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ORIGINAL ARTICLE

Correlation of ultrasound findings with histology, tumor grade, and biological markers in breast cancer

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Abstract

Background and purpose. Ultrasound has been used successfully to differentiate benign and malignant breast lesions. The aim of this study was to investigate the correlation between ultrasound and prognostic indicators in breast cancer such as histological type, tumor grade, and biological markers. *Materials and methods*. Ultrasound findings (shape, margin, orientation, boundary, echo pattern, posterior acoustic feature, and presence of calcifications) of 458 breast cancers were analyzed and correlated with the tumor type, tumor grade, and biological markers by univariate and multivariate logistic regression analyses. The biological markers were estrogen receptor, progesterone receptor, and HER-2/*neu*. *Results*. Invasive cancers displayed more frequently an irregular shape, a not parallel orientation, and a hypoechoic or complex echo pattern than carcinoma *in situ* cases ($p < 0.05$). Poorly differentiated invasive cancers had more frequently not circumscribed margins, an abrupt boundary, and a hypoechoic or complex echo pattern than moderately/well differentiated cancers ($p < 0.05$). Estrogen or progesterone receptor negative cancers more often displayed a hypoechoic or complex echo pattern and HER-2/*neu* positive cancers had more calcifications ($p < 0.05$). *Conclusion*. Ultrasound pattern is correlated with tumor type, tumor grade, and biological markers in breast cancers and it may be useful for prediction of prognosis.

Histological tumor type, grade, and staging are standard prognostic indicators in breast cancer patients [1]. A breast cancer is drug-sensitive, and many drugs have activity. [2]. Biological markers can be used for prediction of the clinical response to medical treatment and for prediction of prognosis [3]. Estrogen receptor (ER), progesterone receptor (PR), and human epithelial growth factor receptor (HER) are common biological markers. ER and PR are localized in the nuclei of epithelial cells and their presence is predictive for response to hormonal therapy [4]. The HER-2/neu gene has a key role in the HER family and this gene regulates normal cell growth. Trastuzumab (Herceptin®) preferentially targets cells that overexpress HER-2/*neu* [5].

Breast ultrasound is widely used as a diagnostic modality for evaluating clinical or radiological suspected abnormalities [6,7] and is an effective screening modality for detecting occult breast cancers in dense breasts [7–9]. Stavros et al. [10] reported that ultrasound has high sensitivity and negative predictive value for diagnosing breast cancers, 98.4% and 99.5%, respectively, and recent advances in ultrasound technology and transducer design permit greater spatial and contrast resolution.

Thus, we investigated correlations between breast ultrasound findings and prognostic indicators in

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breast cancer such as histological tumor type, tumor grade, and biological markers.

Materials and methods

Patients

This study was approved by the institutional review board for human investigation. The soft copy ultrasound examinations of 458 consecutive patients with primary breast cancer were retrospectively evaluated. All cancers were examined from January 2002 to May 2006 and were histologically proven: 435 invasive cancers (389 ductal carcinoma, 20 lobular carcinoma, and 26 others) and 23 DCIS cases. Patient characteristics are shown in Table I. All patients were female and the ages of the patients ranged from 25 to 87 years (mean age, 56 years). On histological examination, the tumor size ranged from 4 to 125 mm (mean size, 21 mm) and 162 of 458 patients had lymph node metastases.

Table I. Patient characteristics.

Characteristic	Number of patients
Age (years)	
≤50	292
>50	166
Tumor type	
Invasive cancer	435
DCIS	23
*Tumor grade of invasive cancer	
Grade 1	84
Grade 2	165
Grade 3	164
Grade X	22
#Tumor classification of DCIS	
Group 1	4
Group 2	6
Group 3	13
Estrogen receptor	
Positive	272
Negative	186
Progesterone receptor	
Positive	270
Negative	188
HER-2/*neu*	
Positive	191
Negative	267

DCIS = ductal carcinoma *in situ*. *Tumor grade of invasive cancer was divided into grade 1 (well differentiated), grade 2 (moderately differentiated), or grade 3 (poorly differentiated) according to the Scarff-Bloom-Richardson System. Grade X was defined as the grade cannot be assessed.
#DCIS cases were classified as group 1 (nonhigh grade DCIS without comedo-type necrosis), group 2 (nonhigh grade DCIS with comedo-type necrosis), or group 3 (high grade DCIS with or without comedo-type necrosis) according to the Van Nuys Classification.

Ultrasound

All patients were examined using a Logiq9 unit (General Electronic Medical Systems, Milwaukee, WI USA) or a HDI 5000 unit (Advanced Technology Laboratories, Bothell, WA USA) using a broadbandwidth (14–5 MHz) and a linear scanhead. One radiologist evaluated all ultrasound images of each tumor on a monitor of the PACS system (StarPACS; Infinitt, Seoul, Korea) and then saved a minimum of two softcopy images from a transverse and a longitudinal plane of each tumor in the TIFF format. In patients with multiple breast cancers, only the largest lesion was considered. The images were labeled with the initials of each patient and with the date of birth. One experienced breast radiologist analyzed the saved electronic figures on a monitor. If a case was unclear, a second breast radiologist was consulted.

Tumor characteristics were assessed using the BI-RADS®-Ultrasound lexicon [11] and an appropriate reference [10]. The characteristics considered were shape (round or oval vs. irregular), margin (circumscribed vs. not circumscribed), orientation (parallel vs. not parallel to skin), boundary (abrupt interface vs. echogenic halo), echo pattern (hypoechoic or complex vs. isoechoic or hyperechoic), posterior acoustic feature (shadowing or combined posterior acoustic feature vs. no posterior acoustic feature or enhancement), and the presence of calcifications within a mass. "Not circumscribed" margins were defined when the margin was indistinct, spiculated, angular, or microlobulated.

Histological examination

The breast specimens were formalin-fixed, paraffin-embedded tissue blocks subsequently stained with hematoxylin and eosin. Histological tumor types were divided into invasive cancers and ductal carcinoma *in situ* (DCIS). Invasive cancer was graded as grade 1 (well differentiated), grade 2 (moderately differentiated), or grade 3 (poorly differentiated) according to the Scarff-Bloom-Richardson System [12]. DCIS cases were classified as group 1 (nonhigh grade DCIS without comedo-type necrosis), group 2 (nonhigh grade DCIS with comedo-type necrosis), or group 3 (high grade DCIS with or without comedo-type necrosis) according to the Van Nuys Classification [13].

Formalin-fixed, paraffin-embedded tissue sections were stained by immunohistochemical with appropriate antibodies for (a) ER (antibody SP1, Neomarker, Fremont, CA, USA), dilution 1:100,

30 minutes incubation at room temperature; (b) PR (antibody PgR 636, DAKO, Carpinteria, CA USA), dilution 1:20, 30 minutes incubation at room temperature; and (c) HER-2/*neu* (antibody TAB250, Zymed, San Francisco, CA USA), dilution 1:200, 1 hour incubation at room temperature. ER and PR were scored positive [14,15] if more than 10% or tumor cells were immunoreactive by evaluation of 10 random microscopic fields comprising at least 1 000 tumor cells. HER-2/*neu* status was graded as 0, 1+, 2+, and 3+, and 3+ was determined as positive [16].

Statistical analysis

For correlations we performed univariate logistic regression models and expressed the odds ratio (OR) with 95% confidence intervals (CI), and also performed multivariate regression analysis. P-values lower than 0.05 were considered statistically significant. We also correlated five biological markers with tumor type and grade on a histological examination using the χ^2 test. Analyses of the data were determined by a statistician using statistical software (SAS/STAT software, version 6.12; SAS Institute, Cary, NC USA).

Results

Biological markers correlated with the histological grade in invasive cancers (Table II). ER negativity, PR negativity, and HER-2/*neu* positivity were more frequent in grade 3 invasive cancers than in grade 2/grade 1 invasive cancers ($p < 0.0001$). There was no significant difference between invasive cancers and DCIS for the presence of the biological markers ($p > 0.05$).

Results of the univariate and multivariate regression models comparing the ultrasound findings of the 458 breast cancers are presented in Table III–VII. Differences were seen in shape, orientation, and echo pattern between the invasive cancers and DCIS (Table III). An irregular shape (72% vs. 35%), a not parallel orientation (42% vs. 9%), and a hypoechoic or complex echo pattern (92% vs. 6%) were more frequent in invasive cancers when compared with the DCIS cases.

Table IV demonstrates a correlation of the ultrasound findings with tumor grades of the invasive cancers. There were significant differences in margin, boundary, and echo pattern between grade 3 and grade 2/grade 1 invasive cancers by multivariate regression analysis ($p < 0.05$). Not circumscribed margins (90% vs. 87%) (Figure 1), an abrupt boundary (57% vs. 43%) (Figures 1 and 2), and a hypoechoic or complex echo pattern (95% vs. 91%) (Figure 2) were more frequent in grade 3 invasive cancers than in grade 2/grade 1 invasive cancers.

In the 23 DCIS cases, tumor classification was correlated with the presence of calcifications on ultrasound. Calcifications were more frequent in group 3 DCIS cases (10/13, 69%) than in group 2/group 1 DCIS cases (1/10, 10%) ($p < 0.05$).

A hypoechoic or complex echo pattern was more frequent in ER or PR negative cancers (96% in ER negative cancers, 94% in PR negative cancers) when compared with ER or PR positive cancers (87% in ER negative cancers, 88% in PR negative cancers) (Table V and Table VI) (Figures 1–3). HER-2/*neu* positivity correlated with the presence of calcifications (46% vs. 19%, $p < 0.0001$) (Table VII) (Figure 1).

Discussion

The major role of breast ultrasound is to diagnose early breast cancers. Ultrasound can differentiate benign and malignant breast lesions and detect

Table II. Correlation of the biological markers with tumor type and tumor grade.

	Tumor type			Tumor grade		
Biological markers	Invasive	DCIS	p-value	Grade 3	Grade 1, 2	p-value
Estrogen receptor						
Positive	259	13	0.7739	51	194	< 0.0001
Negative	176	10		113	55	
Progesterone receptor						
Positive	256	14	0.8479	62	180	< 0.0001
Negative	179	9		102	69	
HER-2/*neu*						
Positive	178	13	0.1392	93	75	< 0.0001
Negative	257	10		71	174	

Invasive = invasive cancer. DCIS = ductal carcinoma *in situ*.

Table III. Tumor type and ultrasound findings of the breast cancers.

	Tumor type		Univariate analysis	Multivariate analysis	
Ultrasound findings	Invasive	DCIS	p-value	p-value	OR (95% CI)
Shape					
Oval, round	123	15	0.0005	0.0141	0.271 (0.095–0.768)
Irregular	312	8			
Orientation					
Parallel	252	21	0.0065	0.0442	0.196 (0.040–0.959)
Not parallel	183	2			
Margin					
Circumscribed	54	4	0.4868	0.3772	1.780 (0.495–6.398)
Not circumscribed	381	19			
Boundary					
Abrupt	216	16	0.0696	0.4014	1.160 (0.529–4.893)
Halo	219	7			
Echo pattern					
Hypoechoic, complex	400	15	0.0001	0.0072	4.131 (1.468–11.621)
Isoechoic, hyperechoic	35	8			
Posterior acoustic features					
None, enhancement	211	13	0.4552	0.8389	1.108 (0.411–2.985)
Shadowing, combined	224	10			
Calcifications					
Present	129	10	0.1654	0.2445	0.559 (0.210–1.489)
Absent	306	13			

Invasive = invasive cancer. DCIS = ductal carcinoma *in situ*. OR (95% CI) = odds ratio (95% confidence interval).

Table IV. Tumor grade and ultrasound findings of invasive breast cancers.

	Tumor grade		Univariate analysis	Multivariate analysis	
Ultrasound findings	Grade 3	Grade 1, 2	p-value	p-value	OR (95% CI)
Shape					
Oval, round	50	62	0.2120	0.22	1.4 (0.807–2.473)
Irregular	114	187			
Orientation					
Parallel	97	139	0.5044	0.4	0.807 (0.495–1.314)
Not parallel	67	110			
Margin					
Circumscribed	17	33	0.3799	0.0495	0.483 (0.234–0.998)
Not circumscribed	147	216			
Boundary					
Abrupt	93	107	0.0065	0.0031	2.111 (1.286–3.464)
Halo	71	142			
Echo pattern					
Hypoechoic, complex	156	226	0.1055	0.0339	2.552 (1.074–6.068)
Isoechoic, hyperechoic	8	23			
Posterior acoustic features					
None, enhancement	85	116	0.2972	0.5625	1.140 (0.731–1.777)
Shadowing, combined	79	133			
Calcifications					
Present	50	72	0.7311	0.8550	1.043 (0.662–1.645)
Absent	114	177			

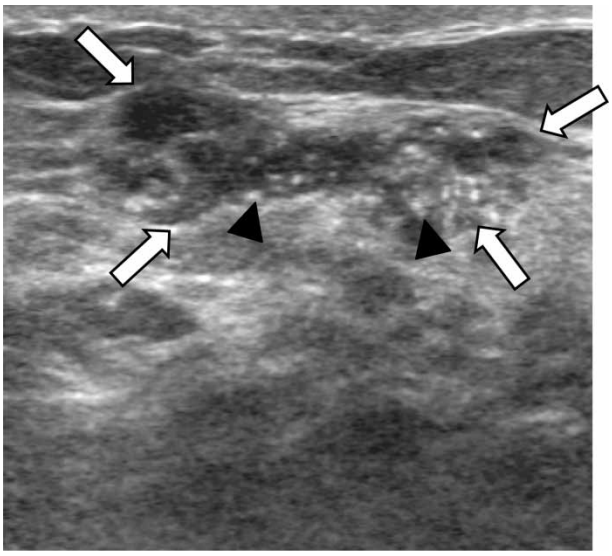

Figure 1. A 37-year-old female with a grade 3 invasive ductal carcinoma. An ultrasound image demonstrates an irregular shaped, not circumscribed marginated, isoechoic mass (arrows) with an abrupt boundary and internal calcifications (arrowheads). On a histological examination, the cancer was ER and PR positive and HER-2/*neu* positive.

occult breast cancers in dense breasts [7–10]. The goal of this study was to determine any correlation between ultrasound findings and prognostic indicators for breast cancers. Multiple logistic regression models demonstrated that tumor type, tumor grade, and the presence of biological markers had a significant impact on the ultrasound findings. Invasive cancers had more frequent breast cancers with an irregular shape, a not parallel orientation and a hypoechoic or complex echo pattern when compared with DCIS cases. These results are comparable to previous studies [17,18]. An irregular shape, a not parallel orientation, and hypoechoic or complex echo pattern are the typical malignant features of solid breast masses [10]. DCIS cases often have less of these typically malignant features; thus, radiologists or sonographers may misinterpret the lesion as being benign. Chen et al. [17] have reported that the internal echo pattern was the most significant factor to differentiate invasive cancers and DCIS cases. Correlations of tumor grade and ultrasound findings in previous studies have varied. Lamb et al. [19] described that high grade invasive cancers were more likely to demonstrate posterior acoustic enhancement and a well defined margin on ultrasound. Watermann and colleagues [20] reported that tumor grading showed no correlation with the examined ultrasound criteria. In our study, the tumor grade of invasive cancers influenced the ultrasound findings. Our results revealed that a not circumscribed margin, an abrupt boundary, and a hypoechoic or complex echo pattern were more frequent in grade 3 than in grade 1–2 invasive cancers. Calcifications on ultrasound were more frequent in group 3 DCIS than group 1-2DCIS. However, the number of DCIS cases was few, 23. The most common feature of DCIS on mammography is microcalcifications. Linear branching or pleomorphic microcalcifications have a high predictive value for the high grade comedo type DCIS [21].

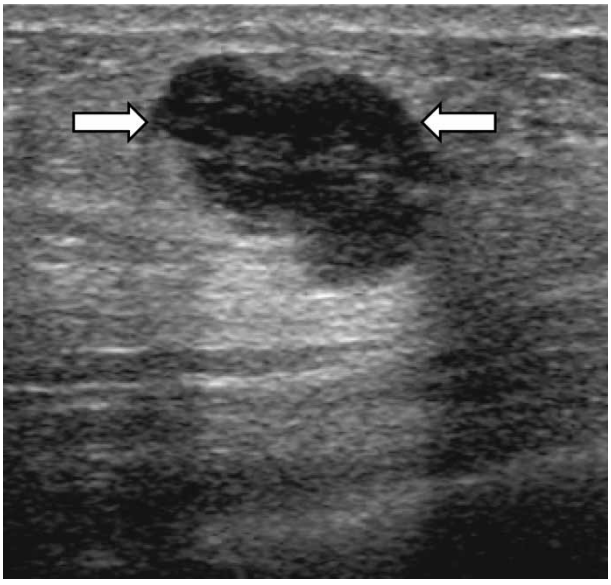

Figure 2. A 42-year-old female with a grade 3 invasive ductal carcinoma. Ultrasound shows an irregular shaped, circumscribed marginated, hypoechoic, parallel orientated mass (arrows) with an abrupt boundary and no internal calcifications. The cancer was ER and PR negative, and HER-2/*neu* negative.

ER, PR, and HER-2/*neu* expression has prognostic and therapeutic value in breast cancer. Our results revealed that all three biological markers correlated with the ultrasound findings. ER and PR demonstrated a significant correlation with echo pattern and a hypoechoic or complex echo pattern was seen more often in cancers with ER or PR negativity. Cancers with ER or PR positivity respond to hormonal therapy and have a relatively good prognosis. Thus, our findings suggest that an echo pattern noted on ultrasound is related with prognosis in breast cancer.

Assessment of HER-2/*neu* positivity is important for the establishment of a treatment plan and the prediction of prognosis in patients with primary breast cancer. HER-2/*neu* is a cell membrane receptor with growth-regulating activity and overexpression of HER-2/*neu* plays a direct role in oncogenic transformation. Overexpression of the HER-2/*neu* gene is associated with a number of adverse prognostic factors, including tumor size, axillary lymph node metastasis, hormone receptors,

Table V. Estrogen receptor and ultrasound findings of the breast cancers.

	Estrogen Receptor		Univariate analysis	Multivariate analysis	
Ultrasound findings	Pos	Neg	p-value	p-value	OR (95% CI)
Shape					
Oval, round	74	64	0.0996	0.4015	0.802 (0.479–1.343)
Irregular	198	122			
Orientation					
Parallel	150	123	0.0190	0.2227	0.747 (0.467–1.194)
Not parallel	122	63			
Margin					
Circumscribed	33	25	0.6793	0.7490	1.114 (0.575–2.161)
Not circumscribed	239	161			
Boundary					
Abrupt	126	106	0.0253	0.1782	0.724 (0.452–1.159)
Halo	146	80			
Echo pattern					
Hypoechoic, complex	237	178	0.0033	0.0002	0.205 (0.090–0.470)
Isoechoic, hyperechoic	35	8			
Posterior acoustic features					
None, enhancement	123	101	0.0566	0.1161	0.713 (0.468–1.087)
Shadowing, combined	149	85			
Calcifications					
Present	78	61	0.3467	0.1469	0.725 (0.470–1.119)
Absent	194	125			

Pos = positive. Neg = negative. OR (95% CI) = odds ratio (95% confidence interval).

Table VI. Progesterone receptor and ultrasound findings of the breast cancers.

	Progesterone receptor		Univariate analysis	Multivariate analysis	
Ultrasound findings	Pos	Neg	p-value	p-value	OR (95% CI)
Shape					
Oval, round	78	60	0.4876	0.9467	1.018 (0.611–1.694)
Irregular	192	128			
Orientation					
Parallel	156	117	0.3392	0.9311	0.980 (0.615–1.560)
Not parallel	114	71			
Margin					
Circumscribed	31	27	0.3628	0.5291	0.812 (0.425–1.552)
Not circumscribed	239	161			
Boundary					
Abrupt	128	104	0.0961	0.1842	0.728 (0.456–1.163)
Halo	142	84			
Echo pattern					
Hypoechoic, complex	238	177	0.0337	0.0064	0.353 (0.167–0.746)
Isoechoic, hyperechoic	32	11			
Posterior acoustic features					
None, enhancement	124	100	0.1263	0.1725	0.749 (0.494–1.135)
Shadowing, combined	146	88			
Calcifications					
Present	79	60	0.5432	0.2838	0.792 (0.516–1.214)
Absent	191	128			

Pos = positive. Neg = negative. OR (95% CI) = odds ratio (95% confidence interval).

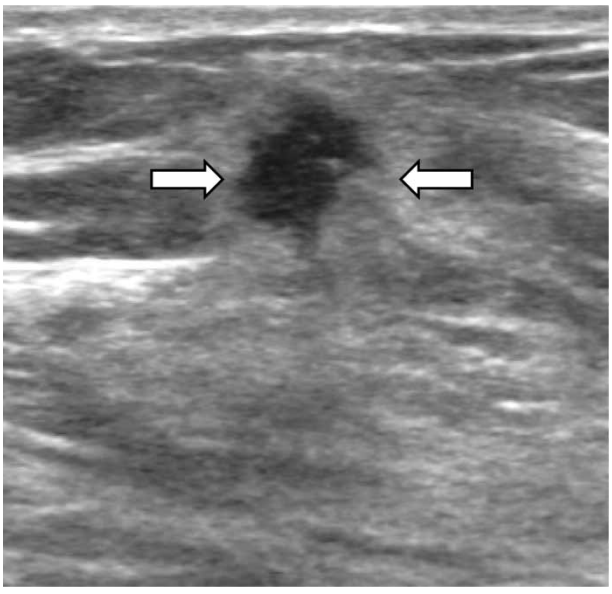

Figure 3. A 44-year-old female with a grade 2 invasive ductal carcinoma. Ultrasound shows an irregular shaped, not circumscribed marginated, hypoechoic, not parallel orientated mass (arrows) with an echogenic halo boundary. The cancer was ER and PR positive, and HER-2/*neu* negative.

and tumor grade [16]. In this study, expression of the HER-2/*neu* oncogene strongly correlated with presence of calcifications on ultrasound. A correlation between the overexpression of the HER-2/*neu* oncogene and calcifications was also reported by mammography in previous studies [22,23]. Seo et al. [22] described that fine linear morphology and diffuse distribution of calcifications on mammography were more frequent in breast cancers with HER-2/*neu* overexpression and the histological tumor grade in invasive cancers and that DCIS cases correlated with HER-2/*neu* overexpression. Thus, presence of calcifications on mammography or on ultrasound might be related to prognosis. One limitation of the HER-2/*neu* oncogene assessment in the current study was that we only used immunohistochemical methods. HER-2/*neu* status was graded as 0, 1+, 2+, and 3+, and only 3+ was determined as positive. A study using a large patient cohort by Yaziji et al. [24] reported that for cancers with a weak positive immunohistochemical result, 17% of the 2+ staining cases were HER-2/*neu* positive by fluorescence *in situ* hybridization (FISH) [24]. However, FISH was not available at our hospital.

Our results are based on a retrospective analysis. To avoid bias, we included all consecutive patients who underwent breast cancer surgery and preoperative breast ultrasound, and all examinations were reviewed by one experienced investigator who was blinded to the clinical data. In conclusion, findings on breast ultrasound correlate with the histological tumor type,

Table VII. HER-2/*neu* oncogene and ultrasound findings of the breast cancers.

	HER-2/*neu*		Univariate analysis	Multivariate analysis	
Ultrasound findings	Pos	Neg	p-value	p-value	OR (95% CI)
Shape					
Oval, round	52	86	0.2521	0.5229	0.842 (0.497–1.427)
Irregular	139	181			
Orientation					
Parallel	115	158	0.8243	0.8908	1.034 (0.641–1.668)
Not parallel	76	109			
Margin					
Circumscribed	22	36	0.5334	0.6184	1.186 (0.606–2.318)
Not circumscribed	169	231			
Boundary					
Abrupt	97	135	0.9624	0.8970	0.968 (0.595–1.575)
Halo	94	132			
Echo pattern					
Hypoechoic, complex	174	241	0.7620	0.5109	1.267 (0.625–2.568)
Isoechoic, hyperechoic	17	26			
Posterior acoustic features					
None, enhancement	87	137	0.2242	0.7717	1.065 (0.694–1.635)
Shadowing, combined	104	130			
Calcifications					
Present	88	51	<.0001	<.0001	3.716 (2.398–5.758)
Absent	103	216			

Pos = positive. Neg = negative. OR (95% CI) = odds ratio (95% confidence interval).

tumor grade and biological markers in breast cancers and the use of breast ultrasound may be useful for predicting prognosis. Further studies are warranted with a large population to confirm our results.

Acknowledgements

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