Received:
09 December 2018

Revised:
18 February 2019

Accepted:
27 February 2019

<https://doi.org/10.1259/bjr.20181032>

Cite this article as:

Yamaguchi K, Hara Y, Kitano I, Hamamoto T, Kiyomatsu K, Yamasaki F, et al. Tumor-stromal ratio (TSR) of invasive breast cancer: correlation with multi-parametric breast MRI findings. *Br J Radiol* 2019; **92**: 20181032.

FULL PAPER

Tumor-stromal ratio (TSR) of invasive breast cancer: correlation with multi-parametric breast MRI findings

¹KEN YAMAGUCHI, MD, ²YUKIKO HARA, MD, ²ISAO KITANO, MD, ³TAKAHIRO HAMAMOTO, MD, ⁴KAZUMITSU KIYOMATSU, MD, ⁵FUMIO YAMASAKI, MD, ¹RYOKO EGASHIRA, MD, ¹TAKAHIKO NAKAZONO, MD and ¹HIROYUKI IRIE, MD

¹Department of Radiology, Faculty of Medicine, Saga University, Saga, Japan

²Department of Radiology, Saga Central Hospital, Saga, Japan

³Ajisai Clinic, Ekimaechuo, Saga, Japan

⁴Department of Surgery, Saga Central Hospital, Saga, Japan

⁵Department of Pathology, Saga Central Hospital, Saga, Japan

Address correspondence to: Dr Ken Yamaguchi

E-mail: yamaguk@cc.saga-u.ac.jp

Objective: To correlate the tumor-stromal ratio (TSR) of invasive breast cancer and MRI findings.

Methods: This study was approved by our institutional review board. 126 consecutive patients with surgically proven invasive breast cancer were included. All patients underwent MRI exams including short-tau inversion-recovery (STIR) T_2 weighted imaging, diffusion-weighted imaging (DWI) and post-contrast dynamic imaging. The mean signal intensity (SI) and apparent diffusion coefficient (ADC) value of each lesion were measured. To objectively evaluate the STIR images, the ratio of the SI of the lesion to the muscle (L/M ratio) was also measured. Percentages of MRI kinetic parameters obtained from dynamic images were also measured. The TSR was defined as the percentage of the stromal component, and categorized into high-stroma ($\geq 50\%$) and low-stroma ($< 50\%$) groups. Inter-group differences in

the SI, L/M ratio, ADC value and percentages of kinetic parameters were examined.

Results: The SI and L/M ratio of the high-stroma group were significantly lower than those of the low-stroma group (208.64 vs 331.86 for SI, 5.69 vs 9.31 for L/M ratio) ($p < 0.001$). The high-stroma group had significantly lower percentages of a washout pattern (25% vs 34.7%) ($p = 0.012$) and significantly higher percentages of a persistent pattern (36.92% vs 28.26%) ($p = 0.044$). There were no significant correlations between the TSR and ADC value.

Conclusion: STIR and dynamic sequence of breast MRI reflects the stromal component of invasive breast cancer.

Advances in knowledge: This is the first study to correlate TSR and MRI findings. STIR and post-contrast dynamic study correlated with the stromal component of breast cancer.

INTRODUCTION

Breast MRI has played many important roles in breast cancer management.^{1–6} In addition to its general assistance in breast cancer diagnosis and staging, MRI has more recently been adapted for use in classifications for molecular subtypes of breast cancers.^{7,8} Breast cancer is a heterogeneous disease. Its malignant behavior is based on many kinds of molecular markers including angiogenesis, cell proliferation, tumor metabolism and hormone receptor status. In addition to these molecular markers, fibrosis of breast cancer has been a focus in the field of breast cancer pathology.^{9,10} Several pathological studies have reported that cancer associated stroma, which mainly consist of fibroblasts and extracellular matrix, influences tumor malignant behavior including progression, invasion and metastasis, and Cancer Associated Fibroblasts

(CAFs) that exist in the cancer stroma increase the fibrous stromal component. This increased stromal component and proteases which is secreted from both cancer cells and mesenchymal cells cause epithelial tissue disruption and extracellular matrix remodeling.^{9,10} Several pathological studies also reported that the tumor-stromal ratio (TSR) of invasive breast cancer is a poor prognostic factor, which means that prognosis of breast cancer with high stroma component is much worse than that with low stroma component.^{9,10} MRI has high tissue resolution and its images reflect the stromal components of the tumor.^{11,12} Only few studies have reported a correlation between stromal components, particularly fibrosis of breast cancer, and MRI images.^{11,13,14} However, there is no study to

Table 1. MRI parameters

	STIR T_2 WI with FS	T_1 WI with FS	DWI ($b = 0, 800$)	Dynamic study with FS (One pre and six post-contrast series)
Orientation	Coronal	Coronal	Axial	Coronal
Sequence	SE/IR	SE	ss-EPI	GR
TR/TE	7100/76	672/10	3000/75	5.53/2.1
Flip angle (°)	170	75	90	14.87
Echotrain length	11	1	1	1
Matrix	384 × 230	384 × 230	128 × 70	387 × 176
Thickness (mm)	5	5	5	1.3
Voxel size (mm)	0.8 × 0.6 × 5.0	0.8 × 0.5 × 5.0	3.3 × 2.5 × 5.0	1.2 × 0.8 × 1.3

DWI, diffusion-weighted imaging; FS, Fat Suppression; GR, Gradient Echo; SE, Spin Echo; STIR, Short-Tau Inversion-Recovery; T_1 WI, T_1 weighted imaging; T_2 WI, T_2 weighted imaging; ss-EPE, Single shot-Echo Planar Imaging.

correlate TSR and MRI findings. The purpose of our study was to examine the correlation between the TSR of invasive breast cancer and MRI findings.

METHODS AND MATERIALS

Patients

This retrospective study was approved by the institutional review board at saga central hospital and ajsai clinic, and written informed consent was waived. From January 2013 to December 2015, 190 patients with surgically and histopathologically proven breast lesions underwent breast MRI at saga central hospital and ajsai clinic. Of these, we excluded benign cases, DCIS cases, cases undergoing neoadjuvant chemotherapy before surgery, cases without complete pathological data and cases with technical error (severe artifact and failure of fat suppression). In addition, if disease was multifocal, only the index lesion was used for analysis.

MRI technique

During the study period, all examinations were performed using a 1.5 T MR system (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany) with a dedicated two-channel breast coil. The sequence parameters are shown in Table 1. In the dynamic study, the contrast material was injected intravenously [0.1 mmol/kg of gadoterate meglumine (Magnescope, Fuji Pharma, Tokyo)] and followed by a 20 ml saline flush by hand injection. Although hand injection was performed, injection rate was set at 2 ml s⁻¹ with using a stopwatch. In the dynamic contrast-enhanced study, the first post-contrast phase was scanned just after the contrast material injection.

Pathology

Based on a previous study,⁹ the TSR was defined as the percentage of stromal cells in tumor tissue and was retrospectively measured by one breast pathologist (30 years of experience in breast pathology). Obvious necrosis, mucin deposition area and area with *in situ* components were ignored. Based on the results, patients were categorized into either a high-stroma (stromal cell ≥ 50%) or low-stroma (stromal cell < 50%) group. These analyses were performed using the most invasive part of the whole slide based on a previous study.⁹

Postprocessing and statistical analysis

Two breast radiologists (21 and 12 years of experience in breast MRI, respectively) manually traced the region of interest (ROI) in the invasive breast cancer on STIR images with consensus, and the mean signal intensity (SI) of each lesion was measured. Although obvious necrosis, mucin deposition area and area with *in situ* components were ignored and the most invasive part of whole slide was used in pathological analysis, these components could not be completely distinguished from other stromal components in MRI images. Therefore, each ROI was placed over as much of the lesion as possible on the slice showing the maximum diameter. For objective evaluation, the ratio of the SI of the lesion to the pectoralis muscle (L/M ratio) was also measured. The area of each ROI of muscle was set up to 38.76 mm². Similarly, the ROI was traced on an apparent diffusion coefficient (ADC) map based on the DWI, and the ADC value of each lesion was measured. In addition, the distribution of kinetic parameters in terms of the percent volume for six kinetic types (slow, medium and fast at the early phase; persistent, plateau and washout at the delayed phase) relative to the two-dimensional segmented tumor at the slice of maximum diameter was also semi-automatically measured using a scatter-plotting system at a dedicated workstation (PMview; JMAC, Sapporo, Japan).

In correlations between stroma group and various prognostic markers of invasive breast cancer, we used the χ^2 test for the statistical evaluation of the relationship between high- or low-stroma group and estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), nuclear grade, histological grade, intrinsic subtype and lymph node (LN) status. We also used the Wilcoxon rank sum test for the statistical evaluation of the relationship between high- or low-stroma group and progression marker (ki 67).

In correlations between stroma group and MRI findings (SI, L/M ratio, percentages of kinetic component and ADC value), we used the Wilcoxon rank sum test. In addition, Spearman's rank correlation test was used for the statistical evaluation of the relationship between SI, L/M ratio and percentages of kinetic component with percentages of stromal components. *p*-values < 0.05 were considered significant. If there was

Table 2. Correlations between high- or low-stroma group and various prognostic markers of invasive breast cancer

		High-stroma (<i>n</i> = 57)	Low-stroma (<i>n</i> = 69)	<i>P</i> value
ER	Positive	51	56	0.22
	Negative	6	13	
PgR	Positive	45	52	0.676
	Negative	12	17	
HER2	Positive	7	8	1
	Negative	50	61	
Progression marker (Ki67)		10% (median)	15% (median)	0.098
Nuclear grade	1	33	37	0.541
	2	13	13	
	3	11	19	
Histological grade	1	15	17	0.484
	2	35	38	
	3	7	14	
Intrinsic subtype	Luminal A	38	34	0.101
	Luminal B	13	22	
	HER2-positive	3	2	
	TN	3	11	
Lymph node metastasis	positive	13	11	0.328
	negative	44	58	

ER, estrogen-receptor; TN, Triple Negative.

significance, receiver operating characteristic (ROC) analysis was additionally used to evaluate the diagnostic performance of each value.

RESULTS

Totally, 126 patients (median age: 55, range: 29–90 years old) with 126 invasive breast cancers were included in this study.

All pathology data were based on pathological reports. Of the 126 invasive breast cancers, there were 111 cases of invasive ductal carcinoma, 7 cases of mucinous carcinoma, 2 cases of invasive lobular carcinoma, 2 cases of invasive micropapillary carcinoma, 1 case of invasive carcinoma with mixed ductal and lobular components, 1 case of apocrine carcinoma, 1 case of solid papillary carcinoma and 1 case of invasive cribriform carcinoma. The median size of these carcinomas was 20 mm (range 5–100 mm). These invasive breast cancers were classified into four intrinsic subtypes according to the St. Gallen International Expert Consensus 2013.¹⁵ Of the 126 cases, 72 were classified as luminal A-like type, 35 as luminal B-like type, 5 as human epidermal growth factor receptor 2 (HER2)-positive type, and 14 as triple-negative cancer.

Correlations between the high- or low-stroma group and different prognostic markers of invasive breast cancer are shown in Table 2. There were no significant correlations between stroma group and any prognostic markers of invasive breast cancer.

The SI of the high-stroma group (median: 208.64) was significantly lower than that of the low-stroma group (median: 331.36) ($p < 0.001$). In addition, the L/M ratio of the high-stroma group (median: 5.69) was significantly lower than that of the low-stroma group (median: 9.31) ($p < 0.001$). In ROC analysis, the sensitivity and specificity for differentiating the high-stroma group from the low-stroma group using a cutoff L/M ratio of 7.87 were 92.98 and 66.67%, respectively. In Spearman's rank correlation test, there were significant correlation between percentages of stromal components and SI or L/M ratio (correlation coefficient; -0.5546 and -0.6241 , respectively. $p > 0.0001$ in each value). Correlations between percentage of stromal components and SI or L/M ratio are shown in Figure 1. The high-stroma group had significantly lower percentages of a washout pattern (median: 25 vs 34.7%) ($p = 0.012$) and significantly higher percentages of a persistent pattern (median: 36.92 vs 28.26%) ($p = 0.044$). In ROC analyses, the sensitivity and specificity for differentiating the high-stroma group from low-stroma group using 31.37 as the cutoff percentage of washout pattern were 66.67 and 59.42%; using 34.33 as the cutoff percentage of persistent pattern, they were 54.39 and 66.67%, respectively. In Spearman's rank correlation test, there were not significant correlation between percentages of stromal components and percentages of six (fast, medium, slow, washout, plateau and persistent) kinetic component (correlation coefficient; 0.0377 , -0.0272 , -0.0855 , -0.0221 , 0.0143 and -0.014 , respectively. p -value; 0.6755 , 0.7625 , 0.3411 ,

Figure 1. Correlations between percentage of stromal components and SI or L/M ratio. There were negative correlations between percentage of stromal components and SI or L/M ratio. SI, signal intensity.

0.8061, 0.8739 and 0.8762, respectively). There was no significant correlation between the TSR and ADC value.

Correlations between high- or low-stroma group and the SI, L/M ratio, distribution of kinetic parameters and ADC value of invasive breast cancer are shown in Table 3. Representative MRI images of the high- and low-stroma group are shown in Figures 2 and 3.

DISCUSSION

Recently, the tumor microenvironment including fibrosis has been a focus in pathological studies, with accumulating evidence that this tumor microenvironment influences malignant tumor behavior including progression, invasion and metastasis.¹⁶ Many components (fibrosis, adipocytes, inflammation, etc.) are included in the tumor microenvironment. Among them, several studies have focused on tumor fibrosis and reported that the TSR of invasive breast cancer is a poor prognostic factor. CAFs that exist in the cancer stroma increase the fibrous stromal component. This increased stromal component and proteases which is secreted from both cancer cells and mesenchymal cells cause epithelial tissue disruption and extracellular matrix

remodeling.^{9,10} Although there were no significant correlations between stromal group and any prognostic markers of invasive breast cancer in this study, fibrosis of breast cancer may be independent prognostic factor.

In this study, we showed that STIR and post-contrast dynamic study images of breast MRI are correlated with the stromal component of invasive breast cancer (TSR). Several previous studies have reported correlations between MRI findings and fibrosis of breast cancer.^{11,13,14} Matsubayashi et al reported that the degree of stromal fibrosis was correlated with the lesion-to-muscle SI ratio and that T_2 weighted or STIR images reflect fibrous changes with a low SI, the same trend found in our results.¹¹ Indeed, in not just in breast cancer, but also in other type of tumor, it has also been reported that tumors with a rich fibrous component tend to show low SI in T_2 weighted images.^{17,18}

Matsubayashi et al also reported that the degree of fibrosis correlated with the post-contrast dynamic enhancement pattern.¹¹ Similarly, in our present study, the stroma-associated percentage of the invasive breast cancer was correlated with the

Table 3. Correlations between high- or low-stroma group and SI, L/M ratio, distribution of kinetic parameters and ADC value of invasive breast cancer

		High-stroma (<i>n</i> = 57)	Low-stroma (<i>n</i> = 69)	<i>p</i> -value
SI		208.64 (89.75–410.1)	331.36 (115.25–1529.13)	<u><0.001</u>
L/M ratio		5.69 (2.4–10.7)	9.31 (2.91–49.86)	<u><0.001</u>
Percentages of kinetic component	Fast	77.11% (0–100)	82.21% (29.15–97.84)	0.152
	Medium	22.06% (0–100)	14.4% (1.29–60.18)	0.107
	Slow	1.49% (0–24.72)	1.37% (0–22.22)	0.834
	Washout	25% (0–93.18)	34.7% (0–80.54)	<u>0.012</u>
	Plateau	33.33% (0–100)	33.84% (6.36–58.49)	0.977
	Persistent	36.92% (0–100)	28.26% (6.37–93.18)	<u>0.044</u>
ADC value		1.04 (0.409–1.498)	1.039 (0.609–2.219)	0.598

ADC, apparent diffusion coefficient; SI, signal intensity.

ADCs are given in $\times 10^{-3} \text{ mm}^2$.

Values of MRI findings are presented as median and values in () are minimum-maximum values.

Figure 2. A 65-year-old female with invasive ductal carcinoma (high-stroma group). A post-contrast, fat-suppressed, coronal T_1 weighted image shows an irregular-shaped mass with an irregular margin and homogeneous enhancement (a). In the STIR image, the mass showed low intensity (left side-panel). Its signal intensity was 143.2 and the L/M ratio was 4.05 (b). In color-coded dynamic enhanced MRI (left side-panel), the mass showed a predominantly persistent pattern (blue: persistent pattern; green: plateau pattern). In scatter plotting graph (right side-panel), the mass also showed a predominantly persistent pattern (washout: 9.6%; plateau: 25.42%; persistent: 64.97%) (c). In the ADC map, the ADC value of the mass was $0.543 \times 10^{-3} \text{ mm}^2$ (d). In the photomicrograph, the mass was revealed to have a rich fibrous component (e). ADC, apparent diffusion coefficient; STIR, short-tau inversion-recovery.

terms of the delayed-phased kinetic pattern. In brief, the high-stroma group had significantly lower percentages of a washout pattern (25% vs 34.7%) and higher percentages of a persistent pattern (36.92% vs 28.26%). They reported that the enhancement ratio of Early to Delayed images (E/D ratio) in tissues with moderate fibrosis is significantly lower than that in tissues with minimal fibrosis.¹¹ Contrast material is filled in the third space of tissue,¹⁹ so it is speculated that gradual enhancement of the delayed phase is larger in stroma-rich tissue compared to stroma-poor tissue.

In this study, there was no significant correlation between the TSR and ADC value. Ko et al studied the relationship between the ADC

Figure 3. A 59-year-old female with invasive ductal carcinoma (low-stroma group). A post-contrast, fat-suppressed, coronal T_1 weighted image showed an oval-shaped mass with a circumscribed margin and heterogeneous enhancement (a). In the STIR image, the mass was high intensity, with a signal intensity of 552.1 (left side-panel) and the L/M ratio was 15.27 (b). In color-coded dynamic enhanced MRI (left side-panel), the mass predominantly showed a washout pattern (orange: washout pattern; green: plateau pattern). In scatter plotting graph (right side-panel), the mass also showed a predominantly washout pattern (washout: 55.52%; plateau: 35.23%; persistent: 12.25%) (c). In the ADC map, the ADC value of the mass was $0.961 \times 10^{-3} \text{ mm}^2$ (d). In the photomicrograph, the mass was revealed to have a scant fibrous component (e). ADC, apparent diffusion coefficient; STIR, short-tau inversion-recovery.

values and TSR in ER-positive breast cancer.¹³ In their study, ADC values were significantly lower in the stroma-poor group.¹³ They speculated that stroma-poor tumors have greater cellularity, which causes a subsequent decrease in ADC values.¹³ In contrast, our study showed no significant correlation. This difference may be due to the differences in study populations. They recruited only ER-positive breast cancers.¹³ On the other hand, our study included all types of invasive breast cancers to recruit large numbers. Numbers included both studies were also different. Further studies with large numbers are needed.

Recently, therapies aimed at CAFs and fibrosis in breast cancer have been examined at both *in vitro* and *in vivo* levels.^{20,21} These studies used pirfenidone, which is used for the treatment of idiopathic

pulmonary fibrosis as an antifibrotic drug. Takai et al reported that CAFs promoted tumor growth, fibrosis and lung metastasis with transforming growth factor- β activation and that pirfenidone inhibited fibrosis on an *in vitro* level.²⁰ They also reported that pirfenidone inhibited *in vivo* tumor growth and lung metastasis in combination with doxorubicin.²⁰ Polydorou et al reported that pirfenidone reduced collagen and hyaluronan levels in breast cancer.²¹ As a result, blood vessel function and perfusion increased, and the antitumor efficacy of doxorubicin improved.²¹ Thus, antifibrotic drugs may be beneficial in clinical settings. In such a situation, MRI which can evaluate tumor fibrosis could be used as monitor of the response to antifibrotic therapy.

Our study has some limitations. One is the lack of detailed pathologic correlation. If possible, we have to confirm that location of fibrosis in pathology is corresponds with low signal intensity area in STIR image and persistent pattern in dynamic MRI. A second

limitation is that we used a 1.5 T MR system with a two-channel breast coil. If we used a 3 T MR system with a higher channel breast coil for a higher signal-to-noise ratio, more meaningful results could be obtained. A third limitation is that our workstation could only calculate two-dimensional segmentation. If three-dimensional segmentation could be calculated, more meaningful results could be obtained. A fourth limitation is the relatively small number of cases ($n = 126$). Although some significant results were obtained, more meaningful results could be obtained with a larger number of cases.

In conclusion, the high-stroma group of invasive breast cancer had significantly lower SI and L/M ratio compared to the low-stroma group. The high-stroma group also had lower percentages of a washout pattern and higher percentages of a persistent pattern. STIR and post-contrast dynamic study images of breast MRI were correlated with the stromal component of invasive breast cancer.

REFERENCES

1. Fischer U, Kopka L, Brinck U, Korabiowska M, Schauer A, Grabbe E. Prognostic value of contrast-enhanced MR mammography in patients with breast cancer. *Eur Radiol* 1997; **7**: 1002–5. doi: <https://doi.org/10.1007/s003300050240>
2. Fischer U, Kopka L, Grabbe E. Breast carcinoma: effect of preoperative contrast-enhanced MR imaging on the therapeutic approach. *Radiology* 1999; **213**: 881–8. doi: <https://doi.org/10.1148/radiology.213.3.r99dc01881>
3. Van Goethem M, Schelfout K, Kersschot E, Colpaert C, Verslegers I, Biltjes I, et al. MR mammography is useful in the preoperative locoregional staging of breast carcinomas with extensive intraductal component. *Eur J Radiol* 2007; **62**: 273–82. doi: <https://doi.org/10.1016/j.ejrad.2006.12.004>
4. Lehman CD, Gatsonis C, Kuhl CK, Hendrick RE, Pisano ED, Hanna L, et al. MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer. *N Engl J Med* 2007; **356**: 1295–303. doi: <https://doi.org/10.1056/NEJMoa065447>
5. Orel SG, Schnall MD. MR imaging of the breast for the detection, diagnosis, and staging of breast cancer. *Radiology* 2001; **220**: 13–30. doi: <https://doi.org/10.1148/radiology.220.1.r01jl3113>
6. Yamaguchi K, Schacht D, Sennett CA, Newstead GM, Imaizumi T, Irie H, et al. Decision making for breast lesions initially detected at contrast-enhanced breast MRI. *AJR Am J Roentgenol* 2013; **201**: 1376–85. doi: <https://doi.org/10.2214/AJR.12.8953>
7. Trop I, LeBlanc SM, David J, Lalonde L, Tran-Thanh D, Labelle M, et al. Molecular classification of infiltrating breast cancer: toward personalized therapy. *Radiographics* 2014; **34**: 1178–95. doi: <https://doi.org/10.1148/rg.345130049>
8. Yamaguchi K, Abe H, Newstead GM, Egashira R, Nakazono T, Imaizumi T, et al. Intratumoral heterogeneity of the distribution of kinetic parameters in breast cancer: comparison based on the molecular subtypes of invasive breast cancer. *Breast Cancer* 2015; **22**: 496–502. doi: <https://doi.org/10.1007/s12282-013-0512-0>
9. de Kruif EM, van Nes JGH, van de Velde CJH, Putter H, Smit VTHBM, Liefers GJ, et al. Tumor-stroma ratio in the primary tumor is a prognostic factor in early breast cancer patients, especially in triple-negative carcinoma patients. *Breast Cancer Res Treat* 2011; **125**: 687–96. doi: <https://doi.org/10.1007/s10549-010-0855-6>
10. Dekker TJA, van de Velde CJH, van Pelt GW, Kroep JR, Julien J-P, Smit VTHBM, et al. Prognostic significance of the tumor-stroma ratio: validation study in node-negative premenopausal breast cancer patients from the EORTC perioperative chemotherapy (POP) trial (10854). *Breast Cancer Res Treat* 2013; **139**: 371–9. doi: <https://doi.org/10.1007/s10549-013-2571-5>
11. Matsubayashi RN, Imanishi M, Nakagawa S, Takahashi R, Akashi M, Momosaki S, et al. Breast ultrasound elastography and magnetic resonance imaging of fibrotic changes of breast disease: correlations between elastography findings and pathologic and short tau inversion recovery imaging results, including the enhancement ratio and apparent diffusion coefficient. *J Comput Assist Tomogr* 2015; **39**: 94–101. doi: <https://doi.org/10.1097/RCT.000000000000155>
12. Tozaki M, Fukuda K, Suzuki M. Dynamic high-spatial-resolution MR imaging of invasive ductal carcinoma: influence of histological scirrhous component on Mr descriptors. *Magn Reson Med Sci* 2006; **5**: 137–46. doi: <https://doi.org/10.2463/mrms.5.137>
13. Ko ES, Han B-K, Kim RB, Cho EY, Ahn S, Nam SJ, et al. Apparent diffusion coefficient in estrogen receptor-positive invasive ductal breast carcinoma: correlations with tumor-stroma ratio. *Radiology* 2014; **271**: 30–7. doi: <https://doi.org/10.1148/radiol.13131073>
14. Van Goethem M, Hufkens G, Verslegers I, Van Marck V, Biltjes I, Parizel PM. The fibrotic focus in MR-mammography. *Eur J Radiol* 2012; **81 Suppl 1** (Suppl 1): S179–S180. doi: [https://doi.org/10.1016/S0720-048X\(12\)70073-6](https://doi.org/10.1016/S0720-048X(12)70073-6)
15. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2013. *Ann Oncol* 2013; **24**: 2206–23. doi: <https://doi.org/10.1093/annonc/mdt303>
16. Korkaya H, Liu S, Wicha MS. Breast cancer stem cells, cytokine networks, and the tumor microenvironment. *J Clin Invest* 2011; **121**: 3804–9. doi: <https://doi.org/10.1172/JCI57099>
17. Imaoka I, Wada A, Kaji Y, Hayashi T, Hayashi M, Matsuo M, et al. Developing an Mr imaging strategy for diagnosis of ovarian masses. *Radiographics* 2006; **26**:

- 1431–48. doi: <https://doi.org/10.1148/rg.265045206>
18. Braschi-Amirfarzan M, Keraliya AR, Krajewski KM, Tirumani SH, Shinagare AB, Hornick JL, et al. Role of imaging in management of desmoid-type fibromatosis: a primer for radiologists. *Radiographics* 2016; **36**: 767–82. doi: <https://doi.org/10.1148/rg.2016150153>
19. Bellin M-F, Van Der Molen AJ. Extracellular gadolinium-based contrast media: an overview. *Eur J Radiol* 2008; **66**: 160–7. doi: <https://doi.org/10.1016/j.ejrad.2008.01.023>
20. Takai K, Le A, Weaver VM, Werb Z. Targeting the cancer-associated fibroblasts as a treatment in triple-negative breast cancer. *Oncotarget* 2016; **7**: 82889–901. doi: <https://doi.org/10.18632/oncotarget.12658>
21. Polydorou C, Mpekris F, Papageorgis P, Voutouri C, Stylianopoulos T. Pirfenidone normalizes the tumor microenvironment to improve chemotherapy. *Oncotarget* 2017; **8**: 24506–17. doi: <https://doi.org/10.18632/oncotarget.15534>