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What is the effect of advanced diagnostic methods on sensitivity and survival in the multiple breast cancers? A systematic analysis and comparison

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ABSTRACT

The sensitivities of the advanced diagnostic methods appear to be higher than the conventional methods and do have the potential to prolong survival, in multiple (multifocal and multicenter) breast cancers. Thus, the aim of this study is to compare the sensitivities of advanced and conventional diagnostic methods and to reveal their effects on survival. The studies published about diagnosis and treatment methods in multiple breast cancer in literature were searched, analyzed, and the sensitivities obtained with advanced and conventional diagnostic methods were compared, and the results were evaluated statistically. The sensitivity obtained with the advanced diagnostic methods in multiple breast cancers was found to be significantly higher than the conventional methods ($p < 0.05$). The high sensitivities obtained with advanced diagnostic methods were found to have a high potential for survivial prolongation in multiple breast cancers. The use of advanced diagnostic methods in breast cancer screening programs, the investigation of tumor foci with molecular methods, increases the rate of diagnosis in multiple breast cancers. In the treatment of multiple breast cancers, a personalized treatment plan is made with the diagnosis of the molecular structure of the tumor foci. Thus, the recurrence rates are reduced, the survival is prolonged.

Key words: Multiple breast cancer; Sensitivity; Diagnosis; Treatment

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INTRODUCTION

Multiple breast cancers (MBC) occur quite frequently. In a study conducted by Badillo et al., it was reported that in 22 studies comprising 67,557 women multifocality was found as 9,5%.[1] MBCs may show different molecular structure, clinical course, different prognosis compared to unifocal breast cancers (UBC). Molecular tumoral heterogeneity is observed in MBCs and they may exhibit different biological behaviors compared to tumors in homogeneous molecular structure. Accordingly, the rate of survival in MBCs may differ from UBCs. Therefore, it is very important to make a molecular diagnosis for every cancer focus in MBCs.

The conventional diagnostic methods (CDM) for screening in BC are ultrasonography (USG) and mammography (MG).[2] Advanced diagnostic methods (ADM) are generally utilized in a limited number of patient groups, such as BC cases under follow-up. Noninvasive ADMs used to reveal the tumor foci in MBCs are; magnetic resonance imaging (MRI),[3] diffusion weighted imaging MRI,[4] contrast enhanced MG, contrast enhanced MRI,[5] magnetic resonance MG,[6] micro-computer tomography (micro-CT),[7] digital breast tomosynthesis with 3-D multi-leison channellized hotelling observer technique,[8] dynamic contrast enhanced breast MRI.[9]

Invasive ADMs used to reveal the molecular structure of the tumor in MBCs are; expression of miRNAs (miR-429,

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miR-182-5p, miR-96-5p) in tissue,[10] antigen Ki-67 (encoded by MK167 gene),[11] expression of long non-coding RNAs in tissue (C19orf33, C3orf52, C15orf48, C4orf19),[12] BRCA2 mutation carrier,[13] ErbB2 expression,[14] Vit-D receptor,[15] differential expression of ABCC11 and ABCB5 genes,[16] many other gene expression profiles.[17]

ADMs in MBCs have a high potential to increase sensitivity, and thus prolonged survival. The aim of this study is to compare the sensitivity of CDMs and ADMs in MBCs and to reveal the effects of ADMs on survival.

MATERIALS AND METHODS

The studies published about the diagnosis and treatment methods in MBCs (Table 1) were searched, analyzed, sensitivity rates obtained with advanced (GpA)[3-6,9] and conventional (GpB)[2] diagnostic methods were compared, and the results were evaluated statistically.

The criteria for inclusion of studies using ADM and CM in diagnosis of MBCs in our study are as follows:

1. The study was carried out in MBCs,
2. The use of noninvasive methods that can be used as screening tests,
3. The number of samples in the studies carried out is high and specific,
4. The work done has been done in the last 10 years.

Using these filtration criteria: Google Scholer, Scopus, Pubmed, ScienceOpen, BioMed Central, Academic Index, and relevant publications were included in our study.

SPSS (Statistical Package for the Social Sciences) 23.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, while continuous measurements were summarized as mean and standard deviation and the range, minimum-maximum were also given where necessary. Shapiro-Wilk test was used to determine whether the parameters in the study showed normal distribution. In comparing the continuous measurements between the groups, the distributions were checked and the Mann-whitney U test was used in those which did not show normal distribution. Statistical significance level was taken as 0.05 in all tests.

RESULTS

Table 1 shows the sample numbers, diagnostic method, years of study, and ethnicity in the studies included in our study.

The comparision of the percent sensitivities of ADMs (GpA) and CDMs (GpB) is shown in Figure 1. The sensitivities obtained with ADMs in MBCs was significantly higher ($p < 0.05$) compared to CDMs (Table 1).

The forest plot view of the sensitivity rates obtained by ADM and CM diagnostic methods in MBC cases is shown in Figure 2.

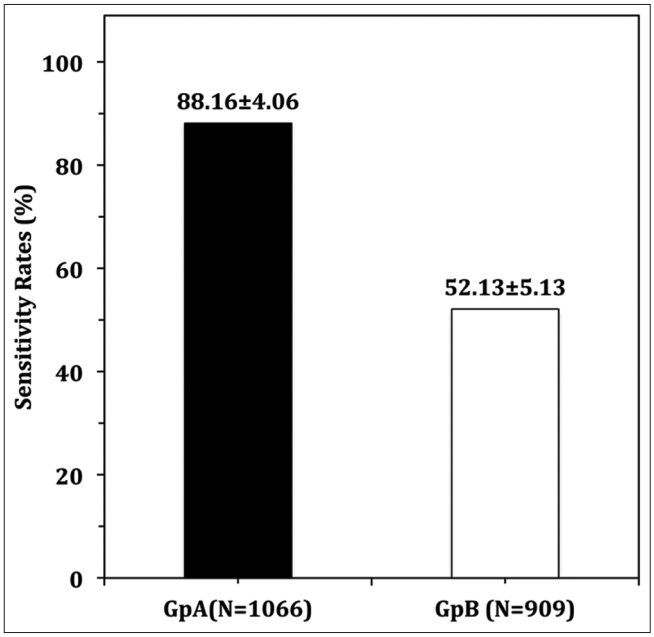

Figure 1: The comparison of the percent mean sensitivities of advanced diagnostic methods (GpA) and conventional diagnostic methods (GpB) is shown

Table 1: The number of samples in the studies included in our study, the method of diagnosis, the years of the study, and information on ethnicity

Authors	Ref. No	Sample No.	Sample Type	Sample Years	Ethnicity
Kim et al.	5	168	CEDMG	Nov 2016-Oct 2017	Korean
Kim et al.	5	168	CEMRI	Nov 2016-Oct 2017	Korean
Song et al	4	76	DCE-MRI	Jul 2014- Feb 2015	Korean
Song et al	4	76	DCE-MRI+DWI	Jul 2014- Feb 2015	Korean
Derias et al.	3	289	MRI	Jan 2011-Dec 2013	UK
Bakhtawar et al.	6	289	MRI+MG	Jan 2015-Feb 2016	Iranian
Bozzini et al.	2	303	USG	Oct 2000-Oct 2004	Italy
Bozzini et al.	2	303	USG +MG	Oct 2000-Oct 2004	Italy
Bozzini et al.	2	303	MG	Oct 2000-Oct 2004	Italy

Combined USG + MG applications in CDMs; the sensitivity increased significantly ($p < 0.05$) compared to the single ones[2] but however, in combined DCE-MRI + DWI, sensitivity was lower than DCE-MRI[4] (Table 2). Among the ADMs, the highest sensitivity (98.6 %) in MBCs was obtained with diffusion weighted imaging MRI method[4] and the lowest sensitivity (45.5%) in MBCs was provided in the MG method[2] (Table 2), (Figure 2). The accuracy and p values of invasive molecular diagnostic methods in MBCs are shown in (Table 3).[10,11,13,17]

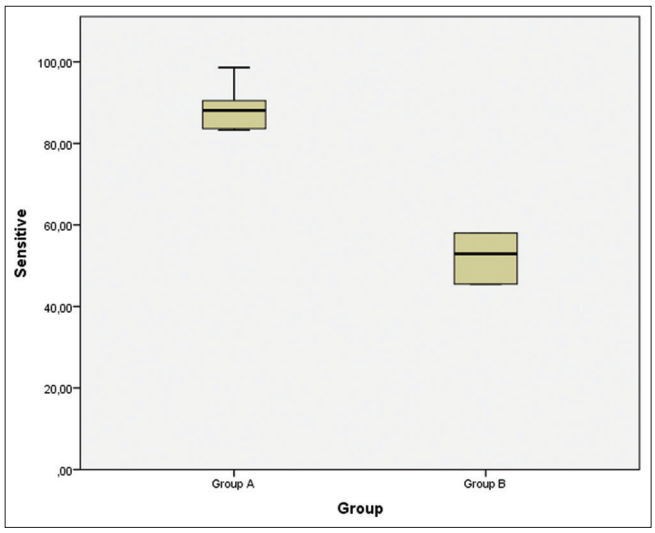

Figure 2: Forest plot of sensitivities obtained in diagnostic studies of ADM and CM in MBC cases

Table 2: The sensitivities of advanced (GpA) and conventional (GpB) diagnostic methods in multiple breast cancers

Group	N	% Sensitivity Rates (Mean ± S.D.)	p
Group A	1066	88.16 ± 4.06	P ≤ 0.001
Group B	909	52.13 ± 5.13	

Table 3: Comparison of sensitivities provided with advanced and conventional diagnostic methods in multiple breast cancers

Method	N	Mean ± S.D.	Range	References
CEDMG	168	83.45 ± 0.15	83.30 – 83.60	Kim et al.
CEDMRI	168	83.45± 0.15	83.30 – 83.60	Kim et al.
DCE-MRI	76	98.60 ± 0.00	98.60 – 98.60	Song et al.
DCE-MRI+DWI	76	90.00 ± 0.00	90.00 – 90.00	Song et al.
MRI	289	88.10 ± 0.00	88.10 – 88.10	Derias et al.
MRI+MG	289	90.50 ± 0.00	90.50 – 90.50	Bakhtawar et al.
USG	303	52.90 ± 0.00	52.90 – 52.90	Bozzini et al.
MG+USG	303	58.00 ± 0.00	58.00 – 58.00	Bozzini et al.
MG	303	45.50 ± 0.00	45.50 – 45.50	Bozzini et al.
Total	1975	71.58 ± 18.54	45.50 – 98.60	

DISCUSSION

MBCs might multifocal (MF) or multicentric (MC). In a study conducted by Kanumori et al., they compared clinical findings, subtypes, estrogen receptor (ER), progestron receptor (PR), HER2, tumor size, triple negative BC (TNBC) types in 1231 UBC, 169 MF, 95 MC BC cases.[18] According to the results of their study, MCBCs showed more aggressive clinical course than MFBCs, tumor (T) was larger, more common in young people, regional lymph node metastasis (RLNM) and lymphovascular invasion, they reported that RLNM is the only independent predictive factor, and because of these different properties, MF and MC are diseases of different biological character.[18]

Diagnoses are important because MBCs generally show different clinical course and survival compared to UBCs and different treatment methods are performed accordingly.

Alexander et al., in 79 MF cases of BC; reported that there was more tumor focus and regional lymph node metastasis in these cases due to the high tendency to lymphovascular invasion.[19] In a meta analysis, Houvenaeghel et al., performed that overall survival (OS) was shorter in MFMC BCs than UBCs.[20] Lang et al., in 3441 UBC and 156 MFMC BC cases; they reported that the prognosis was worse, T was greater, RLNM and Ki-67 was higher in MFMC BC cases.[11] Fang et al., in 10 studies BC compared to the data provided in 19,272 patients; they reported that local recurrence (LR) was higher in MBC cases.[21]

However, Karakaş et al., 323 MFMC BC; UBC and MFMC compared disease-free survival (DFS) and OS rates in BCs and reported no significant difference between them.[22] Jivanovic et al., compared 5-year survival in 83 MBC and 501 UBC cases and did not find a statistically significant difference.[23] In a study by Fushimi et al., they compared 136 MFBC cases and 598 UBC cases, they reported that the only factor affecting prognosis was T size.[24]

One of the factors that increases the importance of diagnosing in MBC cases; is the possibility of tumoral heterogeneity and accordingly grade heterogeneity. In a study by Duan et al., 16 of 146 MFMC BC cases had tumoral heterogeneity (different molecular phenotype).[25] According to the authors, OS and DFS were shorter in MFMC BC cases than in UBC cases.[25]

According to the authors, it has been reported that molecular phenotyping can be performed in all MBC cases and recurrence rates can be reduced and DSS can be prolonged with appropriate therapeutic approaches.[25]

In a study by Boros et al., in 806 MFMC BC cases; compared the histological type of the tumor with the histological grade

and RLNM of the primary tumor from Nottingtam and found that it showed intertumoral heterogeneity.[26]

In a retrospective study conducted by Mosbah et al., in 205 MFMC BC cases in which 178 cases were of the same grade and 89% were of the same histological type; they reported that immunohistochemical findings were the same in 86% of cases.[27] Ilic et al., reported that the immunohistochemical parameters were largely the same in 334 ILBC patients and that there was no tumor heterogeneity.[28]

However, Norton et al., in 11 MFMC infiltrative lobular BC (ILBC) patients with the same immunohistochemical findings (ER+, HER2-); they investigated tumor heterogeneity by examining 730 gene expression profiles, pathway activations, and 80 gene copy numbers.[17] According to the results of their study, they found that 35 genes were upregulated and 34 genes were downregulated. These results demostrate that there may be heterogeneity between tumor foci in MBC cases and that only immunohistochemical findings are not sufficient in determining tumor heterogeneity.[17]

The most important factor affecting the prognosis in MBCs is tumor heterogeneity (molecular phenotype differences of the tumor) and can be seen intertumorally, intratumorally or among patients.[17]

In this study conducted by Norton on MF ILBC patients, more than half of the 730 gene expression analyzes detected tumoral heterogeneity in all 3 forms.

According to the results of this study, it has been reported that tumoral heterogeneity in MF ILBC patients is the most important factor hiding potential prognostic factors.[17]

Uthamalingam et al., studied on pathologically proven 124 UBC and 49 MF/MC BC cases and they found that 16 of 49 MF/MC BC cases showed intertumoral heterogeneity (32.65%), and they reported that thus, each focus should be evaluated separately in MF/MC cases.[29] In a prospective study by Onisai et al., 198 cases of UBC, 31 MF, and 6 MC were evaluated, and it was reported that staging should be done according to the most aggressive focus in MBCs.[30]

According to the authors, in MBC cases with intertumoral heterogeneity, inadequate treatment rates can be reduced by staging patients not according to the largest single tumor, but according to the most aggressive tumor and cumulative tumor burden.[30]

Desmedt et al., investigated genetic heterogeneity in 36 ductal MFBC cases, where ER and HER 2 values and grades were the same.[31]

Genetic heterogeneity has been shown in 12 of the cases oncological mutations. For this reason, they reported that personalized molecular diagnosis and treatment should be performed in MFBC cases.[31] However, in a study by Grabenstetter et al., they could not find molecular and biological heterogeneity in 53 ipsilateral MBC cases with the same histological structure.[32]

Since different treatment methods are applied in MBC and UBC cases, increased sensitivity in diagnosis with ADMs and MBC cases; it also has a high potential to affect the choice of treatment methods.

In a retrospective study conducted by Winters et al., in 24 studies, the mean follow-up period was 59.5 months in 3537 ipsilateral MBC cases.[33] They reported that there was no statistically significant difference in local recurrence rates (LRR) between patients with breast conservative therapy (BCT) and mastectomy (M), but many of these studies were of moderate quality and biased, and thus, for the sake of clarity more randomized studies were needed.[33]

In a study by Massanat et al., they reported that BCT is not contraindicated in selected cases in MF/MC BCs.[34] In a similar study, Koppiker et al., proposed extreme oncoplasty (EO) instead of BCT in MF/MC cases.[35] Nijenhuis et al., reported that BCT may performed in most MF/MC cases.[36] Tan et al., performed BCT in 35 of 41 MF/MC cases, reported that only 1 patient had distant metastases after a 45-month follow-up.[37] Many authors have reported that BCT can be performed in some selected MF/MC cases.[20,34,37,38] However, in a study conducted by Edwards et al., 414 of 567 cases with BCT were reviewed, and histological tumor positive margin was found in 23%, and residual tumor was found in 61 cases.[39]

In a study by Akbulut et al., miR-429 expression was shown to increase only in MBCs, while miR-182-5p and miR-96-5p expression increased in both MBC and UBCs.[10]

In a study by Lameijer et al., 3.1% cases were recalled on 130338 screening mammograms, 6.4% of them had an ipsilateral new tumor focus and 21.5% of these tumor foci were found malignity.[40] Many of these cases have been reported to be MF/MC BC.[36]

In another study conducted by Lai et al., 1468 BC cases were divided into 2 groups, only MG and USG were performed in GpA patients, and in GpB patients in addition to MG and USG, MRI was performed.[41] In the same study; BCT were performed in GpA, M were performed in GpB cases. Surgical margin tumor positivity was found 9.0% in GpA and 5.0% in GpB.[41] MF/MC cases were significantly higher in GpB patients than in GpA.[41]

In this study, when sensitivities were compared in the diagnosis of MBCs, it was found that a higher sensitivity ($p < 0.05$) was obtained with ADMs compared to CDMs (Table 2), (Figures 1-2).

In several studies, tumor foci were found to exhibit molecular biological heterogeneity in MBCs.[17,26,29-31] According to the results obtained in this study, the most sensitive method among CDMs is the combined USG + MG method (58.0%)(Table 2). Interestingly, however, the sensitivity in DCE-MRI + DWI combined ADM has been reported to be lower (90.0%) than the DCE-MRI method (98.6)[4] (Table 3), (Figure 3).

According to the findings provided in these studies, tumor foci and molecular structure of all foci can be widely determined in MBCs (Table 4). According to the findings of some authors included in this study, tumoral heterogeneity could be detected in tissue by molecular marker analysis in many MBC cases with the same immunohistochemical findings.[17,26,30,31] It has been demonstrated by these studies that immunohistochemical tests, which has been an important method in determining prognosis and treatment methods for many years, can not always adequately explain the molecular biological structure of the tumor. This case is an important proof that advanced diagnostic methods significantly affect prognosis and treatment. However, all of these diagnostic tests that are used to determine the molecular structure of the tumor in MBCs are invasive techniques.

In this study, a study with molecular markers in serum was not found in the MBCs in the literature. With ADMs in MBC patients; detection of tumor positivity at the surgical margin,[39,41] local recurrence,[21,39,40] possibility of another tumor focus in a different biological structure,[19,21,26] or a different stage,[25,29,30] the application rate of wrong or inappropriate treatment methods will decrease,[34,41] personalized treatment will be provided,[10,31] and the survival will be prolonged.[11,20,24,25]

In a study conducted by Hu, the relationship between sociodemographic index (SDI), incidence of BC and mortality was examined.[42] According to the results of the study; BC incidence and mortality have been observed to increase, especially in countries with low SDI. One of the most important reasons for this is the lack of access to ADMs in these countries.[42]

In countries with poor socioeconomic status, the diagnostic method in which the highest sensitivity and specificity rates can be achieved at the lowest cost in MBCs: MRI +MG.[3,6,42] Based on the Markov model by Kaiser, only mammography and MRI + MG were compared for the BC diagnostic

Table 4: Accuracy and p values in diagnostic tests performed with biomarkers in multiple breast cancers tissues reported in the literature

Biomarkers	MBC	UBC	p	Refences
miR-429 (UR only in MBC)	26	31	0.161	Akbulut et al.
miR-182-5p (UR both in MBC and UBC)	26	31	<0.001	Akbulut et al.
miR-96b-5p (UR both in MBC and UBC)	26	31	0.938	Akbulut et al.
miR- 1 -3p (DR both in MBC and UBC)	26	31	0.001	Akbulut et al.
miR-10b-5p (DR both in MBC and UBC)	26	31	0.001	Akbulut et al.
ABCC11 (UR in MBC)	156	130	<0.05	Lang et al.
ABCB5 (DR in MBC)	156	130	<0.05	Lang et al.
C19orf33, C3orf52, C15orf48 (UR in MBC)	156	130	<0.05	Lang et al.
4orf19 (DR in MBC)	156	130	<0.05	Lang et al.
BRCA2 (UR in MBC)	52	159	<0.001	McCrorie et al.
35 gene (UR)	11	-	<0.05	Norton et al.
34 gene (DR)	11	-	<0.05	Norton et al.

DR, Downregulated; UR, Upregulated; MBC, Multiple breast cancer; UBC, Unifocal breast cancer

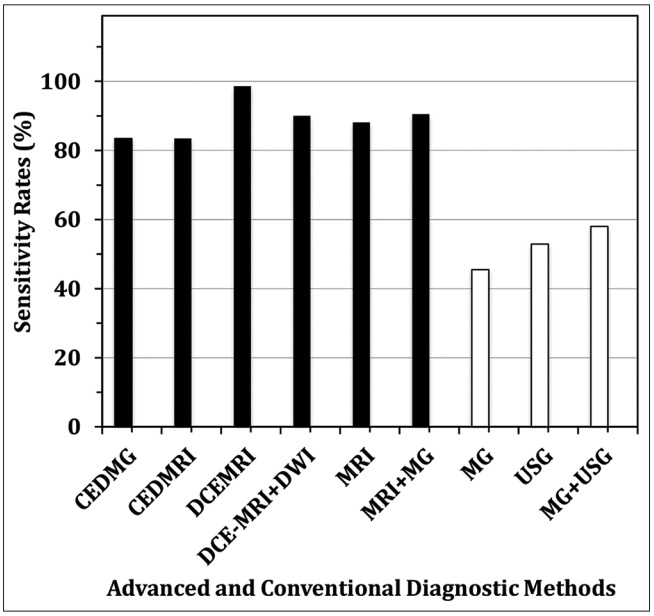

Figure 3: The comparison of percent sensitivities obtained with advanced (ADMs) and conventional diagnostic methods (CDMs) in multiple breast cancers is shown

screening test in the medium risk group, as a result, the sensitivities between 70-100% specivities between 70-100% and overall efficiency (cost-effectiveness) were found to be between 4.68-4.70 QALYs in MRI+MG.[43]

In a study by Artigues for the first time on this subject; cir miRNA-30b-5p analysis in serum is the easiest to apply, noninvasive, highest sensitivity (78.3%) and specificity (72.3%), cost-effective diagnosis and screening method that can be effective in all types of BCs and early stages.[44] Despite

these results, this study was not included among ADMs in our study because it was not performed in MBC cases.

The limitation of our study is that a noninvasive, cost-effective molecular diagnosis method that can determine tumor phenotypes in MBC patients, screening and personalized treatment programs can be applied, is not available in the literature and cannot be included in our study.

CONCLUSION

Using ADMs in BC screening programs, investigation of tumor foci by molecular methods; increases the diagnostic rates of MBCs. In MBCs, a personalized treatment plan is made with the diagnosis of the molecular structure of the tumor foci before treatment. Thus, the recurrence rates are reduced, the survival is prolonged. However, more studies are needed in order to reveal ideal molecular diagnostic methods in MBCs.

Abbreviations

ADM: Advanced diagnostic methods; BC: Breast cancer; BCT: Breast cancer therapy; CDM: Conventional diagnostic methods: DCE: Dynamic contrast enhaced MRI: DWI: Diffusion weighted imaging: EO: Extreme oncoplasty; ILBC: Infiltrative lobular breast carcinoma; LRR: Local reoccurence rate; M: Mastectomy; MBC: Multiple breast cancer; MC: Multicentric cancer; MF: Multifocal cancer; MG: Mammography; Micro-CT: Micro-computor tomography; MRI: Magnetic resonance imaging; RLNM: Regional lymph node metastasis; TNBC: Triple negative breast cancer; UBC: Unifocal breast cancer; USG: Ultrasonography; SDI: Sociodemographic index.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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