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Original Research

Breast magnetic resonance imaging use in patients undergoing neoadjuvant chemotherapy is associated with less mastectomies in large ductal cancers but not in lobular cancers☆

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Breast cancer;
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Abstract ***Background:*** To assess the impact of breast magnetic resonance imaging (MRI) use on surgical outcome per histological breast cancer subtype in patients treated with neoadjuvant chemotherapy.
Patients and methods: All patients aged 18–70 years who underwent neoadjuvant chemotherapy for stage I–III invasive breast cancer in the Netherlands in the years 2011–2013 were identified from the Netherlands Cancer Registry. Patients with cT4 tumours were excluded from the analysis. Use of breast MRI and impact on surgical treatment, resection margins and detection of contralateral breast cancer were analysed by multivariable analyses.
Results: Breast MRI was performed in 2879 (83.9%) out of 3433 patients treated with neoadjuvant chemotherapy. Younger age (odds ratio [OR] 1.42; 95% confidence interval [CI] 1.17–1.71 for 18–50 years compared with 50–70 years), larger tumour stage (OR 1.46 [95% CI 1.15–1.86] for cT3, compared to cT1–2 tumours) and multifocality (OR 1.30; 95% CI 1.04–1.61, versus unifocality) were associated with increased breast MRI use. In ductal breast cancer, after stratification for cT-status, breast MRI use is associated with a significant lower OR for mastectomy as final surgery in cT3 tumours (OR 0.45, 95% CI 0.21–0.99). Resection margin involvement and detection of contralateral breast cancer were not associated with breast MRI use.
Conclusion: In patients treated with neoadjuvant chemotherapy, the use of breast MRI was associated with a reduced mastectomy rate, particularly in patients with large invasive ductal breast tumours but not in patients with lobular breast cancer.

1. Introduction

For the treatment of early breast cancer, neoadjuvant chemotherapy is increasingly being used. Neoadjuvant chemotherapy has the potential to downstage the tumour and the axillary lymph nodes. This may facilitate breast conserving therapy and may obviate the need for extensive axillary treatment in selected patients [1]. Moreover, the time window created by neoadjuvant chemotherapy offers the opportunity for counselling and analysis of germ line mutations, which supports more careful planning of the desired type of breast surgery and is of particular importance in young patients [2]. In addition, it allows evaluation of clinical tumour response to systemic treatment and—in case of no response—an early switch of systemic therapy [3,4].

In patients undergoing surgery without neoadjuvant systemic therapy, magnetic resonance imaging (MRI) has generally shown to increase the number of mastectomies [5–9]. However, studies addressing the impact of breast MRI on surgical outcome specifically in lobular breast cancer reported conflicting results [6–9].

Only few and small studies have addressed breast MRI use in neoadjuvant treated patients in relation to mastectomy rates as surgical outcome [10–13]. Straver *et al.* examined breast MRI exams in 208 patients, with an underestimation of tumour size by MRI in 35 patients and an overestimation in 9 patients, with an overall accuracy of MRI for surgical treatment selection of 83% [10]. Similar findings were seen by others [11–13]. However, these studies were too small to assess the impact of breast MRI on mastectomy rates in patients undergoing neoadjuvant chemotherapy.

The current study was performed to analyse the variables associated with breast MRI use in patients with invasive breast cancer treated with neoadjuvant chemotherapy and the impact of breast MRI use on performing mastectomy as first surgical procedure after neoadjuvant chemotherapy in all patients and per histologic subtype (ductal versus lobular breast cancer). In addition, we analysed presence of a positive surgical margin status after the first surgical procedure and treatment with final mastectomy including those who had first undergone breast conserving therapy. Finally, we assessed the detection rate of contralateral breast cancer in patients treated with neoadjuvant chemotherapy.

2. Patients and methods

2.1. Patients

Patients were selected from the Netherlands Cancer Registry (NCR), which is hosted by the Comprehensive Cancer Organization. All patients newly diagnosed with stage I–III invasive breast cancer in the Netherlands in the period 2011–2013, who underwent neoadjuvant chemotherapy followed by surgery were included. Patients aged under 18 years or over 70 years of age at primary diagnosis, patients undergoing neoadjuvant endocrine therapy and patients with cT4 tumours (and

thereby a smaller chance of breast conservative treatment) were excluded.

2.2. Data collected

The following variables were collected: age at diagnosis, breast MRI use prior to chemotherapy, pre-treatment clinical T-stage, pre-treatment clinical N-stage, type of breast surgery (mastectomy or lumpectomy as first or final surgical procedure after neoadjuvant chemotherapy) and surgical margin status (only after lumpectomy); and from the pathology reports, multifocality, histological type, histological grade, oestrogen receptor (ER) status, progesterone receptor (PR) status and human epidermal growth factor receptor 2 (HER2 status) were collected.

Clinical T-stage was based on the maximum tumour diameter as measured on MRI (preferred if available), mammography or ultrasonography. Clinical N-stage was based on radiological examination as well as cytological or histological examination (if available) of the regional lymph nodes. Grading of invasive carcinoma was scored according to the Nottingham (Elston–Ellis) modification of the Scarf–Bloom–Richardson grading system. Positivity of ER and PR was defined as at least 10% of immunostained nuclei of tumour cells. HER2 status was considered positive in case of HER2 3+ (strong and complete membranous expression in >30% of tumour cells) or HER2 2+ (weak complete membranous expression in >10% of tumour cells) confirmed with positive fluorescence *in situ* hybridisation. If pathological variables (e.g. grading) were not available from the core needle biopsy these were assessed on final pathology. In line with the Dutch guideline, margin involvement is classified as focal (i.e. less than 4 mm) and more than focal (i.e. more than 4 mm). Re-excision is advised in case of more than focal margin involvement. In the present study, margin involvement means more than focal involvement.

All second primary invasive and non-invasive cancers diagnosed in the contralateral breast within three months after the diagnosis of the first breast cancer in the period 2011–2013 were included and considered as synchronous contralateral breast cancers.

The NCR covers the data for all newly diagnosed *in situ* and invasive tumours. The NCR has specialised trained registrars who derive these data from hospital records of patients with a cancer diagnosis. Because of the thorough registrar training and computerised consistency checks, the quality of the data is considered high.

2.3. Statistical analyses

The study population was divided into a non-MRI group and an MRI group according to MRI use prior to chemotherapy. Differences in patient characteristics and disease characteristics between the two groups were tested using χ^2 test for categorical variables. Patients with synchronous contralateral breast cancer were included as two separate 'patients' and the analyses were performed on a tumour level.

Multivariable logistic regression analysis was performed to determine the association between breast MRI use and the following co-variates: year of diagnosis, age at diagnosis, clinical tumour size, clinical nodal status, ER, PR and HER2 status, tumour grade, histological type and multifocality. Multivariable logistic regression analyses were performed to test the association between breast MRI use and the following outcomes: treatment with mastectomy as final surgical procedure (versus breast conserving therapy), presence of a positive surgical margin after breast conserving therapy and diagnosis of contralateral breast cancer.

The analyses on mastectomy as final surgical procedure were performed for the total group of invasive breast cancers and for ductal and lobular cancers separately.

Statistical tests were two-sided, and $P < 0.050$ was considered statistically significant. SAS® version 9.3 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

3. Results

3.1. Patient characteristics

In the period 2011–2013, a total of 3433 patients diagnosed with cT1–3 invasive breast cancer were treated with neoadjuvant chemotherapy and included in the present study. Median age of the included patients at the time of diagnosis was 49 years (range 22–69 years). The ER/PR status was positive in 69.1% and HER2 status was positive in 23.7% of patients; 27.4% of the tumours were multifocal and 12.3% were of lobular histology. Breast MRI prior to chemotherapy was performed in 3156 (83.9%) of patients (Table 1). In 82.0% of patients, the neoadjuvant chemotherapy consisted of an anthracycline–taxane combination.

3.2. Factors influencing breast MRI use

Patients aged younger than 50 years were 1.4 times more likely to undergo MRI compared to patients aged 50–69 years (odds ratio [OR] 1.42, 95% confidence interval [CI] 1.17–1.71; Table 1). Patients with larger tumours were also more likely to undergo breast MRI (OR for cT3 as compared to cT1–2 = 1.46, 95% CI 1.15–1.86). Multifocality was also associated with more frequent MRI use (OR 1.30; 95% CI 1.04–1.61). Between hospitals, MRI use varied from 66.3% to 80.3% of patients undergoing neoadjuvant chemotherapy.

Table 1
Baseline characteristics and multivariable analysis of MRI use in invasive breast cancer treated with neoadjuvant chemotherapy and diagnosed in 2011–2013 in the Netherlands.

Characteristics	Invasive breast cancer (n = 3433)						
	MRI use No	%	MRI use Yes	%	OR	95% CI	P
Year of incidence							
2011	160	17.2	771	82.8	1 (Ref)		
2012	179	16.9	883	83.2	1.04	0.82–1.32	0.75
2013	215	14.9	1225	85.1	1.26	1.00–1.58	0.05
Age group (years)							
<50	298	18.8	1286	81.2	1 (Ref)		
50–69	256	13.9	1593	86.2	1.42	1.17–1.71	<0.001
Clinical tumour stage[a]							
cT1–2	449	17.5	2124	82.6	1 (Ref)		
cT3	100	12.1	728	87.9	1.46	1.15–1.86	0.00
Clinical nodal stage[b]							
cN0	210	17.5	991	82.5	1 (Ref)		
cN1–3	340	15.3	1879	84.7	1.12	0.92–1.35	0.27
Histological type[c]							
Ductal	477	16.4	2429	83.6	1 (Ref)		
Lobular	58	13.7	364	86.3	1.21	0.89–1.66	0.23
Grade							
Good	17	13.2	112	86.8	1 (Ref)		
Intermediate	147	24.0	465	76.0	0.45	0.26–0.78	0.00
Poor	104	19.6	426	80.4	0.60	0.34–1.06	0.08
Unknown	286	13.2	1876	86.8	0.92	0.54–1.57	0.77
ER/PR/HER2 status[d]							
ER+ or PR+, and HER2−	274	14.5	1611	85.5	1 (Ref)		
ER+ or PR+, and HER2+	65	13.4	422	86.7	1.28	0.9–1.72	0.10
ER− and PR−, and HER2−	114	17.3	546	82.7	1.03	0.80–1.32	0.85
ER− and PR−, and HER2+	55	16.8	272	83.2	0.97	0.70–1.34	0.86
Multifocality[e]							
No	373	15.6	2024	84.4	1 (Ref)		
Yes	128	13.6	813	86.4	1.30	1.04–1.61	0.02

NAC, neoadjuvant chemotherapy; MRI, magnetic resonance imaging; ER, oestrogen receptor; PR, progesterone receptor; HER2, HER2-receptor.
[a] cT-status missing in 32 patients.
[b] cN status missing in 13 patients.
[c] Histological type missing in 90 patients.
[d] ER/PR/HER2 status missing in 74 patients.
[e] Multifocality missing in 95 patients.

3.3. Mastectomy as final surgical procedure

In 3394 patients, the final surgical procedure was known and of all patients treated with neoadjuvant chemotherapy, 1820 (53.6%) were treated with a mastectomy as final surgical procedure.

In Table 2, the ORs of all parameters and mastectomy as final surgical procedure are shown. Table 3 shows the ORs of all parameters and mastectomy as final surgical procedure per histological type. After correcting for year of breast cancer incidence, age, clinical tumour size, clinical nodal status, ER, PR and HER2 status, tumour grade and multifocality, breast MRI use was associated with a lower rate of mastectomies performed as final surgical procedure after neoadjuvant chemotherapy in patients with invasive breast cancer (OR 0.89, 95% CI 0.73–1.09) as compared to those with no breast MRI use (Table 2). This is particularly applicable to the invasive ductal breast cancers. After stratification for cT-status in ductal breast cancer, breast MRI use is associated with a significant lower OR for mastectomy as final surgery in cT3 tumours (OR 0.45, 95% CI 0.21–0.99). In cT1–2 invasive ductal tumours, breast MRI use is associated with an OR of mastectomy as final surgery of 0.95 (95% CI 0.75–1.20).

3.4. Surgical margins

In total, 103 patients (3.3%) had margin involvement after breast conserving surgery as first surgical procedure. Of these, 88 (85%) underwent breast MRI.

After multivariable correction, a non-significant trend was observed between the use of breast MRI and a reduced presence of a positive surgical margin in patients with invasive breast cancer that were treated with breast conserving surgery (OR 0.60; 95% CI 0.32–1.10; Table 2).

Table 2
Multivariable analysis of outcomes in invasive breast cancer treated with neoadjuvant chemotherapy and diagnosed in 2011–2013 in The Netherlands.

Variables	Margin involvement for breast conserving surgery as first surgical procedure			Mastectomy as final surgery			Contralateral breast cancer		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
MRI									
No	1 (Ref)			1 (Ref)			1 (Ref)		
Yes	0.60	0.32–1.10	0.10	0.89	0.73–1.09	0.27	0.84	0.50–1.40	0.51
Year of incidence									
2011	1 (Ref)			1 (Ref)			1 (Ref)		
2012	1.53	0.83–2.83	0.17	1.09	0.89–1.33	0.40	1.16	0.67–2.01	0.59
2013	1.37	0.76–2.44	0.29	0.86	0.72–1.03	0.11	1.21	0.73–2.01	0.46
Age group (years)									
50–69	1 (Ref)			1 (Ref)			1 (Ref)		
<50	1.12	0.71–1.77	0.63	1.66	1.43–1.94	<0.001	0.83	0.55–1.24	0.36
Clinical tumour stage									
cT1–2	1 (Ref)			1 (Ref)			1 (Ref)		
cT3	2.66	1.49–4.72	<0.001	5.64	4.60–6.92	<0.001	0.37	0.19–0.72	0.00
Clinical nodal stage									
cN0	1 (Ref)			1 (Ref)			1 (Ref)		
cN1–3	1.34	0.83–2.15	0.23	1.17	1.00–1.37	0.05	0.34	0.22–0.51	<0.001
Histology									
Ductal	1 (Ref)			1 (Ref)			1 (Ref)		
Lobular	4.53	2.67–7.67	<0.001	2.16	1.67–2.79	<0.001	1.20	0.68–2.12	0.53
Other	1.13	0.25–5.06	0.87	1.48	0.92–2.37	0.11	1.43	0.50–4.07	0.51
Tumour grade									
Good	1 (Ref)			1 (Ref)			1 (Ref)		
Intermediate	2.36	0.67–8.33	0.18	1.07	0.70–1.63	0.77	0.84	0.30–2.34	0.73
Poor	1.29	0.31–5.44	0.73	1.59	1.03–2.46	0.04	0.93	0.31–2.84	0.90
Unknown	1.12	0.33–3.82	0.86	1.25	0.84–1.85	0.28	1.12	0.44–2.87	0.82
ER, PR and HER2 status									
ER+ or PR+, and HER2−	1 (Ref)			1 (Ref)			1 (Ref)		
ER+ or PR+, and HER2+	0.41	0.18–0.92	0.03	0.99	0.79–1.24	0.92	0.49	0.24–1.00	0.05
ER− and PR-, and HER2−	0.14	0.04–0.44	<0.001	0.91	0.74–1.12	0.36	0.33	0.16–0.66	0.00
ER− and PR−, and HER2+	0.36	0.12–1.02	0.05	1.00	0.77–1.31	0.98	0.26	0.08–0.82	0.02
Multifocality									
No	1 (Ref)			1 (Ref)			1 (Ref)		
Yes	0.96	0.55–1.67	0.88	2.93	2.46–3.49	<0.001	0.84	0.52–1.35	0.48

MRI, magnetic resonance imaging; ER, oestrogen receptor; PR, progesterone receptor; HER2, HER2-receptor.

Regardless of MRI use, the presence of a positive surgical margin after breast conserving surgery was significantly higher in patients with lobular breast cancer as compared to patients with ductal cancer (OR 4.53; 95% CI 2.67–7.67), in patients with cT3 tumours as compared with cT1–2 tumours (OR 2.66; 95% CI 1.49–4.72; Table 2). No significant relation was found for multifocal tumours and presence of a positive surgical margin.

3.5. Contralateral breast cancer

Overall, 102 (3.0%) contralateral breast cancers were detected by breast MRI.

No significant association was found, however, between breast MRI use and the frequency of being diagnosed with contralateral breast cancer in patients treated with neoadjuvant chemotherapy (Table 2).

Detection of contralateral breast cancer was associated with the size and with ER/PR/HER2 status of the index breast tumour (Table 2).

4. Discussion

In this large cohort study in the Netherlands, breast MRI was used in approximately 80% of patients younger than 70 years old who were treated with neoadjuvant chemotherapy. Important parameters associated with breast MRI use during neoadjuvant chemotherapy were larger tumour size and presence of multifocality. A small majority of patients treated with neoadjuvant chemotherapy underwent a mastectomy as final surgical procedure (53.6%). Although we did not observe a significantly lower rate of mastectomies as final surgical procedure when breast MRI was performed in patients with invasive ductal cancer, we did

Table 3
Multivariable analysis of mastectomy as final surgery in breast cancer tumours treated with neoadjuvant chemotherapy and diagnosed in 2011–2013 in The Netherlands according to histological subtype.

Variables	Invasive ductal breast cancer			Invasive lobular breast cancer		
	OR	95% CI	P	OR	95% CI	P
MRI						
No	1 (Ref)			1 (Ref)		
Yes	0.87	0.70–1.09	0.22	1.03	0.52–2.06	0.93
Year of incidence						
2011	1 (Ref)			1 (Ref)		
2012	1.14	0.92–1.41	0.22	0.75	0.41–1.39	0.36
2013	0.83	0.68–1.01	0.06	1.20	0.67–2.17	0.54
Age group (years)						
50–69	1 (Ref)			1 (Ref)		
<50	1.66	1.41–1.96	<0.001	0.76	0.46–1.26	0.28
Clinical tumour stage						
cT1–2	1 (Ref)			1 (Ref)		
cT3	5.28	4.23–6.59	<0.001	9.82	5.21–18.49	<0.001
Clinical nodal stage						
cN0	1 (Ref)			1 (Ref)		
cN1–3	1.17	0.99–1.38	0.07	1.11	0.67–1.83	0.69
Tumour grade						
Good	1 (Ref)			1 (Ref)		
Intermediate	1.02	0.64–1.63	0.93	1.35	0.43–4.22	0.60
Poor	1.59	0.99–2.55	0.05	1.11	0.15–8.52	0.92
Unknown	1.22	0.79–1.89	0.36	1.60	0.55–4.68	0.39
ER, PR and HER2 status						
ER+ or PR+, and HER2−	1 (Ref)			1 (Ref)		
ER+ or PR+, and HER2+	1.03	0.81–1.30	0.83	0.58	0.22–1.51	0.26
ER− and PR−, and HER2−	0.89	0.72–1.11	0.29	1.77	0.35–8.86	0.49
ER− and PR−, and HER2+	1.03	0.78–1.35	0.85	0.25	0.04–1.79	0.17
Multifocality						
No	1 (Ref)			1 (Ref)		
Yes	3.19	2.64–3.85	<0.001	1.44	0.87–2.39	0.15

MRI, magnetic resonance imaging; ER, oestrogen receptor; PR, progesterone receptor; HER2, HER2-receptor.

observe that tumour size plays an important role. After stratification for cT-status, breast MRI use was associated with a significant lower OR for mastectomy as final surgery in patients with cT3 tumours, but not in those with cT1 or cT2 tumours. MRI use did not influence the number of mastectomies in patients with invasive lobular cancer. Breast MRI use therefore did not appear to be of value for patients with lobular cancer treated with neoadjuvant chemotherapy to increase the possibility of breast conserving surgery.

In our large population-based study, the rate of surgical margin involvement in patients who underwent breast conserving surgery after neoadjuvant chemotherapy was 3.3% (2.8% with breast MRI versus 3.8% without breast MRI), which is comparable to what we observed in our prior MRI study in patients treated with primary surgery (4.0%). The low irradicality rate in our study as compared to other studies may in part be explained by different definitions of surgical margins [14]. Most importantly, despite our more liberal definition of radicality, we have a low local recurrence rate in the Netherlands [14].

Of note, despite the fact that breast MRI was more frequently used in lobular breast cancer, the presence of a positive surgical margin after breast conserving surgery was more than fourfold higher in patients with lobular breast cancer as compared to patients with ductal cancer. Moreover, breast MRI use was not associated with a significant decrease in margin involvement. We hypothesise that neoadjuvant chemotherapy results in a more scattered response in lobular cancer in contrast to a more concentric response in ductal cancer, which could result in less clearly defined tumour delineation in MRI exams in lobular cancers [15,16]. Hence, this may explain why breast MRI use does not reduce the number of mastectomies and neither the presence of margin involvement in lobular breast cancer in contrast to the results in ductal breast cancer. As far as we know, no other studies focussed on the role of MRI use in patients with lobular breast cancer treated with neoadjuvant chemotherapy with respect to surgical outcome.

The strength of our study was the use of a large cohort of patients derived from a population-based database. Limitations of our study are inherent to its retrospective and observational design: several coded parameters were based on pathological findings after surgery (instead of coding based on the radiological assessment), such as multifocality. In this retrospective analysis, it could therefore not be assessed whether or

not multifocality was already clinically diagnosed and if so, with which imaging modality it was detected. In addition, 'bias by indication' may have occurred since, for example, in younger patients neoadjuvant chemotherapy is more frequently advised with MRI being performed because of response evaluation of the neoadjuvant treatment. These young patients may have been more often BRCA 1–2 mutation carriers, information that was not available in the registry, which could have masked the true impact of breast MRI on mastectomy rates. Reversely, patients who did not undergo breast MRI might have had decided already for mastectomy. If such confounding by indication might be the case for patients with ductal cancer, the impact of MRI might be lower than presented, whereas for patients with lobular cancer it actually becomes stronger. Obviously, randomly assigning yes or no breast MRI to patients treated with neoadjuvant chemotherapy would provide the most reliable information on impact of MRI use on type of surgery. However, such a design is probably not feasible anymore since MRI use is already implemented in daily practice.

Notwithstanding the shortcomings, we think that the current observations provide valuable insights on the effect of using breast MRI in breast cancer patients treated with neoadjuvant chemotherapy on a nationwide level.

In conclusion, important parameters associated with breast MRI use in patients treated with neoadjuvant chemotherapy were younger age, larger tumour size, lobular histology and presence of multifocality. Patients had a significantly reduced number of mastectomies when they had undergone breast MRI scanning prior to chemotherapy, especially in the case of large ductal breast cancer, without compromising the surgical margin. Therefore, breast MRI is recommended for patients treated with neoadjuvant chemotherapy especially in those with large ductal breast cancer if preferring breast conservative treatment.

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Conflict of interest statement

None declared.

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