Original article

Population-based study of the effect of preoperative breast MRI on the surgical management of ductal carcinoma *in situ*

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Background: **Determinants of the use of breast MRI in patients with ductal carcinoma *in situ* (DCIS) in the Netherlands were studied, and whether using MRI influenced the rates of positive resection margins and mastectomies.**

Methods: **All women aged less than 75 years, and diagnosed with DCIS between 2011 and 2015, were identified from the Netherlands Cancer Registry. Multivariable logistic regression analyses were performed, adjusting for incidence year, age, hospital type, DCIS grade and multifocality.**

Results: **Breast MRI was performed in 2382 of 10 415 DCIS cases (22·9 per cent). In multivariable analysis, patients aged less than 50 years, those with high- or intermediate-grade DCIS and patients with multifocal disease were significantly more likely to have preoperative MRI. Patients undergoing MRI were more likely to have a mastectomy, either as first surgical treatment or following breast-conserving surgery (BCS) in the event of positive margins (odds ratio (OR) 2·11, 95 per cent c.i. 1·91 to 2·33). The risk of positive surgical margins after BCS was similar for those with *versus* without MRI. The secondary mastectomy rate after BCS was higher in patients who had MRI, especially in women aged less than 50 years (OR 1·94, 1·31 to 2·89). All findings were similar for low- and intermediate/high-grade DCIS.**

Conclusion: **Adding MRI to conventional breast imaging did not improve surgical outcome in patients diagnosed with primary DCIS. The likelihood of undergoing a mastectomy was twice as high in the MRI group, and no reduction in the risk of margin involvement was observed after BCS.**

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Introduction

In the past 25 years, the incidence of ductal carcinoma *in situ* (DCIS) has increased rapidly, especially among women aged 50–74 years, owing to the introduction of the breast cancer screening programmes and the widespread implementation of full-field digital mammography (FFDM). In the Netherlands, DCIS incidence has increased from six per 100 000 women in 1989 to 30 per 100 000 women in 2015[1,2].

In most patients, DCIS is not palpable and presents as morphologically suspicious calcifications on FFDM. However, because FFDM often underestimates DCIS size, resection margins are frequently positive after breast-conserving surgery (BCS)[3,4]. Figures collected by the Dutch Institute for Clinical Auditing on patients treated with BCS in 2015 showed positive resection margins in 19·4 per cent of those with DCIS *versus* 3 per cent of patients with invasive breast cancer[5]. Involved resection margins are associated with a twofold increased risk of ipsilateral breast recurrences, of which half are invasive, compared with negative margins[6,7]. Although positive resection margins can be treated by secondary surgery, re-excisions are a source of physical burden, anxiety and worse cosmesis for the patient.

Previous studies[8–10] have shown that adding breast MRI to FFDM leads to a more accurate assessment of the extent of DCIS compared with FFDM alone. MRI might therefore reduce the rate of margin involvement and limit the need for additional surgery after BCS. A meta-analysis[11]

including patients with biopsy-proven DCIS from two RCTs and seven observational cohort studies, however, found no effect of MRI on margin involvement, need for re-excision or mastectomy rate. Sample sizes of individual studies were generally small and not all relevant surgical outcomes were determined in these nine studies, limiting the interpretation of the overall effect. Moreover, the estimated impact on positive margins was dominated by the largest study, whereas all other surgical outcomes were based on the smaller studies.

The aim of this study was to analyse determinants of the preoperative use of breast MRI in patients with pure DCIS, and its impact on the type of primary surgery, surgical resection margins and need for re-excision after BCS in a large population-based cohort.

Methods

This was a population-based study including all women aged less than 75 years and treated with surgery for pure DCIS of the breast diagnosed in the Netherlands between 2011 and 2015. DCIS was diagnosed using stereotactic, ultrasound- or MRI-guided core needle or vacuum-assisted biopsies, with a preference for the latter.

According to Dutch guidelines[12] at that time, preoperative imaging comprised FFDM and ultrasonography in all patients, with breast MRI being considered in patients with high-grade DCIS preferring BCS, unclear tumour size, or if there was suspicion of microinvasion based on the preoperative biopsy. The presence of positive margins after primary surgery was, and still is, an indication for re-excision. To assess the use and impact of breast MRI, the study population was categorized into an MRI and a no-MRI group.

Data collection

Patients were identified from the database of the Netherlands Cancer Registry (NCR). Patients are included in the NCR database after notification by the nationwide Dutch Pathology Archive of Histo- and Cytopathology. Specially trained data managers collect the data from the patients' files in all Dutch hospitals. Only patients with pure DCIS in the resection specimen were included in this study.

The following variables were used in the present analysis: age at diagnosis, hospital type (university, teaching, general), histological grade (low, intermediate, high, unknown), multifocality (yes, no), use of preoperative breast MRI (yes, no), type of primary surgery (BCS, mastectomy), surgical margin involvement after BCS (none, focal (4 mm or less), more than focal (more than 4 mm)) and use of secondary surgery after BCS (none, re-excision, mastectomy).

Study endpoints

The study endpoints were more than focal margin involvement after BCS for DCIS, the combination of focal and more than focal margin involvement after BCS, primary and overall mastectomy rates, and secondary surgery (re-excision or mastectomy) after BCS.

Statistical analysis

Multivariable logistic regression analyses were undertaken to determine the association between the use of MRI and the following co-variables: year of incidence, hospital type, age at diagnosis, tumour grade and multifocality. The associations between MRI and primary and final mastectomy were established for all patients, and adjusted for year of incidence, age group, hospital type, tumour grade and multifocality. In patients who underwent initial BCS, multivariable logistic regression analyses were performed to examine the association between MRI and surgical outcomes, including margin involvement, secondary surgery (re-excision or mastectomy) and secondary mastectomy. Analyses were stratified by age at diagnosis (less than 50 *versus* 50–74 years) because younger women tend to have more dense glandular tissue with a higher chance of background enhancement on MRI[13]. This may influence the diagnostic accuracy of MRI in detecting DCIS. Analyses were furthermore stratified by histological grade (low *versus* intermediate/high) because this factor is also known to affect the accuracy of MRI[9,14–16].

Results

Patient characteristics associated with use of breast MRI

In the interval 2011–2015, a total of 10 173 patients were diagnosed with 10 415 DCIS lesions. The majority of the lesions were diagnosed at age 50–74 years (84·7 per cent), were of intermediate or high grade (79·0 per cent) and were primarily treated with BCS (70·8 per cent) (*Table 1*). MRI was used in 2382 lesions (22·9 per cent); this varied between 20·4 per cent in 2013 and 25·6 per cent in 2015. MRI was used in 38·8 per cent of women aged less than 50 years and 20·0 per cent of those aged 50–74 years (*Table 2*). In multivariable analyses, age at diagnosis, DCIS grade and multifocality remained independent factors associated with use of MRI (*Table 2*).

Mastectomy

Mastectomy as the first surgical procedure was performed in 29·2 per cent of patients, and more often in women

Table 1 Patients with ductal carcinoma *in situ* diagnosed in the Netherlands, 2011–2015, according to use of MRI

	Total ($n = 10\,415$)	MRI ($n = 2382$)	No MRI ($n = 8033$)
Year of diagnosis			
2011	1900 (18·2)	419 (17·6)	1481 (18·4)
2012	2016 (19·4)	450 (18·9)	1566 (19·5)
2013	2265 (21·7)	462 (19·4)	1803 (22·4)
2014	2046 (19·6)	491 (20·6)	1555 (19·4)
2015	2188 (21·0)	560 (23·5)	1628 (20·2)
Hospital type			
University	1227 (11·8)	321 (13·5)	906 (11·3)
Teaching	4536 (43·6)	1081 (45·4)	3455 (43·0)
General	4640 (44·6)	975 (40·9)	3665 (45·6)
Unknown	12 (0·1)	5 (0·2)	7 (0·1)
Age (years)			
< 50	1594 (15·3)	618 (25·9)	976 (12·1)
50–74	8821 (84·7)	1764 (74·1)	7057 (87·9)
DCIS grade			
Low	1581 (15·2)	254 (10·7)	1327 (16·5)
Intermediate	3545 (34·0)	799 (33·5)	2746 (34·2)
High	4682 (45·0)	1203 (50·5)	3479 (43·3)
Unknown	607 (5·9)	126 (5·3)	481 (6·0)
Multifocality			
No	9416 (90·4)	2090 (87·7)	7326 (91·2)
Yes	779 (7·5)	264 (11·1)	515 (6·4)
Unknown	220 (2·1)	28 (1·2)	192 (2·4)
Primary surgery			
BCS	7375 (70·8)	1303 (54·7)	6072 (75·6)
Mastectomy	3040 (29·2)	1079 (45·3)	1961 (24·4)
Margin involvement after BCS	$n = 7375$	$n = 1303$	$n = 6072$
None	5512 (74·7)	981 (75·3)	4531 (74·6)
Focal	876 (11·9)	148 (11·4)	728 (12·0)
More than focal	563 (7·6)	120 (9·2)	443 (7·3)
Unknown	424 (5·7)	54 (4·1)	370 (6·1)
Secondary surgery after BCS	$n = 7375$	$n = 1303$	$n = 6072$
No further surgery	6076 (82·4)	1027 (78·8)	5049 (83·2)
Re-excision	704 (9·5)	130 (10·0)	574 (9·5)
Mastectomy	595 (8·1)	146 (11·2)	449 (7·4)

Values in parentheses are percentages. DCIS, ductal carcinoma *in situ*; BCS, breast-conserving surgery.

Table 2 Multivariable analysis of predictors for the use of MRI in patients with ductal carcinoma *in situ*

	No. who had MRI*	Odds ratio†‡
Year of diagnosis		
2011	419 (22·1)	1·00 (reference)
2012	450 (22·3)	1·02 (0·87, 1·19)
2013	462 (20·4)	0·91 (0·78, 1·06)
2014	491 (24·0)	1·13 (0·97, 1·31)
2015	560 (25·6)	1·24 (1·07, 1·44)§
Hospital type		
University	321 (26·2)	1·42 (1·22, 1·66)§
Teaching	1081 (23·8)	1·19 (1·08, 1·32)§
General	975 (21·0)	1·00 (reference)
Age (years)		
< 50	618 (38·8)	2·56 (2·28, 2·88)§
50–74	1764 (20·0)	1·00 (reference)
DCIS grade		
Low	254 (16·1)	1·00 (reference)
Intermediate	799 (22·5)	1·59 (1·35, 1·86)§
High	1203 (25·7)	1·92 (1·64, 2·23)§
Unknown	126 (20·8)	1·29 (1·01, 1·65)§
Multifocality		
No	2090 (22·2)	1·00 (reference)
Yes	264 (33·9)	1·72 (1·47, 2·02)§

Values in parentheses are *percentages and †95 per cent confidence intervals. ‡Some 230 patients with unknown hospital type and/or unknown multifocality were excluded from the multivariable analysis. DCIS, ductal carcinoma *in situ*. §$P < 0·050$ (multivariable logistic regression analysis).

who had undergone breast MRI (odds ratio (OR) 2·22, 95 per cent c.i. 2·00 to 2·45) (*Table 3*). Findings were similar by age and DCIS grade. MRI was also associated with a significantly increased risk of final mastectomy (OR 2·11, 1·91 to 2·33).

Margin involvement

Of patients who underwent BCS as first surgical procedure and with known margin status, 19·5 per cent had margin involvement (*Table 4*). MRI use was not associated with a lower risk of margin involvement overall (OR 0·99, 95 per cent c.i. 0·85 to 1·16), or with a lower risk of more than focal margin involvement (OR 1·13, 0·90 to 1·40). Findings with respect to margin involvement were similar in women aged less than 50 years and those aged 50–74 years, and for low- and intermediate/high-grade DCIS.

Secondary surgery

Secondary surgery and mastectomy were performed in 17·5 and 8·1 per cent respectively of patients who were primarily treated with BCS. The likelihood of secondary surgery after BCS was slightly higher in the MRI group (OR 1·17, 95 per cent c.i. 1·00 to 1·37), irrespective of age or DCIS grade (*Table 4*). The risk of secondary mastectomy after BCS was also slightly higher in the MRI group (OR 1·32, 1·07 to 1·63), irrespective of DCIS grade (*Table 4*). The risk of secondary mastectomy in the MRI group was increased in women aged less than 50 years (OR 1·94, 1·31 to 2·89), but not among those aged 50–74 years (OR 1·12, 0·87 to 1·44).

Table 3 Effect of preoperative breast MRI on primary and final mastectomy in all patients with ductal carcinoma *in situ*, by age and tumour grade

	Primary mastectomy		Final mastectomy	
	% of women	Odds ratio	% of women	Odds ratio
All women*	29·2		34·9	
No MRI	24·4	1·00 (reference)	30·0	1·00 (reference)
MRI used	45·3	2·22 (2·00, 2·45)§	51·4	2·11 (1·91, 2·33)§
Age < 50 years†	43·8		52·5	
No MRI	35·6	1·00 (reference)	43·4	1·00 (reference)
MRI used	56·8	2·14 (1·72, 2·67)§	66·7	2·33 (1·85, 2·92)§
Age 50–74 years†	26·6		31·7	
No MRI	22·9	1·00 (reference)	28·1	1·00 (reference)
MRI used	41·3	2·23 (1·99, 2·50)§	46·1	2·05 (1·83, 2·29)§
Low-grade DCIS‡	17·0		21·1	
No MRI	14·3	1·00 (reference)	18·0	1·00 (reference)
MRI used	31·1	2·59 (1·88, 3·57)§	37·4	2·51 (1·85, 3·40)§
Intermediate/high-grade DCIS‡	32·0		38·2	
No MRI	27·0	1·00 (reference)	33·2	1·00 (reference)
MRI used	47·7	2·18 (1·96, 2·43)§	53·8	2·28 (2·05, 2·54)§

Values in parentheses are 95 per cent confidence intervals. Analyses were adjusted for: *incidence year, age group, hospital type, ductal carcinoma *in situ* (DCIS) grade and multifocality; †incidence year, hospital type, DCIS grade and multifocality; ‡incidence year, age group, hospital type and multifocality. §$P < 0{\cdot}050$ (multivariable logistic regression analysis).

Table 4 Effect of preoperative breast MRI on surgical outcomes after primary breast-conserving surgery for ductal carcinoma *in situ*, by age and grade

	Margin involvement focal or more than focal*		Margin involvement more than focal*		Secondary surgery		Secondary mastectomy	
	% of women	Odds ratio	% of women	Odds ratio	% of women	Odds ratio	% of women	Odds ratio
All women†	19·5		7·6		17·5		8·1	
No MRI	19·3	1·00 (reference)	7·3	1·00 (reference)	16·7	1·00 (reference)	7·4	1·00 (reference)
MRI used	20·6	0·99 (0·85, 1·16)	9·2	1·13 (0·90, 1·40)	21·0	1·17 (1·00, 1·37)¶	11·2	1·32 (1·07, 1·63)¶
Age < 50 years‡	24·0		12·3		26·1		15·4	
No MRI	24·0	1·00 (reference)	11·1	1·00 (reference)	24·6	1·00 (reference)	12·2	1·00 (reference)
MRI used	24·0	1·00 (0·70, 1·42)	15·0	1·41 (0·91, 2·20)	29·6	1·19 (0·85, 1·67)	22·9	1·94 (1·31, 2·89)¶
Age 50–74 years‡	18·9		7·0		16·3		7·1	
No MRI	18·7	1·00 (reference)	6·9	1·00 (reference)	15·8	1·00 (reference)	6·8	1·00 (reference)
MRI used	19·7	1·00 (0·84, 1·18)	7·7	1·04 (0·81, 1·35)	18·8	1·16 (0·97, 1·38)	8·2	1·12 (0·87, 1·44)
Low-grade DCIS§	11·7		4·3		10·5		5·0	
No MRI	11·5	1·00 (reference)	4·1	1·00 (reference)	9·9	1·00 (reference)	4·3	1·00 (reference)
MRI used	13·1	1·04 (0·63, 1·71)	6·3	1·31 (0·64, 2·70)	14·3	1·20 (0·73, 1·97)	9·1	1·77 (0·95, 3·29)
Intermediate/high-grade DCIS§	22·1		8·6		19·7		9·1	
No MRI	22·0	1·00 (reference)	8·3	1·00 (reference)	19·0	1·00 (reference)	8·5	1·00 (reference)
MRI used	22·7	1·02 (0·87, 1·21)	9·9	1·15 (0·91, 1·45)	22·9	1·21 (1·02, 1·43)	11·7	1·27 (1·01, 1·59)

Values in parentheses are 95 per cent confidence intervals. *Patients with unknown margin status were excluded from the analyses. Analyses were adjusted for: †incidence year, age group, hospital type, ductal carcinoma *in situ* (DCIS) grade and multifocality; ‡incidence year, hospital type, DCIS grade and multifocality; §incidence year, age group, hospital type and multifocality. ¶$P < 0{\cdot}050$ (multivariable logistic regression analysis).

Discussion

This population-based study included 10 173 women diagnosed with primary DCIS in the Netherlands between 2011 and 2015. Preoperative breast MRI, in addition to conventional breast imaging, in patients with DCIS did not reduce the risk of positive resection margins, but increased the secondary surgery rate after primary BCS and doubled the overall mastectomy rate.

An important finding of this study is that preoperative MRI increased the odds of having mastectomy as primary surgery in all age groups (fully adjusted OR 2·22, 95 per cent c.i. 2·00 to 2·45). A similar effect was found in the meta-analysis by Fancellu and colleagues[11], in which the age-adjusted OR was 1·8 (1·2 to 2·7), based on five studies including 598 patients. This result can partly be explained by the fact that, in some patients, extensive, multifocal and multicentric disease can be detected more accurately by MRI[15,17], and so patients unsuitable for BCS can be identified. MRI, however, also tends to overestimate the size of the lesion in 17–47 per cent of patients[14,18], increasing the likelihood of unnecessary mastectomies. Another explanation may be that more patients choose to undergo mastectomy owing to increased anxiety caused by false-positive MRI findings in other quadrants of the breast[19].

In this study, MRI use was not associated with the likelihood of positive resection margins after BCS (adjusted OR 0·99, 0·85 to 1·16). This result confirms the finding of the previous meta-analysis[11], where the age-adjusted OR was 1·1 (0·6 to 1·9) based on five studies including 2688 patients. DCIS mostly manifests as non-mass-like enhancement with inconsistent dynamic features (from plateau to wash-out, to persistent enhancement curves)[20,21], sometimes making it challenging to distinguish it from regular background parenchymal enhancement and to determine the extent of DCIS[9]. Another reason may be that metabolic activity in intraductal cancer cells and angiogenesis around the affected ducts is too low for gadolinium uptake, especially in low-grade DCIS, and so remains below the enhancement threshold currently used in breast MRI[22,23]. FFDM-detected DCIS is not visible on MRI in 17–30 per cent of patients[24]. Consequently, for these patients MRI cannot add information on the size or growth pattern[16].

MRI is currently the most accurate imaging technique for estimating the size of DCIS, although it has limitations as described above[19]. Why does this not then translate into any improvement in surgical outcomes in patients treated with BCS? Probably the most important reason is that DCIS is not palpable, and that the breast consists mostly of soft and mobile tissue, with only a few anatomical structures to orientate on. Various techniques have been developed to help the surgeon localize non-palpable lesions. During the study interval, the localization methods most often used in the Netherlands were the wire-guided and iodine-125 seed-guided techniques. FFDM with or without MRI, and with or without a localization procedure, provides the only guidance for the surgeon to determine which tissue needs to be resected. These images are made with the breast in a different position to that on the operating table, making extrapolation of the exact position and growth pattern of the DCIS difficult during surgery. Gombos and colleagues[25] showed considerable deformity of the breast and change in tumour position between MRI in the supine and prone positions. Sakakibara and co-workers[26] reported a lower rate of positive resection margins after MRI in the supine position than in the prone position in patients with DCIS. Another reason why MRI does not improve the surgical outcome in patients treated with BCS is the growth pattern of DCIS, following the linear and branching pattern of the ductal system. It is unlikely that in a short period of time imaging techniques will be able to visualize one or a few pathological ducts. Even if possible, defining all borders of abnormal tissue with a localization procedure will not be feasible. Techniques that help the surgeon to distinguish normal from abnormal tissue during surgery will probably lead to a faster decrease in the risk of positive resection margins.

If there were a subgroup in which MRI had a positive effect on surgical outcomes of DCIS, one might expect it to be the younger patient group, because in general FFDM images are harder to interpret owing to higher breast density. In women aged less than 50 years, DCIS is more likely to be detected by clinical symptoms than by screening, and is more often larger and of higher grade when diagnosed[27,28]. This, together with a higher risk of local recurrence among younger patients treated with BCS in comparison with older patients[27,29], and increasing possibilities and improved techniques for immediate breast reconstruction, may explain the higher mastectomy rate in this age group, irrespective of the use of MRI. In the present study, women aged less 50 years who underwent MRI had the highest primary mastectomy rate and the lowest BCS rate, which might suggest better selection by use of MRI. However, this did not result in a lower risk of positive resection margins after BCS, indicating that MRI also has no additional value in these younger patients. Among younger patients, those who had MRI during the diagnostic process were more likely to undergo secondary mastectomy in the event of involved margins than those who did not have MRI. The reason for this is not clear. A possible explanation is that a larger amount of DCIS was expected to be left in the breast when MRI was not able to predict

the extent or growth pattern of the DCIS in this subgroup more accurately in comparison with conventional imaging.

A strength of the present study, besides the large patient population, is the use of data from the NCR, which is known to have high-quality data. However, like most retrospective studies, this study also has some limitations. An important limitation is that the reasons for performing MRI were unavailable, neither was information on radiological and pathological size of DCIS. As more patients with high-grade DCIS underwent MRI, it is possible that there was selection of larger tumours in the MRI group[30]. With larger DCIS comes a higher risk of positive resection margins[30,31] and a higher risk of primary mastectomy. This can mimic the effect of MRI in this patient group. In addition, information about MRI sequence protocols used, experience of the radiologists and localization procedures employed were not available in this study. Furthermore, it was not possible to determine whether MRI use changed surgical treatment decisions and, if it did, whether this was appropriate. In the meta-analysis by Fancellu and colleagues[11], 16 (95 per cent c.i. 6 to 35) per cent of 298 patients had a change in initial surgical treatment based on preoperative MRI findings. In the COMICE trial[32], MRI led to an accurate treatment decision in 79 per cent of patients compared with histopathological findings. The ratio between appropriate and inappropriate mastectomy was 1 : 1. It is also unknown how other factors, such as patient or surgeon preference, or how patients were informed about adjuvant radiotherapy or about safety of BCS in comparison with mastectomy, influenced the surgical decision-making.

At present, there is no convincing indication for the use of preoperative MRI in patients diagnosed with DCIS. MRI increases costs[33], causes stress and anxiety for patients owing to additional uncertain or false-positive findings[34], and does not lead to a better surgical outcome. For a definitive conclusion, it is advised to wait for the results of studies with large patient numbers investigating the long-term impact of MRI on local recurrence and survival, for example using follow-up data from this cohort. If preoperative breast MRI is being considered, the European Society of Breast Cancer Specialists guidelines[35] state that women should be informed about the uncertainties, and possible advantages and disadvantages, of MRI before being scheduled for this examination.

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