Original Article

Background Parenchymal Enhancement and Fibroglandular Tissue Proportion on Breast MRI: Correlation with Hormone Receptor Expression and Molecular Subtypes of Breast Cancer

Mesut Öztürk[1], Ahmet Veysel Polat[1], Yurdanur Süllü[2], Leman Tomak[3], Ayfer Kamalı Polat[4]

[1]Department of Radiology, Ondokuz Mayıs University School of Medicine, Samsun, Turkey
[2]Department of Pathology, Ondokuz Mayıs University School of Medicine, Samsun, Turkey
[3]Department of Medical Biostatistics, Ondokuz Mayıs University School of Medicine, Samsun, Turkey
[4]Department of General Surgery, Ondokuz Mayıs University School of Medicine, Samsun, Turkey

ABSTRACT

Objective: To assess the relationship between background parenchymal enhancement (BPE) and fibroglandular tissue (FGT) proportion on breast magnetic resonance imaging (MRI) and hormone receptor expression and molecular subtypes in invasive breast cancer.

Materials and Methods: This retrospective study enrolled 75 breast cancer patients who underwent breast MRI before treatment. T1-weighted images were reviewed to determine the FGT proportion, and contrast-enhanced fat-suppressed T1-weighted images were reviewed to determine BPE. Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2-neu (HER2) status, and molecular subtypes of the tumors were compared with the BPE and FGT proportions.

Results: Women with high BPE tended to have increased rate of ER and PR positive tumors (p=0.018 and p=0.013). FGT proportion was associated with ER positivity (p=0.009), but no significant differences between FGT proportion and PR positivity were found (p=0.256). There was no significant difference between HER2 status and any of the imaging features (p=0.453 and p=0.922). For premenopausal women, both FGT proportion and BPE were associated with molecular subtypes (p=0.025 and p=0.042). FGT proportion was also associated with BPE (p<0.001).

Conclusion: In women with invasive breast cancer, both high FGT containing breasts and high BPE breasts tended to have ER positive tumors.

Keywords: Breast neoplasms, magnetic resonance imaging, molecular subtypes, enhancement, hormone receptor

Introduction

Breast cancer is the most common malignancy of women with a life-time risk up to 12% in USA (1). It is the second most common cause of death from cancer in women (2). In recent years, advancement in the knowledge of the biology of breast cancer has contributed to better understanding the nature of the disease. For therapeutic reasons, breast cancer is divided into four different molecular subtypes using molecular biomarkers: estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor 2 (HER2). Four molecular subtypes are identified: Luminal A, Luminal B, HER2 positive, and Triple Negative (3). Different subtypes present with distinct epidemiological risk factors, distinct disease prognoses, and different responses to systemic and local therapy (4-8). This knowledge has opened a new door in disease management toward personalized therapy. For example, luminal A cancers require hormonotherapy whereas triple negative tumors respond better to chemotherapy (3). Trastuzumab, which is directed against the HER2-neu receptor, is considered in the treatment of HER2 positive tumors (3). Luminal A and luminal B subtypes are more likely to develop bone metastases whereas triple negative subtypes are more likely to develop lung and brain metastases (9).

Breast MRI is a common diagnostic tool in the management of breast diseases. It can be used for screening in a high-risk population, for determining the disease extent, or for problem solving to contribute in discordant results of mammography, ultrasonography or clinical findings. FGT proportion, which refers to the proportion of FGT to fat tissue of the breast, and BPE, which refers to the enhancement of normal breast parenchyma after contrast agent administration, are two imaging features of breast MRI. Breast density which reflects FGT composition is a well-known risk factor for breast malignancy. Women having a high amount of FGT content are also more likely to develop breast cancer (10). Similarly, a recent study reported that moderate or marked BPE is associated with a greater risk of developing breast cancer than minimal or mild BPE (11). Considering those known risk factors and the spectrum of breast cancers, one may suspect that FGT proportion and BPE of the same molecular subtypes may have some common properties. If this relationship is demon-

strated, we may further increase our knowledge of which mechanism the FGT proportion and BPE influence the risk of developing breast cancer. Furthermore, it could be used for guiding the initial treatment planning and predicting the disease prognosis. This is still unclear and more studies are needed to determine whether the FGT proportion or BPE can predict receptor positivity, which also determines the molecular subtypes of the breast cancer. Therefore, in this retrospective study, we aimed to demonstrate whether there is any correlation between the FGT proportion and BPE of cancerous breast tissue and hormone receptor expression and molecular subtypes of invasive breast cancer.

Materials and Methods

This study was approved by the institutional review board. Owing to the retrospective nature of the study, the requirement for informed consent was waived.

Patient selection and characteristics

Retrospective analysis of the medical records between January 2010 and April 2016 of our university hospital computer database was queried. A total of 115 patients who had pre-treatment breast MRI were identified. Of these, 40 patients were excluded from the study because of unavailable or poor quality of MR images (n=5), previous history of breast cancer (n=13), unknown receptor status (n=12), and unknown menopausal status (n=10). The remaining 75 cases were enrolled in the study. Eligible patients had not used any hormone replacement or anti-hormonal therapy within the 12 months before the MRI was performed. Clinical indications for breast MRI were either for problem solving after inconclusive breast ultrasound or mammography or for planning of the surgical approach preoperatively.

It is a routine daily practice for our breast diseases imaging department to conduct a questionnaire survey of the patients who are admitting for any breast examination. Patients are asked about their menopausal status, history of hormonal therapy, and presence of history of any previous breast cancer. Data about those information were collected from this archive.

Breast MRI technique and MRI interpretation

Breast MRI examinations were performed using two different 1.5 T MRI systems (Achieva; Philips Healthcare, Best, the Netherlands and Siemens Magnetom Symphony Quantum, Erlangen, Germany). All patients were examined in the prone position on a dedicated bilateral breast coil. Routine MRI protocol including axial T1-weighted turbo spin echo sequence and axial T1-weighted fat-suppressed dynamic contrast-enhanced 3D spoiled gradient echo sequence were obtained from all the patients (Table 1). A standard dosage of 0.1 mmoL/kg contrast agent was administered using an automatic injector with a flow rate of 2 mL/s following 20 ml of saline flush. One pre-contrast and five post-contrast image series for every one minute were obtained. After image acquisition, subtracted images were obtained by subtracting pre-contrast images from contrast-enhanced ones on a pixel-by-pixel basis.

A radiologist with six years of experience in breast imaging interpreted the MRI examinations. The FGT proportion was determined by using axial T1-weighted MR images. BPE was determined by using the first post-contrast T1-weighted subtracted images. The radiologist was blinded to the hormone receptor expression and molecular subtypes of the tumors, age, and menopausal status of the patients.

The MRI examinations were read according to the lexicon of the American College of Radiology Breast Imaging and Reporting Data System (BIRADS) (12). Axial T1-weighted images were evaluated to deter-

Table 1. Parameters of the MRI examinations

Parameters	Scanner 1[1]		Scanner 2[2]	
	T1-weighted TSE[3]	T1-weighted 3D SGE[4]	T1-weighted TSE[3]	T1-weighted 3D SGE[4]
TR/TE (ms)	412 / 10	6.9 / 3.4	510 / 11	4.6 / 1.4
Slice thickness (mm)	3	1	4	1
FOV (mm)	340	340	320	320
Matrix size (mm)	340 x 270	340 x 337	288 x 384	336 x 448
Flip Angle	90	12	90	10
NEX	2	1	2	1

[1] : Achieva; Philips Healthcare, Best, the Netherlands

[2] : Siemens Magnetom Symphony Quantum, Erlangen, Germany

[3] : Axial T1-weighted turbo spin echo sequence

[4] : Axial T1-weighted fat-suppressed 3D spoiled gradient echo sequence

TR/TE: repetition time / echo time; FOV: field of view; NEX: number of excitation; MRI: magnetic resonance imaging
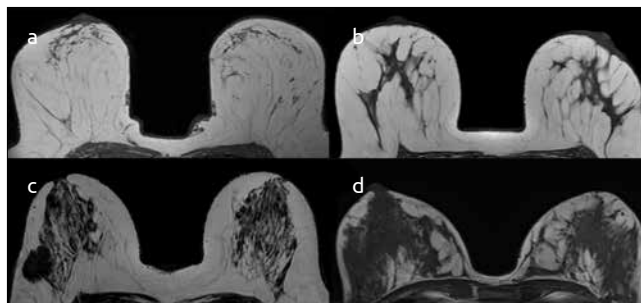

Figure 1. a-d. Axial T1-weighted images demonstrate the classification of the breasts according to FGT proportion; BIRADS a: almost entirely fat (a); BIRADS b: scattered FGT (b); BIRADS c: heterogeneous FGT (c); BIRADS d: extreme FGT (d)
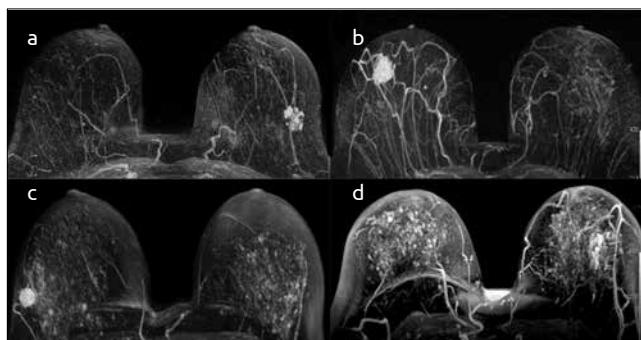

Figure 2. a-d. Axial fat-suppressed T1-weighted dynamic, contrast-enhanced MR images show different breast tissues with minimal (a), mild (b), moderate (c), and marked (d) BPE

mine the FGT proportion. Breast compositions were separated into four categories based on a visual assessment of the FGT proportion of the breast: BIRADS a: almost entirely fat; BIRADS b: scattered FGT; BIRADS c: heterogeneous FGT; BIRADS d: extreme FGT (Figure 1). BPE of the breast parenchyma was visually assessed and graded as minimal, mild, moderate, or marked (Figure 2).

Table 2. Demographic data, MRI features, hormone receptor expression and molecular subtypes of breast cancer

Characteristics	Number (%)
Cases (Number)	75
Premenopausal	49 (65.3)
Postmenopausal	26 (34.6)
Breast Density on MRI	
BIRADS a	16 (21.3)
BIRADS b	19 (25.3)
BIRADS c	19 (25.3)
BIRADS d	21 (28.0)
Background Parenchymal Enhancement	
Minimal	34 (45.3)
Mild	11 (14.7)
Moderate	16 (21.3)
Severe	14 (18.7)
Pathology	
Invasive Ductal Carcinoma	62 (82.7)
Ductal Carcinoma in Situ	4 (5.3)
Invasive Lobular Carcinoma	4 (5.3)
Mucinous Carcinoma	3 (4)
Tubulolobulary Carcinoma	1 (1.3)
Papillary Carcinoma	1 (1.3)
Estrogen Receptor	
Positive	60 (20)
Negative	15 (80)
Progesterone Receptor	
Positive	53 (70.7)
Negative	22 (29.3)
HER2	
Positive	28 (37.3)
Negative	47 (62.7)
Molecular Subtypes	
Luminal A	40 (53.3)
Luminal B	20 (26.7)
HER2 Enriched	8 (10.7)
Triple Negative	7 (9.3)

BIRADS: Breast Imaging and Reporting Data System; HER2: Human Epidermal Growth Factor 2-neu; MRI: magnetic resonance imaging

Pathologic data collection, hormone receptor expression, and molecular subtypes of breast cancer
Pathology results of the cases were reviewed to identify ER, PR, and HER2 status. ER and PR positivity were determined via immuno-histochemical analysis. Tumors were classified ER or PR positive if at least 1% positive staining was observed (13). The evaluation of HER2 status was based on the guidelines of the American Society of Clinical Oncology College of American Pathologists (ASCO/CAP) and was classified as negative, undetermined, or positive. Silver in situ hybridization (SISH) was performed on undetermined cases with an automatized system (Ventana Benchmark XT, Ventana Medical Systems, Illkirch, France) (14).

Lesions were classified into four subtypes according to immuno-cytochemical characteristics: Luminal A (ER+ and/or PR+, plus HER2–), Luminal B (ER+ and/or PR+, plus HER2+), HER2 enriched (ER– and PR–, plus HER2+) and Triple Negative (ER– and PR–, plus HER2–) (15).

Statistical analysis
For statistical analysis, ACR breast composition categories a and b (almost entirely fatty and scattered FGT) were combined and identified as fatty breast tissue, categories c and d (heterogeneous FGT and extreme FGT) were combined and identified as high fibroglandular breast tissue. Breasts with minimal or mild BPE were classified as low BPE breasts; breasts with moderate or marked BPE were classified as high BPE breasts. Statistical analyses were performed with Statistical Package for the Social Sciences 18.0 (SPSS Inc.; Chicago, IL, USA) for windows. The frequencies were compared, using the Pearson Chi-square, Continuity Correction Chi-square, and Fisher Exact test. One proportion test (z test) was used to compare MRI imaging features and molecular subtypes of breast cancer. A p value less than 0.05 was considered as statistically significant.

Results

MRI features, immunohistochemical characteristics, and molecular subtypes of the cases are summarized in Table 2. Among 75 patients with invasive breast cancer, 49 women were premenopausal (65%) and 26 women were postmenopausal (35%). Mean age of the study population was 46.7 years (range: 27–77). Among 75 patients with invasive breast cancer, molecular subtypes of the lesions were 40 for Luminal A (53.3%), 20 for Luminal B (26.7%), 8 for HER2 enriched (10.7%), and 7 for Triple Negative (9.3%). Thirty-five patients had fatty breast tissue (breast composition categories a and b), and 40 patients had high fibroglandular breast tissue (breast composition categories c and d). In terms of BPE: 45 cases were low BPE breasts (minimal + mild) and 30 cases were high BPE breasts (moderate + marked).

The association of BPE with ER and PR positivity was found to be statistically significant (p=0.018 and p=0.013 respectively; Table 3). High BPE breasts tended to have increased rate of ER and PR positive tumors. Of the 30 high BPE cases, 28 (93.3%) were ER positive and 26 (86.7%) were PR positive. We performed subgroup analysis for premenopausal and postmenopausal women separately and the association was again found to be statistically significant for premenopausal women (p=0.011 and p=0.021).

In terms of FGT proportion, we found significant differences with ER positivity (p=0.009) whereas no significant difference with PR positivity was found (p=0.256). Thirty-seven of 40 women (92.5%) with high fibroglandular breasts had ER positive tumors. The analysis again was found to be statistically significant for premenopausal women (p=0.005). There was no correlation between HER2 status and any of the imaging features (p=0.453 and p=0.922).

Table 3. Association of hormone receptor expression with FGT proportion and BPE

		Estrogen Receptor			Progesterone Receptor			HER2 Status		
		ER- (%)	ER+ (%)	p	PR- (%)	PR+ (%)	p	HER2- (%)	HER2+ (%)	p
All Patients	FGT proportion			0.009			0.256			0.453
	Fatty	12 (34.3)	23 (65.7)		13 (37.1)	22 (62.9)		24 (68.6)	11 (31.4)	
	High Fibroglandular	3 (7.5)	37 (92.5)		9 (22.5)	31 (77.5)		23 (57.5)	17 (42.5)	
	BPE			0.018			0.013			0.922
	Low BPE	13 (28.9)	32 (71.1)		18 (40)	27 (60)		28 (62.2)	17 (37.8)	
	High BPE	2 (6.7)	28 (93.3)		4 (13.3)	26 (86.7)		19 (63.3)	11 (36.7)	
Premenopausal Patients	FGT proportion			0.005			0.050			0.974
	Fatty	7 (41.2)	10 (58.8)		8 (47.1)	9 (52.9)		12 (70.6)	5 (29.4)	
	High Fibroglandular	2 (6.3)	30 (93.8)		6 (18.8)	26 (81.3)		21 (65.6)	11 (34.4)	
	BPE			0.011			0.021			1.000
	Low BPE	8 (33.3)	16 (66.7)		11 (45.8)	13 (54.2)		16 (66.7)	8 (33.3)	
	High BPE	1 (4)	24 (96)		3 (12)	22 (88)		17 (68)	8 (32)	
Postmenopausal Patients	FGT Proportion			0.628			0.668			0.090
	Fatty	5 (27.8)	13 (72.2)		5 (27.8)	13 (72.2)		12 (66.7)	6 (33.3)	
	High Fibroglandular	1 (12.5)	7 (87.5)		3 (37.5)	5 (62.5)		2 (25)	6 (75)	
	BPE			1.000			1.000			0.635
	Low BPE	5 (23.8)	16 (76.2)		7 (33.3)	14 (66.7)		12 (57.1)	9 (42.9)	
	High BPE	1 (20)	4 (80)		1 (20)	4 (80)		2 (40)	3 (60)	

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor 2-neu; BPE: background parenchymal enhancement

Considering the associations of the molecular subtypes of breast cancer and FGT proportion and BPE, we found significant differences between molecular subtypes and FGT proportion for the whole study population (p=0.014), but no significant difference was found between molecular subtypes and BPE (p=0.087) (Table 4). When we re-performed a subgroup analysis for premenopausal women and postmenopausal women separately, in the premenopausal group both FGT proportion and BPE were found to be associated with molecular subtypes (p=0.025 and p=0.042). All of the six triple negative tumors were seen in low BPE breasts. Luminal A and luminal B subtypes tended to be seen in high fibroglandular breasts. In the postmenopausal group, no significant differences between molecular subtypes and any of the imaging features were found (p=0.860 and p=0.055).

Fibroglandular tissue proportion was associated with BPE (p<0.001; Table 5). Among 35 cases with fatty breasts, 31 (88.6%) showed minimal or mild BPE. Twenty-six of 40 women with high fibroglandular breasts (65%) demonstrated moderate or marked BPE. When we re-performed the statistical analysis for premenopausal and postmenopausal group separately, we found significant correlation in each group again (p=0.002 and p=0.020, respectively).

Discussion

Breast tissue consists of two components: fat and FGT. Radiologically, the ratio of FGT to fat tissue is an issue of interest because it strongly

increases the risk of having breast cancer. BPE, which is the enhancement of normal FGT on breast MRI, was also shown to be a risk factor for breast cancer (11). BPE may vary depending on which phase of the menstrual cycle the MRI is performed, because the FGT is very sensitive to hormonal influence. Progesterone with its mitogenic activity induces FGT proliferation (16). Estrogen may induce vasodilation and may increase vascular permeability by its histamine-like effect (16). The combination of these two hormone effects may result in increased FGT proportion and high BPE.

In accordance with previously published studies, breast density and BPE were reported to be associated with tumor characteristics. In a cohort study, high breast density was shown to increase the risk of ER and PR positive tumors (17). Another study reported that mammographic density was strongly related to ER positivity (18). According to a recently published study, breast density was associated with ER and PR positivity whereas BPE was independent of tumor characteristics for Asian patients (19). Our study demonstrated a significant association between BPE and ER and PR positivity. Women with high BPE tended to have ER and PR positive tumors. When we repeated our analysis for premenopausal women, we again found a significant correlation with a lower p value for ER. Our results also demonstrated that high fibroglandular breasts were more likely to have ER-positive tumors. This may suggest that estrogen has a stronger influence than progesterone on the pathogenesis of breast cancer.

Table 4. Association of molecular subtypes of breast cancer with BPE and FGT proportion

Molecular subtype	BPE			FGT Proportion		
	Low (%)	High (%)	p	Fatty (%)	High Fibroglandular (%)	p
All Patients			0.087			0.014
Luminal A	21 (52.5)	19 (47.5)	0.875	18 (45.0)	22 (55.0)	0.636
Luminal B	11 (55.0)	9 (45.0)	0.824	5 (25.0)	15 (75.0)	0.041
HER2 Enriched	6 (75.0)	2 (25.0)	0.289	6 (75.0)	2 (25.0)	0.289
Triple Negative	7 (100)	0 (0)	0.016	6 (85.7)	1 (14.3)	0.125
Premenopausal Patients			0.042			0.025
Luminal A	10 (37.0)	17 (63.0)	0.248	7 (25.9)	20 (74.1)	0.019
Luminal B	6 (46.2)	7 (53.8)	1.000	3 (23.1)	10 (76.9)	0.092
HER2 Enriched	2 (66.7)	1 (33.3)	1.000	2 (66.7)	1 (33.3)	1.000
Triple Negative	6 (100.0)	0 (0)	0.031	5 (83.3)	1 (16.7)	0.219
Postmenopausal Patients			0.860			0.055
Luminal A	11 (84.6)	2 (15.4)	0.022	11 (84.6)	2 (15.4)	0.022
Luminal B	5 (71.4)	2 (28.6)	0.453	2 (28.6)	5 (71.4)	0.453
HER2 Enriched	4 (80.0)	1 (20.0)	0.375	4 (80.0)	1 (20.0)	0.375
Triple Negative	1 (100.0)	0 (0.00)	1.000	1 (100.0)	0 (0)	1.000

BPE: background parenchymal enhancement; HER2: human epidermal growth factor 2-neu

Table 5. Association of BPE and FGT proportion

FGT Proportion	BPE		
	Low BPE (%)	High BPE (%)	p
All Patients			<0.001
Fatty	31 (88.6)	4 (11.4)	
High Fibroglandular	14 (35.0)	26 (65.0)	
Premenopausal Patients			0.002
Fatty	14 (82.4)	3 (17.6)	
High Fibroglandular	10 (31.3)	22 (68.8)	
Postmenopausal Patients			0.020
Fatty	17 (94.4)	1 (5.6)	
High Fibroglandular	4 (50.0)	4 (50.0)	

BPE: background parenchymal enhancement

Previously published studies have found that postmenopausal hormone therapy, nulliparity, and late-onset pregnancies were associated with increased mammographic density (20-23). These hormone-related factors were also found to be associated with ER+ /PR+ tumors (24, 25). In our study, high fibroglandular breast tissues were more common among luminal A and luminal B tumors. As luminal subtypes of the breast cancers are also ER and/or PR positive tumors, the pathway that increases FGT proportion may also include the mechanism of developing the luminal subtype of breast cancer. Similar to FGT proportion, it may be hypothesized that increased BPE may increase the risk of developing hormone receptor-positive tumors. Our findings demonstrating that ER and PR positivity associated with BPE confirmed this hypothesis, but when the question of molecular subtypes arises, our results demonstrated no significant association between BPE and molecular subtypes. Separating the groups for premenopausal and postmenopausal patients and re-performing the analysis revealed that there were significant differences between BPE and molecular subtypes in premenopausal women. This finding again may be due to the hormonally active state of premenopausal patients. But as there was no association in the whole study group, BPE may not have a significant influence on determining the molecular subtype. More studies are needed to confirm these results.

We found a significant association between FGT proportion and BPE. Significant correlation was present both in postmenopausal and premenopausal groups with a lower p value in premenopausal patients. This finding may be due to the hormonally active state of premenopausal women. It is recommended to perform breast MRI within the second week of the menstrual cycle to reduce the enhancement of normal breast parenchyma (26, 27). However, some experts' opinion is to disregard the phase of the cycle if the imaging is performed for the staging of a known malignancy (28). Previous studies demonstrated no correlation between breast density and BPE when the breast MRI of the patient has been adjusted for the menstrual cycle (16, 29). However, there is one publication that reported significant correlation of the breast density and BPE when the MRI examination was performed without adjusting for the menstrual phase (30). Our study confirms their findings. As our study population also composed of patients with known malignancy or patients with high suspicion of malignancy, we also didn't consider the patients' phase of the menstrual cycle when the imaging was performed.

Our study has several limitations. It was a single center and single reader study. It was also a retrospective study, which may cause selection bias. Interpretation of BPE and FGT proportion were subjective entities, which were determined according to the visual assessment of enhancing glandular tissue and FGT proportion. Moreover, we have studied a population of a small size (75 cases) especially for the subgroups like triple negative, therefore the statistical significance of these findings might be inconclusive.

Conclusion

We conclude that, in women with invasive breast cancer, both high fibroglandular breasts and high BPE breasts tended to have ER positive tumors.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Owing to the retrospective nature of the study, the requirement for informed consent was waived.

Peer-review: Externally peer-reviewed

Author Contributions: Consept - M.O., A.V.P., Y.S., L.T., A.K.P.; Design - M.O., A.V.P., Y.S., L.T., A.K.P.; Supervision - M.O., A.V.P., Y.S., L.T., A.K.P.; Data Collection and/or Processing - M.O., A.V.P.; Analysis and/or Interpretation - M.O., A.V.P., L.T.; Literature Review - M.O., A.V.P.; Writer - M.O., A.V.P., Y.S., L.T., A.K.P.; Critical Review - M.O., A.V.P., Y.S., L.T., A.K.P.

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