



LONG-TERM SURVIVAL EFFECTS OF PREOPERATIVE BREAST MRI IN PATIENTS WITH BREAST-CONSERVING SURGERY

Ahmet Serkan Ilgun¹, Dauren Sarsenov², Gul Alco³, Alper Ozturk⁴, Filiz Agacayak⁵, Filiz Elbuken⁶, Zeynep Erdogan⁷, Kezban Nur Pilanci⁸, Cetin Ordu⁹, Fatma Aktepe¹⁰, Gursel Soybir¹¹ and Vahit Ozmen¹²

¹Department of Surgery, Demiroglu Bilim University, Istanbul, Turkey;

²Department of Surgery, Mater Dei Hospital, Msida, Malta;

³Department of Radiation Oncology, Gayrettepe Florence Nightingale Hospital, Istanbul, Turkey;

⁴Department of Surgery, Biruni University Medical School, Istanbul, Turkey;

⁵Department of Radiology, Istanbul Florence Nightingale Hospital, Istanbul, Turkey;

⁶Department of Radiology, Yeditepe University Medical School, Istanbul, Turkey;

⁷Physical Therapy and Rehabilitation Center, Biruni University Medical School, Istanbul, Turkey;

⁸Department of Medical Oncology, Memorial Bahcelievler Hospital, Istanbul, Turkey;

⁹Department of Medical Oncology, Gayrettepe Florence Nightingale Hospital, Istanbul, Turkey;

¹⁰Department of Pathology, Sisli Memorial Hospital, Istanbul, Turkey;

¹¹Department of Surgery, Sisli Memorial Hospital, Istanbul, Turkey;

¹²Department of Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

SUMMARY – The benefit of breast magnetic resonance imaging (MRI) in breast-conserving surgery (BCS) is unclear. Our study compared breast cancer patients with and without preoperative breast MRI and their long-term oncologic outcomes are reported. A total of 1378 BCS cases with early breast cancer between 1996 and 2017 were reviewed. Patients with carcinoma *in situ* or neoadjuvant treatment or having breast MRI after tumor excision were excluded. Of 1378 patients, 270 (19.5%) had preoperative MRI. There were no significant differences regarding T and N stage and molecular subtypes between the groups. Surgical margins were significantly wider in the breast MRI group. Five-year overall survival (OS) was 96.9% in the MRI group and 94.3% in the control group, and this difference was not significant ($p=0.11$). Five-year local-regional recurrence-free survival (LRFS) was not significantly different either (98.8% and 96.5%, respectively, $p=0.41$). When analyses were repeated only for patients with hormone receptor-negative or triple-negative breast cancer, there was still no significant difference in OS, LRFS, or disease-free survival. In conclusion, MRI does not seem necessary in all patients undergoing BCS. New prospective randomized controlled trials are needed to determine appropriate use of preoperative MRI and its effects on oncologic outcomes in early breast cancer patients.

Key words: *Breast cancer; Breast MRI; Breast-conserving surgery; Overall survival; Local failure; Oncologic outcome*

Introduction

Surgical treatment of breast cancer has evolved from radical mastectomy to breast-conserving surgery (BCS). Today, BCS with additional radiation therapy is the treatment of choice for early breast cancer¹⁻³. By further

Correspondence to: *Ahmet Serkan Ilgun, MD, FEBS, Istanbul Florence Nightingale Hospital İzzetpaşa Mah, Abide-i Hürriyet Cd No:166, 34381 Şişli/İstanbul, Turkey*
E-mail: ilgunserkan@yahoo.com

Received December 15, 2020, accepted August 23, 2021

developing oncoplastic surgical techniques, huge tumors can be treated without mastectomy with satisfying cosmetic results⁴. However, with the more frequent use of BCS, multifocality and close/positive surgical margins have become an actual problem that requires re-excisions or mastectomy⁵. Patients with multifocality, positive lymphovascular invasion, positive axillary lymph nodes, or positive surgical margins are more likely to have residual tumors in re-excision or mastectomy specimens than others⁶. Re-excision or mastectomy could be avoided in some patients with close margins with favorable factors such as unifocal tumors or node-negative diseases⁶. Additional surgical procedures result in physical and psychological stress, extended hospital stays, and a higher likelihood of complications such as infections, hematomas, seromas, and fat necrosis⁷.

In patients who undergo BCS, the traditional preoperative imaging modalities of the breast are mammography and ultrasound. However, it is known that other invisible tumor foci beyond 2 cm the index tumor are present in up to 16%-27% of patients⁸. Magnetic resonance imaging (MRI) is more sensitive in detecting additional foci of disease than mammography and clinical breast examination^{9,10}. Furthermore, preoperative evaluation with MRI in patients with high breast density may help find additional tumor(s) and obtain precise tumor size and localization¹¹. Therefore, the use of preoperative contrast-enhanced MRI may better identify candidates for BCS and reduce re-excision and recurrence rates after surgery. On the other hand, MRI in the preoperative setting may cause increased mastectomy rates or unnecessary biopsies¹². It is also expensive and can cause delays in treatment¹³.

Our study aimed to evaluate the effect of preoperative MRI on long-term survival in patients undergoing BCS in our breast department.

Patients and Methods

In this retrospective institutional review board-approved study, 1704 patients having undergone BCS for early-stage breast cancer in Istanbul Florence Nightingale Breast Health Center between 1996 and 2017 were identified. After excluding patients diagnosed with carcinoma *in situ*, those who underwent neoadjuvant treatment, had breast MRI after tumor excision, underwent mastectomy due to broad margin involvement after BCS, or were not followed up after surgery, 1378 patients remained and composed the entire study

group. Two hundred and seventy patients had preoperative MRI and made up the MRI group. The patients underwent breast MRI for diagnostic purposes or determination of suitability for BCS before or after diagnostic core biopsy. The control group was made up of 1108 patients without preoperative breast MRI. All surgical treatments were performed according to oncologic principles at the time by a single surgeon. Re-excision was done if intraoperative or postoperative specimen examination showed positive or close (<2 mm) surgical margin(s). All patients were evaluated and discussed in the multidisciplinary tumor board regarding adjuvant treatment options. Locoregional recurrence was defined as any local failure in the ipsilateral breast or regional lymphatic fields. Disease-free survival (DFS) was defined as the period from diagnosis to the first disease recurrence at a local, regional or distant site, or the diagnosis of contralateral breast cancer.

Categorical variables of patients and tumor characteristics were compared using Pearson's χ^2 -test or Mann-Whitney U test, as appropriate. The log-rank test was used to compare differences between survival curves derived by the Kaplan-Meier method. The Cox proportional hazard regression was used to model clinical outcomes such as overall survival (OS), local recurrence-free survival (LRFS), and DFS after BCS. All p-values from two-sided tests and a p-value ≤ 0.05 were considered statistically significant. Statistical analyses were performed with SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA).

Results

Of 1378 patients, 270 (19.5%) had preoperative MRI. The patient median age was 50 (range, 23-88) years, and patients with preoperative MRI were significantly younger than patients in the control group (44 (26-81) *vs.* 51 (23-88), respectively, $p < 0.001$). Preoperative MRI use increased after 2010 and became significantly higher after 2015 (Table 1).

There were 62 (23.3%) patients with multifocal tumors in the MRI group. Breast MRI could identify multifocal disease with 79% sensitivity and 77% specificity. Also, MRI could predict axillary lymph node involvement with 37.5% sensitivity and 88% specificity.

There were 48 (3.5%) patients who underwent re-excision after lumpectomy. Out of 48 patients, 45 (4.2%) patients were in the non-MRI group, whereas only three (1.1%) patients were in the MRI group ($p = 0.017$).

Table 1. Patient and tumor characteristics

	Control group, n (%)	Study group, n (%)	p-value
Years			<0.001*
1996-2000	23 (2.1)	0	
2000-2004	96 (8.7)	4 (1.5)	
2005-2009	271 (24.5)	11 (4.1)	
2010-2014	526 (47.5)	136 (50.4)	
2015-2017	192 (17.3)	120 (44.1)	
Age (yrs)	51 (23-88)	44.5 (26-81)	<0.001 ^φ
Age group (yrs)			<0.001*
20-29	20 (1.8)	4 (1.5)	
30-39	126 (11.4)	67 (24.8)	
40-49	335 (30.2)	117 (43.3)	
50-59	288 (26.0)	46 (17.0)	
60-69	216 (19.5)	30 (11.1)	
70-79	100 (9)	5 (1.9)	
80-89	23 (2.1)	1 (0.4)	
T stage			0.94*
T1	638 (57.6)	154 (57)	
T2	449 (40.5)	110 (40.7)	
T3	21 (1.9)	6 (2.2)	
N stage			0.81*
N0	711 (64.2)	169 (62.6)	
N1	238 (21.5)	64 (23.7)	
N2	94 (8.5)	20 (7.4)	
N3	65 (5.9)	17 (6.3)	
Margin width (mm)	10 (0-40)	6 (0-20)	<0.001 ^φ
Re-excision			0.017*
No	1034 (95.8)	262 (98.9)	
Yes	45 (4.2)	3 (1.1)	
Tumor histopathology			0.44*
Invasive ductal	866 (80)	217 (80)	
Invasive lobular	77 (7)	14 (5)	
Other	139 (13)	39 (15)	
Unifocal/multifocal disease			<0.001*
Unifocal	946 (87.7)	204 (76.7)	
Multifocal	145 (13.3)	62 (23.3)	
Molecular subtype			0.44*
Lum A	430 (40.0)	96 (35.8)	
Lum B	467 (43.5)	123 (45.9)	
Her2 +	60 (5.6)	13 (4.9)	
TNBC	117 (10.9)	36 (13.4)	

* χ^2 -test; ^φMann-Whitney U test; TNBC = triple-negative breast cancer

Table 2. Survival: univariate analysis

	n	OS	p-value	LRF5	p-value	DFS	p-value
Preoperative breast MRI			0.11*		0.41*		0.09
No	1108	94.3%		96.5%		92.8%	
Yes	270	96.9%		98.8%		98%	
Age (yrs)			0.30*		0.09*		0.52
<40	218	95%		94.5%		92.6%	
≥40	1160	94%		97.1%		93.8%	
T stage			0.006*		0.16*		0.015*
T1	792	97%		97.3%		95%	
T2	559	90%		96%		91.7%	
T3	27	95.5%		94.1%		84.5%	
LN involvement			0.003*		0.26*		0.024*
no	880	96.3%		97.1%		94.4%	
yes	498	91.3%		96.1%		91.8%	
HG			0.023*		0.058*		0.002*
I+II	705	96.7%		98.7%		97%	
III	620	92.7%		95%		90.5%	
LVI			0.001*		0.51*		0.024*
No	722	96.6%		97.7%		95.7%	
Yes	614	92.5%		96.3%		91.8%	
ER			<0.001*		<0.001*		<0.001*
(-)	266	87.5%		89.4%		86.4%	
(+)	1096	96.4%		98.6%		95.2%	
PR			<0.001*		<0.001*		0.024*
(-)	404	90.1%		92.8%		90.5%	
(+)	957	96.4%		98.5%		94.7%	
Her2			0.42*		0.02*		0.28*
(-)	1078	94%		97.7%		94.5%	
(+)	256	97.2%		93.5%		90.8%	
Molecular subtype			<0.001*		<0.001*		0.007*
Lum A	526	97.8%		99.2%		96.3%	
Lum B	590	94.3%		97.8%		94%	
Her2 +	73	84.2%		84%		84%	
TNBC	153	85%		92.1%		89.3%	
Hormone receptor			0.001*		<0.001*		0.001*
(-)	226	89%		89.5%		87.7%	
(+)	1116	96%		98.5%		95.1%	

*Kaplan-Meier method; OS = overall survival at 5 years; LRF5: local recurrence-free survival at 5 years; DFS = disease-free survival at 5 years; MRI = magnetic resonance imaging; LN = lymph node; HG = histologic grade; LVI = lymphovascular invasion; ER = estrogen receptor; PR = progesterone receptor; TNBC = triple-negative breast cancer

There were no significant differences regarding T and N stage, histopathologic types, or molecular subtypes between the two groups. However, surgical margins were significantly wider in patients without preoperative breast MRI (Table 1).

Our median follow-up time was 56 (1-267) months. Among 1378 patients, 103 patients died during the follow-up period. Five-year OS rates were 96.9% in the MRI group and 94.3% in the control group, and this difference was not significant (p=0.11) (Table 2). When the analyses were repeated only for patients younger than 40, there was no survival difference between the two groups either (p=0.71).

In univariate analyses, T stage, lymph node involvement, histologic grade, lymphovascular invasion, estrogen receptor (ER) and progesterone receptor (PR) negativity significantly affected OS (Table 2).

In multivariate analyses, only hormone receptor negativity, lymph node involvement, and presence of lymphovascular invasion were significantly related to OS (Table 3).

Table 3. Overall survival: multivariate analysis

	HR	95% CI	p-value
Preoperative MRI (+ vs. -)	0.439	0.17-1.09	0.081
Molecular subtype			
Lum A vs. TNBC	0.306	0.171-0.548	<0.001
Lum B vs. TNBC	0.408	0.237-0.7	0.001
Hormone receptor (- vs. +)	2.26	1.428-3.605	0.001
LVI (+ vs. -)	1.83	1.108-3.032	0.018
LN involvement (+ vs. -)	1.57	1.001-2.489	0.049

TNBC = triple-negative breast cancer; LVI = lymphovascular invasion; LN = lymph node; MRI = magnetic resonance imaging; HR = hazard ratio; CI = confidence interval

During the follow-up, 56 (4%) patients developed locoregional recurrence. Five-year LRFS rates were not significantly different between the two groups (96.5%

and 98.8%, respectively, p=0.418) (Table 2). Only triple-negative and HER-2 (+) molecular subtypes were significantly related to lower LRFS rate (Table 4). In multivariate analyses, only hormone receptor negativity had significant adverse effects on LRFS (Table 4). Sixty-one patients developed systemic recurrence during follow-up, and DFS rate was 98% in the MRI group and 92.8% in the control group (p=0.099).

Table 4. Locoregional recurrence: multivariate analysis

	HR	95% CI	p-value
Preoperative MRI (+ vs. -)	0.569	0.17-0.81	0.35
Molecular subtype			
TNBC vs. Lum A	2.653	0.17-0.79	0.01
TNBC vs. Lum B	2.716	0.18-0.84	0.017
TNBC vs. Her 2	2.042	0.84-4.78	0.113
Her2+ vs. Lum A	5.443	2.37-12.47	<0.001
Her2+ vs. Lum B	5.027	2.19-11.5	<0.001
Hormone receptor (- vs. +)	3.655	2.022-6.610	<0.001
HG (1+2 vs. 3)	1.416	0.60-3.30	0.42
LN involvement (+ vs. -)	1.438	0.79-2.60	0.23
Age (yrs) (<40 vs. ≥40)	0.76	0.38-1.55	0.46

TNBC = triple-negative breast cancer; LN = lymph node; HG = histologic grade; MRI = magnetic resonance imaging; HR = hazard ratio; CI = confidence interval

Of 153 patients with triple-negative disease, 36 (23.5%) patients had preoperative MRI. Three of them died of systemic metastases, and one of them developed local recurrence. There was no significant difference regarding OS and LRFS rates between patients with triple-negative breast cancer in the two groups. When analyses were repeated only for patients with hormone receptor-negative disease, there was no significant between-group difference in OS, LRFS, or DFS (Table 5).

Table 5. Survival analysis in patients with hormone receptor negative disease

	n	OS	p-value	LRFS	p-value	DFS	p-value
Preoperative MRI (+)	49	90.3%	0.97	97.3%	0.25	97.3%	0.34
Preoperative MRI (-)	177	89.3%		88.5%		86.2%	

OS = overall survival at 5 years; LRFS = local recurrence-free survival at 5 years; DFS = disease-free survival at 5 years; MRI = magnetic resonance imaging

Discussion

This study analyzed 270 patients with preoperative breast MRI out of 1378 patients diagnosed with clinically early-stage breast cancer and having undergone BCS. We were specifically interested in clinical outcomes such as OS, LRFs, and DFS between patients with and without preoperative MRI.

Clinical use of preoperative breast MRI gradually increased over time and significantly after 2010 in patients having undergone BCS (Table 1). This increase in MRI use might be related to change in the screening mammography age from 50 to 40 in 2010; this arrangement was made because half of the breast cancer patients in Turkey were younger than 50 years¹⁴. The increase in free cancer screening programs, early detection, education centers, and mobile screening systems increased the early diagnosis of breast cancer in young women with dense breasts. Thus, it contributed to the more frequent use of breast MRI. Furthermore, technological improvements and easy access to MRI may have played a part. Breast MRI better visualizes the affected and contralateral breast in the preoperative setting and improves local control by detecting additional cancer.

Multiple studies have demonstrated that breast MRI detects foci of cancer not seen with other imaging modalities in 10% to nearly 30% of cases^{10,11}.

In their study, Liberman *et al.* found that MRI imaging identified additional ipsilateral cancer sites in 27% of women, and the yield was highest in women with a family history of breast cancer or infiltrating lobular histology of index cancer¹⁰. In another study evaluating the impact of preoperative MRI on BCS by Pengel *et al.*¹⁵, incomplete excision rate was not significant between the MRI and non-MRI groups even though the MRI group had lower rates (13.8% *vs.* 19.4%). In the same study, when stratified according to tumor type rather than lobular histology, incompletely excised infiltrating ductal carcinoma was significantly associated with absence of breast MRI¹⁵. In a randomized control trial (COMICE), Turnbull *et al.* showed that reoperation rates in patients with preoperative MRI were not lower than in patients without MRI¹⁶. In our study, the MRI group margin width was significantly lower than in the control group (6 mm *vs.* 10 mm). This could be owing to development of breast cancer treatment with a decreased adequate surgical margin width and the recent 'no ink on tumor' approach, and the fact that relatively newly diagnosed

patients more frequently had MRI. Our overall re-excision rate was 3.5%. This relatively low rate could result from delicate intraoperative specimen evaluation by a very experienced breast pathologist. The re-excision rate in our study was significantly lower in the MRI group. It may have been due to better preoperative assessment resulting in reduced rates of incomplete excision.

Another critical issue in the clinical use of preoperative breast MRI is its possible benefits in oncologic outcomes. However, controversies exist whether detecting additional cancers by breast MRI is beneficial for survival. The possible effects of preoperative MRI on breast cancer local control are doubtful since randomized trials of BCS and mastectomy have demonstrated nearly equivalent results^{17,18}. In their retrospective study, Fisher *et al.* demonstrated decreased locoregional recurrence in patients undergoing BCS with preoperative MRI in a 40-month follow-up¹⁹. On the other hand, two other retrospective studies showed no local recurrence or overall survival improvements if preoperative breast MRI was performed^{20,21}. Vapiwala *et al.* did not find a survival advantage of preoperative MRI in patients undergoing BCS in their 13-year follow-up²⁰. Similarly, in a study by Sung *et al.*, survival benefit or local failure difference was not determined in their 8-year follow-up²¹. Both studies included not only patients with invasive cancer but also patients with noninvasive disease. In another retrospective study examining patients over age 65 who underwent BCS, no significant difference in breast cancer-specific survival and OS were found between those who had preoperative breast MRI and those who did not²². To the best of our knowledge, no randomized prospective trial has been conducted on long-term oncologic effects of preoperative breast MRI. However, the Alliance A11104 Clinical Trial from the American College of Radiology Imaging Network (ACRIN) is still ongoing²³. This ongoing study included only triple-negative and HER-2(+) molecular subtypes due to relatively low recurrence rates in patients with luminal subtypes. In their study, Gervais *et al.* defined a high-risk subgroup consisting of 39 patients with triple-negative and 30 patients with HER-2 (+) tumors. They investigated ipsilateral breast tumor recurrence in high-risk patients with or without preoperative breast MRI. Although ipsilateral breast tumor recurrence was higher in patients without preoperative breast MRI, the difference was

not significant (11.8% *vs.* 3.3%; $p=0.3$)²⁴. In our study, patients with triple-negative and HER-2(+) subtypes were grouped as a hormone receptor-negative subgroup. OS, LRFS, or DFS rates were not significantly different between the MRI and non-MRI groups (Table 5).

In our study, which included only patients with invasive breast cancer, there was no significant difference in tumor stage, tumor histologic features, or molecular subtypes, even though patients in the MRI group were significantly younger. Moreover, preoperative MRI was not associated with a statistically significant improvement in long-term oncologic outcomes. Since most patients with preoperative MRI were treated after 2010, we repeated our analyses only for those patients; preoperative breast MRI was still not associated with significant improvements in OS, LRFS, or DFS in these patients.

In the light of our current findings, we believe that preoperative MRI is not necessary to improve oncologic outcomes in all patients undergoing BCS. Since our study had limitations such as retrospective design and lack of adjuvant chemotherapeutic agent usage data, there might still be a subgroup of patients who can benefit from preoperative breast MRI. New prospective randomized controlled trials are necessary to determine the appropriate use of preoperative MRI for BCS patients and its effects on LRFS and OS rates in early breast cancer patients.

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Sažetak

DUGOROČNI UČINAK PRIJEOPERACIJSKE MAGNETSKE REZONANCIJE NA PREŽIVLJENJE U BOLESNICA S POŠTEDNOM OPERACIJOM RAKA DOJKE

A.S. Ilgun, D. Sarsenov, G. Alco, A. Ozturk, F. Agacayak, F. Elbuken, Z. Erdogan, K.N. Pilanci, C. Ordu, F. Aktepe, G. Soybir i V. Ozmen

Koristi od magnetske rezonancije (MR) kod operativnog zahvata kojim dojka ostaje očuvana u većoj ili manjoj mjeri (*breast-conserving surgery*, BCS) ostaju nejasne. U ovoj studiji uspoređene su bolesnice s rakom dojke u kojih je napravljena prijeoperacijska MR i one bez MR (kontrolna skupina) te se navode njihovi dugoročni onkološki ishodi. Pregledani su podatci za 1378 žena s ranim rakom dojke podvrgnutih BCS između 1996. i 2017. godine. Bolesnice s karcinomom *in situ* ili neoadjuvantnim liječenjem ili pak one kod kojih je učinjena MR nakon ekscizije tumora nisu uključene u istraživanje. Od 1378 bolesnica prijeoperacijska MR učinjena je u njih 270 (19,5%). Nije bilo značajnih razlika između dviju skupina s obzirom na T i N stadij te molekularne podtipove karcinoma. Kirurške granice bile su značajno šire u skupini s MR. Petogodišnje ukupno preživljenje bilo je 96,9% u skupini s MR i 94,3% u kontrolnoj skupini; ova razlika nije bila značajna ($p=0,11$). Petogodišnje preživljenje bez lokalnog-regionalnog recidiva (*local-regional recurrence-free survival*, LRFS) također se nije značajno razlikovalo između dviju skupina (98,8% odnosno 96,5%, $p=0,41$). Kad su analize ponovljene samo za bolesnice s rakom dojke negativnim na receptore ili trostruko negativnim rakom dojke nisu utvrđene nikakve značajne razlike u ukupnom preživljenju, LRFS ili preživljenju bez bolesti. Zaključno, izgleda da MR nije potrebno raditi u svih bolesnica u kojih se planira BCS. Nova prospektivna randomizirana kontrolirana istraživanja su potrebna kako bi se utvrdila odgovarajuća primjena prijeoperacijske MR te njezini učinci na onkološke ishode u bolesnica s ranim rakom dojke.

Ključne riječi: *Rak dojke; MR dojke; Poštedna operacija dojke; Ukupno preživljenje; Lokalni neuspjeh; Onkološki ishod*