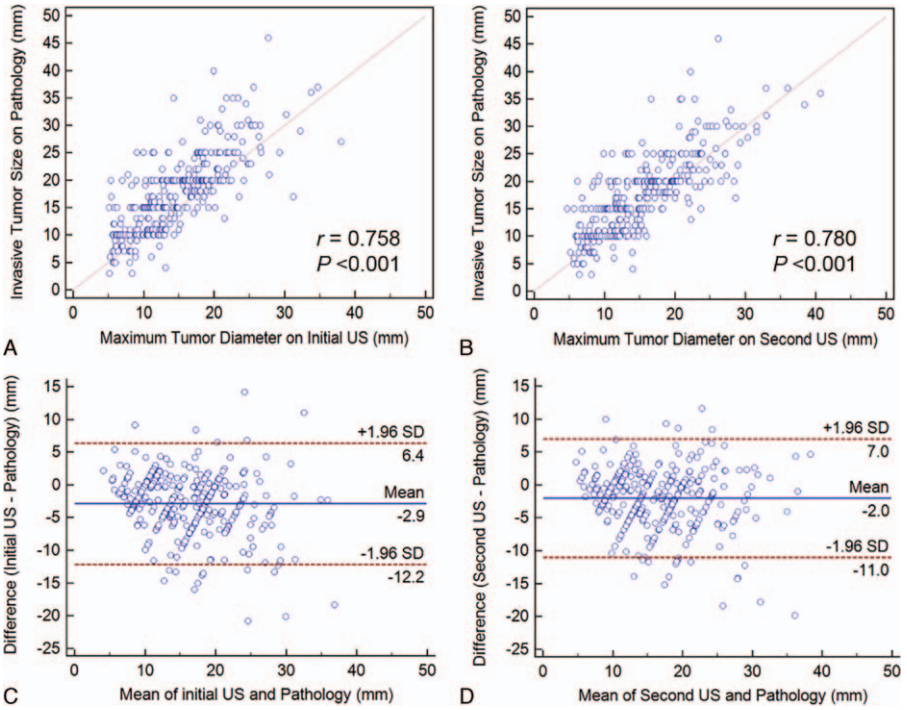

Figure 3. Correlations and agreements between maximum tumor diameters measured on breast US and pathology. Both maximum tumor diameters measured on initial US (A) and second US (B) showed strong linear correlations with invasive tumor size on pathology with slightly higher correlation coefficients for the second US ($r = 0.780$) than the initial US ($r = 0.758$). On Bland–Altman plots, the mean difference (solid lines) between maximum tumor diameters on US and pathology was 2.9 mm for initial US (C) and 2.0 mm for second US (D). The range between 95% limits of agreement (dashed lines) was 18.6 mm for the initial US (C) and 18.0 mm for the second US (D).

changed during wait times for surgery from the patients' perspective.

With regard to the interobserver agreement for tumor diameter measurement, almost perfect agreement was found among the 3 radiologists (ICC, 0.892–0.955). It is known that tumor size assessment by US is accurate and is well correlated with pathologic tumor size, although US slightly underestimates tumor size.[29] In our study, the second US examinations are performed after percutaneous core needle biopsy. Despite concerns over the biopsy effect, which may hamper accurate size measurements, there was a trend toward slightly better correlation between the second US size and pathologic size ($r=$ 0.758) than between the initial US size and pathologic size ($r=$ 0.780). In addition, the difference in tumor diameters with pathology was slightly smaller for the second US (2.0 ± 4.6 mm) than the initial US (2.9 ± 4.7 mm).

The degree of tumor diameter change between diagnosis and surgery (2.1 ± 2.6 mm for triple negative breast cancers and $0.4 \pm$ 1.6 mm for luminal A breast cancers) as well as the tumor diameter difference between US and pathology (2.9 ± 4.7 mm for initial US vs. pathology and 2.0 ± 4.6 mm for second US vs. pathology) was very small in our study. This may have been because of the relatively short time interval between diagnosis and surgery (median, 31 days; range, 8–78 days) at our institution.[1] A previous study by Wagner et al[2] used the difference between the initial imaging size and pathologic size as a surrogate for tumor size progression and reported that the median difference from baseline sonographic tumor size to surgery was 1 mm (range, 75 mm smaller to 83 mm larger at surgery) with modest time intervals. However, they pointed out that assessing the change in tumor size as measured by imaging at diagnosis to the size on imaging immediately before surgery may allow more uniform comparison of disease progression. At our institution, preoperative breast US is routinely performed 1 day before surgery in all breast cancer patients to mark accurate disease extent. Therefore, we can compare tumor diameters on serial US images acquired at the time of diagnosis and surgery and thereby calculate tumor growth rates during wait times for surgery. According to our results, breast cancers showed different growth rates according to the tumor characteristics, although the tumor size change was small in the short time interval. Breast cancers having fast tumor growth rates may present marked tumor progression if the surgery is delayed longer than usual. Therefore, efforts to reduce wait times for surgery should be pursued especially for breast cancers with high tumor growth rates such as triple negative or HER2-positive breast cancers, which may be discriminated from luminal breast cancers through IHC staining for HR status or characteristic imaging features at diagnosis.[30,31]

Our study has several limitations. First, this was a retrospective study performed at a single center, and as we excluded patients who had received neoadjuvant chemotherapy or patients with multifocal or diffuse breast cancers, more advanced stage cancers were not evaluated. Second, we did not evaluate the interobserver variability of US data acquisition. Variability within data acquisition could occur as a result of minor changes in patient's position or the degree of compression. Therefore, we only included cases with serial US image sets in the same probe direction to reduce the bias from inadequate data acquisition. As automated 3-dimensional US scanners are currently installed in many institutions, they could be used to monitor changes in tumor diameter and tumor volumes during wait times for surgery.[32,33] Lastly, the patient series reported in this study was relatively recent with insufficient follow-up data. This reflects our current practice, but does not allow us to determine the effect of tumor growth rates on the patients' long-term outcomes of disease-free and overall survival. In this regard, however, a recent study by Yoo et al[14] demonstrated that SGR measured by US was associated with disease-free survival in breast cancer patients, particularly in the subgroup of patients with an initial tumor size >2 cm.

In conclusion, invasive breast cancers with aggressive molecular subtypes showed faster tumor growth rates and more frequent upgrading of clinical T stage during wait times for surgery. Therefore, it is highly desirable to minimize wait times for surgery in breast cancer patients particularly with triple negative or HER2-positive molecular subtypes.

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References

[1] Bleicher RJ, Ruth K, Sigurdson ER, et al. Preoperative delays in the US Medicare population with breast cancer. J Clin Oncol 2012;30:4485–92.
[2] Wagner JL, Warneke CL, Mittendorf EA, et al. Delays in primary surgical treatment are not associated with significant tumor size progression in breast cancer patients. Ann Surg 2011;254:119–24.
[3] Nessim C, Winocour J, Holloway DP, et al. Wait times for breast cancer surgery: effect of magnetic resonance imaging and preoperative investigations on the diagnostic pathway. J Oncol Pract 2015;11:e131–138.
[4] Bilimoria KY, Ko CY, Tomlinson JS, et al. Wait times for cancer surgery in the United States: trends and predictors of delays. Ann Surg 2011;253:779–85.
[5] Richards MA, Westcombe AM, Love SB, et al. Influence of delay on survival in patients with breast cancer: a systematic review. Lancet 1999;353:1119–26.
[6] Bleicher RJ, Ruth K, Sigurdson ER, et al. Time to surgery and breast cancer survival in the United States. JAMA Oncol 2016;2:330–9.
[7] McCahill LE, Privette A, James T, et al. Quality measures for breast cancer surgery: initial validation of feasibility and assessment of variation among surgeons. Arch Surg 2009;144:455–62.
[8] Del Turco MR, Ponti A, Bick U, et al. Quality indicators in breast cancer care. Eur J Cancer 2010;46:2344–56.
[9] Kaufman CS, Shockney L, Rabinowitz B, et al. National Quality Measures for Breast Centers (NQMBC): a robust quality tool: breast center quality measures. Ann Surg Oncol 2010;17:377–85.
[10] Liederbach E, Sisco M, Wang C, et al. Wait times for breast surgical operations, 2003-2011: a report from the National Cancer Data Base. Ann Surg Oncol 2015;22:899–907.
[11] Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869–74.
[12] Weedon-Fekjaer H, Lindqvist BH, Vatten LJ, et al. Breast cancer tumor growth estimated through mammography screening data. Breast Cancer Res 2008;10:R41.
[13] Ryu EB, Chang JM, Seo M, et al. Tumour volume doubling time of molecular breast cancer subtypes assessed by serial breast ultrasound. Eur Radiol 2014;24:2227–35.
[14] Yoo TK, Min JW, Kim MK, et al. In Vivo Tumor Growth Rate Measured by US in Preoperative Period and Long Term Disease Outcome in Breast Cancer Patients. PLoS One 2015;10:e0144144.
[15] Mehrara E, Forssell-Aronsson E, Ahlman H, et al. Specific growth rate versus doubling time for quantitative characterization of tumor growth rate. Cancer Res 2007;67:3970–5.
[16] Mehrara E, Forssell-Aronsson E, Ahlman H, et al. Quantitative analysis of tumor growth rate and changes in tumor marker level: specific growth rate versus doubling time. Acta Oncol 2009;48:591–7.
[17] Tot T, Gere M, Pekar G, et al. Breast cancer multifocality, disease extent, and survival. Hum pathol 2011;42:1761–9.
[18] Mendelson EB. ACR practice parameter for the performance of a breast ultrasound examination. http://www.acr.org/Quality-Safety/Standards-Guidelines/PracticeGuidelines-by-Modality/Breast-Imaging/~/media/ACR/Documents/PGTS/guidelines/US_Breast.pdf. Accessed on January 3, 2016.

[19] Millet I, Bouic-Pages E, Hoa D, et al. Growth of breast cancer recurrences assessed by consecutive MRI. BMC Cancer 2011;11:155.
[20] Mendelson EB, Bohm-Velez M, Berg WA, et al. Breast Imaging Reporting and Data System. BI-RADS: ultrasound. Reston, VA: American College of Radiology; 2013.
[21] Sickles EA, D'Orsi CJ, Bassett LW, et al. Breast Imaging Reporting and Data System, BI-RADS: mammography. 5th ed. Reston, VA:American College of Radiology; 2013.
[22] Elston CW, 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 2002;41:154–61.
[23] Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual. 7th edNew York:Springer; 2010.
[24] Dowsett M, Nielsen TO, A'Hern R, et al. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst 2011;103:1656–64.
[25] Hammond ME, Hayes DF, Dowsett M, et al. 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;28:2784–95.
[26] Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007;25:118–45.
[27] Goldhirsch A, Wood WC, Coates AS, et al. 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: 1736–47.
[28] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.
[29] Bosch AM, Kessels AG, Beets GL, et al. Preoperative estimation of the pathological breast tumour size by physical examination, mammography and ultrasound: a prospective study on 105 invasive tumours. Eur J Radiol 2003;48:285–92.
[30] Wang Y, Ikeda DM, Narasimhan B, et al. Estrogen receptor-negative invasive breast cancer: imaging features of tumors with and without human epidermal growth factor receptor type 2 overexpression. Radiology 2008;246:367–75.
[31] Kojima Y, Tsunoda H. Mammography and ultrasound features of triple-negative breast cancer. Breast Cancer 2011;18:146–51.
[32] Lee MC, Gonzalez SJ, Lin H, et al. Prospective trial of breast MRI versus 2D and 3D ultrasound for evaluation of response to neoadjuvant chemotherapy. Ann Surg Oncol 2015;22:2888–94.
[33] Brem RF, Tabar L, Duffy SW, et al. Assessing improvement in detection of breast cancer with three-dimensional automated breast US in women with dense breast tissue: the SomoInsight Study. Radiology 2015; 274:663–73.