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Breast Cancer in the Elderly: Is MRI Helpful?

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Abstract

Background—Appropriate use of MRI in elderly breast cancer (BC) patients remains unclear; we sought to identify the indications and implications of MRI use in our elderly BC population.

Methods—Women 70 years of age or older at first BC diagnosis with an MRI performed at our institution either perioperatively or in follow-up were included from a prospectively maintained database from 2000-2010. Univariate logistic regression was used to test associations with upgrade (additional ipsilateral, contralateral, new cancer, or recurrence) following perioperative MRI.

Results—305 BCs were imaged in 286 patients. 133 were imaged with MRI in the perioperative setting alone, 88 had only follow-up MRIs after BC treatment, and 65 had both. Indications for perioperative MRI include: extent of disease evaluation (155; 78%); abnormal imaging (13; 7%); protocol (13; 7%); occult primary (10; 5%); high-risk screening (5; 3%); and abnormal physical exam (2; 1%). MRI upgrade for occult primary cases was 4/10 (40%; 95% confidence interval [CI], 12.2-73.8%) and 14/181 (7.7%; 95% CI, 4.3-12.6%) for perioperative MRIs performed for extent of disease evaluation. Analysis of imaging and tumor characteristics failed to find significant predictors of upgrade. 369 postoperative follow-up MRIs were performed in 148 patients with a median of 2 MRIs per patient (range, 1-8), and identified 7 upgrades (1.9%; 95% CI, 0.8-3.9%).

Conclusion—MRI had the greatest benefit in women presenting with an occult primary cancer and minimal additional benefit in elderly patients with breast cancer undergoing MRI imaging for extent of disease evaluation or in follow-up.

Keywords

breast cancer; elderly; MRI

INTRODUCTION

Controversy exists regarding the use of perioperative breast MRI in the general breast cancer (BC) population.¹⁻⁵ While there are no guidelines for the appropriate use of MRI in the newly diagnosed BC patient, utilization has been increasing in recent years⁶; however, there remains scant data supporting improved outcomes in women imaged with perioperative MRI. Recent population-based studies have reported perioperative breast MRI use within subsets of BC patients and show 7-10% of patients aged >70 years undergo MRI⁷⁻⁹, with rates as high as 27% by 2007 in elderly women.⁸ While population-based registry data show increasing MRI use within the elderly BC population, information regarding the clinical indication and outcomes from MRI use in this patient population is lacking. With projections showing nearly 20% of the U.S. population 65 years of age¹⁰ by 2030, there is increasing interest in determining the optimal imaging and treatment of BC in elderly women. Here we identify the indications and implications of MRI use, both in the perioperative and postoperative setting, in women aged 70 years at time of BC diagnosis.

METHODS

Following Memorial Sloan-Kettering Cancer Center (MSKCC) institutional review board approval, women aged 70 years at time of first BC diagnosis were identified from a prospectively maintained database from 2000-2010. Women with a breast MRI performed at MSKCC, either perioperatively or in follow-up, were included. Data on patient, tumor, and treatment characteristics were collected: age at surgery; breast or ovarian cancer family history; tumor histology (ductal carcinoma in situ [DCIS], DCIS with microinvasion, invasive lobular carcinoma; invasive ductal carcinoma; other); means of diagnosis (imaging; physical exam; other/incidental); estrogen receptor (ER) status; progesterone receptor status, HER2/neu status; final surgery (lumpectomy, mastectomy); number of re-excisions; radiation therapy (RT); radiation boost to tumor bed; neoadjuvant chemotherapy or endocrine therapy; adjuvant chemotherapy or endocrine therapy; lymph node status; and mammographic density (predominately fatty; scattered fibroglandular; heterogeneously dense; extremely dense). MRI imaging characteristics were collected, including date and timing of MRI defined as perioperative (prior to cancer diagnosis, following cancer diagnosis but prior to surgery, or after surgery in the perioperative period) or postoperatively in follow-up. Indication was assessed for each perioperative MRI and up to three follow-up MRIs, and included extent of disease evaluation for known cancer, high-risk screening, physical exam abnormality, follow-up from prior cancer, protocol, abnormal imaging work-up, occult primary or other. MRI results were categorized as: negative; known-cancer only; additional ipsilateral cancer identified; new contralateral cancer identified; new cancer or local recurrence which was mammographically occult; additional lesion identified but not biopsied. It was determined if additional biopsies were performed based on MRI results; if so, pathology was recorded. Upgrade was defined as a mammographically occult cancer identified by MRI. Patient charts were reviewed for date of last follow-up and status at last follow-up (no evidence of disease; died of disease; died other cause/unknown; alive with disease). Recurrence events and dates of recurrence as first events were captured for local, regional, or distant metastasis. Date of subsequent contralateral breast cancer (CBC) was recorded.

Clinical and demographic factors were summarized using median, mean, and range for continuous covariates, and frequency and percent for categorical covariates. Univariate logistic regression was used to assess associations between selected covariates, and upgrade of disease associated with a perioperative MRI. Kaplan-Meier methods were used to estimate overall survival (OS) and recurrence-free survival (RFS), which were measured from date of definitive surgery. Cumulative incidence of CBC following surgery was estimated using competing-risks methodology, with death as a competing event. Patients with bilateral cancer at diagnosis were excluded from CBC calculations. Cumulative incidence of local, regional, and distant recurrence were estimated using competing-risks methodology with time to first event defined as time from final surgery to the earliest local, regional, or distant recurrence or death. Time-to-event analyses were limited to patients with perioperative MRI since it could not be known at time of surgery whether patients would receive a follow-up MRI. Statistical analysis was done in SAS 9.2 (SAS Institute, Cary, NC) and R 3.0.1 (R Foundation, Vienna, Austria) using the survival() and cmprsk() packages. P-values <0.05 were considered significant.

RESULTS

305 BCs were imaged in 286 women (19 synchronous bilateral BCs) who underwent MRI at MSKCC between 2000-2010. 133 (47%) were imaged with MRI in the perioperative period alone, 88 (31%) had only follow-up MRIs after their BC treatment, and 65 (23%) had both perioperative and follow-up MRIs. Table 1 summarizes patient and tumor characteristics. Patient population median age was 73 years (range, 70-90), 63% of cancers were diagnosed by imaging and 36% by physical exam abnormalities. 86% of tumors were ER⁺, 30% were lymph node⁺, and 71% treated with lumpectomy. Table 1 shows mammographic density; 87% of women had scattered fibroglandular or heterogeneously dense breast tissue, only 7% had predominantly fatty breast density, and 6% had extremely dense breast tissue. Table 2 summarizes treatment characteristics.

Perioperative MRI

198 women underwent a perioperative MRI, representing 9% (198/2198) of all women aged 70 years during this 11-year period at MSKCC. Indications for the 198 perioperative breast MRIs were: 155 (78%) for extent of disease evaluation for a known cancer; 13 (7%) for work-up of abnormal imaging before biopsy; 13 (7%) for intraoperative RT protocol requirement; 10 (5%) for an occult primary cancer; 5 (3%) for high-risk screening; 2 (1%) for an abnormal physical exam with negative conventional imaging. For the remainder of the results and discussion, the indications of “extent of disease evaluation”, “work-up of abnormal imaging”; and “protocol” were combined into the category “extent of disease evaluation” as all of these women represent a similar clinical scenario with either a known cancer or abnormal mammogram followed by MRI to evaluate disease extent. Perioperative MRI timing was: 17 (9%) prior to biopsy; 131 (66%) following cancer diagnosis but before surgery; 50 (25%) after the initial surgery in the perioperative period.

Perioperative MRI upgrade rates were examined separately for women with an occult primary tumor (n=10) and women who underwent MRI for extent of disease evaluation

(n=181). MRI upgrade for occult primary cases was 40% (4/10; 95% confidence interval (CI), 12.2-73.8%), significantly higher than the upgrade rate of 7.7% (14/181; 95% CI, 4.3-12.6%) for MRIs performed for extent of disease evaluation ($p=0.023$). Of 181 MRIs done for extent of disease evaluation, 43 (24%) led to a biopsy; 29 (67.4%) resulted in benign pathology, and 14 (32.6%) resulted in malignant pathology. One MRI identified both an additional ipsilateral cancer and a new contralateral cancer, for a total of 15 lesions (7 ipsilateral cancers consisting of 1 DCIS and 6 invasive tumors [size range, 4.5-12.0mm], and 8 contralateral cancers consisting of 3 DCIS and 5 node-negative invasive cancers [size range, 5-12mm]). All additional ipsilateral malignancies were identified in a separate quadrant of the breast from the index tumor and therefore represent multicentric disease. Analysis of imaging and tumor characteristics failed to find significant predictors of MRI upgrade (Table 3), although tumor size had a borderline significant p -value for incremental tumor size increases of 1cm (hazard ratio, 1.47; 95% CI, 1.00-2.18; $p=0.05$).

Follow-up MRI

148 women underwent 369 postoperative MRIs for follow-up. The median number of follow-up MRIs per patient was 2 (range, 1-8). 7 upgrades were identified from all follow-up MRIs (1.9%; 95% CI, 0.8-3.9%), 6 were identified in a patient's first follow-up MRI, and 1 was identified in a second follow-up MRI. No upgrades were identified in any subsequent third through eighth follow-up MRI (Table 4).

Patient Outcomes

Subsequent cancer rates were assessed among women imaged with perioperative MRI. At 5.0 years median follow-up, 5-year incidence of local, regional, and distant recurrence was 3.9%, 0.6%, and 4%, respectively. Five-year CBC incidence was 3.7% (2.0, 5.3). Five-year OS and RFS were 91.1% and 84.7%, respectively (FIG. 1). Within a cohort of 62 women with node-negative, ER⁺, T1 tumors treated with lumpectomy, there was 1 local and 1 regional recurrence. For this select population, 5-year OS was 93.6% (95% CI, 86.7-100.0) and 5-year RFS was 91.8% (95% CI, 84.3-100).

DISCUSSION

Our single-institution experience with MRI use in elderly BC patients mirrors that seen from large population-based studies, with 9% of women aged ≥ 70 years having undergone a perioperative MRI from 2000-2010. While few women underwent perioperative MRI for problem solving, most (91%) were obtained to evaluate extent of disease for a known cancer or mammographic abnormality. Perioperative breast MRI has the theoretic benefit of improving surgical planning or long-term outcomes by identifying mammographically occult tumor foci. MRI's ability to identify additional multifocal or multicentric disease has been widely published and is summarized in large meta-analyses by Houssami et al¹¹ and Plana et al¹², who report additional ipsilateral disease identified by MRI in 16% and 20% of cases, respectively. The individual studies in these reviews include patients with median ages ranging from 49-60 years. In our patient population aged ≥ 70 years, the additional ipsilateral disease identification rate was 3.9% for those MRIs performed for extent of disease evaluation. Two prospective, randomized trials^{13,14} and other retrospective single-

institution studies¹⁵⁻¹⁹ have not found improvements in re-excision and locoregional recurrence rates in women imaged with MRI at time of BC diagnosis. Given the lack of improved outcomes in the general BC population and substantially lower rates of ipsilateral MRI cancer detection in this population, additional MRI findings in this elderly population will likely not lead to improvements in surgical or recurrence outcomes.

Another argument for routine use of perioperative MRI is to identify mammographically occult CBC. In our elderly BC patient cohort, the CBC identification rate was 4.4%, similar to the 4.1% of patients diagnosed with an MRI-detected synchronous CBC reported in the meta-analysis of 3253 women with a unilateral BC who underwent MRI in addition to conventional imaging.²⁰ If indeed MRI was responsible for detecting clinically relevant CBC, a decrease in metachronous CBC development should be seen. Four retrospective single-institution studies reported on metachronous CBC rates in women imaged with and without MRI at the time of their index cancer; all reported low (0.5-6.0%) CBC rates.^{15,19,21,22} While studies by Fischer et al²¹ and Kim et al²² report significantly decreased CBC rates in women imaged with MRI, the absolute difference in CBC rates between women imaged with and without MRI was only 1-2%. Given the similar metachronous CBC rates seen in women imaged with or without MRI, it raises the possibility that MRI is detecting clinically irrelevant disease, either because it is appropriately treated with systemic therapy, which is known to decrease CBC rates^{23,24}, or because of indolent tumor biology. Our elderly BC population had a 3.7% 5-year metachronous CBC rate, similar to that reported in the SEER database²⁵ (3% at 5 years) in a population of 134,501 women with stage 0-2 BC between 1973-1996, a time period when perioperative MRI was not routine practice.

Within our elderly population, women presenting with an occult primary BC had the most benefit from MRI imaging. MRI identified a primary breast tumor in 4/10 (40%) of women presenting with this unusual clinical circumstance. <1% of all BCs present with an axillary metastasis and breast primary that is occult by physical exam, mammography, and ultrasound.²⁶ Historically, the breast was treated with either a total mastectomy or whole-breast RT, but MRI imaging has altered treatment options for many women presenting with an occult primary tumor. In de Bresser et al's meta-analysis of 220 women with an occult primary BC from 8 retrospective studies, MRI identified a suspicious breast lesion in 72% of cases (sensitivity, 90%; specificity, 31%). When MRI identified a primary breast lesion in patients without metastatic disease, 21-60% were able to undergo breast-conserving therapy.²⁷ A negative MRI also provides reassurance that a large tumor burden is unlikely and that a patient may be safely treated with an axillary dissection and whole-breast irradiation. 75% (3/4) of patients in our study in whom MRI identified a primary breast tumor were successfully treated with a lumpectomy and axillary dissection. In this rare clinical scenario, MRI has become standard imaging to attempt localization of the primary tumor and to allow standard surgical treatment of the breast.

Updated ASCO practice guidelines recommend imaging women with a history of BC with annual mammography and note that breast MRI is not recommended in routine surveillance.²⁸ While there are limited data examining the routine use of follow-up MRI in BC patients, a systematic review of 10 case series comparing MRI with other imaging

modalities to diagnose BC recurrence in patients with clinical suspicion for recurrence concluded that MRI has not proven to be superior to standard assessment; however, MRI may be beneficial when additional information is required after conventional imaging.²⁹ Our results show that routine follow-up MRIs had a low yield, with a 1.9% total upgrade rate, and a 1% upgrade rate (2/199) among follow-up MRIs performed for routine postop surveillance in rounds 1 or 2 (rounds where indication data were available). Conversely, MRIs obtained to evaluate an abnormal physical exam or abnormal imaging resulted in superior malignancy detection, indicating that MRI may aid clinical problem solving.

The overall outcomes of this elderly BC population were excellent; however this evaluation is limited given the lack of a comparison control group. While comparing our study population to a known elderly BC cohort, we identified all patients with ER⁺, node-negative tumors ≥ 2 cm who were treated with lumpectomy, and compared this cohort's outcomes to the randomized controlled trial results of Hughes et al evaluating the benefit of RT to lumpectomy in women aged ≥ 70 years in the CALGB C9342 trial.³⁰ 62 women met these criteria; 83% were treated with adjuvant endocrine therapy; 85% were treated with adjuvant RT. One local and 1 regional recurrence were observed in this cohort. The cumulative incidence of locoregional recurrence at median follow-up of 5.0 years within this cohort was 1.8%. Among 636 women randomized to RT plus tamoxifen or tamoxifen alone in CALGB C9342, 5-year locoregional recurrence actuarial rates were 1% and 4% within the radiation and no-radiation groups, respectively. This study's patient accrual dated from 1994-1999, a time when perioperative MRI use was not routine. While rates of locoregional control were high and similar between our study and the patients enrolled in CALGB C9342, OS differed. In our comparable contemporary patient population selected for MRI, 5-year OS was 92% versus 86-87% in the Hughes et al trial. This highlights the possible selection bias for women chosen to undergo MRI in our study. While the overall patient, tumor, and treatment characteristics, including distribution of breast density³¹, are those expected within an elderly BC population, physicians possibly selected healthier women deemed eligible for adjuvant therapy for MRI imaging. Another study limitation is its acquisition of clinical data by retrospective chart review.

In conclusion, elderly women presenting with an occult primary tumor benefitted the most from perioperative MRI. Our results support the routine use of MRI in the work-up of women presenting with this unusual clinical scenario. However, perioperative and follow-up MRI for our elderly BC patients resulted in low upgrades for the identification of additional malignancy, questioning the benefit of MRI in these settings.

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Synopsis

In our elderly breast cancer population, we find that MRI had the greatest benefit in women presenting with an occult primary cancer and minimal additional benefit in elderly patients with breast cancer undergoing MRI imaging for extent of disease evaluation or in follow-up.

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FIG. 1. Recurrence and survival outcomes. **A** Local, regional, and distant recurrence; **B** Contralateral breast cancer; **C** Recurrence-free survival; **D** Overall survival

TABLE 1

Patient and tumor characteristics

Factor	n=305
Age, years	Median, 73 (range, 70-90)
Means of diagnosis Breast Imaging Physical abnormality Other/incidental	191 (62.6%) 109 (35.7%) 5 (1.6%)
Mammographic density (n=301) Predominately fatty Scattered fibroglandular tissue Heterogeneously dense Extremely dense	21 (7%) 96 (32%) 166 (55%) 18 (6%)
Tumor size (n=255)	Median, 1.2cm (range, 0.1-7.0)
Histology DCIS +/- microinvasion Invasive ductal carcinoma Invasive lobular carcinoma Other	44 (14%) 181 (59%) 68 (22%) 12 (4%)
ER positive (n=263)	225 (86%)
PR positive (n=261)	159 (61%)
HER2/neu overexpressing (n=245)	17 (7%)
Lymph node positive (n=278)	83 (30%)

DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor

TABLE 2

Treatment characteristics

Treatment	n=305
Final surgery (n=304) Lumpectomy Mastectomy	217 (71%) 87 (29%)
Radiation following lumpectomy (n=217)	169 (78%)
Neoadjuvant chemotherapy	11 (4%)
Neoadjuvant endocrine therapy	5 (2%)
Adjuvant chemotherapy (n=298)	81 (27%)
Adjuvant endocrine therapy (n=291)	200 (69%)

TABLE 3

Univariate analysis for predictors of MRI upgrade among perioperative MRIs done for extent of disease evaluation (n=181)

Factor	Odds ratio (95% CI)	p-value
Mammographic density	2.89 (0.26-32.35)	0.82
Predominately fatty (versus scattered fibroglandular)	1.66 (0.43-6.40)	
Heterogeneously dense (versus scattered fibroglandular)	1.44 (0.14-15.13)	
Extremely dense (versus scattered fibroglandular)		
Means of diagnosis *	1.53 (0.49-4.78)	0.46
Imaging (versus physical exam finding)		
Timing of MRI	1.31 (0.35-4.92)	0.69
Before surgery (versus after surgery in perioperative period)		
Histology **	2.27 (0.48-10.66)	0.30
Ductal (versus lobular)		
DCIS	0.60 (0.07-4.84)	0.63
DCIS only (versus invasive)		
Tumor size	1.47 (1.00-2.18)	0.05
ER status	2.00 (0.25-16.20)	0.52
Positive (versus negative)		
PR status	1.14 (0.35-3.64)	0.83
Positive (versus negative)		
HER2 status	NA ***	0.60 ***

CI, confidence interval; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor

* 2/181 patients with other/incidental means of diagnosis were excluded from this model

** 24/181 patient with metaplastic/other invasive or pure mucinous/colloid/medullary/tubular/papillary carcinoma/other or DCIS history are excluded from this model

*** No patient with HER2 overexpressing tumor had an upgrade, so cannot report odds ratio. P-value is from Fisher's exact test.

TABLE 4

Postoperative follow-up MRIs

	No. of MRIs	New cancers / recurrences identified	Upgrade rate
Round 1 of post-op MRI			
Follow-up prior cancer	120	2	1.7%
Abnormal physical exam	17	3	17.6%
Abnormal imaging	3	1	33.3%
Known new cancer/recurrence	2	0	0%
Evaluate for implant rupture	1	0	0%
Total	148	6	4.1%
Round 2 of post-op MRI			
Follow-up prior cancer	79	0	0%
Abnormal physical exam	2	1	50%
Total	81	1	1.2%
Rounds 3-8 of post-op MRI			
Total*	140	0	0%
Total (rounds 1-8 of post-op MRI)			
All indications	369	7	1.9%

* Indication data were not available for MRIs done in round 3 and later.