Published in final edited form as:
Ann Surg Oncol. 2014 December ; 21(13): 4133–4138. doi:10.1245/s10434-014-3852-x.

Rate of Contralateral Prophylactic Mastectomy is Influenced by Preoperative MRI Recommendations

Chang Xia, MD, PhD [Fellow],
Division of Hematology, Oncology and Blood and Marrow Transplantation, Department of Internal Medicine, University of Iowa

Mary C. Schroeder, PhD [Assistant Professor],
Department of Pharmacy Practice and Science, College of Pharmacy, University of Iowa

Ronal J. Weigel, MD, PhD [Professor],
Department of Surgery, University of Iowa

Sonia L. Sugg, MD [Clinical Professor], and
Department of Surgery, University of Iowa

Alexandra Thomas, MD [Clinical Associate Professor]
Division of Hematology, Oncology and Blood and Marrow Transplantation, Department of Internal Medicine, C32 GH, 200 Hawkins Drive, University of Iowa, Iowa City, IA 52242, (319) 356-2148 PHONE, (319) 353-8383 FAX

Alexandra Thomas: alex-thomas@uiowa.edu

Abstract

Background—Women with breast cancer increasingly undergo contralateral prophylactic mastectomy (CPM). We evaluate the relationship between pre-operative magnetic resonance imaging (MRI) findings and CPM. Other clinicopathologic variables associated with CPM choice, and the pathology found in the contralateral breast, are also reported.

Methods—Newly diagnosed breast cancer patients were prospectively enrolled in the University of Iowa Breast Molecular Epidemiology Resource. Patients with Stage 0-III breast cancer who underwent mastectomy for the index cancer were eligible for this analysis. Univariate logistic regression and a multivariate model were used to identify factors predictive of CPM.

Results—Among 134 patients (mean age 54.9), 53 (39.6%) chose CPM. On univariate analysis patients undergoing CPM were more likely to have a pre-operative breast MRI (64.2% vs. 39.5%, p=0.006) and to have follow-up testing recommended for the contralateral breast (28.3% vs. 4.9%, p=0.001). Univariate analysis also associated CPM with younger age (p<0.0001), *BRCA* testing (p<0.0001), *BRCA* mutation (p=0.034) and reconstruction performed (p=0.001). Median age of youngest child at diagnosis varied significantly between the CPM (15.9 years) and the non-CPM (24.3 years) groups (p=0.0018). On multivariate analysis, MRI follow-up recommendation, young age, reconstruction and HER-2 positivity of the index cancer were significantly associated with

Correspondence to: Alexandra Thomas, alex-thomas@uiowa.edu.
All Authors report no conflict of interest

CPM. Of the CPM specimens, one (1.8%) had ductal carcinoma in situ (DCIS), which had not been identified on MRI.

Conclusions—Abnormal findings in the contralateral breast on preoperative MRI, as well as, young age, reconstruction and HER-2 positive status correlated with CPM choice in this cohort. Occult malignancy was rare.

Introduction

Women with newly diagnosed unilateral breast cancer increasingly elect to undergo contralateral prophylactic mastectomy (CPM).[1-4] A variety of tumor and patient characteristics contribute to the decision to pursue aggressive surgery to lower the perceived risk of future cancer. The majority of women choosing this procedure, however, have no known genetic susceptibility or other strong risk factors for a second breast cancer.

For most patients, risk of death is greater from the primary breast tumor, not from a future second malignancy in the contralateral breast. Studies report rates of contralateral breast cancer between 0.5 to 0.75% per year.[5] In older series, contralateral cancers account for 2.5% of breast cancer deaths.[6] Contemporary systemic treatments further decrease the risk of developing cancer in the contralateral breast.[7-9] For average risk women with breast cancer, contralateral prophylactic mastectomy appears to offer little or no survival benefit.[10-13] A recent Cochrane review found no overall survival benefit to the prophylactic procedure.[14] However, the CPM rate continues to rise.

Pre-operative MRI has been evaluated as a factor contributing to higher CPM rates. Some reviews show that women who undergo breast MRI elect both mastectomy on the affected side and CPM with greater frequency.[12,15,16] Although MRI has high sensitivity for the detection of multifocal, multicentric, or synchronous contralateral breast cancers, there is increasing evidence that breast MRI confers no advantage with respect to attainment of negative margins, or lower rates of reoperation.[17-19] Additionally, the high incidence of false positive MRI findings could be of clinical relevance. Women with a new diagnosis of cancer may elect more aggressive treatment due to the perception of a possible malignant lesion in the contralateral breast.

To assess factors contributing to a decision to undergo CPM, we used a dataset of prospectively enrolled, consecutive patients with newly diagnosed unilateral breast cancer. The goal of this analysis was to characterize the relationship between a pre-operative MRI and the patient's decision to pursue CPM, with specific attention to the rate of contralateral MRI findings for which follow-up is recommended and the choice to undergo CPM.

Patients and Methods

Study Population

Patient and clinical data were obtained from Breast Molecular Epidemiology Resource (B-MER) of the University of Iowa. Newly diagnosed breast cancer patients were prospectively enrolled from April 2010 through March 2013. Women were included in this cohort if they underwent mastectomy for the index breast cancer. Patients who were diagnosed with

bilateral breast cancer prior to pre-operative MRI were excluded. The University of Iowa Institutional Review Board approved this study.

Prophylactic mastectomy is defined as removal of the contralateral breast within 12 months of definitive mastectomy. Recommended follow-up of the contralateral breast MRI is defined as the recommendation for any imaging or procedure on the contralateral breast other than immediate ultrasound evaluation.

Statistical Analysis

Univariate logistic regression was used to identify factors predictive of undergoing CPM. A multivariate logistic regression model was fitted to examine the relationship between MRI and CPM, after adjusting for recommendation for MRI follow-up, age, whether the patient's youngest child was under the age of 6 at diagnosis, *BRCA* testing, *BRCA* test result for those who received testing, family history, nodal status, history of benign biopsies, receptor status (Hormone receptor (HR), Human Epidermal Growth Factor Receptor 2 (HER-2), and triple negative breast cancer (TNBC)), body mass index, and reconstruction performed. All p values were 2-tailed, and values of $p \leq 0.05$ were considered significant. All statistical analyses were completed using Stata Statistical Software: release 12 (StataCorp LP., College Station, Texas).

Results

Patient Characteristics

Among 134 patients who underwent mastectomy, 53 underwent CPM. Characteristics of both cohorts are shown in Table 1. No patients had undergone prior mantle radiation. A single patient who was diagnosed with synchronous bilateral breast cancer was excluded from analysis.

Preoperative breast MRI was completed in 66 (49.3%) of the patients. Patient age and tumor size were not predictive of the likelihood of undergoing an MRI on univariate analysis (p=0.217 and 0.774, respectively). Of these imaging studies, 19 (28.8%) found areas of concern in the contralateral breast for which immediate biopsy, or follow-up imaging in six months was recommended. Indications for the pre-operative breast MRI and follow-up recommendations for the contralateral breast are shown in Table 2.

Predictors for undergoing CPM

On univariate analysis patients undergoing preoperative MRI were more likely to choose CPM (OR = 2.74, p=0.006) (Table 3). Those women who were given a recommendation for a follow-up test were even more likely to pursue CPM (OR= 7.60, p=0.001). Univariate analysis also revealed associations between choice of CPM and younger <50 years, reconstruction performed, and *BRCA* testing. Women with children under the age of 6 were more likely to elect CPM, though this relationship did not achieve statistical significance. The average age of the youngest child between the two groups (15.9 years for CPM group and 24.3 years for unilateral mastectomy group) was statistically different (p=0.002).

On multivariate logistic regression, MRI follow-up recommendation, patient age and reconstruction remain significant (Table 4). HER2 status of the index breast cancer also achieved significance in this analysis. The indications for MRI did not correlate with CPM on multivariate analysis and did not change the significance of the other variables.

Histological findings in mastectomy and CPM

CPM was performed at the time of index mastectomy in 94% of the patients. The pathological findings within the CPM specimens included 34 proliferative disease without atypia and one proliferative disease with atypia. A single case of DCIS was found in the contralateral breast, which was not detected on the pre-operative MRI.

Discussion

In this series of prospectively enrolled patients with breast cancer, factors associated with CPM on multivariate evaluation were young age, follow-up recommendation of the pre-operative breast MRI, reconstruction and HER2 positivity in the index cancer. At our institution, we do not recommend CPM based on tumor histology, receptor status, age, imaging findings, or symmetry after reconstruction. In fact our surgeons and oncologists specifically counsel patients on the low risk of developing contralateral breast cancer and lack of survival benefit with CPM. In patients with BRCA or other predisposing high-risk gene mutations, and in those who have received chest wall radiation, the risk of contralateral breast cancer is specifically discussed to aid in their decision for surgery.

We found that a recommendation for follow-up evaluation of the contralateral breast led to a markedly increased rate of CPM, adding to existing knowledge on the role of MRI in surgical decision-making. Previous work reported pre-operative MRI as a predictor of CPM.[12,15,16] Here, pre-operative MRI itself was not an independent predictor of CPM in multivariate analysis. Rather, it was an abnormal finding on pre-operative MRI in the contralateral breast that was associated with a seven-fold increase in the likelihood of electing CPM. This is consistent with the retrospective report of almost 3,000 patients in which additional biopsies based on MRI findings, were associated with higher CPM rates.[20] This work extends the concept, looking not just at biopsies, but also at the perception that there may be an area of concern and that further testing will be needed at some future time.

We also evaluated age of youngest child at diagnosis as a possible independent risk factor for CPM, as some have reported that social and cultural factors contribute to higher CPM.[21,22] We noted in our study cohort that age of youngest child was lower in women who chose to undergo CPM. Thus we hypothesized that it was not patient young age, but having young children at home that might lead to CPM choice. We included it as a covariate in the multivariate model. We describe age 6 because it is the cutoff age when children go to kindergarten; however, we also ran sensitivity analyses with the following age cutoffs: 4,6,10,12,18. None were significant.

In this recent cohort, HER2 positive status of the index cancer, on multivariate analysis, correlated with the decision for CPM. Earlier series pre-date HER2 testing, and would not be able to evaluate the association of HER2 status with CPM. This finding that HER2 status

influences CPM needs to be confirmed. Very recent reports suggest that HER2 positive breast cancer is more often multifocal or multicentric, and more likely to have associated extensive ductal carcinoma in situ, than HER2 negative disease.[23] This could lead to more frequent failed breast conservation, which has been associated with CPM.[20] Furthermore, the perception of more serious disease could have contributed to the decision for CPM.

Family history of breast cancer, defined in this dataset as a first-degree family member with breast cancer, correlated with CPM choice but did not achieve statistical significance. Multiple retrospective studies have previously associated family history with CPM, though family history is frequently defined more broadly.[4,12,20] A positive BRCA test did not correlate with CPM choice in this series, likely due to small numbers.

The CPM rate in this cohort of women diagnosed from 2010 to 2013 was 39.6%. This rate is markedly higher than seen in most series, which generally begin at earlier time points. A review of the National Cancer Data Base found that women from the Midwest and women treated at academic institutions are more likely to undergo CPM.[24] Women enrolled in the University of Iowa B-MER were from one of the states included in the Midwest and generally, but not exclusively, were treated at our academic center. We are a regional referral center for breast reconstruction, which may bias our population. Indeed reconstruction remained an independent predictor of CPM on multivariate analysis. Still, the CPM rate reported by Yao et al for 2002 was 9.4%.[24] Our more recent data suggest that the trend of women selecting this elective procedure is not ebbing.

This series found a single case of DCIS in the contralateral breast, which was not detected on MRI. An occult carcinoma rate of 1.8% is in keeping with other series where clinically and mammographically occult contralateral breast cancer is found 2-3% of cases.[15,25] In all cases, the abnormal MRI findings, for which follow-up was recommended, did not represent malignancy.

Limitations to this work include a relatively small series of patients and the fact that patients were enrolled at a single academic institution. However, the data is significant in that it may be more representative of surgery in rural states. Some patients may have chosen CPM for symmetry given their planned unilateral mastectomy, though there are other options for obtaining cosmetic balance. Further, such patients would have been less likely to be influenced by an abnormal MRI finding, if they had already made an aesthetic decision.

The high rate of CPM, and the factors contributing to selection of this aggressive surgical choice, reported here occurs in the setting of an academic multidisciplinary breast program with physicians routinely counseling patients on the lack of survival benefit for a contralateral procedure. These results add to evidence that can be used to counsel women on the risks and benefits of CPM, particularly in the context of abnormalities found in the contralateral breast on pre-operative MRI. This expanding literature will hopefully provide more information for evidence-based discussions between physicians and patients during the stressful period of diagnosis and treatment planning.

References

1. Yao K, Stewart AK, Winchester DJ, Winchester DP. Trends in contralateral prophylactic mastectomy for unilateral cancer: a report from the National Cancer Data Base, 1998-2007. Ann Surg Oncol. Oct; 2010 17(10):2554–2562. [PubMed: 20461470]
2. Tuttle TM, Habermann EB, Grund EH, Morris TJ, Virnig BA. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J Clin Oncol. Nov 20; 2007 25(33):5203–5209. [PubMed: 17954711]
3. Tuttle TM, Jarosek S, Habermann EB, et al. Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. J Clin Oncol. Mar 20; 2009 27(9):1362–1367. [PubMed: 19224844]
4. Arrington AK, Jarosek SL, Virnig BA, Habermann EB, Tuttle TM. Patient and surgeon characteristics associated with increased use of contralateral prophylactic mastectomy in patients with breast cancer. Ann Surg Oncol. Oct; 2009 16(10):2697–2704. [PubMed: 19653045]
5. Kurian AW, McClure LA, John EM, Horn-Ross PL, Ford JM, Clarke CA. Second primary breast cancer occurrence according to hormone receptor status. J Natl Cancer Inst. Aug 5; 2009 101(15): 1058–1065. [PubMed: 19590058]
6. Bernstein JL, Lapinski RH, Thakore SS, Doucette JT, Thompson WD. The descriptive epidemiology of second primary breast cancer. Epidemiology. Sep; 2003 14(5):552–558. [PubMed: 14501270]
7. Nichols HB, Berrington de Gonzalez A, Lacey JV Jr, Rosenberg PS, Anderson WF. Declining incidence of contralateral breast cancer in the United States from 1975 to 2006. J Clin Oncol. Apr 20; 2011 29(12):1564–1569. [PubMed: 21402610]
8. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. May 14-20; 2005 365(9472):1687–1717. [PubMed: 15894097]
9. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol. Dec; 2010 11(12): 1135–1141. [PubMed: 21087898]
10. Bedrosian I, Hu CY, Chang GJ. Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients. J Natl Cancer Inst. Mar 17; 2010 102(6):401–409. [PubMed: 20185801]
11. Boughey JC, Hoskin TL, Degnim AC, et al. Contralateral prophylactic mastectomy is associated with a survival advantage in high-risk women with a personal history of breast cancer. Ann Surg Oncol. Oct; 2010 17(10):2702–2709. [PubMed: 20853163]
12. Chung A, Huynh K, Lawrence C, Sim MS, Giuliano A. Comparison of patient characteristics and outcomes of contralateral prophylactic mastectomy and unilateral total mastectomy in breast cancer patients. Ann Surg Oncol. Aug; 2012 19(8):2600–2606. [PubMed: 22396004]
13. Peralta EA, Ellenhorn JD, Wagman LD, Dagis A, Andersen JS, Chu DZ. Contralateral prophylactic mastectomy improves the outcome of selected patients undergoing mastectomy for breast cancer. Am J Surg. Dec; 2000 180(6):439–445. [PubMed: 11182394]
14. Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst Rev. 2010; (11):CD002748. [PubMed: 21069671]
15. Miller BT, Abbott AM, Tuttle TM. The influence of preoperative MRI on breast cancer treatment. Ann Surg Oncol. Feb; 2012 19(2):536–540. [PubMed: 21751044]
16. Sorbero ME, Dick AW, Beckjord EB, Ahrendt G. Diagnostic breast magnetic resonance imaging and contralateral prophylactic mastectomy. Ann Surg Oncol. Jun; 2009 16(6):1597–1605. [PubMed: 19330381]
17. Bleicher RJ, Ciocca RM, Egleston BL, et al. Association of routine pretreatment magnetic resonance imaging with time to surgery, mastectomy rate, and margin status. J Am Coll Surg. Aug; 2009 209(2):180–187. quiz 294-185. [PubMed: 19632594]
18. Turnbull L, Brown S, Harvey I, et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. Lancet. Feb 13; 2010 375(9714):563–571. [PubMed: 20159292]

19. Morris EA. Should we dispense with preoperative breast MRI? Lancet. Feb 13; 2010 375(9714): 528–530. [PubMed: 20159274]

20. King TA, Sakr R, Patil S, et al. Clinical management factors contribute to the decision for contralateral prophylactic mastectomy. J Clin Oncol. Jun 1; 2011 29(16):2158–2164. [PubMed: 21464413]

21. Rosenberg SM, Tracy MS, Meyer ME, et al. Perceptions, knowledge, and satisfaction with contralateral prophylactic mastectomy among young women with breast cancer: a cross-sectional survey. Ann Intern Med. Sep 17; 2013 159(6):373–381. [PubMed: 24042365]

22. Guth U, Myrick ME, Viehl CT, Weber WP, Lardi AM, Schmid SM. Increasing rates of contralateral prophylactic mastectomy - a trend made in USA? Eur J Surg Oncol. Apr; 2012 38(4): 296–301. [PubMed: 22305274]

23. Morrow M. Personalizing extent of breast cancer surgery according to molecular subtypes. Breast. Aug; 2013 22(Suppl 2):S106–109. [PubMed: 24074769]

24. Yao K, Winchester DJ, Czechura T, Huo D. Contralateral prophylactic mastectomy and survival: report from the National Cancer Data Base, 1998-2002. Breast Cancer Res Treat. Dec; 2013 142(3):465–76. [PubMed: 24218052]

25. Lehman CD, Gatsonis C, Kuhl CK, et al. MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer. N Engl J Med. Mar 29; 2007 356(13):1295–1303. [PubMed: 17392300]

Synopsis

Rates of contralateral prophylactic mastectomies (CPM) continue to rise. On multivariate analysis, we find a pre-operative MRI with follow-up recommendation, young age, reconstruction and HER2 status all independently affect the decision of whether to undergo CPM.

Ann Surg Oncol. Author manuscript; available in PMC 2015 December 01.

Table 1

Patient characteristics by surgery

	No CPM (n=81)		CPM (n=53)		
	No.	**% of No CPM**	**No.**	**% of CPM**	***p* value**
Age					
Mean		58.9		48.8	
Range		32-85		34-74	<0.001
Age					
<50 years	12	14.8	23	43.4	<0.001
≥ 50 years	69	85.2	30	56.6	
Obese (BMI ≥ 30)					
No	46	56.8	34	64.2	0.400
Yes	35	43.2	19	35.9	
Nodal Status					
Negative	45	55.6	32	60.4	0.584
Positive	36	44.4	21	39.6	
History of benign biopsies					
No	59	77.6	45	86.5	0.208
Yes	17	22.4	7	13.5	
Family history					
No	60	76.0	38	73.1	0.714
Yes	19	24.0	14	26.9	
BRCA testing done					
No	67	82.7	22	41.5	<0.001
Yes	14	17.3	31	58.5	
BRCA Mutation Carrier*					
No	13	92.9	25	80.6	0.295

	No CPM (n=81)		CPM (n=53)		
	No.	**% of No CPM**	**No.**	**% of CPM**	***p* value**
Yes	1	7.1	6	19.4	
Youngest child < 6 years old					
No	75	92.6	47	88.7	0.442
Yes	6	7.4	6	11.3	

Abbreviations: CPM, contralateral prophylactic mastectomy; BMI, body mass index

*For those who received testing (N=45).

Table 2

Indications for MRI and Contralateral Follow-up Recommendations

	No.	% of MRI
Indication for MRI		
Recommended to further work up mammogram and US findings	8	12.1
Dense breasts/high risk surveillance	9	13.6
Lobular cancer	16	24.2
Patient referred with an MRI	6	9.1
Surgical planning	13	19.7
Response to chemotherapy	14	21.2
Contralateral follow-up of MRI recommended	19	28.8
Follow up imaging in 6 MO (MRI or US)	6	9.1
Immediate biopsy	8	12.1
Immediate ultrasound and then MRI in 6 MO	5	7.6

Ann Surg Oncol. Author manuscript; available in PMC 2015 December 01.

Ann Surg Oncol. Author manuscript; available in PMC 2015 December 01.

Table 3

Univariate Analysis

Variable	CPM		OR	*p* value	95% CI
	No	Yes			
Age					
<50 years	12	23	7.5	<0.0001	3.306, 17.013
≥ 50 years	69	30			
Breast MRI					
No	49	19	2.74	0.006	1.338, 5.611
Yes	32	34			
MRI follow-up recommended					
No	77	38	7.6	0.001	2.36, 24.468
Yes	4	15			
Reconstruction performed					
No	46	13	3.98	0.001	1.828, 8.669
Yes	32	36			
Obese (BMI ≥ 30)					
No	46	34	0.98	0.361	0.931, 1.026
Yes	35	19			
Nodal Status					
Negative	45	32	0.82	0.581	0.406, 1.658
Positive	36	21			
History of benign biopsies					
No	59	45	0.54	0.209	0.206, 1.413
Yes	17	7			
Family history					
No	60	38	1.16	0.711	0.522, 2.592
Yes	19	14			

Variable	CPM		OR	*p* value	95% CI
	No	Yes			
HR positive					
No	17	18	0.52	0.097	0.237, 1.127
Yes	64	35			
HER2 positive					
No	61	33	2.46	0.066	0.941, 6.453
Yes	9	12			
TNBC					
No	70	42	1.85	0.217	0.696, 4.926
Yes	9	10			
BRCA testing done					
No	67	22	6.74	<0.0001	3.049, 14.916
Yes	14	31			
BRCA mutation*					
No	13	25	3.12	0.315	0.339, 28.742
Yes	1	6			
Youngest child < 6 years old					
No	75	47	1.6	0.441	0.486, 5.239
Yes	6	6			

Abbreviations:CPM, contralateral prophylactic mastectomy; OR, odds ratio; CI, confidence internal; MRI, magnetic resonance imaging, BMI, body mass index, HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer.

*For those who received testing (N=45).

Table 4

Multivariate Analysis

Variable	level	OR	p-value	95% CI
Age	<50 vs ≥50 years	23.08	0.001	3.713, 143.486
Breast MRI	Yes vs No	1.27	0.732	0.328, 4.893
MRI follow-up recommended	Yes vs No	6.79	0.043	1.058, 43.63
Reconstruction performed	Yes vs No	5.25	0.018	1.329, 20.728
Obese (BM ≥ 30)	Yes vs No	2.93	0.131	0.726, 11.818
Nodal Status	Pos vs Neg	1.53	0.527	0.41, 5.711
History of benign biopsies	Yes vs No	1.02	0.981	0.204, 5.087
Family history	Yes vs No	2.6	0.225	0.555, 12.217
HR positive	Yes vs No	2.61	0.515	0.146, 46.602
HER2 positive	Yes vs No	21.82	0.011	2.026, 234.864
TNBC	Yes vs No	10.32	0.17	0.369, 288.371
BRCA testing done	Yes vs No	1.16	0.846	0.254, 5.308
BRCA mutation	Yes vs No	18.15	0.062	0.86, 383.077
Youngest child < 6 years old	Yes vs No	0.16	0.096	0.018, 1.388

Abbreviations: OR, odds ratio; CI, confidence interval; MRI, Magnetic resonance imaging; BMI, body mass index; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer;