Correlation of Tumoral Prognostic Factors by Sonoelastography Score in Patients to be Operated Due to Breast Cancer

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Abstract Predictability of pre-op prognosis on patient with a diagnosis of breast cancer is quite valuable for the choice of both surgical technique and adjuvant therapy. With the aim of evaluation of sonoelastography score utility in this respect, correlation of tumoral prognostic factors by sonoelastography score in patients to be operated due to breast cancer was analyzed on our study. Pre-op sonoelastography results and tumoral histopathological properties of 60 patients operated with a diagnosis of breast cancer in 2011 at Adnan Menderes University Faculty of Medicine General Surgery Department were analyzed retrospectively. As an elastography scoring method, “Tsukuba scoring system” was used. Statistically significant differences ($p < 0.05$) were determined between tumor grade and Ki-67 analyzed as prognostic factor with tumors reported as sonoelastography score 4 and score 5, on the other hand there were no statistically significant differences between tumor size, positivity of axillary lymph nodes, significance of lymphovascular invasion, p-53 positivity, CerbB-2 positivity, hormone receptor positivity, tumor histologic type and applied surgical technique between tumors reported as elastography score 4 and score 5. ($p > 0.005$). Foresee ability of prognostic factors correlation by sonoelastography score will

be guide way for the choice of surgery technique, determination of adjuvant therapy and patient follow-up.

Keywords Breast cancer · Elastography · Prognostic factors

Introduction

Earlier mammary ultrasonography (US) was a limited diagnostic procedure for discrimination of cystic and solid lesions, but in recent years it has become a developed diagnostic method which provides the evaluation and classification of bulk and cystic lesions [1, 2]. Using the breast imaging and reporting data system (BI-RADS™) in gray scale US, lesion form, margin characteristics, location, echo structure, posterior acoustic characteristics, effects on peripheral breast tissue, and existence of microcalcification are evaluated [3]. Ophir et al. proposed a new method called elastography in 1991 [4]. Because of the hardness of malignant lesions according to the peripheral tissues, different amount of pressure is applied to different areas [5]. It is based on the differences in tissue sizes as a result of mechanical pressure applied to tissues by US probe. In malignant tumors, between pre- and postcompression there were no differences in distances between two small points signed in the tissue layer, but in normal tissues and benign lesions distances became shorter. Imaging of distance differences between pre- and postcompression is called “elastography”. For this evaluation, a software is used in which soft lesions seem to be bright, hard lesions seem to be dark and malignant lesions are more specific than benign lesions. On the other hand tissues seem to be in different color spectrum according to their hardness [6–11]. Yet, there is no agreement on the method or classification which has the most clinical applicability. The main limitations are the differences between observers reported in the last studies and default of standards on how to apply compression during the study. In breast cancer, natural course after diagnoses differs in patients. On follow-up

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it is found that tumor relapses in a short time in patients who have the same tumor diameter after surgery and adjuvant therapy, but on the other hand some patients live a healthy life. Thence, prognostic factors are used to expect the clinically and biologically tumor behavior difference. They are useful tools for determination of high-risk breast cancer patients. These factors are tumor diameter, axillary lymph node invasion, histologic tumor type, histologic grade, hormone receptor positivity (estrogen and progesterone receptors), tumor proliferation speed (mitosis, thymidine labeling index, S-phase reaction, immunohistochemical labels), and molecular prognostic factors (enzymes, *CerbB-2*, oncosuppressor genes).. In the past few years, researches have been performed on the utility of the sonoelastography technique for malignant benign separation of bulks. But we didn't see any study on the existence of predictive power of prognosis and the relations with prognostic factors belonging to tumor of this technique.

Materials and Methods

Surgery was performed in 60 patients with breast cancer at the General Surgery Department at Adnan Menderes University in 2011. As a result of postoperative histopathologic analyses and preoperative sonoelastography scores of these patients, tumoral properties were analyzed retrospectively (Table 1) as an elastography scoring method; “Tsukuba scoring” was used.

Elastographic Study

To all cases, at the same stage, gray scale US and real-time elastography analysis were made. All researches were done at the Acuson Antares (Siemens/Mountain View, CA, ABD) machine by using 7–13 mHz matrix linear transducer. In gray scale US research, lesion localization, size of lesion, border properties, echogenicity, homogeneity, acoustic permeability, exposure on breast tissue, and existence of microcalcification were evaluated. After gray scale analysis, the ultrasound probe lubricated with gel was placed on the breast at transverse plan, and the lesion was displayed in an optimal way to see. Prob was kept as static as possible and without pressure. By dividing the screen into two parts, gray scale scene and at the other part real-time elastography scene, it was displayed including the sampling window lesion, peripheral breast tissue, pectoralis muscle, and subcutaneous fat plans. The data of tissue elasticity in analysis area were saved as color image. Color coding from soft tissue to hard tissue was blue-green-yellow-red. After supplying the optimal image, images were saved as both motion and static.

Elastographic Classification

Elastography data were scored by using Itoh et al. scoring systems. It was defined as: if the lesion was coded blue

Table 1 Histopathological features and sonoelastography scores of tumors

Case number: 60	Score 4 <i>n</i> =18 (%)	Score 5 <i>n</i> =42 (%)	<i>p</i> value
Primary tumor (T)			0,124
T ₁	8 (44.4)	30 (71.4)	
T ₂	8 (44.4)	9 (21.4)	
T ₃	2 (11.1)	3 (7.1)	
Hysthologic type			
Invasive ductal carcinoma	15 (83.3)	34 (80.9)	0,570
Invasive papillary carcinoma	0	4 (9.5)	0,230
Invasive lobular carcinoma	1 (5.5)	0	0,300
Tubular carcinoma	2 (1.1)	4 (9.5)	0,186
Grade			0,001
I	7 (38.8)	1 (2.3)	
II	11 (61.1)	41 (97.6)	
III	0	0	
Axillary lymph node involvement			0,340
pN -	6 (33.3)	23 (54.7)	
pN +	12 (66.6)	19 (45.2)	
1–3	3 (25)	4 (21)	
>3	9 (75)	15 (78.9)	
Receptor situation			0,115
ER+PR +	11 (61.1)	27 (64.2)	
ER+PR -	5 (27.7)	4 (9.5)	
ER–PR +	0	7 (16.6)	
ER–PR -	2 (11.1)	4 (9.5)	
Presence of lymphovascular invasion			0,516
(+)	14 (77.7)	34 (80.9)	
(–)	4 (23.3)	8 (19)	
CerbB2			0,344
Score 0	9 (50)	17 (40.4)	
Score 1	4 (22.2)	7 (16.6)	
Score 2	3 (16.6)	9 (21.4)	
Score 3	2 (11.1)	9 (21.4)	
P53			0,070
(+)	0	7 (16.6)	
Ki67			0,002
(+)	6 (33.3)	1 (2.3)	
Applied surgical technique			
BCS+SLNB	5 (27.7)	23 (54.7)	
BCS+AD	5 (27.7)	8 (19)	
MRM	7 (38.8)	11 (26.1)	
SM+SLNB	1 (5.5)	0	

ER estrogen receptor, *PR* progesterone receptor, *BCS* breast conserving surgery, *SLNB* sentinel lymph node biopsy, *AD* axillary lymph node dissection, *SM* simple mastectomy

means “score 1”, if the lesion was coded blue-red mosaic pattern means “score 2”, if the peripheral of the lesion was blue and center of it was coded red means “score 3”, if the lesion was fully coded red but the peripheral of it was coded

blue means “score 4”, and if the lesion and its peripheral were coded red means “score 5” (Fig. 1).

Gray scale US analysis data were grouped by using the BI-RADS classification. According to elastography analysis, scores 1, 2, and 3 were accepted as benign, and scores 4 (Fig. 2) and 5 (Fig. 3) were accepted as malignant. Cases composing this research group were classified as scores 4 and 5 in elastography analysis.

Statistical analysis

For data analysis, chi-squared test was used. For $p < 0.05$, all results were accepted statistically significant.

The study was reviewed by the appropriate medical ethics committee and was performed in accordance with the medical ethics standards laid down in an appropriate version of the 1964 Declaration of Helsinki. The Institute's Protocol Review Board approved the study.

Findings

18 tumors (30 %) of 60 female patients ($n=60$) operated due to breast cancer were classified as score 4, and 42 tumors of them (70 %) were classified as score 5. According to tumor size, 38 patients (63.3 %) were evaluated as T1, and 17 patients (28.3 %) were evaluated as T2, and five of them (8.3 %) were evaluated as T3. 30 (71.4 %) tumors evaluated as score 5 were evaluated as T1, nine (21.4 %) of them were evaluated as T2, three (7.1 %) of them were evaluated as T3, eight (44.4 %) of score 4 were evaluated as T1, eight (44.4 %) of them were evaluated as T2, and two (11.1 %) of them were evaluated as T3. On statistical evaluation, in terms of tumor size (T) between scores 4 and 5 groups there was no statistical significant relation ($p > 0.05$). On evaluation of axillary lymph node involvement in 12 (66.6 %) patients of score 4 and 19 (45.2 %) patients of score 5, the lymph nodes came out to be positive. Lymph nodes were positive in 31 (51.6 %) patients, and between scores 4 and 5 groups there was no statistically significant relation ($p > 0.05$). Invasive ductal carcinoma (81.6 %) was the most seen histological type followed by tubular carcinoma (10 %), invasive papillary carcinoma (6.6 %), and invasive lobular carcinoma

(1.6 %), and between histological type and scores 4 and 5 groups there was no statistically significant relation ($p > 0.05$). Eight (13.3 %) grade I tumors of 7 (87.5 %) were classified as score 4 and 52 (86.6 %) grade II tumors of 41 (78.8 %) were classified as score 5. Between grades I-II and scores 4 and 5 tumors, there was a statistically significant difference ($p < 0.05$). By the time CerbB-2 and Ki-67 positiveness was analyzed according to dye properties, a statistically significant relation was defined only between Ki-67 positiveness and scores 4 and 5 ($p < 0.05$). By the time tumors were evaluated in terms of hormone receptor positivity, ER positiveness was in 47 tumors (78.3 %), PR positiveness was in 45 (75 %), ER and PR positiveness was in 38 (63.3 %), and ER and PR negative was in 6 (10 %). With the hormone receptor status between scores 4 and 5, there was no statistically significant relation ($p > 0.05$). Lymphovascular invasion existence was totally stated in 48 (80 %) patients; it was determined as 80.9 % in score 5 tumors and 77.7 % in score 4 tumors. With lymphovascular existence, there were no statistically significant relation between scores 4 and 5 ($p > 0.05$). Modified radical mastectomy was applied to 18 patients (30 %), breast conserving surgery was applied to 41 patients (68.3 %), sentinel lymph node sampling was applied to 29 patients (48.3 %) and axillary lymph node dissection was applied to 31 patients (51.6 %).

Discussion

In a research in Japan in 2010, it was emphasized that distinction of malignant and benign lesions could be made safely by real-time elastography as a new US technique. According to the results of this research, the elastography method could show malignant or benign lesions in women who have bulk in the category of BI-RADS 4 [12]. According to traditional US, definition of such bulk is “suspicious lesion” or “it is advised to do biopsy”. The applied technique means for such group patients to relieve from unnecessary breast biopsy.

In tender age group, especially premenopausal period and hormone replacement therapy taking women, due to dense breast structure, cancer determination sensibility of mammography decreases prominently. As a complementary examination, US increases the cancer determination sensibility

Fig. 1 Tsukuba scoring

Fig. 2 Heterogeneous hypoechoic solid lesion with irregular contours was seen at the examination of gray scale US of 66-year-old female patient. Entire lesion is red coded at elastography examination (score 4). Histopathological diagnosis: invasive ductal cancer

prominently in dense breast structured women population whose mammographic sensibility is decreased, and it provides additional information such as multifocality and multicentricity, which changes the treatment plan. Studies in recent years emphasized that elastography added to conventional analyses increases the specificity of US, and it would be an important device for malignant-benign discrimination. The limitation of elastography analysis is the variability between executives. Moon et al. made a computerized elastogram study on 100 breast bulks [8]. By using a computer-aided diagnosis program on segmented image, borders, differences between front-back length, total area, and differences on hardness of bulks were evaluated. Writers achieved 85 % sensibilities, 88 % specificity, 87 % diagnostic correctness, and 90 % negative predictive. Regner et al., along similar lines but also taking account of differences between executives, concluded that elastography has potential on differentiation of breast tissue lesions [7]. Itoh et al. suggested a classification method according to the differences of color spectrum obtained on a dynamic form [13]. By using the five-pointed classification system, they evaluated 111 lesions. Scores 1, 2, and 3 were accepted as benign, and scores 4 and 5 were accepted as malignant. Writers found 86.5 % sensibilities, 89.9 % specificity, and 88.3 % diagnostic correctness. Scaperrotta et al. applied more basic three-pointed systems developed on the basis of classification system used by Itoh et al., and they obtained 80 % sensibility and 80.9 % specificity levels similar to US study [11]. As a main limitation of elastography, writers determined that it was executive dependent and due to this it

varied from. To learn suitable technique in all studies, education and experience were necessary.

In recent years, researches have been performed on the use of the elastography technique on discrimination of malignant and benign bulks [14–16]. But no study searching the existence of predictive power of prognosis and relation with tumoral prognostic factors of this technique is found in the literature. At the time of diagnosis, prognostic factors giving true information about the course of disease can be determined without any therapy, and this evaluation in clinic will prevent patients from taking unnecessary therapies. Besides, predetermination of tumors, which will be aggressive, is very important for the choice of a surgical procedure, determination of adjuvant therapy, and follow-up. Although there were deaths due to disease with very small tumors, obtaining a long-term survival with large tumors and even with distant metastases stepped up efforts to identify the prognostic factors affecting the course of the disease [17]. From here, by the time we examine the tumor size (T) of prognostic factors, 71.4 % of score 5 tumors and 44.4 % of score 4 tumors were determined as T1. The average pathological size of score 4 tumors was 2.35 cm, and the average pathological size of score 5 tumors was determined as 1.72 cm. As is known in patients with breast cancer, a better prognosis is expected in the lymph node negative group in comparison with the lymph node positive group. Also, in the lymph node positive group, the number of metastatic lymph nodes emerges as an important prognostic parameter. In our study, axillary lymph node involvement is examined. In score 4 tumors, lymph node positivity was seen as %66.6

Fig. 3 Spiculated and significant hypoechoic solid lesion was seen at gray scale US of 53-year-old female patient. It was also seen in elastography examination; lesion and peripheral breast tissue are red coded (score 5). Histopathological diagnosis: invasive ductal cancer

in the same group, while there was more than three lymph node involvement rate and was seen as 75 %. In score 5 tumors, lymph node positivity was seen as 45.2 %, while there was more than three lymph node involvement rate and was seen as 78.9 %. Between scores 4 and 5 tumors, there was no statistically significant difference in terms of tumor size being small and rate of lymph node involvement being less. In the examination of histological types of tumors, invasive ductal carcinoma (83.3 % and 80.9 %) was the most seen in scores 4 and 5 tumors. The statistically significant difference between histological tumor types and scores 4 and 5 was not determined.

In the evaluation of lymphovascular invasion existence, it was determined as 77.7 % in score 4 tumors and 80.9 % in score 5 tumors. There are studies that show lymphovascular invasion is a prognostic factor, which increases deaths relating to both relapse and breast cancer.

Seven (38.8 %) grade 1 tumors and 11 (61.1 %) grade 2 tumors were defined as score 4, and 1 (2.3 %) grade 1 tumor and 41 (97.6 %) grade 2 tumors were defined as score 5. In breast cancer, histological grades appear as a strong prognostic factor, but it is a subjective parameter.

According to many studies, it is determined that prognosis is worse in situations like there were *CerbB-2* (HER-2), *Ki-67*, *p-53* positivity, and decreased estrogen and progesterone receptor existence in breast cancer [18, 19]. *CerbB-2* is an oncoprotein and when its expression increases, grade increases and prognosis gets worse in breast cancer. Moreover, it was emphasized that in the event *CerbB-2* is positive, recurrence risk will be higher [20, 21]. In our study, in score 4 tumors, *CerbB-2*, *Ki-67*, *p-53*, and hormone receptor positivity were found as 50 %, 33.3 %, 0 %, and 61.1 %, respectively, and in score 5 tumors the same parameters were determined as 59.6 %, 2.3 %, 16.6 %, and 64.2 %, respectively. When surgical procedures applied to tumors were examined, it was seen that breast conserving surgery (BCS) was applied to 55.5 % and sentinel lymph node biopsy (SLNB) was applied to 33.3 % of score 4 tumors. BCS was applied to 73.8 % and SLNB was applied to 54.7 % of score 5 tumors. Modified radical mastectomy applied case number was 38.8 % in score 4 tumors and 26.1 % in score 5 tumors. Between applied surgical techniques and scores 4 and 5 tumors, there was no statistically significance. It was seen that due to the fact that tumor size is small and lymph node involvement is less in group score 5, breast conserving surgery (78.3 %) and sentinel lymph node sampling (54.7 %) were done. With the evaluation of tumor histopathology relating these patients for early breast cancer, high tumor grade, presence of lymphovascular invasion, *CerbB-2* positivity, and excessive accumulation of *p-53* were detected. This means that if patients undergo breast conserving surgery with no axillary dissection, there will be more recurrence rate and poor prognosis. As a result, today significant benefits can be achieved from prognostic factors for some

clinical pictures. These can be expressed as the identification of patients who will benefit from systemic therapy after local treatment and patients who need more aggressive treatment due to poor prognosis. We consider that in order to determine these features in advance, the use of the elastography scoring system can give important clues about biological behaviors of tumors and can be a guide for the treatment plan.

References

1. Kaplan SS (2001) Clinical utility of bilateral whole-breast US in the evaluation of women with dense breast tissue. *Radiology* 221:641–649
2. Stavros AT, Thickman D, Rapp CL, Dennis MA, Parker SH, Sisney GA (1995) Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. *Radiology* 196:123–134
3. American College of Radiology (2003) Breast Imaging Reporting and Data System (BIRADS), ultrasound, 4th edn. American College of Radiology, Reston
4. Ophir J, Céspedes I, Ponnekanti H, Yazdi Y, Li X (1991) Elastography: a quantitative method for imaging the elasticity of biological tissues. *Ultrason Imaging* 13:111–134
5. Cho N, Moon WK, Park JS, Cha JH, Jang M, Seong MH (2008) Nonpalpable breast masses: evaluation by US elastography. *Korean J Radiol* 9:111–118
6. Burnside ES, Hall TJ, Sommer AM et al (2007) Differentiating benign from malignant solid breast masses with US strain imaging. *Radiology* 245:401–410
7. Regner DM, Hesley GK, Hangiandreou NJ et al (2006) Breast lesions: evaluation with US strain imaging—clinical experience of multiple observers. *Radiology* 238:425–437
8. Moon WK, Chang RF, Chen CJ, Chen DR, Chen WL (2005) Solid breast masses: classification with computer-aided analysis of continuous US images obtained with probe compression. *Radiology* 236:458–464
9. Zhi H, Ou B, Luo BM et al (2007) Comparison of ultrasound elastography, mammography, and sonography in the diagnosis of solid breast lesions. *J Ultrasound Med* 26:807e15
10. Tohno E, Ueno E (2008) Current improvements in breast ultrasound, with a special focus on elastography. *Breast Cancer* 15:200–204
11. Scaperrotta G, Ferranti C, Costa C et al (2008) Role of sonoelastography in non-palpable breast lesions. *Eur Radiol* 18:2381–2389
12. Satake H et al (2011) Ultrasound elastography can identify patients who need breast biopsies, study. *AJR Am J Roentgenol* 196 (1):202–209
13. Itoh A, Ueno E, Tohno E et al (2006) Breast disease: clinical application of US elastography for diagnosis. *Radiology* 239:341–350
14. Hatzung G, Grunwald S, Zygmunt M et al (2010) Sonoelastography in the diagnosis of malignant and benign breast lesions: initial clinical experiences. *Ultraschall Med* 31:596–603
15. Navarro B, Ubeda B, Vallespi M et al (2011) Role of elastography in the assessment of breast lesions: preliminary results. *J Ultrasound Med* 30:313–321
16. Lee JH, Kim SH, Kang BJ et al (2011) Role and clinical usefulness of elastography in small breast masses. *Acad Radiol* 18:74–80
17. Fisher B, Fisher ER (1996) Transmigration of lymph nodes by tumor cells. *Science* 152:1397–1398

18. Walker RA, Lees E, Webb MB, Dearing SJ (1996) Breast carcinomas occurring in young women (<35 years) are different. *Br J Cancer* 74:1796–1800
19. Sjogren S, Inganas M, Lindgren A, Holmberg L, Bergh J (1998) Prognostic and predictive value of c-erbB-2 overexpression in primary breast cancer, alone and in combination with other prognostic markers. *J Clin Oncol* 16:462–469
20. Leal CB, Schmitt FC, Bento MJ et al (1995) Ductal carcinoma in situ of the breast; histological categorization and its relationship to ploidy and expression of hormone receptors, p53 and c-erbB-2 protein. *Cancer* 75:2123–2131
21. Albonico G, Querzoli P, Ferretti S et al (1996) Biophenotypes of breast carcinoma in situ defined by image analysis of biological parameters. *Pathol Res Pract* 192:117–123