The impact of preoperative breast MRI on surgical planning in women with incident breast cancer

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Thesis for the degree of Master of Public Health Sciences

University of Iceland

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HÁSKÓLI ÍSLANDS

Áhrif segulómunar af brjóstum á skurðaðgerðaráform kvenna sem eru nýgreindar með brjóstakrabbamein

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Ritgerð til meistaragráðu í lýðheilsuvísindum

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Ágrip

Inngangur: Segulómun af brjóstum kvenna sem greinst hafa með brjóstakrabbamein hefur nýlega verið innleidd á Íslandi. Erlendar rannsóknir sýna að með segulómun megi finna fleiri mein en með röntgenmynd af brjóstum og getur það breytt fyrirhugaðri meðferð á formi skurðaðgerðar.

Markmið: Markmið rannsóknarinnar er að kanna hvaða áhrif segulómunin hefur á skurðaðgerðaráform kvenna sem eru nýgreindar með brjóstakrabbamein á Íslandi.

Aðferðir: Rannsóknin er lýsandi tilfellarannsókn á 284 konum sem komu í segulómun af brjóstum á árunum 2007 og 2008 á Landspítala Háskólasjúkrahúsi. Bornar voru saman niðurstöður röntgenmynda og segulómana af brjóstum. Ef niðurstöður segulómunar voru frábrugðnar niðurstöðum röntgenmynda mat skurðlæknir hvort skurðaðgerðaráform hefðu breyst.

Niðurstöður: Hjá 43 (15.1%) konum fundust fleiri mein með segulómun en með röntgenmynd af brjóstum. Hjá 23 (8.1%) konum var meinið í sama brjósti og hið þekkta æxli en hjá 17 (6%) í hinu brjóstinu. Hjá þremur konum (1%) voru mein í báðum brjóstum á segulómun en engin mein höfðu sést á röntgenmynd. Skurðaðgerðaráform breyttust hjá 20 konum (7%) vegna niðurstöðu segulómunarinnar. Gerð var stærri aðgerð á sama brjósti hjá níu konum (3.2%) og 11 (3.9%) konur fóru í aðgerð á báðum brjóstum í stað aðgerðar á öðru brjósti.

Ályktun: Þessi rannsókn staðfestir að með segulómun megi finna mein, bæði góðkynja og illkynja, sem ekki greinast á röntgenmynd af konum með brjóstakrabbamein. Þessi mein geta breytt skurðaðgerðaráformum hjá um helmingi þeirra.

Abstract

Introduction: Routine breast Magnetic Resonance Imaging (MRI) has recently been introduced in Iceland as a preoperative examination of patients with incident breast cancer. Previous studies report that additional lesions not detected on mammography can be identified with MRI, which may result in revised surgical planning.

Objectives: The aim of this study is to determine if additional findings on preoperative breast MRI changed the planned surgical treatment.

Methods: This is a descriptive case series of 284 female patients who underwent breast MRI in the years 2007 and 2008 at Landspitali-University Hospital, Reykjavík, Iceland. The results of mammography and breast MRI were compared for each patient. If an additional lesion was detected on breast MRI, a breast surgeon evaluated if the planning of the surgical treatment was altered.

Results: An additional lesion was detected on breast MRI in 43 women (15.1%). In 23 women (8.1%) the additional lesion was found in the ipsilateral breast and in 17 (6%) in the contralateral breast. In three women (1%) the breast MRI showed bilateral lesions that were not detected on mammography. Due to the MRI findings surgical planning was changed in 20 women (7%). A wider unilateral excision was performed in nine women (3.2%) and in 11 cases (3.9%) bilateral surgery was performed instead of unilateral.

Conclusion: The results of this study confirm previous reports that preoperative breast MRI detects additional lesions, benign and malignant, in a substantial number of breast cancer patients and can alter the surgical treatment in approximately half of these patients.

Þakkir

Í meistaranámsnefndinni eru Hildur Einarsdóttir röntgenlæknir, Lára G. Sigurðardóttir læknir og doktorsnemi í lýðheilsuvísundum og Unnur Anna Valdimarsdóttir dósent. Þeim færir höfundur kærar þakkir fyrir góða leiðsögn, lærdómsríkt samstarf og ómetanlega aðstoð við gerð verkefnisins. Samstarfsaðili að verkefninu er Kristján Skúli Ásgeirsson brjóstaskurðlæknir, höfundur færir honum sérstakar þakkir fyrir að sýna verkefninu mikinn áhuga og veita höfundi aðstoð við þann hluta sem ekki var á hans færi að framkvæma sjálfur. Söru Birgisdóttur nýbakaðri móður, geislafræðingi og meistaranema í lýðheilsuvísindum þakkar höfundur fyrir skemmtilegt og lærdómsríkt samstarf við söfnun og skráningu gagna í rannsóknina.

Margir aðrir einstaklingar aðstoðuðu höfund við gerð rannsóknarinnar og vill höfundur færa þeim aðilum sérstakar þakkir. Þetta eru þau: Vigdís Pétursdóttir sérfræðingur á rannsóknarstofu í meinafræði við Landspítala Háskólasjúkrahús fyrir aðstoð og aðgang að meinafræðiskýrslum, Magnús Baldursson röntgenlæknir í Domus Medica og Leitarstöðinni fyrir aðstoð og aðgang að röntgensvörum úr brjóstamyndatökum, Hjalti Már Þórisson og Maríanna Garðarsdóttir röntgenlæknar fyrir yfirlestur og góðar ábendingar. Einnig þakkar höfundur yfirmönnum myndgreiningardeildar Landspítalans fyrir hvatningu, skilning og veitta námsdaga í náminu.

Að lokum vill höfundur þakka eiginmanni sínum, fjölskyldu og vinum fyrir ríka þolinmæði, hvatningu og stuðning við vinnslu þessa verkefnis.

Rannsóknin var unnin á Landspítala Háskólasjúkrahúsi.

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List of Abbreviations

ACS	American Cancer Society
AJCC	The American Joint Committee on Cancer
BCS	Breast Conserving Surgery
BI-RADS-MRI	Breast Imaging Reporting and Data System Atlas
BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
DCIS	Ductal Carcinoma In Situ
FLASH	Fast Low Angle SHot
ICR	Icelandic Cancer Registry
ICS	Icelandic Cancer Society
IDC	Invasive Ductal Carcinoma
ILC	Invasive Lobular Carcinoma
LCIS	Lobular Carcinoma In Situ
LUH	Landspitali University Hospital
MRI	Magnetic Resonance Imaging
NCI	The National Cancer Institute
TE	Echo Time
TNM	Tumor – lymph Node - Metastasis
TR	Repetition Time

THEORETICAL BACKGROUND

Breast cancer is the most common cancer among women worldwide and accounts for 23% of all cancer combined (1). This also holds true in Iceland with 182 new cases diagnosed in 2007 and 204 in 2008 (2). The number of new breast cancer cases in Iceland has increased over the past decades. The Icelandic Cancer Registry (ICR) reported an age-standardized incidence rate of 77.3 per 100,000 for breast cancer in the period 1994 – 1998, while ten years later, in the period 2004 – 2008 the age-standardized incidence rate was up to 91.6 per 100,000. Despite the higher incidence, the death rate has decreased (3).

In the last decades breast MRI has been introduced in the preoperative evaluation of breast cancer as a complement to existing methods. This article focuses on the impact of breast MRI on surgery in patients newly diagnosed with breast cancer.

1 Breast cancer

1.1 Characteristics and stage

Breast cancer can be noninvasive or invasive. In *noninvasive (in situ) breast cancer* the cancer cells have not spread from their place of origin through the normal breast tissue barrier. The most common type is ductal carcinoma in situ (DCIS), which is confined to the lining of the milk ducts. Lobular carcinoma in situ (LCIS), which is confined to the milk glands, is more rare. In *invasive (infiltrating) breast cancer,* the cancer cells have spread outside the breast tissue barrier that lines a duct or lobule, invading the surrounding tissue. The cancer cells can then metastasize to other parts of the body, to the lymph nodes via the lymphatic system and via the bloodstream to distant organs. The two major types of invasive breast cancer are ductal carcinoma (IDC) that is the most common type and lobular carcinoma (ILC). Less

common form of invasive breast cancers are medullary, tubular and mucinous carcinoma (4,5).

A staging system is a standardized way to summarize information about how far a cancer has spread. It can be used to assess the patient's prognosis and to decide treatment. The TNM system from the American Joint Committee on Cancer's (AJCC), is most commonly used to stage breast cancer. It is based on the size of the tumor (T), whether lymph nodes are involved or not (N), and whether the cancer has spread beyond the breast (M). Based on the TNM system breast cancer is classified as Stage 0-4 (6).

Stage 0 refers to non-invasive cancer (carcinoma *in situ*). In Stage I the tumor measures 2 cm or less and has not spread to the lymph nodes. In stage IIA the tumor measures 2 cm or less and has spread to the axillary lymph nodes, or the tumor measures 2 - 5 cm but has not spread to the axillary lymph nodes. In stage IIB the tumor measures either 2 - 5 cm and has spread to the axillary lymph nodes, or measures over 5 cm and has not spread to the axillary lymph nodes. Stage IIIA-C is used for tumor of any size, even when no tumor is found in the breast, if the cancer has spread to axillary lymph nodes, to lymph nodes near the breastbone or the collarbone. Stage IIIA-C is also used if the tumor has spread to the chest wall or the skin of the breast. In stage IV the cancer has metastasized to other organs of the body, most often to the bones, lungs, liver or brain (6,7).

1.2 Survival rate

Breast cancer is most effectively treated in its early stages. This is well demonstrated by the reported five-year survival rate of 100% for stage 0 and I, 86% for stage II, 57% for stage III, and 20% for stage IV disease (8). These figures illustrate the importance of early detection.

The reported survival rate is different from country to country. Women in low-resource countries generally present with breast cancer at higher stages compared to women in high-

resource countries and consequently have lower survival rate (9). The National Cancer Institute reported that overall five-year relative survival rate among American women diagnosed with breast cancer 1996 to 2006 was 89% , 90.2% for white women and 77.5% for black women (10). In England the survival rate was 82% for women diagnosed with breast cancer 2001 to 2006 (11) and in Sweden the reported survival rate was 87.8% in 2007 (12).

The prognosis for breast cancer patients in Iceland has improved over the past decades. The five-year survival rate for the period 1985 – 1994 was 79%, but increased to 90% in the years 1995 – 2004 (13).

1.3 Treatment

Therapy for breast cancer can either be surgery, chemotherapy, radiotherapy or hormonal therapy; or any combination of these methods, depending on the patient´s needs (14).

1.3.1 Surgery

The aim with surgery is to excise the tumor along with the surrounding tissue. In mastectomy the whole breast is removed. Breast-conserving surgery (BCS) is a less radical procedure in which the tumor with its surrounding tissue is removed. This type of procedure includes lumpectomy. In both mastectomy and BCS, lymph node removal can be included (9,15).

1.3.2 Radiotherapy

In radiotherapy high-energy x-rays are used for curative or adjuvant treatment. Radiotherapy is targeted to the breast to destroy any cancer cells that may have been left at surgery, to reduce the risk of recurrence. In some cases radiation is also delivered to the loco-regional lymph nodes (16,17).

1.3.3 Chemotherapy

Chemotherapy is used to inhibit the growth of cancer cells, either by affecting cell division or by eradicating the cancer cells. With endocrine therapy**,** the action of hormones that stimulate cancer growth in estrogen receptor-positive cancer cells is inhibited. Tamoxifen, which is an antagonist of the estrogen receptor in breast tissue, has been the most commonly used anti-estrogen therapy for estrogen receptor-positive breast cancer in pre- and post-menopausal women. Aromatase inhibitors block the synthesis of estrogens and are alternate treatment to tamoxifen in post-menopausal women. There are several other types of endocrine therapy (9,16).

1.3.4 Adjuvant therapy

Adjuvant therapy refers to any additional treatment, usually given after surgery when all detectable disease has been removed when there remains a statistical risk of relapse. Radiotherapy and/or systematic therapy (chemotherapy and/or hormonal therapy) are commonly given as an adjuvant treatment after surgery for a breast cancer (17,18).

1.3.5 Neo-adjuvant therapy

Neo-adjuvant therapy refers to the administration of a therapeutic agent prior to the main therapy, which is usually surgery in case of breast cancer. The aim is to reduce the size and extent of the cancer so less extensive surgery can be performed, for example breast-conservation surgery instead of mastectomy (18).

1.4 Risk factors

The cause of breast cancer is still undefined, but epidemiological research has found association with genetic, biological, environmental and lifestyle risk factors. Estrogens play a major role in the causal mechanism of breast cancer. Women with increased amount estrogen exposure in reproductive life, that is women with history of early menstruation age, short

intervals between menstruations, and later menopause than average (51 years old), are at increased risk. The risk of breast cancer is furthermore negatively associated with the number of pregnancies and length of breast-feeding, that is periods when estrogen exposure is opposed with progesterone exposure. Hormone replacement therapy (HRT) is also a known risk factor. Women with family history of breast cancer (first- or second-degree relative) are at increased risk and some in this group will have mutation in the BRCA1 and BRCA2 genes.(19-22).

Physical activity and healthy life style can lower the risk. Alcohol intake and obesity are established risk factors (20). Some studies have indicated that a high fat diet may increase risk, while others have not found any evidence for the association between diet and breast cancer (22).

1.5 Screening

1.5.1 Self-examination

Cancer organizations worldwide encourage self-examination monthly. Self-examination along with screening mammography is the most effective way to detect breast cancer at its early stages. A woman who palpates her breast regularly on the seventh to tenth day of her menstrual cycle, when the breast tissue is soft and fairly homogeneous, is more likely to notice a new lump in her breast (20).

1.5.2 Mammography

Mammography is an x-ray examination of breast tissue that obtains high quality images while using a very low dose of ionizing radiation. The level of radiation is usually standardized, based on national and international guidelines. It is performed with the breast tissue compressed to optimize image quality. The screening examination includes two special projections on each breast, craniocaudal view and mediolateral oblique view (23).

The National Cancer Institute (NCI) and the American Cancer Society (ACS) recommend mammography as the method of choice to screen for nonpalpable, clinically occult breast cancer in all women 40 years and older as well as in younger women with certain risk factors (23,24). In Sweden the recommendations are similar. The Swedish Cancer Society recommends screening mammography for all women at the age 40 to 74 years but there are regions in Sweden were the age span has been shortened to 50 years to 69 years by the local health government. The recommended interval varies from 18 - 24 months (25).

In 1987 mammographic screening was launched in Iceland. Almost all examinations are performed at the screening center of the Icelandic Cancer Society (ICS) or at their mobile mammography unit that is used in the rural areas. A small number of women are examined at Akureyri Hospital outside the ICS program. The ICS recommends screening mammography biannually for all women aged 40 to 69 years. The participation rate in the screening program has been between 61 - 63% since 1994 (26).

When a screening examination reveals abnormal findings or when a patient presents with symptoms, further imaging is warranted. The woman will undergo triple assessment that is diagnostic mammography, breast ultrasonography and clinical breast examination. If cancer is still suspected after imaging and/or clinical examination, a fine-needle biopsy is performed (26). If the biopsy shows cancer cells the patient is referred to the Landspitali University Hospital (LUH) where further treatment is planned.

In the mid-2008 the screening center of the ICS began to use digital mammography (Mammomat Inspiration, Siemens Medical solution, Erlangen, Germany) instead of conventional mammography (screen-film mammography) (26). Studies that have compared digital mammography with conventional mammography report no difference in breast cancer detection rate between digital and conventional mammography in the general population.

However, the researchers concluded that women with dense breasts might benefit from having a digital rather than conventional mammography (27).

2 Breast Magnetic Resonance Imaging

Since January 2007 most women diagnosed with primary breast cancer in Iceland have been offered preoperative breast magnetic resonance imaging (breast MRI). As far as we are aware it is unique that almost a whole population is offered this examination. At the present, breast MRI in Iceland is performed at one center, the Department of Radiology at the Landspitali University Hospital (LUH).

2.1 Indications

The most common indication for breast MRI at LUH is preoperative staging directly after diagnosis. Less common indications are evaluation of the extent of disease after breast conserving surgery, assessment of response to chemotherapy and inconclusive findings on mammography. Screening of patients with high-risk for hereditary breast cancer is also performed.

2.2 Contraindications

The most common contraindications for MRI are cardiac pacemaker, implanted neurostimulator, implanted hearing prosthesis, some models of brain aneurysm clips, and some cardiac prosthetic valves (28). Overweight individuals and those suffering from claustrophobia might not be able to undergo the examination.

2.3 The breast MRI examination

At LUH breast MRI is performed on a 1.5 T magnet (Magnetom Avanto, Siemens Medical solution, Erlangen, Germany) with a dedicated bilateral breast surface coil. The patient is examined in prone position that ensures good image quality and limits physiologic motion such as breathing that may cause image artifacts. The examination requires administration of

a gadolinium contrast agent. Studies have shown that breast MRI examination without contrast agent is of limited diagnostic value (29). Exception from the use of gadolinium contrast is when the examination is only performed to evaluate suspected leak of breast prosthesis.

The imaging protocol and parameters are the following: First, axial T2-weighted turbo spin-echo images (TR; 4000/ TE; 100) of both breasts are obtained. The slice thickness is 3 mm without any gap. Then axial T1-weighted images of both breasts are acquired before and after intravenous contrast injection. A 3D FLASH imaging with a fat-selective inversion for fat suppression (TR; 4.19 / TE; 1.22) is performed with a slice thickness of 0.9 mm and 0.18 mm gap. One T1 serie is performed before contrast injection, and then a bolus injection of 0.1 mmol/kg (max 15 mL) of gadopentetate dimeglumine (Magnevist, Bayer Schering Pharma AG, Berlin, Germany) and a 20 mL saline solution flush is given, followed by five sequential T1 contrast-enhanced series.

The pre-contrast image is then subtracted from the corresponding post-contrast image with standard software subtraction function available on the console. The sequence is called dynamic because imaging of the same area is repeated multiple times after contrast administration. The examination takes approximately 15 minutes.

2.4 Sensitivity of breast MRI

The role of breast MRI has been studied and debated since contrast-enhanced breast MRI was introduced in 1985. The major concern is the high sensitivity and low specificity (23).

Breast MRI is used in the preoperative setting for newly diagnosed breast cancer patients to define tumor extent and to search for other focuses of malignancy. For this purpose breast MRI is highly sensitive (>90%) when compared to mammography (50-60%) (30). Current

reports on breast MRI's sensitivity lie between 89% and 100% for all invasive cancers and between 93% and 100% for ILC (31,32).

Several studies report that breast MRI in women with newly diagnosed breast cancer identifies additional, otherwise undetected synchronous tumors in up to 30% of patients (33-36). New lesions detected with breast MRI are more commonly found in the ipsilateral breast than in the contralateral. The detection of an additional lesion varies. Studies have reported detection of additional lesions in the ipsilateral breast in 4.2 - 27% of cases (33,36,37) and in 3.6 – 6.5% of cases in the contralateral breast (34,38,39).

2.5 Accuracy of breast MRI

Although breast MRI is highly sensitive it lacks specificity and accuracy. The specificity reported for breast cancer is quite variable, ranging from 37 – 100%. False-positive result may be caused by benign conditions such as fibroadenoma, fibrocystic disease and atypical ductal hyperplasia (23).

Several studies have pointed out that breast MRI can overestimate tumor size when compared to pathology measurements (40,41). Onesti *et al*. reported that breast MRI overestimated mean tumor size in 35.2% of all tumors by an average of 0.63 cm. This overestimation was reported primarily for large tumors (>2.0 cm). The author suggested that if breast MRI shows a lesion that measures over 2 cm, a correlation of the findings with other imaging techniques should be performed (41).

2.6 Effect on treatment decision

The detection of additional lesions on breast MRI may influence the type of surgical treatment planned based on previous findings on mammography and ultrasound. However, a change in treatment plan is usually not based on breast MRI findings alone. If an additional lesion is detected it is usually analyzed with further imaging and/or biopsies.

Therapy plans have in some studies been revised in up to 44% of patients (42,43) and a change in surgical treatment has been reported in 11 – 31% of patients (34,38,44,45). Bilmora *et al.* reported that due to breast MRI the surgical treatment was changed in 36 of 155 breast cancer cases (23.2%). Of those, mastectomy was performed in 10 patients (6.5%) who originally were candidates for breast conserving surgery (BCS), 21 patients (13.5%) required wider excision and 5 patients (4.5 %) underwent additional contralateral surgery (44).

2.7 Criticism of the breast MRI examination

The use of preoperative breast MRI in breast cancer remains controversial. Criticism about its use in this setting include increased cost, lack of proven clinical benefit and overestimation of disease leading to overtreatment (46,47).

The main argument against preoperative MRI is that the breast MRI overestimates the disease, with high rates of false-positive findings and overestimation of tumor size. Blair *et al*. reported that the MRI findings resulted in overestimation of disease extent which resulted in unnecessary mastectomy in 8.7% of patients (30). Schelfout reported that 4.4% patients underwent unnecessary wider excisions and 1.5% underwent unnecessary biopsies (43).

The cost-effectiveness of breast MRI and its overall effect on patient survival are still unknown. The COMICE trial (Comparative effectiveness of MRI in breast cancer trial) (48,49) is the first randomized trial to assess whether preoperative breast MRI in early-stage breast cancer can decrease reoperation rates and provide data about quality of life and health economic assessments. The COMICE study is not completed but primary results have not indicated any benefit from preoperative breast MRI. The results show that the addition of MRI to the conventional triple assessment has no benefit on the reduction of reoperation rate (49). The authors also found no differences in health-related quality of life between the groups 12 months after surgery, and no significant difference in costs. However, the question of

recurrence and overall survival is still unanswered and the role of preoperative breast MRI has not yet been defined (48,49).

2.8 Impact on public health

It is important to map the effect of preoperative breast MRI on treatment decision and outcome in women with primary breast cancer. Although the examination has been performed routinely in Iceland for almost four years, the effect on the surgical procedures performed has not been evaluated.

3 Aim

The aim of this study is to determine the effect of routine breast MRI on surgery for incident breast cancer in Iceland. The proportion of additional lesions detected with MRI in the ipsilateral and the contralateral breast compared to mammography will be examined. Furthermore, it will be evaluated whether the MRI findings resulted in altered surgical treatment plan.

Article

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The impact of preoperative breast MRI on surgical planning in women with incident breast cancer in Iceland

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Introduction

Breast cancer is the most common cancer among women worldwide and accounts for 23% of all cancer combined (1). This also holds true in Iceland with approximately 200 new cases diagnosed annually (2,3).

The role of breast magnetic resonance imaging (MRI) in evaluating breast disease has been studied and debated since contrast-enhanced breast MRI was introduced in 1985 (23). Breast MRI is used in the preoperative setting to define tumor extent and to search for other foci of malignancy in newly diagnosed patients. For this purpose breast MRI is highly sensitive (>90%) when compared to mammography (50-60%) (30,31,32).

Several studies report that breast MRI of women with incident breast cancer identifies additional, otherwise undetected synchronous tumors in up to 30% of patients (33-36). Additional lesions detected with breast MRI are more commonly found in the ipsilateral breast than in the contralateral breast. Studies have reported detection of additional lesions in the ipsilateral breast in 4.2 - 27% of cases (33,36,37) and in the contralateral breast in 3.6 – 6.5% of cases (34,38,39).

Planning of surgical treatment is based on mammography, ultrasound, clinical examination and needle biopsy and detection of an additional lesion with breast MRI may change the plan. A revised surgical plan based on the MRI findings has been suggested to be applicable in 11 – 31% of breast cancer patients (34,38,44,45).

Since January 1st 2007 all women diagnosed in Iceland with incident breast cancer have been offered preoperative breast MRI at Landspitali-University Hospital (LUH), which is the only radiological facility equipped to perform breast MRI in Iceland. As far as we are aware, it is unique that almost whole population is offered this kind of preoperative examination.

Women living in the northern part of the country are examined and treated outside screening center at the Icelandic Cancer Society (ICS) and LUH. Although the MRI examination is now performed routinely it has not been addressed whether the implement of breast MRI has an effect on the surgical treatment of incident breast cancer in Iceland.

The aim of this study is to determine the effect of routine breast MRI on surgery for incident breast cancer in Iceland. The proportion of additional lesions detected with MRI in the ipsilateral and the contralateral breast compared to mammography will be examined. Furthermore, it will be evaluated whether the MRI findings resulted in altered surgical treatment plan.

Materials and methods

Study design and selection of cases

This study represents a case series of breast cancer patients who underwent preoperative breast MRI examination in 2007 and 2008 at the LUH. A total of 386 women were diagnosed with breast cancer in Iceland during the study period (2).

All participants met the following initial inclusion criteria: (1) female gender, (2) primary breast cancer diagnosis, (3) no history of neoadjuvant chemotherapy before breast MRI, and (4) the MRI examination preceded surgery. To identify the eligible cases, all breast MRI reports from the study period were reviewed. Of the 386 incident cases**,** 326 (84.5%) underwent breast MRI during the study period. A total of 302 met the initial inclusion criteria (Fig. 1). Later in the study after having reviewed mammography, breast MRIs and pathology reports, 18 patients were excluded for the following reasons: the mammography or pathology report was unavailable, motion artifacts on the breast MRI made analysis impossible, or chemotherapy preceded the surgery. Altogether, 284 breast cancer patients remained in the study or 73.6% of the total population (N=386) of incident female breast cancer cases during the two year study period.

Study material and data extraction

The following original reports were analyzed for the remaining 284 patients: mammography reports from the screening center at ICS, breast MRI reports from the Department of Radiology at LUH, and pathology reports from the Department of Pathology at LUH. The information extracted from the reports was tumor location, number of tumors and histology type.

Evaluation of breast MRI and mammography

For each patient the results of the mammography and the breast MRI were compared. The result of the breast MRI was assumed to have no effect on the surgery if there were no additional lesions detected on the breast MRI. If additional lesions were detected, a breast surgeon reviewed the findings. The surgeon answered a questionnaire (Appendix 1) regarding whether and what additional examinations were conducted, and whether the examination confirmed the results of breast MRI or not. Moreover, the surgeon recorded if and how the surgical treatment changed as a result of additional findings on the breast MRI.

Statistical analysis

SPSS (Statistical Package for Social Sciences) software version 17.0 was used for analysis. Due to the nature of the study, statistical analysis was limited to basic descriptive methods.

Ethical considerations

The study was approved by the National Bioethics Committee of Iceland and The Icelandic Data Protection Authority.

Results

Demographics

This case series consists of 284 women, all of whom were diagnosed with incident breast cancer during the study period. The mean age at presentation was 59 years (range 29 – 86 years) (Table 1).

Surgical treatment

All patients were treated with surgical resection or biopsy. The majority underwent unilateral breast-conserving surgery (BCS) (63%, n=179) or unilateral mastectomy (29.2%, n=83). Eighteen patients (6.3%) underwent bilateral breast tissue resection, four had bilateral mastectomy (1.4%) and in eight patients bilateral BCS (2.8%) was performed (Table 1).

Pathological findings

Benign or negative findings

No malignancy was found at the histopathological examination in eight patients (2.8%) of whom seven were diagnosed with benign lesion. In six of these women with benign tumor, a lesion was described both on the breast MRI and the mammography report. The remaining one patient had a benign lesion that was not observed on mammography but detected during clinical examination and on breast MRI. Six of the patients underwent BCS and one underwent bilateral mastectomy.

In one patient no histopathological abnormality was found. The clinical examination showed indentation of the skin overlying the breast and therefore malignancy was suspected and patient underwent core biopsy. In this case no lesion was detected on breast MRI or mammography.

In situ carcinoma

Twenty patients (7%) had in situ disease, whereof 18 were ductal carcinoma in situ (DCIS), and two were lobular carcinoma in situ (LCIS). The disease was confined to one breast in all of the twenty patients (Table 2).

In the patients with LCIS a fibrocystic disease was also described at the histopathological examination. In both cases, breast MRI and mammography described ipsilateral lesions, but much smaller than reported at the histopathological examination.

Invasive carcinoma

A total of 256 patients were diagnosed with invasive carcinoma (90.1%). Of those, 244 (95.3%) had cancer confined to one breast and 12 (4.7%) had cancer diagnosed in both breasts (Table 2). The majority of patients or 201 (78.5%) had ductal type disease, 26 (10.2%) had the lobular type and 29 (11.3%) were diagnosed with tubular-, mucinous- or mixed type disease.

Comparison of breast MRI and mammography

The comparison of findings on breast MRI and mammography are summarized in Fig. 2. Additional lesions not observed on mammography but detected on breast MRI were found in 43 patients (15.1%). In 23 patients (8.1%) an additional lesion was found in the ipsilateral breast and in 17 patients (6%) in the contralateral breast. In three patients (1%) the breast MRI showed bilateral lesions that were not observed on mammography but these lesions were identified with clinical breast examination or ultrasound (a note from the surgeon). Of those, one patient was diagnosed with bilateral invasive mixed carcinoma that was identified with clinical breast examination. The other two patients were diagnosed with ipsilateral invasive ductal carcinoma and contralateral benign lesion both of which were identified with ultrasound before the breast MRI.

The impact of breast MRI on surgical treatment

The surgical treatment of 20 patients (7.0%) was changed as a result of the breast MRI. The change in surgical treatment is summarized in Table 3. In 12 patients the decision was made after re-evaluation with ultrasound and biopsy. In six patients the decision was made after repeated ultrasound only and in the remaining two patients the change was based on the breast MRI findings alone (Fig. 3).

Additional lesion in the ipsilateral breast

The planned surgery was changed for nine (39%, 3.2% of the total) of the 23 patients with additional lesion in the ipsilateral breast. Of these, seven underwent mastectomy instead of BCS and two had wider BCS.

In all except one of these cases the additional lesion proved to be malignant. Six cases were diagnosed with ductal cancer and two cases with mixed lobular cancer. One patient was diagnosed with lobular cancer but the additional lesion turned out to be benign (false-positive).

The mean age at presentation for women in this group was 57 years (range of 41 – 76 years).

Additional lesion in the contralateral breast

The surgical treatment planned was changed for eleven (65%, 3.9% of the total) of the 17 patients with bilateral lesions on breast MRI but unilateral on mammography. Eight of these 11 patients were diagnosed with bilateral invasive cancer. Two patients were diagnosed with fibroadenoma in the contralateral breast and one patient was diagnosed with papillomatosis.

In eight patients the surgery was altered from unilateral to bilateral BSC. In one case, a lesion diagnosed as benign was excised at the patient´s request. The change in surgical

treatment is summarized in Table 3. For the remaining six patients diagnosed with an additional lesion in the contralateral breast (2.1%) the additional lesions were interpreted as benign and no change in surgical treatment was made. In three of these patients ultrasound examination and biopsy were performed. In the other three, no additional investigations were performed and the additional lesion was diagnosed as benign on the basis of the MRI findings alone.

The mean age at presentation for women in this group was 63 years (range of 43 – 83 years).

Additional procedures due to benign lesions

Nine of the 43 additional lesions (21%, 3.2% of total) that resulted in further imaging and surgical procedures turned out to be benign. These nine lesions lead to repeated ultrasound (n = 2), repeated ultrasound and biopsy (n = 3) or surgical resection (n = 4). Therefore, surgical procedures, such as wider excision or biopsy, was performed in 2.5% (n = 7) of the women due to a benign lesion detected on breast MRI.

Discussion

The present study was performed to determine the effect of presurgical evaluation with routine breast MRI on the surgical treatment for incident breast cancer in Iceland. The main findings are that additional lesions were found in 15.1% of patients and the surgical procedure was altered in almost half of these or 7 % of the cases.

The proportion of additional lesions found with breast MRI in this study (15.1%) is considerably lower than has previously been reported. The detection of an additional lesion varies but several studies have reported that breast MRI can detect cancer that is occult to mammography in up to 30% of patients (33-36). This discrepancy might be explained by high quality of the mammography screening program at the ICS, which was launched in 1987. On the contrary, in 2007 and 2008 the LUH had relatively short experience of breast MRI. However, the most reasonable explanation might be that breast MRI was offered to almost all women diagnosed with breast cancer and therefore performed in an unselected population. Tendulkar *et al.* conducted an unselected cohort study of breast cancer patients diagnosed at a single large institution (36). The cohort was composed of incident cases diagnosed either with invasive breast cancer or DCIS. An additional lesion was found in 4.2% of the ipsilateral and 1.5% of the contralateral breast. Those figures are similar to our findings. This center routinely conducts breast MRI on virtually all patients who are diagnosed with incident breast cancer, as opposed to many other institutions who reserve the breast MRI for patients in whom additional disease may be suspected (36).

The breast MRI resulted in revision of the surgical treatment planned for 7% of the patients and that is lower than previously reported (11 – 31%) (34,38,44,45). The reason may be that fever additional lesions were found in our study compared to the other centers. This holds true when both changes in the ipsilateral and contralateral breast surgery are summarized.

However, when only the revision of surgery for the contralateral breast (3.9%) is considered, the proportion is comparable to prior studies (3.6 – 6.5%) (34,38,39).

In this study roughly half of the additional lesions that were detected with breast MRI (8.1%) were found in the ipsilateral breast. Some authors argue that undetected small additional tumors in the ipsilateral breast need not be of clinical relevance (47). The reason is that patients who are treated with BCS generally receive postoperative radiotherapy of the whole breast, or if mastectomy is performed the additional lesion is removed anyway. However, these arguments are not valid regarding detection of lesions in the contralateral breast. An additional lesion was detected in the contralateral breast in 17 patients. Nine of these additional lesions were benign and eight were invasive carcinoma.

Of the twelve patients who were diagnosed with bilateral invasive carcinoma, eight had an additional lesion identified on breast MRI and not observed on mammography. Without the breast MRI these additional lesions might not have been detected until later and consequently a worse prognosis would be expected. These findings do support the use of breast MRI in the preoperative setting. However, even if the use of breast MRI was beneficial for this group there are other cases in which the benefit may be questionable. As a result of the breast MRI unnecessary surgical procedures such as wider excision or biopsies were performed in 2.5% of the women, which is a lower proportion than previously reported. In a prospective study of 204 incident breast cancer patients who underwent preoperative breast MRI, 5.9% of the patients underwent unnecessary surgical procedures based on the breast MRI findings (43).

The breast MRI resulted in further imaging in 8.1% of the patients in the present study and in 5.3% of the patients an additional biopsy was performed. These additional procedures can delay surgical treatment. Although unlikely to affect the course of the disease, the delayed treatment may cause patient anxiety. Anxiety associated with finding an additional lesion on

breast MRI, even if it turns out to be benign, can influence the patient decision when the type of surgery is selected. For example, in this study one patient requested a wider excision despite the benign nature of the additional lesion detected by the breast MRI.

Study strengths and limitations

The main strength of this study is that it is population based, comprising 284 histologically verified cases in almost a whole nation and a geographically defined area (Iceland). The study covers 73.6% of the incident female breast cancer cases during a two-year study period. Only a small proportion of Icelandic women in a geographically defined area (Akureyri) are examined and treated outside ICS and LUH.

All of the mammographic examinations in this study were performed and evaluated at a single center (ICS). Moreover, all of the breast MRI´s were performed at LUH with an up to date MRI scanner and a standardized protocol, evaluated by two radiologists. The surgical procedures and histopathological examinations were also performed at a single institution (LUH). The histopathology reports were standardized regarding the main characteristics of the tumors and constructed for research purposes.

This study has some limitations. The breast MRI reports were not constructed with the view that they would be used for research studies and the reports were not standardized. For research purposes the BI-RADS-MRI (Breast Imaging Reporting and Data System Atlas), that is a breast MRI lexicon to describe lesion architecture and enhancement characteristics, would have been helpful (50).

The fact that a breast surgeon´s was a part of the study (review of the alterations in the surgery) might involve information bias, since some of the patients are well known to him. Furthermore, the results of ultrasound and clinical breast examination that are a part of the usual triple assessment of breast cancer were not taken into account. For example, it is not

known whether some of the additional lesions found on breast MRI had previously been observed with ultrasound or clinical breast examination. This is of importance since it has been suggested that combined mammography, clinical examination and breast MRI might be more sensitive than any other individual test or combination of tests (51).

Despite these limitations, we feel that this data is an important addition to the existing literature as they reflect the daily experience of clinicians treating breast cancer patients in Iceland.

Conclusion

The results of this study confirm previous reports that preoperative breast MRI detects additional lesions, benign and malignant, in a substantial number of breast cancer patients and can alter the surgical treatment in approximately half of these patients. However, routine breast MRI resulted in some unnecessary additional imaging and/or biopsies, and in some patients more extensive surgery.

Fig. 1. Flowchart of the selection process

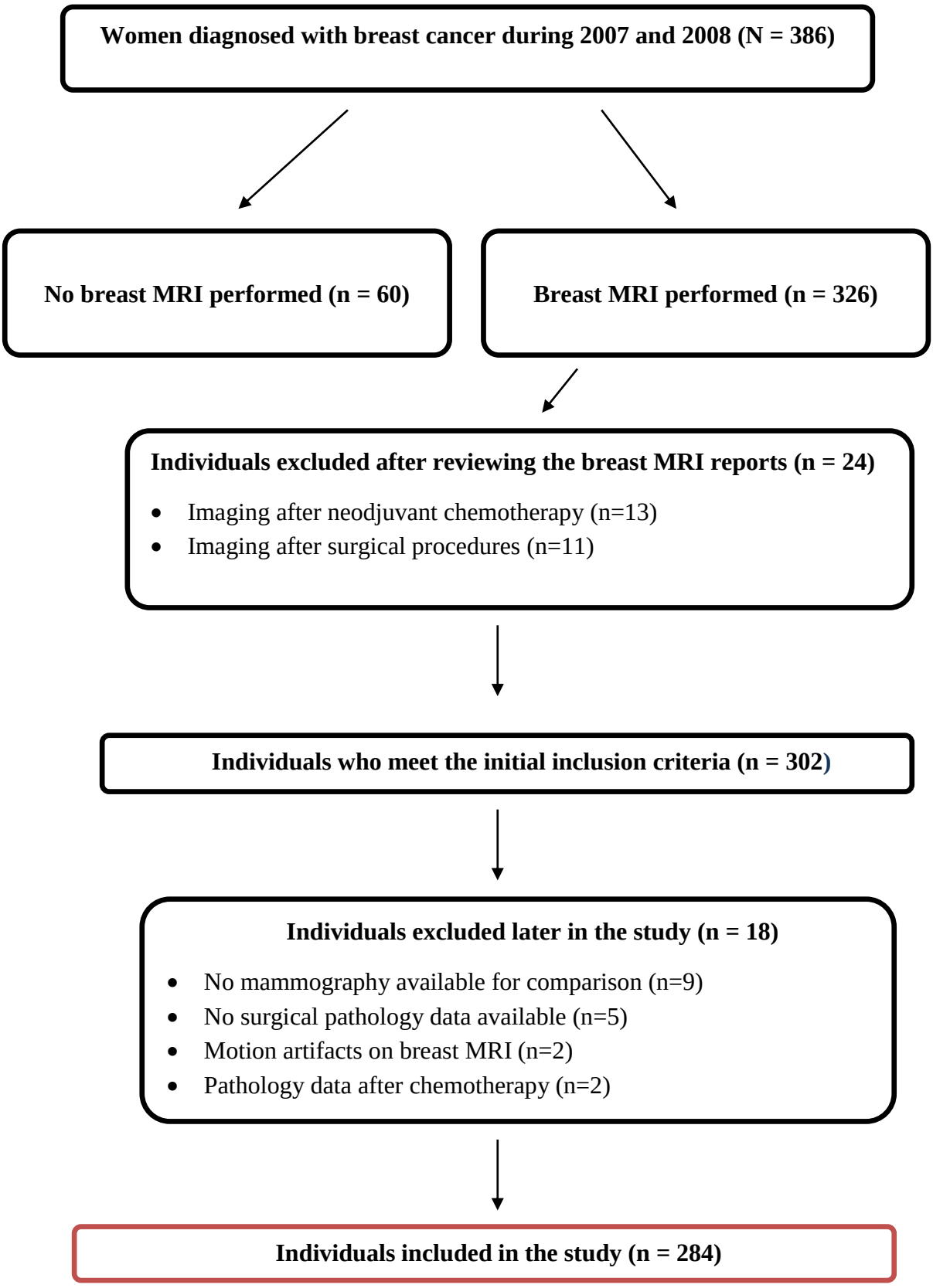

Fig. 2. Comparison of the breast MRI and mammography (N= 284)

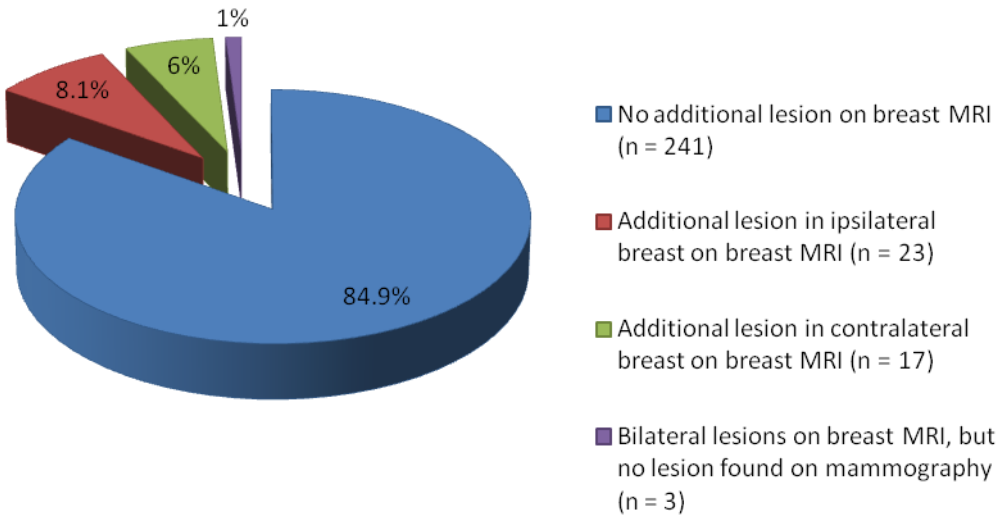

Fig. 3. Flowchart for work-up of an additional lesion on the breast MRI.

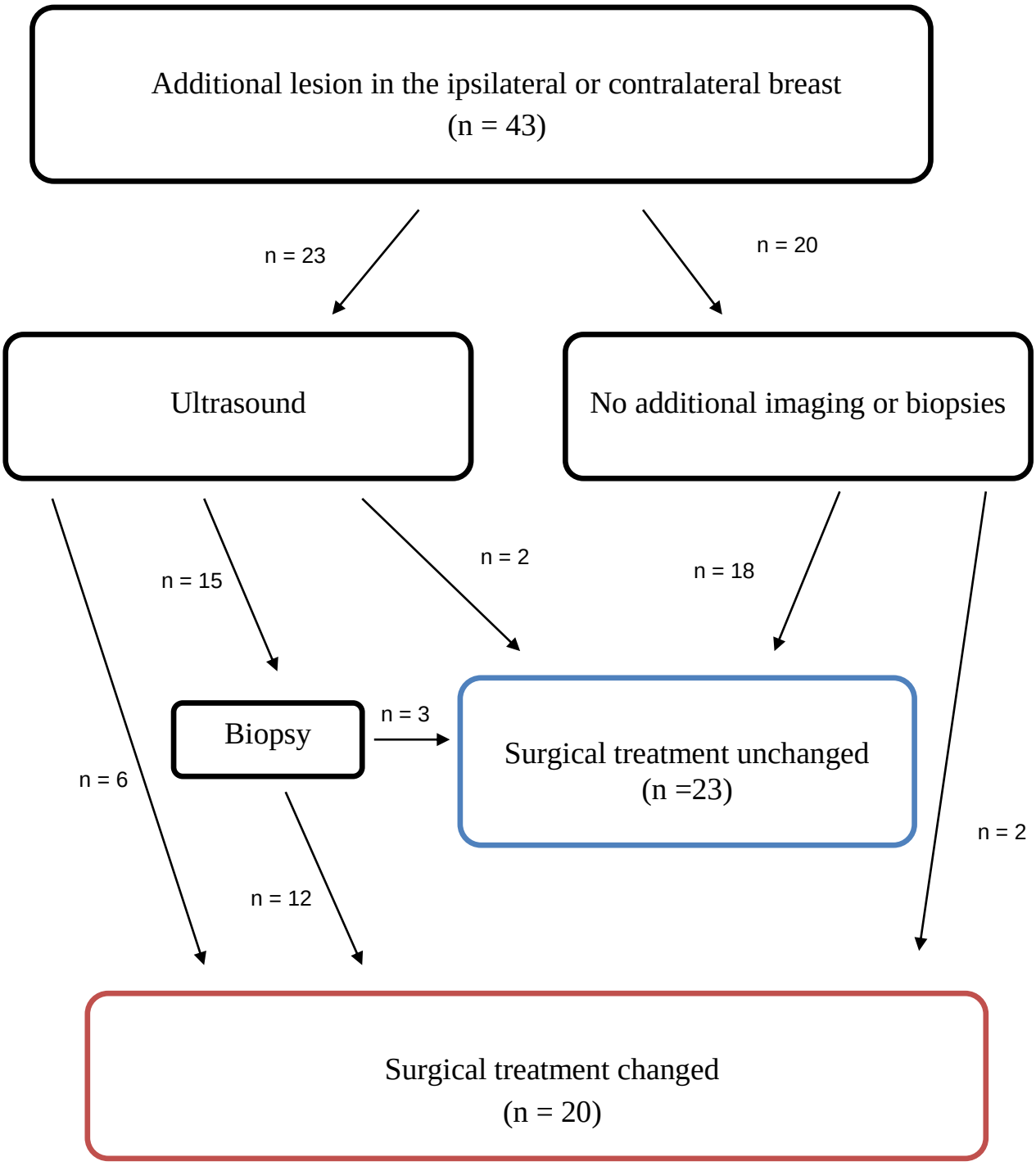

Table 1. Characteristics of the women diagnosed with breast cancer

Patients N=284	**n (%)**
Age (years)	
Mean age 58.6 (range 29-86)	
<40	10 (3.5)
40-49	54 (19)
50-59	92 (32.4)
60-69	77 (27.1)
≥ 70	51 (18)
Surgical treatment	
Unilateral resection	
Mastectomy	83 (29.2)
Breast-conserving surgery	179 (63)
Biopsy	4 (1.4)
Bilateral resection	
Bilateral mastectomy	4 (1.4)
Bilateral breast-conserving surgery	8 (2.8)
Mastectomy and breast-conserving surgery	3 (1.1)
Mastectomy and biopsy	1 (0.4)
Breast-conserving surgery and biopsy	2 (0.7)

Table 2. Histopathologic diagnoses

Patients N=284	**n (%)**
Negative (no tumor detected)	1 (0.35)
Benign (fibrocystic disease/fibroadenoma)	7 (2.5)
In situ carcinoma	
Ductal carcinoma in situ	18 (6.3)
Lobular carcinoma in situ	2 (0.7)
Invasive unilateral carcinoma	
Ductal carcinoma	195 (68.7)
Lobular carcinoma	25 (8.8)
Tubular carcinoma	3 (1.1)
Mucinous carcinoma	2 (0.7)
Mixed type	19 (6.7)
Invasive bilateral carcinoma	
Ductal carcinoma	6 (2.1)
Lobular carcinoma	1 (0.35)
Mixed ductal and mucinous carcinoma	1 (0.35)
Mixed ductal and lobular carcinoma	3 (1.0)
Mixed ductal, lobular and tubular	1 (0.35)

Table 3. Change in the surgical treatment based on the breast MRI findings

Patients N = 20	n (%)
New lesion in the ipsilateral breast	
Breast-conserving surgery changed to mastectomy	7 (2.5)
Wider-excision breast-conserving surgery	2 (0.7)
New lesion in the contralateral breast	
Ipsilateral breast-conserving surgery changed to bilateral breast-conserving surgery*	8 (2.8)
Ipsilateral mastectomy changed to bilateral mastectomy	1 (0.4)
Ipsilateral breast-conserving surgery changed to mastectomy and contalateral breast-conserving surgery	1 (0.4)
Mastectomy with additional contralateral diagnostic biopsy	1 (0.4)

**One of the surgeries was done at the patient request.*

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Appendix 1

Kennitala sjúklings er: *xxxxxx-xxx* **Case númer:** *xx*

Mammography, fjölda breytinga lýst í svari: *xx*

MRI, fjölda breytinga lýst í svari: *xx*

Viðbótarrannsókn eftir MRI: **Já:**_____ **Nei:**_____

Ef já, hvaða: **US:**_____ **Mammography:**_____ **Biopsy:**_____ **Annað:**_____

Staðfesti sú rannsókn niðurstöður MRI: **Já:**_____ **Nei:**_____

Breyttust meðferðarplön vegna MRI: **Já:**_____ **Nei:**_____

Ef já, hvernig:_____

_____

Athugasemdir:_____

_____