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ORIGINAL ARTICLE – BREAST ONCOLOGY

Breast Pathology Review: Does It Make a Difference?

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ABSTRACT

Background. Breast pathology is a challenging field, and previous work has shown discrepancies in diagnoses, even among experts. We set out to determine whether mandatory pathology review changes the diagnosis or surgical management of breast disease.

Methods. Cases were referred for pathology review after patients presented for surgical opinion to the Dubin Breast Center at Mount Sinai Medical Center over the course of 2 years. Surgical pathologists with expertise in breast disease reviewed slides submitted from the primary institution and rendered a second opinion diagnosis. Comparison of these reports was performed for evaluation of major changes in diagnosis and definitive surgical management.

Results. A total of 306 patients with 430 biopsy specimens were reviewed. Change in diagnosis was documented in 72 (17 %) of 430 cases and change in surgical management in 41 (10 %). A change in diagnosis was more likely to occur in patients originally diagnosed with benign rather than malignant disease (31 vs. 7 %, $p < 0.001$). Twelve (7 %) of 169 specimens initially diagnosed as benign were reclassified as malignant. A malignant diagnosis was changed to benign in 4 (2 %) of 261 cases. Change in diagnosis was less common in specimens originating from commercial laboratories than community hospitals or university hospitals (8, 19, 21 %, $p = 0.023$). Change in management was not dependent on initial institution. Type of biopsy specimen (surgical or core) did not influence diagnostic or management changes.

Conclusions. We recommend considering breast pathology review based on the individual clinical scenario, regardless of initial pathologic diagnosis or originating institution.

Breast pathology is a challenging field, and previous work has shown discrepancies in diagnoses even among experts.[1] Surgical pathology is becoming increasingly subspecialized, and in many large academic centers, specialists in breast pathology review all breast cancer cases. Slide review is an integral component of breast cancer care for patients referred from outside institutions.[1] While pathology review of outside slides is mandatory at some institutions, overall its use is sporadic, implemented on a case-by-case basis, and impractical at institutions that lack breast pathology sub-specialists. Recommendations from prior studies vary, with some advocating mandatory pathology second opinion and others proposing selection criteria to determine which patients should undergo pathology review.[2,3]

The accurate diagnosis of breast cancer and benign disease strongly affects management and decision making for both surgery and adjuvant therapy. We set out to determine whether systematic pathology review changes the diagnosis or surgical management of breast disease. We assessed the role of breast pathology second opinions by breast cancer pathology specialists at our institution and the incidence of change in diagnosis and definitive surgical management. We also sought to determine whether the type of initial institution where slides were originally produced and diagnosis rendered influenced the likelihood of change in diagnosis and opinion.

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METHODS

Cases were referred for pathology review after patients presented for surgical opinion to three attending surgeons at the Dubin Breast Center at Mount Sinai Medical Center over the course of 2 years (January 2010 to January 2012). Cases were consecutive and comprehensive in that all slides from each case were procured for review and represented both core biopsy and surgical excision specimens. Institutional review board approval was obtained for this study as a minimal risk project with waiver of informed consent.

Surgical pathologists with expertise in breast disease reviewed slides submitted from the primary institution and rendered a second opinion diagnosis. Comparison of these reports was performed for evaluation of change in diagnosis. If a discrepancy was noted between the initial pathologic diagnosis and the second opinion, slides were reviewed by an additional pathologist at our institution for interobserver confirmation. Categories of diagnostic change included one benign pathology to another (including fibroadenoma, fibrocystic changes, ductal hyperplasia, atypia, radial scar, papillary lesion, and lobular carcinoma-in situ), benign disease to ductal carcinoma-in situ (DCIS), DCIS to invasive cancer, invasive ductal carcinoma to invasive lobular carcinoma, and change in axillary nodal status. Change in diagnosis that led to change in management were further evaluated, recorded, and categorized. Cases were additionally categorized by primary institution type: university hospital, community hospital, or commercial laboratory. Change in diagnosis and/or management was determined on the basis of initial institution and biopsy type (core or excisional).

When specimens from different sites in a single patient were submitted for review, each site was evaluated independently when comparing for change in pathologic diagnosis. Comparison was made between initial diagnosis and second-opinion diagnosis and both change in diagnosis and subsequent change in surgical management recorded and tested for statistical significance. Univariate analysis was performed by a nonparametric χ^2 (Pearson's Chi square) at the $\alpha = 0.05$ level. Pathologic diagnosis at initial submission was tested as an independent predictor of change in diagnosis as well as change in management. No distinction was made between categories of diagnostic change (benign or malignant) when tested for significance. Both change in diagnosis and change in management were tested as categorical variables. Type of institution from which pathology originated and type of biopsy performed were also tested as independent predictors of change in diagnosis, and change in management. McNemar test ($\alpha = 0.05$ level) was performed to assess for differences between the paired initial and second-opinion diagnoses.

TABLE 1 Changes in diagnosis and management after secondary pathology review

Characteristic	Change in diagnosis ($n = 72$)	Change in management ($n = 41$)
Benign to benign	41 (57 %)	20 (49 %)
Benign to DCIS	12 (17 %)	12 (29 %)
DCIS to benign	4 (6 %)	4 (10 %)
DCIS to invasive cancer	2 (3 %)	2 (5 %)
Invasive cancer to DCIS	2 (3 %)	2 (5 %)
Invasive ductal to invasive lobular cancer (or vice versa)	10 (14 %)	0 (0 %)
Axillary node status	1 (1 %)	1 (2 %)

DCIS ductal carcinoma-in situ

TABLE 2 Changes in diagnosis of benign disease resulting in change in surgical management

Initial diagnosis	Diagnosis on review	Change in management
P + DH	DH only	E → No E
P	DH	E → No E
P	FCC, DH	E → No E
P	FA	E → No E
P	FCC	E → No E
ADH	DH	E → No E (2 patients)
ADH	FA	E → No E (2 patients)
ADH	FCC, DH	E → No E
ADH	FCC	E → No E
ALH	FCC, DH	E → No E
ALH	FCC	E → No E
FA with atypia	FA only	E → No E
FCC	FCC with atypia	No E → E
FCC	ADH, LCIS	No E → E
FA	FA with atypia	No E → E
DH	ADH	No E → E (2 patients)
DH	ALH	No E → E

P papilloma, *DH* ductal hyperplasia, *FCC* fibrocystic change, *FA* fibroadenoma, *ADH* atypical ductal hyperplasia, *ALH* atypical lobular hyperplasia, *LCIS* lobular carcinoma-in situ, *E* surgical excision required, *No E* surgical excision not required

Changes from benign to malignant (upgrade) or malignant to benign (downgrade) were also evaluated and compared for likelihood of change.

RESULTS

A total of 306 patients with 430 total biopsy specimens were reviewed. These comprised 371 core needle biopsy (86 %) and 59 excisional biopsy (14 %) specimens. Submitting diagnosis was benign in 169 cases (39 %) and malignant (either DCIS or invasive cancer) in 261 cases

TABLE 3 Changes in diagnosis from benign disease to malignancy, and vice versa

No. of cases	Initial diagnosis	Diagnosis on review	Biopsy type
5	ADH	DCIS	Core
1	ADH	DCIS	Excision
1	LCIS	DCIS	Core
1	ADH, LCIS	DCIS	Excision
3	LCIS	DCIS	Excision
1	ALH	DCIS	Core
3	DCIS	ADH	Core
1	DCIS	DH	Excision

ADH atypical ductal hyperplasia, *DCIS* ductal carcinoma-in situ, *LCIS* lobular carcinoma-in situ, *ALH* atypical lobular hyperplasia, *DH* ductal hyperplasia

(61 %). Mean patient age was 53.6 years (range 28–86 years). Overall, 72 (17 %) of 430 submitted specimens had a change in diagnosis on secondary pathology review, and of these cases, 41 (57 %) resulted in change in definitive surgical management. Out of all submitted specimens, secondary pathology review resulted in a change in management in 41 (10 %) of 430 specimens, affecting 35 (11 %) of 306 patients (Table 1).

The most common change in diagnosis category was from one benign condition to another, found in 41 (57 %) of 72 patients with a change in diagnosis. Twenty of these resulted in management changes regarding excision (Table 2). Of these 20 patients, 14 had benign diagnoses that resulted in management changes from excision to no excision required. In the majority of benign cases with recommended changes in management, the change in management hinged on determining the absence or presence of a papillary lesion or atypia. These included papilloma with ductal hyperplasia to ductal hyperplasia alone, papilloma to fibroadenoma, and fibroadenoma with atypia to fibroadenoma alone. Change in diagnosis requiring excision when excision was not previously recommended according to the initial diagnosis was found in six patients (Table 2). Change in diagnosis from one benign condition to another accounted for 49 % of the management changes seen overall.

Benign disease was reclassified as DCIS in 12 cases (17 %) (Table 3). The most frequent benign disease to be reclassified as DCIS was atypical ductal hyperplasia (ADH), which occurred in seven specimens. A diagnosis of DCIS was changed to benign in four cases (6 %), most commonly to ADH, which occurred in three specimens. In the three cases that were downgraded from DCIS to ADH, the final pathology after definitive surgical excision revealed biopsy site changes only, without residual atypia or DCIS.

TABLE 4 Change in diagnosis and management stratified by institution type

Change	University hospital ($n = 155$)	Community hospital ($n = 167$)	Commercial laboratory ($n = 108$)	p value
Change in diagnosis	32 (21 %)	31 (19 %)	9 (8 %)	0.023
Change in management	18 (12 %)	18 (11 %)	5 (5 %)	0.130

Change from in situ disease to invasive cancer or the converse was seen in 4 (6 %) of 72 specimens, resulting in a management change for all 4. Changes between invasive ductal and invasive lobular carcinoma were seen in 10 (14 %) of 72 cases but did not translate into a change in management. Axillary nodal status was altered in 1 patient and did result in a management change (Table 1).

Results were then stratified on the basis of benign versus malignant submitting diagnosis. Of the total 430 specimens that were submitted for a second opinion at Mount Sinai Hospital, 169 had an initial diagnosis of benign disease. Benign pathology submitted for review had resultant change in diagnosis in 53 (31 %) of 169. A benign diagnosis was changed to one of malignancy in 12 (7 %) of 169 cases. Of the 261 malignant specimens examined, a change in diagnosis occurred in 19 (7 %). Four patients (2 %) had a diagnostic change from malignant disease to benign. A change in diagnosis was more likely to occur in patients originally diagnosed with benign disease rather than malignant disease (31 vs. 7 %, $p < 0.001$). Specimens initially diagnosed as benign were also more likely to undergo a change in management (19 vs. 3 %, $p < 0.001$).

The likelihood of change in diagnosis was significantly different when comparing type of institution from which pathology originated (Table 4). Change was observed in 32 (21 %) of 155 consultations originating from other university hospitals, 31 (19 %) of 167 from community hospitals, and 9 (8 %) of 108 from commercial laboratories ($p = 0.02$). There was a comparatively low rate of change from commercial laboratories, with community and university hospitals having similar rates of change in diagnosis. Change in management was not dependent on initial institution type and was indicated in 18 (12 %) of 155, 18 (11 %) of 167, and 5 (5 %) of 108 consultations from the same groups, respectively ($p = 0.1$).

The type of biopsy specimen did not influence diagnostic or management changes. Diagnosis was changed in 62 (17 %) of 371 of core needle specimens compared with 10 (17 %) of 59 surgical excisions ($p = 0.9$). Change in management was also similar: 37 (10 %) of 371 and 4 (7 %) of 59, respectively ($p = 0.4$).

DISCUSSION

In the setting of newly diagnosed cancer, pursuing a second opinion is common. In a National Health Interview Survey, 55.7 % of patients newly diagnosed with any type of cancer reported seeking a second opinion.[4] On multivariate analysis, predictors of utilizing a second opinion were Hispanic origin, breast cancer diagnosis, and residence in a non-central city.[4]

Previous reports have documented considerable disagreement in diagnosis among breast pathologists. The well-known but controversial study by Rosai in 1991 was the first to illustrate the point that there is often discordance in diagnosis, even among specialists, particularly when evaluating "borderline epithelial lesions of the breast."[5] Discrepancies in pathologic differentiation between ADH and DCIS have been highlighted in the recent literature. Because ADH and low-grade DCIS share common features, it has been suggested that these entities actually represent a spectrum of pathology rather than distinct diseases.[6] Therefore, a difference in diagnosis among pathologists is not unexpected, and a change in diagnosis as characterized by our study may not be significant.

Many previous studies have found varying rates of change in diagnosis after pathology review. Staradub et al. reviewed 346 cases of diagnosed breast cancer. Pathology or prognostic factors changed in 80 % after secondary review. This study included minor changes and grade discrepancy in the diagnostic change category, partially accounting for this high rate. Surgical management was altered in 7.8 %. Diagnostic changes were seen more frequently in the diagnosis of in situ disease compared with invasive carcinoma. Core versus excisional biopsy did not significantly predict change.[3]

Newman et al. retrospectively reviewed 149 patients referred to a multidisciplinary breast cancer tumor board for changes in imaging interpretation, pathology, and recommended management. They found changes in diagnosis for 43 (29 %) of 149 patients after pathology review. The most common discrepancies involved changes in tumor grade or surgical margin status, and resulted in a change in management for 13 patients (9 %).[7]

Kennecke et al. evaluated 906 patients with node-negative breast cancer or DCIS. Unlike our study, where pathology review was routine, only 45 % of the eligible patients received pathology review. Twenty percent had changes in diagnosis, most frequently grade, lymphovascular invasion, nodal status, and margin status. There was a change in adjuvant systemic or radiotherapy recommendations for 6 % of patients. There were no changes in surgical management reported.[2] This study highlights the important concept that when pathology review is not mandated by hospital policy, it is either patient driven or at the discretion of the treating hospital and physician. In a survey evaluating hospital practices regarding pathology review, 126 hospitals responded, and 50 % reported a policy of mandatory pathology review of slides from outside institutions before surgical intervention. Seventy-five percent of academic tertiary-care centers, 30 % of community hospitals, and 17 % of nonacademic tertiary-care centers reported having a policy mandating pathology review.[8] However, in the current era of rising health care costs and initiatives toward cost containment, mandatory pathology review for all submitted breast specimens for all institutions may not be feasible.

In our experience, systematic secondary review of surgical pathology specimens by specialized breast pathologists altered diagnosis in 17 % and management in 10 % of cases, regardless of biopsy type. Our study did not evaluate grade; only major pathologic changes were assessed. Change in management assessed only definitive surgical management, and resultant changes in adjuvant therapy were not addressed, as they were beyond the scope of this study. Change in adjuvant therapy recommendations would most likely not be as frequent as change in biopsy diagnosis and management because in most cases, surgical pathology from definitive surgical management provides a larger pathology sample from which the true diagnosis and assessment would most likely be made.

Specimens initially labeled as benign were significantly more likely to have a change in diagnosis than those containing malignancy, 31 versus 7 % ($p < 0.001$). Management changes were also significantly more common in the initially benign group. Therefore, secondary pathology review should not be limited to patients with a diagnosis of malignancy.

To our knowledge, this is the first study to stratify pathology second opinion results by original institution type. Pathology specimens initially evaluated at university or community hospitals were more likely to undergo a change in diagnosis than those submitted from commercial laboratories. When cases referred from academic medical centers were compared with those from community hospitals or commercial laboratories, there was no significant difference in the rates of change in management. Multiple prior studies evaluating concordance among pathologists reviewing the same slides found significant variation in diagnosis rendered, even when utilizing the same criteria.[5,9,10] Our findings, in conjunction with these results, support a recommendation for obtaining a second opinion in all cases, regardless of the setting where the original biopsy was performed.

Pathology second opinion is invaluable for a substantial number of patients, but it is not without drawbacks. Secondary slide review adds to health care costs and may delay definitive treatment. On the other hand, pathology review

TABLE 5 Review of prior studies [a]

Study	Year	No. of cases reviewed	Change in diagnosis (%)	Change in management (%)	Notes
Kennecke et al.[2]	2012	405	20	6	Node negative patients only
Newman et al.[7]	2006	149	29	9	
Staradub et al.[3]	2002	346	40	7.8	
Chang et al.[11]	2001	77	4	4	
Kronz et al.[12]	1999	6,171	1.4		All pathology, not only breast
Wells et al.[13]	1998	30	27		Evaluated pathologist discordance
Gupta and Layfield[8]	1998	4,836	1.36		Fine-needle aspiration cytology
Abt et al.[9]	1995	777	9.1	63	
Schnitt et al.[10]	1992	24	42		Evaluated pathologist discordance

[a] Studies are not uniform in design or outcomes

may prevent unnecessary procedures and treatments, thereby ultimately proving to be more cost-effective. A second drawback involves optimal decision making by the patient after a pathology review presents a different diagnosis. Although the pathologists in our study specialize in breast disease, one cannot be certain that the second opinion rendered by our institution was invariably more accurate than the initial diagnosis. Finally, selection bias may confound our results, as presumably more patients with cancer diagnoses or those with benign diagnoses requiring further intervention would seek a second opinion. It is less common for patients with isolated benign disease to present for pathology review. Therefore, it is unknown how many patients with benign disease would have pathologic changes if samples were submitted for a second opinion.

At our medical center, there is a policy of mandatory preoperative pathology review for all slides prepared at outside institutions. On the basis of the results of this study and a review of the literature (Table 5), we recommend considering breast pathology review before decisive management, regardless of initial pathologic diagnosis, originating institution, or specimen type.

DISCLOSURE The authors have no conflicts of interest to disclose.

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