Annals of Surgical Oncology **14**(12):3369–3377
DOI: 10.1245/s10434-007-9530-5

The Predictive Value of Ductography and Magnetic Resonance Imaging in the Management of Nipple Discharge

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Background: Standard evaluation (physical examination, mammography, sonography) often fails to identify an underlying lesion in patients with suspicious nipple discharge. The aim of this study was to determine the predictive value of ductography (DG) and magnetic resonance imaging (MRI) in this setting.

Methods: Using ICD-9 codes, we retrospectively identified 376 patients who presented with suspicious nipple discharge (ND) (1995–2005); 306 patients (68%) had negative standard evaluation.

Results: Among 306 patients, 186 (61%) underwent further evaluation with DG ($n = 163$) and/or MRI ($n = 52$), 35 (11%) underwent major duct excision alone (MDE), and 85 (28%) were followed clinically. Ultimately, 182/306 (59%) patients underwent surgery and/or biopsy. Overall incidence of malignant or high-risk pathology was 15% (46/306). DG was completed in 139/163 (85%) studies and detected 12 cancers and seven high-risk lesions (HRL), but failed to identify four cancers and 2 HRL (PPV 19%, NPV 63%). MRI detected seven cancers and three HRL, but failed to identify one cancer and one HRL (PPV 56%, NPV 87%). MDE alone ($n = 35$) detected five cancers and three HRL. Of all patients not having surgery, (142/306, 41%), one (0.01%) presented with an invasive cancer at 102 months (median follow-up, 6.3 months; range, 0–124 months).

Conclusions: An underlying malignancy was identified in 30/306 (10%) patients with ND and negative standard evaluation. Ductography is a poor predictor of underlying pathology and cannot exclude malignancy. MRI's higher predictive values may allow for improved patient selection and treatment planning; however, MRI should not replace MDE as the gold standard to exclude malignancy in patients with ND and negative standard evaluation.

Key Words: Nipple discharge—Predictive value—MRI—Ductography.

Between 5 and 10% of women presenting for routine examination will report spontaneous nipple discharge,[1,2] and as many as 80% of women will experience at least one episode of nipple discharge during their reproductive years.[3] Although the majority of nipple discharges are caused by benign conditions, such as intraductal papillomas and duct ectasia, an underlying cancer may be present in up to 15% of cases.[4,5,6,7]

The approach to a patient with nipple discharge should begin with a complete clinical history, including age, parity, previous benign breast disease, menstrual history, family history, smoking, and medications. Characteristic features of the discharge, such as color (clear, bloody, white, green/yellow), spontaneity, unilaterality, frequency, and single versus multiple ducts,

Received March 21, 2007; accepted June 27, 2007; published online: September 26, 2007.
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may also help to distinguish between pathological/suspicious discharge and physiological discharge.[8] Following clinical history, standard evaluation includes physical examination, age-appropriate mammography and, in some centers, sonography.

In patients with suspicious nipple discharge and negative standard evaluation, the physician must decide either to manage expectantly, or proceed to major duct excision (MDE). In this setting, MDE aims to be both diagnostic and therapeutic; however, a frequent criticism of this blind approach is that the pathologists may not always identify a discrete causative lesion for the discharge. In addition, MDE may be undesirable for a woman of child-bearing age. Thus, there is a need for a more-effective tool to localize and distinguish between malignant and benign causes of nipple discharge.

Ductography and magnetic resonance imaging (MRI) are among the spectrum of investigations that may have value in this setting. By localizing the causative lesion, ductography increases the yield of diagnostic major duct excision and, in some cases, may allow for selective duct excision. However, it is frequently difficult to perform and its predictive role in the nonoperative setting is limited. Based on the ability of MRI to identify otherwise occult disease, preliminary research suggests that MRI may also have a role in the evaluation of patients with nipple discharge; however, the data is limited.

The aim of this study was to assess the management patterns at our institution regarding patients with clinically significant ND and negative standard evaluation, and to determine the predictive value of ductography and MRI in this setting.

MATERIALS AND METHODS

Using the ICD-9 code for breast symptoms (611.79), we identified 2294 women without a current cancer diagnosis that presented to the Memorial Sloan-Kettering (MSK) Cancer Center breast surgery clinic for evaluation between January 1995 and October 2005. Retrospective chart review revealed that 451 (20%) of these patients presented with a chief complaint of nipple discharge. Following subsequent in-depth review of medical records, 376/451 (83%) patients were considered to have suspicious nipple discharge, defined by the presence of at least one of the following features: spontaneous, unilateral, bloody, persistent, or single-duct discharge. Of these, 306 (81%) had negative standard evaluation [clinical breast examination (CBE)/mammogram/sonography], and this population comprised our study group ($n = 306$). All data was collected by retrospective chart review with the approval of our institutional review board.

Standard clinical parameters were reviewed, including age at presentation, ethnicity, previous history of nipple discharge/benign breast disease or breast cancer, medical history, family history, medications, and smoking. Salient features regarding the nature and duration of the discharge were also collected. Discharge was classified as bloody based on color and/or heme-occult testing if performed by the treating surgeon.

All patients underwent clinical breast examination by a breast surgeon. Mammography was available and confirmed to be negative in 271/306 (89%) patients. Ultrasound was available and confirmed to be negative in 44/306 (14%) patients, and 42 (14%) patients had both negative mammography and ultrasound. All imaging studies performed at an outside facility were reviewed by a dedicated breast radiologist at MSK and repeated as needed. All mammography (MMG) greater than six months old were also repeated. Further management (clinical observation, major duct excision, or additional evaluation) was at the discretion of the treating surgeon. For those patients proceeding to further evaluation with ductography (DG) or MRI, investigations were performed and interpreted at our institution by an experienced radiologist according to previously described protocols.[9,10]

For the purposes of this analysis, the presence of either a filling defect or duct ectasia on ductography was considered suspicious, as this interpretation is an indication for surgery to rule out an underlying cancer or high-risk lesion. Similarly, a breast imaging reporting and data system (BIRADS) MRI score of 4 or 5 was considered suspicious, whereas a BIRADS MRI score of 1, 2, or 3 was considered negative. Pathology reports for those patients proceeding to biopsy and/or surgery were reviewed. A patient was considered to have a false-positive DG or MRI if the excised lesion identified by the investigation did not reveal a carcinoma or a high-risk lesion [lobular carcinoma in situ (LCIS) or atypical ductal hyperplasia (ADH)]. Conversely, a patient was considered to have a false-negative DG or MRI if there was no suspicious finding on DG or MRI, and the pathological specimen revealed either a cancer or a high-risk lesion. For those patients who did *not* proceed to biopsy or surgery, clinical status at last follow-up was obtained from medical records.

All analyses were done with SPSS software (version 11; SPSS Inc., Chicago, IL). The Pearson chi-square

TABLE 1. *Patient characteristics and characteristic features of nipple discharge*

Patient characteristics	$n = 306$ n (%)
Median age, years (rang)	51.3 years (19.8–93.9)
Menopausal status:	
Premenopausal	110 (36%)
Postmenopausal	196 (64%)
Peripartum *(pregnant or within six months of delivery)*	11 (4%)
Family history:	
Breast cancer (any)	98 (32%)
Breast and ovarian cancer.	9 (3%)
Smoker *(current)*	57 (19%)
Medications *(current)*	
OCP	20 (7%)
HRT	24 (8%)
Fertility medications.	1
Benign breast disease	59 (19%)
Ipsilateral	41
Contralateral	18
Previous history of breast cancer	26 (9%)
Ipsilateral	13
Contralateral	13
Median onset ND/duration, weeks (range)	4 weeks (1–520 weeks)
Unilateral ND	275 (90%)
Color of ND	
White/milky	20 (7%)
Clear/serous/pink	90 (29%)
Bloody *(as defined by color or heme-occult if performed)**	165 (54%)
Green/brown	31 (10%)
Spontaneous ND	239 (78%)
Single-duct ND	161 (53%)
Large-volume ND (regular/continuous)	31 (10%)
ND present on the day of CBE	252 (82%)
Persistent ND	211 (69%)

OCP: Oral contraceptive pill, HRT: hormone-replacement therapy

* Heme-occult was performed on 108 patients with non-bloody-colored discharge at the discretion of the treating surgeon. Of these, 62 (57%) had a positive heme-occult and were thus considered to have bloody nipple discharge.

test was used to determine if any clinical variable could predict the presence of underlying malignant pathology.

RESULTS

The clinical characteristics of our population are shown in Table 1. Following negative standard evaluation [CBE, MMG, ultrasound (US)], 186/306 patients (61%) proceeded to further evaluation with ductography and/or MRI. A total of 163 ductograms and 52 MRIs were performed in 186 patients; 29 patients had both DG and MRI. Among the remaining 120 patients, 35 (11%) proceeded directly to MDE, while 85 (28%) were followed clinically

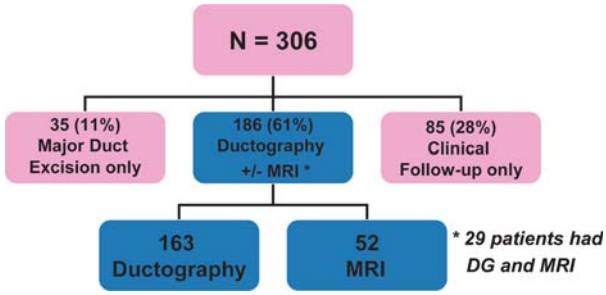

FIG. 1. Management of patients with suspicious nipple discharge after negative standard evaluation. DG, ductography

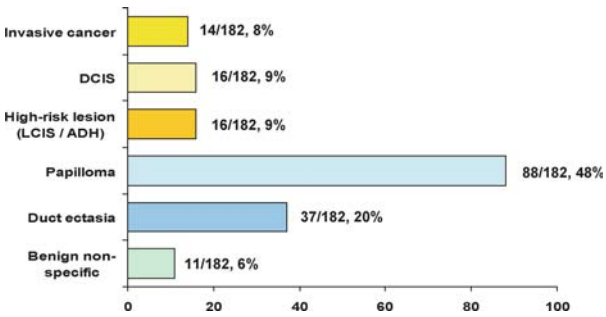

FIG. 2. Histopathological findings: 182/306 (59%). HR, high risk; ND, nipple discharge; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; ADH, atypical ductal hyperplasia

(Figure 1). The median time from presentation to surgery was 1.3 months (range, 0.2–122.8 months). Patients that were selected for clinical follow-up only ($n = 85$) versus further evaluation ($n = 221$) were more likely to be premenopausal (43% vs. 19%, $p < 0.05$) and/or have at least one of the following clinical features: non-bloody ND (74% vs. 45%, $p < 0.001$), milky ND (15% vs. 3%, $p < 0.001$), multi-duct ND (72% vs. 38%, $p < 0.01$), small volume ND (98% vs. 87%, $p < 0.01$) or spontaneous resolution of the ND (73% vs. 15%, $p < 0.001$).

Among the 221 patients selected for further evaluation, 182 (82%) ultimately proceeded to surgery/biopsy while the remaining 39 patients (18%) were followed clinically after negative subsequent evaluation. Within this group, patients selected for biopsy/surgery ($n = 182$) versus clinical follow-up ($n = 39$) were more likely to have: a positive DG (76% vs, 35%, $p < 0.01$); a positive MRI 61% vs. 0%, $p < 0.05$) and/or persistent ND (95% vs. 28%). Histopathological findings for those proceeding to surgery/biopsy are illustrated in Figure 2. The overall incidence of malignant or high-risk pathology was 15%, representing 30 (10%) malignancies and 16 (5%) high-risk lesions (LCIS or ADH). On univariate analysis,

TABLE 2. *Clinical features of patients who had cancer/high-risk lesions compared with those with benign pathology*

	Cancer/high-risk lesion, $n = 46$	Benign, $n = 136$	P
Postmenopausal status	29 (78%)	91 (67%)	≤0.1
Family history of breast cancer (any)	21 (46%)	40 (29%)	≤0.2
Acute onset (≤ 4 weeks)	25 (54%)	87 (64%)	≤1
Unilateral ND	45 (98%)	132 (97%)	≤1
Large volume (regular/continuous) ND	13 (28%)	10 (7%)	≤0.01
Bloody nipple discharge (based on color or heme-occult if performed)	32 (70%)	81 (60%)	≤1
Spontaneous ND	41 (89%)	122 (90%)	≤1
Single duct ND	26 (57%)	46 (34%)	≤0.1
Persistent ND	41 (89%)	129 (95%)	≤1

ND, Nipple discharge

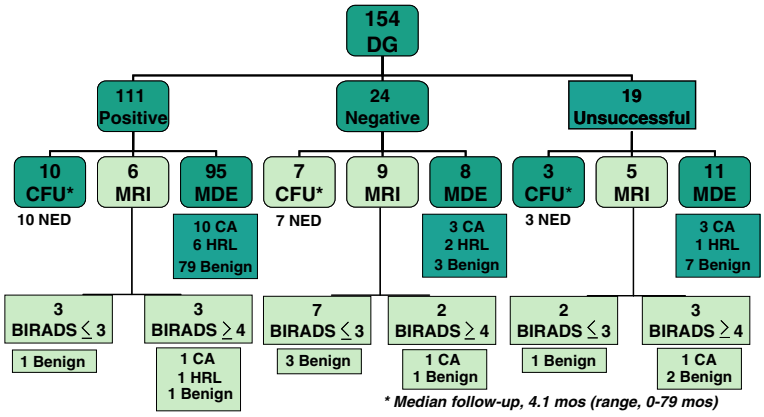

FIG. 3. Outcome for patients that underwent ductography as a first-line test, $n = 154$. DG, ductography; CFU, clinical follow-up; MDE, major duct excision; CA, cancer; HRL, high-risk lesions; BIRADS, breast imaging reporting and data system

the only clinical variable that appeared predictive of malignant/high-risk pathology was large-volume nipple discharge ($p \leq 0.01$) (Table 2).

Diagnostic Ductography

Ductography was the first-line test in 154/163 patients in which it was performed. Successful cannulation was achieved in 135/154 (88%) patients, and an abnormality was detected in 111/135 (82%). The most frequent finding was the presence of one or more filling defects ($n = 100$); duct ectasia was reported in 20 studies. Subsequent management and outcomes for all 154 patients are illustrated in Figure 3.

Ninety-five patients with abnormal DG (95/111, 86%) proceeded directly to MDE (41 with preoperative ductography and needle localization), yielding 10 cancers (5 invasive, 5 ductal carcinoma in situ [DCIS]), 6 high-risk lesions (2 LCIS, 4 atypia), and 79 benign lesions. Six patients (6/111, 5%) with abnormal DG were evaluated further with MRI, and three of six patients were found to have BIRADS ≥ 4 lesions. MDE revealed one invasive cancer (BIRADS 4), one LCIS (BIRADS 5), and one papilloma (BIRADS 5) in these patients. Ten patients (9%) with abnormal ductograms have been followed clinically without event at a median follow-up of 2.7 months (range, 0–30.5 months).

Ductography was negative in 24 patients. Of these, eight (33%) proceeded directly to MDE, yielding three cancers (one invasive, two DCIS), two high-risk lesions (two atypia), and three benign lesions. MRI was obtained in 9/24 (38%) patients, two of whom were considered to have BIRADS ≥ 4 lesions. Subsequent biopsy demonstrated cancer in one of these patients. Seven (30%) patients in this group have been followed clinically without event at a median follow-up of 3.7 months (range, 0.1–79 months).

Ductography was unsuccessful in 19/154 (12%) patients due to either the inability to cannulate the discharging duct, or the absence of active discharge on the day of the examination. The majority of these patients (11/19, 58%) proceeded directly to MDE, yielding three cancers (three DCIS), one high-risk lesion (atypia), and seven benign lesions. MRI was obtained in 5/19 (26%) patients and demonstrated a BIRADS ≥ 4 lesions in three of the five. Subsequent biopsy demonstrated cancer in one of these three

TABLE 3. *Histopathological findings for patients that underwent further evaluation, and correlative predictive values (for malignant/high-risk pathology) for preoperative evaluation*

	No surgery	Invasive CA	DCIS	HRL	Benign	PPV	NPV
Ductography*							
Positive (n = 112)	12 (11%)	6 (5%)	6 (5%)	7 (6%)	81 (72%)	19%	63%
Negative (n = 27)	11 (41%)	2 (7%)	2 (7%)	2 (7%)	10 (38%)		
Incomplete (n = 24) †	4 (17%)	0	4 (17%)	2 (8%)	14 (58%)		
MRI ††							
BIRADS 4/5 (n = 19)	1 (5%)	3 (16%)	4 (21%)	3 (16%)	8 (42%)	56%	87%
BIRADS 1/2/3 (n = 33)	18 (55%)	1 (3%)	0	1 (3%)	13 (39%)		
MDE alone (n = 35)	–	4 (11%)	1 (3%)	3 (9%)	27 (77%)	–	

*Sensitivity 76%, specificity 11%.
†Excluded in analysis of PPV, NPV, sensitivity and specificity
†† Sensitivity 77%, specificity 62%.
CA, cancer; DCIS, ductal carcinoma in situ; MDE, major duct excision; HRL, high-risk lesions; PPV, positive predictive value; NPV, negative predictive value.

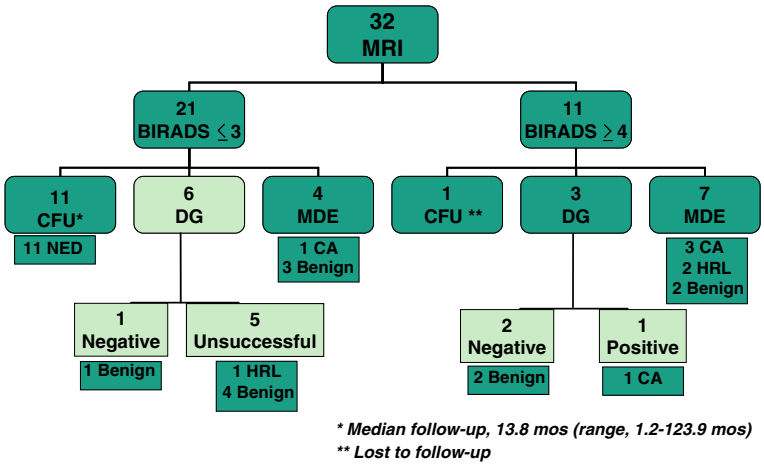

FIG. 4. Outcome for patients that underwent MRI as a first-line test, n = 32. BIRADS, breast imaging reporting and data system; CFU, clinical follow-up; DG, ductography; MDE, major duct excision; CA, cancer; HRL, high-risk lesions

patients. Three (16%) patients in this group have been followed clinically without event at a median follow-up of 5.7 months (range, 5.1–22.7 months).

Results for all 163 patients having DG are illustrated in Table 3. The PPV and NPV of ductography for identifying underlying malignant or high-risk pathology in this population were 19% and 63%, respectively (sensitivity 76%, specificity 11%).

Diagnostic MRI

MRI was the first line test in 32/52 (63%) patients in which it was performed, and yielded a BIRADS ≥ 4 diagnosis in 11/32 (34%) patients. Seven of 11 (64%) patients proceeded directly to MDE, demonstrating one invasive cancer, two DCIS, two high-risk lesions, and two benign lesions. Three of 11 (27%) patients were evaluated further with ductography, which identified a filling defect in one patient that was subsequently excised yielding DCIS, but failed to detect an abnormality in the remaining two patients, both of whom were subsequently found to have benign papillomas. One patient with a BIRADS ≥ 4 MRI declined further work-up.

MRI was negative in 21 patients (BIRADS ≤ 3). Of these, four patients proceeded to MDE, yielding one invasive cancer and three benign lesions. Six (29%) patients were evaluated further with ductography prior to MDE, and the remaining 11/21 (52%) patients have been followed clinically without event at a median follow-up of 13.8 months (range, 1.2–123.9 months). Management and outcomes for all 32 patients having MRI as the first-line test are illustrated in Figure 4.

Among the entire group of 52 patients who underwent MRI (either alone or in conjunction with DG), additional incidental findings were reported in the index breast in 24 (46%) cases. Repeat imaging was recommended and undertaken for all 24 patients, three of whom subsequently required biopsy, yielding

benign results in all three cases. The median number of follow-up scans for these 24 patients was one (range, 1–7), and at last follow-up, no further cancers have been identified. Of 45 women who had bilateral MRI, one required biopsy for a suspicious lesion in the contralateral breast, which ultimately proved to be benign.

The sensitivity, specificity, positive predictive value, and negative predictive value of MRI in this population are illustrated in Table 3.

Major Duct Excision

MDE without additional evaluation was performed in 35 (11%) patients (Figure 1). Surgical excision successfully identified a specific causative pathological lesion in 32 (91%) cases (four invasive cancers, one DCIS, three high-risk lesions, 14 papillomas, 10 duct ectasia). Nonspecific benign findings were reported in the remaining three patients, and there have been no subsequent clinical events in these three patients at a median follow-up of 25.1 months (range, 2.1–89.1 months).

Clinical Follow-Up Only

The remaining 85/306 (28%) patients were followed clinically without further evaluation (Figure 1). At a median follow-up of six months (range, 0–102 months), 62/85 (73%) patients had resolution of their symptoms, and one patient presented with an invasive cancer at 102 months.

DISCUSSION

The majority of patients with suspicious nipple discharge will not have an underlying cancer or high-risk lesion. In our series, we defined suspicious nipple discharge as the presence of at least one of the classical features of pathological nipple discharge (spontaneous, single-duct, bloody, unilateral, persistent ND), and showed that despite negative standard evaluation, an underlying cancer was present in 10% of all patients presenting with ND, and that 5% were found to have a high-risk lesion. Considering only those patients who proceeded to biopsy/surgery (182/306, 59%), 25% of patients (46/182) were found to have an underlying malignant /high risk lesion. Although the referral patterns of patients to our institution (a tertiary referral cancer center) differ from others, these rates are in concordance with those reported in other studies.[3,4,6,11–13] Among 30 patients who were found to have an underlying cancer, the rates of invasive and in-situ disease in our series were almost equivocal. This is in contrast to recently published series that report higher rates of in situ disease in patients presenting with nipple discharge.[6,11–13] Although this my be explained in part by the fact that our institutional rate of DCIS is lower then that seen in the general population (17% versus 23%), longer follow-up will help confirm whether our approach reliably identified all noninvasive underlying malignancies.[14]

As breast surgeons, we rely on preoperative diagnosis to facilitate optimal treatment planning. Unfortunately, in the case of nipple discharge, no one diagnostic study has proved superior to any other in distinguishing between benign and malignant pathology; as a result, these patients can present a diagnostic challenge. Conventional wisdom teaches that the presence of suspicious nipple discharge alone is an indication for surgical excision of the involved duct(s).

As previously outlined, the standard assessment of suspicious nipple discharge includes history, CBE, mammography, and in some centers, sonography. The principal goal of assessment is to identify potentially malignant underlying pathology. A careful clinical history (age, family history, history of benign breast disease/previous breast cancer, parity, etc,) seeks to establish a patient's inherent breast cancer risk.[15] For example, it has been suggested that older women with discharge have a higher incidence of cancer.[16,17] One such paper reported that in the absence of positive findings on standard evaluation, suspicious nipple discharge was due to cancer in less than 3% of patients younger than 40 years old, in 10% of patients between 40 and 60 years old, and in 32% patients over the age of 60.[18] In our study, the incidence of cancer in those age categories was 7%, 9%, and 14%, respectively.

In our population, further evaluation was performed at the discretion of the treating surgeon. While there was a trend toward an increased incidence of malignant or high-risk pathology associated with a family history of breast cancer ($p \leq 0.1$), postmenopausal status ($p \leq 0.2$), and single-duct nipple discharge ($p \leq 0.1$), the only variable that was statistically significant was large-volume nipple discharge. In this setting, large-volume discharge was defined as discharge that was regular, persistent, or continuous. However, this definition is somewhat subjective, which may limit its application in the clinical setting. Bloody nipple discharge, however, is a more-objective variable, and has been shown to be a

strong predictor of underlying malignancy.[19,20] Although some suggest that a conservative approach to non-bloody discharge may be appropriate in patients with negative standard evaluation,[21] the absence of blood does not exclude carcinoma.[22–25] In this series, 47% (14/30) of cancers and 50% (8/16) of high-risk lesions identified were in patients with non-bloody discharge by color alone. While heme-occult testing was positive in a proportion of these patients (4/14 cancers and 4/8 high-risk lesions), 33% (10/30) of cancers and 25% (4/16) of high-risk lesions were identified in patients with heme-occult negative nipple discharge, suggesting that the absence of blood is not helpful in ruling out a malignancy. The failure to identify objective clinical predictors of underlying malignancy in this series highlights the need for consideration of further work-up in patients with suspicious nipple discharge when standard evaluation is negative.

Ductography is a delicate, technically challenging study. Cannulation is only possible if the duct is discharging at the time of the study, and it can be difficult to detect small or flat lesions. Nonetheless, in experienced hands, it can facilitate localization to the site of the intraductal lesion and guide the surgical approach.[11,26–28] This is particularly helpful when one considers that many lesions may be located in the peripheral ducts.[29,30] Unfortunately, its predictive role is less convincing, since a positive study does not differentiate between malignant and benign causes of discharge, and a negative study does not exclude the presence of an underlying carcinoma. In our study, the positive and negative predictive values of ductography were 19% and 63%, respectively (sensitivity, 76%; specificity, 11%). These values are consistent with those of other studies and confirm that there is little role for ductography in distinguishing between malignant and benign causes of nipple discharge.[11,26,31]

Breast MRI, however, has a high sensitivity for both invasive (86% to 100%) and noninvasive disease (40% to 100%), and is emerging as an effective diagnostic technique to identify clinically and mammographically occult cancers.[32] One of the earliest studies evaluating the role of MRI in patients with nipple discharge described 22 patients with nipple discharge and negative mammography, 14 of whom underwent excisional biopsy after MR imaging. MR imaging findings were felt to correlate with histopathologic findings in 10 of the 14 (71%) cases that underwent surgical excision, including the identification of five of six underlying malignancies. The authors concluded that MR imaging may help distinguish between benign and malignant causes of nipple discharge.[33] Others have anecdotally supported this suggestion; however, the data is limited.[34,35] In our population, the positive and negative predictive values of MRI were 56% and 87%, respectively (sensitivity, 83%; specificity, 62%).

While breast MRI is more sensitive than mammography for the detection of breast cancer, its low specificity limits its clinical utility.[36] Diagnostic MRI may detect additional incidental lesions in either the ipsilateral or contralateral breast that require follow-up imaging or biopsy. In this series, additional incidental findings were reported in 46% of scans. All of these patients underwent appropriate workup (three MR-guided biopsies and 56 repeat scans), and no cancer was detected. Yet these incidental findings can have an obvious impact on both the patient and the healthcare delivery system and, as such, should be considered when integrating breast MRI into the evaluation of patients with suspicious nipple discharge.

We recognize that there are many alternative nonoperative investigations for the evaluation of patients with nipple discharge. These include cytological analysis of the nipple discharge fluid (with or without ductal lavage), sonography, and ductoscopy. The use of nipple-fluid cytology to distinguish between patients with cancer and those with benign pathological ND has been a subject of ongoing interest.[37] Current data suggests that cytological examination is only useful when positive, and can have a false-negative rate for cancer of up to 50%.[38,39] In our institution, cytological analysis of the discharge fluid is not standard practice for all patients who present with suspicious ND. Sonography, when positive, may aid localization of the causative lesion but does not reliably distinguish between benign and malignant pathology and as such its role as a sole identifier of breast malignancy remains undetermined.[40] Although some of the patients in this study underwent sonography as part of their initial work-up, we did not evaluate the role of sonography as it is not routinely performed at our institution nor is it considered standard practice in this setting. Finally, while recent interest in ductoscopy as a minimally invasive method for the evaluation of nipple discharge may have potential, there is no data to support that ductoscopic findings can reliably distinguish between benign and malignant pathology.[41] As such, this technique has not been adopted in our institution.

Major duct excision is a straightforward procedure with low morbidity. With the exception of the

younger patient who wishes to breast feed, or perhaps the diabetic patient who may have poor wound healing, it is a very reasonable and appropriate approach to nipple discharge. In the immediate postoperative period, patients may experience some sensory changes over the nipple areolar complex; however, this typically resolves with time. The major criticism of MDE is that in the absence of preoperative findings, it may fail to identify the causative lesion. This has obvious implications if the underlying lesion is malignant or represents a high-risk lesion.[23,42] In our population of 11 patients with nonspecific benign findings post MDE all remain symptom- and cancer-free at last follow-up (median follow-up, 10.8 months; range, 0.7–89.1 months). A similar study assessed long-term outcome (20 years) after blind MDE and concluded that MDE for pathologic nipple discharge was an effective way to diagnose and treat pathologic nipple discharge without missing underlying cancers.[43]

For patients with single-duct nipple discharge, selective duct excision, with or without intraoperative ductoscopy, is a reasonable, less-invasive approach that may minimize postoperative sensory changes and/or preserve the integrity of the ductal system. However, in the absence an actively discharging duct or pre-operative localization of a ductogram finding, selective excision of the ductal system may fail to identify underlying occult disease. Further, while the use of intraoperative ductoscopy may guide the surgeon toward the underlying causative lesion, many ductal carcinomas arise within the peripheral terminal ductal lobular units which are likely to be beyond the reach of the ductoscope.[44,45] As such, when employing a less-invasive approach, it is important that clinical and histopathological findings are concordant and that patients are followed for recurrent symptoms or other signs of residual disease.

In conclusion, for patients with suspicious discharge and negative standard evaluation, cancer remains a significant risk. The failure to identify objective clinical predictors of underlying malignant pathology in this large series highlights that further evaluation should be strongly considered for such patients. Ductography may aid in the localization of an underlying lesion, but it does not distinguish between benign and malignant pathology. Furthermore, a negative ductogram does not reliably exclude an underlying cancer (or high-risk lesion). The higher predictive values of MRI may allow for improved patient selection and treatment planning; however, MRI should not replace MDE as the gold standard to exclude malignancy in patients with suspicious nipple discharge and negative standard evaluation.

REFERENCE

1. Santen RJ, Mansel R. Benign breast disorders. *N Engl J Med* 2005; 353(3):275–85.
2. Newman HF, Klein M, Northrup JD, Ray BF, Drucker M. Nipple discharge: frequency and pathogenesis in an ambulatory population. *NY State J Med* 1983; 83:928.
3. Hughes L, Mansel R, Webster D, Gravelle I. Benign disorders and diseases of the breast London: WB Saunders; 2000.
4. Kilgore AR, Fleming R, Ramos MM. The incidence of cancer with nipple discharge and the risk of cancer in the presence of papillary disease of the breast. *Surg Gynecol Obstet* 1953; 96:649–660.
5. Murad TM, Contesso G, Mouriesse H. Nipple discharge from the breast. *Ann Surg* 1982; 195(3):259–64.
6. Falkenberry SS. Nipple discharge. *Obstet Gynecol Clin North Am* 2002; 29(1):21–9.
7. Bland KI, Copeland EM. The Breast – Comprehensive management of benign and malignant disorders, Third Edition Philadelphia: WB Saunders; 2004.
8. King TA, Carter KM, Bolton JS, Fuhrman GM. A simple approach to nipple discharge. *Am Surg* 2000; 66(10):960–5; discussion 965–6.
9. Van Zee KJ, Ortega Perez G, Minnard E, Cohen MA. Preoperative galactography increases the diagnostic yield of major duct excision for nipple discharge. *Cancer* 1998; 82(10):1874–80.
10. Morris EA. Screening for breast cancer with MRI. *Semin Ultrasound CT MR* 2003; 24:45–54.
11. Florio MG, Manganaro T, Pollicino A, Scarfo P, Micali B. Surgical approach to nipple discharge: a ten-year experience. *J Surg Oncol* 1999; 71(4):235–8.
12. Cabioglu N, Hunt KK, Singletary SE, et al. Surgical decision making and factors determining a diagnosis of breast carcinoma in women presenting with nipple discharge. *J Am Coll Surg* 2003; 196(3):354–64.
13. Adepoju LJ, Chun J, El-Tamer M, Ditkoff BA, Schnabel F, Joseph KA. The value of clinical characteristics and breast-imaging studies in predicting a histopathologic diagnosis of cancer or high-risk lesion in patients with spontaneous nipple discharge. *Am J Surg* 2005; 190(4):644–6.
14. American Cancer Society. Cancer Facts and Figures 2006. Online at: http://www.cancer.org/docroot/STT/content/STT_1x_Cancer_Facts__Figures_2006.asp (accessed June 22, 2007).
15. Goksel HA, Yagmurdur MC, Demirhan B, Isiklar I, Karakayali H, Bilgin N, Haberal M. Management strategies for patients with nipple discharge Langenbecks. *Arch Surg* 2005; 390(1):52–8.
16. Lau S, Kuchenmeister I, Stachs A, Gerber B, Krause A, Reimer T. Pathologic nipple discharge: surgery is imperative in postmenopausal women. *Ann Surg Oncol* 2005; 12(7):546–51.
17. Seltzer MH. Breast complaints, biopsies, and cancer correlated with age in 10,000 consecutive new surgical referrals. *Breast J* 2004; 10(2):111–7.
18. Seltzer MH. The significance of age in patients with nipple discharge. *Surg Gynecol Obstet* 1970; 131(3):519–22.
19. Vargas HI, Romero L, Chlebowski RT. Management of bloody nipple discharge. *Curr Treat Options Oncol* 2002; 3(2):157–61.
20. Sauter ER, Schlatter L, Lininger J, Hewett JE. The association of bloody nipple discharge with breast pathology. *Surgery* 2004; 136(4):780–5.

21. Dillon MF, Mohd Nazri SR, Nasir S, et al. The role of major duct excision and microdochectomy in the detection of breast carcinoma. *BMC Cancer* 2006; 6:164.
22. LaFreniere R. Bloody nipple discharge during pregnancy: a rationale for conservative treatment. *J Surg Oncol* 1990; 43(4):228–30.
23. Leis HP. Management of nipple discharge. *World J Surg* 1989; 13(6):736–42.
24. McLaughlin CW, Coe JD. A study of nipple discharge in the nonlactating breast. *Ann Surg* 1963; 157:810–6.
25. Dawes LG, Bowen C, Venta LA, Morrow M. Ductography for nipple discharge: no replacement for ductal excision. *Surgery* 1998; 124(4):685–91.
26. Tjalma WA, Verslegers IO. Suspicious nipple discharge and breast magnetic resonance imaging. *Breast J* 2004; 10(1):65–6.
27. Funovics MA, Philipp MO, Lackner B, Fuchsjaeger M, Funovics PT, Metz V. Galactography: method of choice in pathologic nipple discharge?. *Eur Radiol* 2003; 13(1):94–9.
28. Lamont JP, Dultz RP, Kuhn JA, Grant MD, Jones RC. Galactography in patients with nipple discharge. *Proc (Bayl Univ Med Cent)* 2000; 13(3):214–6.
29. Hou MF, Huang TJ, Liu GC. The diagnostic value of galactography in patients with nipple discharge. *Clin Imaging* 2001; 25(2):75–81.
30. Dietz JR, Crowe JP, Grundfest S, et al. Directed duct excision by using mammary ductoscopy in patients with pathologic nipple discharge. *Surgery* 2002; 132:582–7.
31. Funovics MA, Philipp MO, Lackner B, Fuchsjaeger M, Funovics PT, Metz V. Galactography: method of choice in pathologic nipple discharge?. *Eur Radiol* 2003; 13(1):94–9.
32. Morris EM, Libermann L. Breast MRI Diagnosis and Intervention New York: Springer; 2005.
33. Orel SG, Dougherty CS, Reynolds C, Czerniecki BJ, Siegelman ES, Schnall MD. Imaging in patients with nipple discharge: initial experience. *Radiology* 2000; 216(1):248–54.
34. Nakahara H, Namba K, Watanabe R, et al. A comparison of MR imaging, galactography and ultrasonography in patients with nipple discharge. *Breast Cancer* 2003; 10(4):320–9.
35. Wahner-Roedler DL, Reynolds C, Morton MJ. Spontaneous unilateral nipple discharge: when screening tests are negative–a case report and review of current diagnostic management of a pathologic nipple discharge. *Breast J* 2003; 9(1):49–52.
36. Fischer U, Kopka L, Grabbe E. Breast carcinoma: Effect of preoperative contrast-enhanced MR imaging on the therapeutic approach. *Radiology* 1999; 213:881–888.
37. West KE. Correlation of nipple aspiration and ductal lavage cytology with histopathologic findings for patients before scheduled breast biopsy examination. *Am J Surg* 2006; 191(1):57–60.
38. Simmons R, Thevarajah S, Brennan MB, Christos P, Osborne P. Methylene blue dye as an alternative to isosulfan blue dye for sentinel lymph node localization. *Ann Surg Oncol* 2003; 10(3):242–7.
39. Das DK, Al-Ayadhy B, Ajrawi MT, et al. Cytodiagnosis of nipple discharge: a study of 602 samples from 484 cases. *Diagn Cytopathol* 2001; 25:25–37.
40. Greene T. A single institution review of new breast malignancies identified solely by sonography. *J Am Coll Surg* 2006; 203(6):894–8.
41. Louie D. Identification of breast cancer in patients with pathologic nipple discharge: does ductoscopy predict malignancy. *Am J Surg* 2006; 192(4):530–3.
42. Moore SW, Pearce J, Ring E. Intraductal papilloma of the breast. *Suvr Med (Sofiia)* 1961; 112:153–158.
43. Nelson RS, Hoehn JL. Twenty-year outcome following central duct resection for bloody nipple discharge. *Ann Surg* 2006; 243(4):522–4.
44. Dietz JR, Kim JA, Malycky JL, et al. Feasibility and Technical Considerations of Mammary Ductoscopy in Human Mastectomy Specimens. *Breast J* 2000; 6(3):161–165.
45. Sharma R. Comparative analysis of minimally invasive microductectomy versus major duct excision in patients with pathologic nipple discharge. *Surgery* 2005; 138(4):591–6; discussion 596–7.