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ORIGINAL PAPER

Triple Test Score for the Evaluation of Invasive Ductal and Lobular Breast Cancer

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Abstract The aim of our study was to compare the preoperative sum score diagnostics of invasive ductal and lobular cancers using three or four diagnostic methods. The novelty of this study is the examination of this phenomenon based on sum score, no such papers can be found in the literature. Ductal cancers have higher score values indicating easier diagnostics, but the difference in distribution of the scores was significant (p=0.0086) only in case of the triple-test. The score values give appropriate opportunity to create their order of diagnostic power which was the same by both histologic types and in their subgroups with low sum-score: the strongest was cytology, followed by mammography, ultrasound and physical examination. No significant difference was found between the two histologic group in their mammographic appearances—stellate, circumscribed, assymmetric distortion or microcalcification—(p=0.0694). In low score subgroup besides the occult forms, structural distortion and indeterminate microcalcifications overweighed the stellate and circumscribed lesions typical for the whole groups. In symptomless cases of both histologic groups only one strongly malignant diagnostic test result warrants the right diagnosis. Summarizing the score distribution of the results in case of four diagnostic tools the higher scores—indicating malignancy—were more frequent in the ductal group compared to the lobular ones. Extra attention has to be paid to rare radiomorphologic appearances and to the most deterministic examination, namely cytology.

Keywords Lobular · Ductal · Breast cancer · Sum-score diagnosis · Triple test · Symptomless

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Introduction

The radiological diagnosis of lobular carcinoma is a challenge [1]. Though it is not more than 5–10% [2] or according to others 8–15% [3, 4] of all breast cancer cases its incidence is increasing [5]. Several studies have proved that compared to the most common ductal carcinoma its prognosis is better [6, 7], specially because its lower proliferative activity [8] but diffuse spreading, multifocality [9] makes diagnosis more difficult. In the past decades mammography, palpation and cytology examination were considered as "triple test" [10, 11] and several papers have proved its usefulness [11, 12] and cost-effectiveness [13]. The score created from the sum of numeric test results of different diagnostic tools is sensitive and accurate to predict the benign or malignant behaviour of the laesion [14]. Former it was applied only in the case of palpable lesions [14, 15] but in the era of the routine use of ultrasound [16, 15] and core biopsy the components of the triple test have changed applied in younger populations omitting X-ray radiation [17, 18]. In screening of women with family history triple test consists of result of mammography, ultrasound and magnetic resonance imaging (MRI) [19].

As it was shown in our earlier paper mammography, ultrasound and clinical examination has the same value in case of both ductal and lobular cancers, but cytology performs significantly better for ductal cancers [20]. In the current study the diagnostic value of the sum score was tested in the two different histologic groups, and in their symptomless low sum-score subgroup. The order of the different modalities were created from their score value in ductal and lobular groups. Radiomorphologic distribution of the histologic groups and subtypes were also compared to define which groups have the highest frequency of difficult to diagnose forms.

Materials and Methods

From January 1 till December 31 2002 331 histologically proven invasive ductal and 65 lobular cancers were diagnosed at the Breast Diagnostic Unit of MaMMa Healthcare Co., 83.6% and 16.4% respectively. As all four examinations were carried out only in 330 invasive ductal cancers, only these were included along with the lobular ones.

Imaging

In each case the complex examination of the breasts included mammography, physical examination, ultrasonography and cytology.

Mammography

Mammography was performed with dedicated equipment (Contour Plus Mammograph (Trex Medical, USA) and FUJI AD-Mammographic-Fine film-screen system was used with FUJI AD-M films. A Mammoray-Compact E. O.S. daylight processing machine was used with extended cycle processing. Each breast was examined in two standard views, (cranio-caudal and mediolateral oblique) and additional views (spot magnifications) were taken when it was necessary for better visualization. Mammographic findings were categorized on the basis of a five-point rating scale describing the degree of suspicion for malignancy according to Breast Imaging Reporting and Data System (BI-RADS) of the American College of Radiology assessment scoring system [21]. Each lesion was classified into the commonly used radiomorphologic categories.

Ultrasonography

Ultrasound examinations were performed on a Diasus-2000 Ultrasound system with 7.5–10 and 16–20 MHz high resolution linear array and former on a Hitachi 4 real-time ultrasound machine equipped with a 7.5 MHz linear transducer. Gray-scale ultrasound evaluation of the breasts and axillary regions were performed with the knowledge of the clinical and mammographic findings.

Cytology

Fine needle aspirations were performed with ultrasound-guidance in majority of cases—88%—but in lack of US appearance it should have done with 2D mammography-guidance. On-site fixed wet and hematoxylin and eosin stained smears were examined.

Image Interpretation and Diagnostic Workup

The results of all examinations were coded in the same manner (from 1 to 5) like mammography: 1 meaning normal tissue, 2 indicates benign change, 3 stands for borderline undefined alteration, 4 is suspected malignant and 5 is used for definitely malignant lesion. This coding provided the possibility of creation a triple test result from different diagnostic methods and a sum score to compare breast carcinomas of different hystologic types and was also used for statistical analysis.

Statistical analysis (of sum score, mean, median and standard deviation) was performed on the two histologic groups with all four (Table 1) and only using three examination modalities (Table 2).

Table 1 The distribution of sum scores of invasive ductal and lobular breast cancer groups in case of four diagnostic modalities

Score	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lobular	0	0	0	0	0	1	0	1	2	1	3	7	5	4	9	6	6	6	4	10
Ductal	0	0	0	0	0	1	4	4	9	9	7	9	15	27	29	46	35	50	33	52

Sum-score, lobular, ductal number of cases

Table 2 The distribution of sum scores of invasive ductal and lobular breast cancer groups in case of three diagnostic modalities

Score	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Lobular	0	0	0	0	1	0	2	3	4	6	8	10	4	9	18
Ductal	0	0	0	1	0	6	6	8	17	8	20	26	63	47	128

Sum-score, lobular, ductal number of cases

The low sum-score "difficult to diagnose" group consists of the cases when the certainty score was 3 (indeterminate) or less according to our own definition. In practice the score was 12 or less in the case of four modalities and 9 or less when only three modalities were used.

The same statistical parameters (sum distribution, mean, median and standard deviation) were also compared in these subgroups.

The diagnostic power of the different diagnostic tools was defined for the whole population and for the subgroups. Those which resulted mostly in 1 with least 5-s and lowest average value were considered the weakest, the strongest was the opposite. The order of power of the diagnostic methods were compared with different histologic groups, low score subgroups with each other, and with its total group. The distribution of the radiomorphologic appearance of ductal and lobular cancers, and their subgroups were evaluated and correlated with histologic results.

Statistical analysis was conducted to demonstrate whether the distribution of score gives significantly different results between the ductal and lobular groups and subgroups.

Mann–Whitney, Chi-square, Mann–Whitney *U*, Pearson Chi-square and M–L Chi-square tests [22, 23] were carried out.

Results

Using all four diagnostic tools there is no significant difference in the distribution of sum-score between ductal and lobular cancers (p=0.0684; Fig. 1), whereas if only three tests were used the difference becomes significant (p=0.0086; Fig. 2).

In the ductal group the mean and median of the sum score was higher with standard deviation and the proportion of lower sum scores is lower independent of the use of four or only three diagnostic tools (Table 3).

In the low sum score—difficult to diagnose group—no significant difference in the code distribution, average, median and standard deviation could have been found based on the histologic result neither in the three nor in the four test groups (Table 4).

The order of diagnostic power of the four or three modality test is shown in Table 5 respectively. Independent from the number of the used diagnostic tools or the

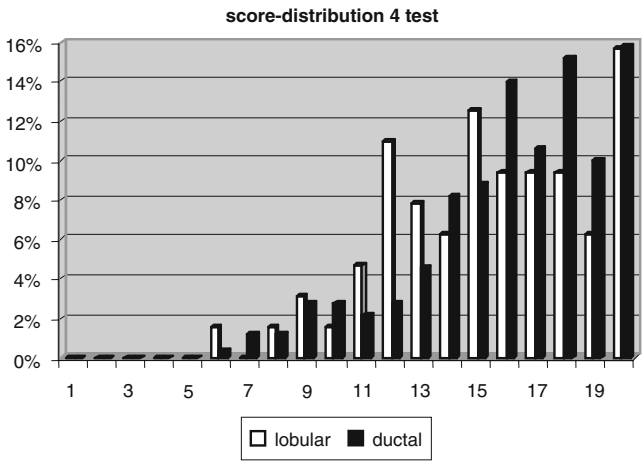

Fig. 1 Sum score distribution of ductal and lobular cancers using four diagnostic modalities

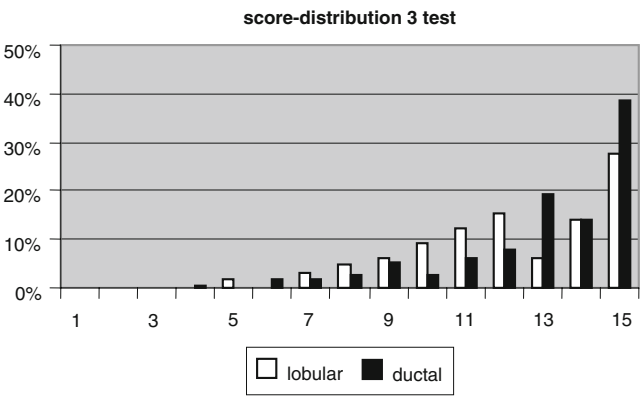

Fig. 2 Sum score distribution of ductal and lobular cancers using three diagnostic modalities

Table 3 Statistical analysis of sum-score diagnostics in case of ductal and lobular total groups

	4 test		3 test	
	Ductal	Lobular	Ductal	Lobular
N	330	65	330	65
Mean	16.15	15.34	13.05	12.19
SD	3.21	3.46	2.34	2.54
Median	17	15.5	14	12
Minimum	6	6	4	5
Maximum	20	20	15	15
Subgroup (%)	13.60	13.60	11.50	15.40

Subgroup in 4 test exam: the score is equal or under 12. Subgroup in 3 test exam: the score is equal or under 9.
SD Standard deviation

histologic type the order was the same: cytology has the best scores. Solely this method has scored always higher than 3 (indeterminate). Cytology was followed by mammography, ultrasound and in case of all four tools physical examination was the weakest. This was true for the whole groups and subgroups as well.

The distribution of radiomorphologic appearance of ductal and lobular total groups is not significantly different (p=0.0994) and the same applies to the ductal and lobular subgroups derived from either three tests (p=0.6306) or four tests (p=0.2587) assessment. Nevertheless both of subgroups show strongly significant difference from its total group: for ductal cancers (p=0.0001) from both the three and four test assessment, whereas in the lobular group (p=0.0139) using four, and p=0.0339 using only three examinations.

In the subgroups those radiomorphologic forms which are well known as diagnostic difficulties like asymmetric density or indeterminate microcalcifications are outweighing the typical stellate and well circumscribed appearances.

From their total group of the same histologic result the difference is significant, but no difference can be found between the two histologic subtypes (Fig. 3).

Discussion

Our study has proved that the radiologic diagnosis of lobular carcinoma is more difficult than the recognition of ductal one when all diagnostic modalities are evaluated together. The well known fact that the sensitivity of mammography is lower in lobular cancers [27, 28] is supported by the evidence from autopsies that multicentricity, multifocality, the presence of satellite lesions [24] and increased likelihood of bilateral synchronicity [25, 26] is more frequent in the this group.

As the main tumour body of a lobular carcinoma has almost the same radio-opacity as normal fibroglandular breast tissue [29] in these cases the proportion on mammographically occult lesions is twofold [32] compared to ductal. The figures vary from 10% [30] to 16% [31] according to different authors. The first novelty of this study is the examination of this phenomenon based on sum score, no such papers can be found in the literature. The other original idea is the use of the 5 scale BI-RADS a coding system for the evaluation of the sum score whereas the previous triple test studies were based on binary coding which simplifies the delicate issue of the limits of diagnostic sensitivity [11, 33]. Subsequently the introduction of the three grade system made possible the definition of a high and low score limit (6 and 4 are the respective values) which makes the diagnosis of malignancy (above the value of 6) and a benign change (below 4) very probable [13, 34, 35]. As the 5 grade BI-RADS scale was used in the current study even better separation of the cases becomes possible as opposed to the previous 3 grade classification with then the maximum value of 9, now in case of three diagnostic tests the range of the scale reaches 15 and using four modalities it goes up to 20. As it was proved in this study, the higher mean and median value with lower standard deviation of the ductal carcinoma cases makes better diagnosis possible as compared to lobular cancers. Summarizing the score distribution of the results in case of four diagnostic tools the higher scores—indicating malignancy—were more frequent in the ductal group compared to the lobular ones, but the significance level of the difference was at the borderline. The code distribution

Table 4 Statistical analysis of the diagnostic results in the low sum-score subgroups

	4 test		3 test	
	Ductal	Lobular	Ductal	Lobular
N	45	15	38	10
Mean	9.91	10.6	7.87	7.9
mean R	2.82	3.00	2.63	2.8
mean K	1.62	1.87		
mean U	2.47	2.53	2.37	2.1
mean C	3.18	3.2	2.87	3
Median R	3	3	3	3
Median K	1	1		
Median U	3	3	3	3
Median C	3	3	3	3

R Mammgraphy, *K* clinical examen, *U* sonography, *C* citology

Table 5 Comparision of efficacy power of the diagnostic modalities in case of total and the low sum-score subgroups of both ductal and lobular cancers

	Ductal			Lobular		
	Total	4 t subgr.	3 t subgr	Total	4 tsubgr.	3 t subgr.
R ave	4.26	2.82	2.63	4.03	3	2.8
R1%	4.5	22.22	29	4.6	6.66	12.5
R5%	55	6.66	5.3	46.15	6.66	0
K ave	3.08	1.62		3.11	1.87	
K1%	22.52	55.55		21.53	46.6	
K5%	19.93	0		23.07	0	
U ave	4.21	2.47	2.37	4.16	2.53	2.1
U1%	3.6	22.22	24	6.15	26.6	50
U5%	52	0	0	47.7	6.66	0
C ave	4.56	3.18	2.87	4.18	3.2	3
C1%	3.9	20	29	7.7	20	25
C5%	77.6	20	15.8	55.4	13.3	12.5

R ave average of the R scores, *4t subgr.* low sum-score subgroup from the 4 test diagnostic, *3t subgr.* low sum-score subgroup from the 3 test diagnostic

became significant between the two histologic groups using the modified triple test: two imaging modalities (mammography and ultrasound) plus cytology.

This proves that leaving out the weakest diagnostic method, clinical examination the difference becomes more pronounced. As it goes well with other author's experience physical examination on its own has low sensitivity [36]. The palpability alone is not an independent indicator, the diameter of the lesion correlated to the nodal state could be evaluated [37]. Knowing the result of the physical examination will not improve the diagnostic sensitivity of mammography [38], but can be crucial in the cases of mammographically occult tumors [39]. Symptomless cases usually come to the front by installation of new ancillary diagnostic methods for example scinti-mammography or MRI in screening of the population with strong family history [40, 41]. Separate score-analysis of symptomless subgroup directly—in order to evaluate diagnostic methods—has not yet been published. There is no significant difference between the symptomless ductal and lobular subgroups examining score distribution, mean, median and standard deviation values. The diagnostic power also does not change within histologic type or between the different groups: cytology is the most effective, followed by mammography and ultrasound, and physical examination is the least effective. The distribution of radiomorphologic appearance is the only field where significant difference could have been found between the subgroup and his whole histologic type, but not between the subgroups of different histology. In the subgroups significantly higher number of mammographically occult forms can be found along with indeterminate microcalcifications, asymmetric density and structural distorsion. The difference is marked (the significance level is a magnitude higher) in the ductal group where the difficult to recognize forms are rare and relatively more frequent in the lobular group.

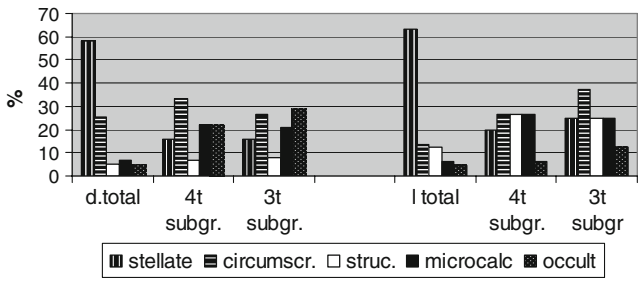

Fig. 3 Radiomorphologic distribution of ductal and lobular cancers in the whole group and in the lower sum score groups; *d.total*—ductalis whole group, *l total*—lobular whole group, *4t subgr*—subgroup from the four-test evaluation, *3t subgr*—subgroup from the three-test evaluation

Conclusion

The main point of our work is that on the basis of sum-score the diagnosis of lobular cancers is more difficult compared to ductal. Analysis of the symptomless, aspecific in appearance subgroups has lead to the conclusion that a malignant result which does not go along with the results of the other modalities or a specific radiomorphologic form can be the only indicator of malignancy so has to be assessed with great care.

Our results predicate further investigations: to analyse the diagnostic accuracy of ductal and lobular cancers in different age-groups, and tumor size. The value of sum-score could be refined by modification of its positive predictive value-weighted power.

Appendix

Table 6 The low score subgroup of ductal cancers using three or four tests

No	3 test duct.					4 test duct.					
	R	U	C	Sum score	Morphology	R	K	U	C	Sum score	Morphology
1	3	3	3	9	A	2	2	2	5	11	C
2	4	4	1	9	S	4	1	4	2	11	S
3	2	2	5	9	C	1	3	3	4	11	X
4	4	4	1	9	S	2	2	2	5	11	C
5	1	3	5	9	X	3	2	3	3	11	C
6	1	3	5	9	X	4	1	1	5	11	M
7	1	3	5	9	X	3	2	3	3	11	C
8	2	2	5	9	C	3	1	3	3	10	A
9	1	4	4	9	X	2	2	2	4	10	C
10	5	3	1	9	C	1	1	3	5	10	X
11	3	3	3	9	C	1	1	3	5	10	X
12	3	3	3	9	C	5	1	3	1	10	C
13	3	3	3	9	A	3	1	3	3	10	A
14	3	3	3	9	A	2	1	3	4	10	M
15	2	3	4	9	M	3	1	3	3	10	M
16	3	3	3	9	M	2	2	2	4	10	C
17	3	3	3	9	C	3	1	3	2	9	S
18	2	2	4	8	C	1	2	2	4	9	X
19	3	3	2	8	S	4	1	1	3	9	M
20	1	3	4	8	X	4	1	3	1	9	S
21	4	1	3	8	M	1	2	1	5	9	X
22	4	3	1	8	S	1	2	3	3	9	X
23	4	1	3	8	C	4	1	1	3	9	C
24	4	3	1	8	M	2	2	2	3	9	C
25	2	2	4	8	C	4	1	3	1	9	M
26	1	2	4	7	X	1	2	2	3	8	X
27	1	1	5	7	X	5	1	1	1	8	M
28	5	1	1	7	M	3	1	1	3	8	M
29	1	3	3	7	X	1	2	2	3	8	X
30	3	1	3	7	M	4	1	1	1	7	S
31	2	2	3	7	C	4	1	1	1	7	M
32	1	2	3	6	X	4	1	1	1	7	S
33	4	1	1	6	S	4	1	1	1	7	M
34	4	1	1	6	M	1	2	2	1	6	X
35	4	1	1	6	S	4	1	4	3	12	S
36	4	1	1	6	M	3	1	3	5	12	C
37	1	2	3	6	X	1	3	3	5	12	X
38	1	2	1	4	X	2	2	3	5	12	C
39						4	4	4	4	12	C
40						3	1	3	5	12	C
41						5	1	3	3	12	S
42						3	3	3	3	12	C
43						3	3	3	3	12	A
44						3	1	4	4	12	M
45						4	4	4	4	12	C

R Score of mammography, *K* score of physical exam, *U* score of sonography, *C* score of cytology,
Radiomorphology—*C* circumscribed, *S* stellate, *M* microcalcification, *A* asymmetric density, *X* occult

Table 7 The low score subgroup of lobular cancers using three or four tests

N	Lobula	3 test				lobular	4 test				
	R	U	C	Sum score	Morphol.	R	K	U	C	Sum score	Morphol.
1	3	3	3	9	A	3	1	3	4	11	A
2	3	3	3	9	A	2	1	3	5	11	C
3	4	1	4	9	M	3	1	3	4	11	A
4	1	3	5	9	X	2	2	2	4	10	C
5	2	2	4	8	C	4	1	1	3	9	S
6	4	1	3	8	S	2	2	2	3	9	C
7	3	4	1	8	C	3	1	1	3	8	S
8	3	1	3	7	S	3	1	1	1	6	M
9	2	2	3	7	C	3	3	3	3	12	A
10	3	1	1	5	M	4	1	3	4	12	M
11						3	3	3	3	12	A
12						4	3	1	4	12	M
13						3	4	4	1	12	C
14						1	3	3	5	12	X
15						5	1	5	1	12	S

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