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Breast Pathology Second Review Identifies Clinically Significant Discrepancies in Over 10% of Patients

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Background: Patients seeking a second opinion or continuation of care at our hospital will routinely have their pathology reviewed prior to initiating treatment. To assess the relevance of this review in patients with breast cancer, we compared original pathology reports submitted during the referral with second-review reports issued at our institution. We also assessed compliance with College of American Pathologists (CAP) requirements regarding inclusion of scientifically validated data elements (SVDE) in these pathology reports.

Methods: We retrospectively studied all 1,970 breast pathology referral cases reviewed during one calendar year. The variables studied were histologic classification; tumor grade, necrosis, size, margin status, lymphatic/vascular invasion, dermal involvement, and biomarker profile (ER, PR, and Her-2). Each variable was rated as "agree," "disagree," "missing information," or "not applicable."

Results: A significant discrepancy, defined as a disagreement that affected patient care, was found in 226 cases (11.47%). Additionally, in 418 resection cases (31.6%), some CAP-checklist specific required information was missing. The most common areas of significant discrepancy were histologic category (66 cases; 33%) and biomarker reporting (50 cases; 25%). The most problematic diagnostic categories were intraductal lesions, lobular carcinoma, metaplastic carcinomas, and phyllodes tumors. Most disagreements in the biomarker-profile category were interpretive, but in 20% of discrepant cases, findings were supported by repeat immunohistochemical analysis.

Conclusions: Our results confirm the value and utility of obtaining a second opinion to optimize patient care. Changes in diagnoses obtained after second review should be interpreted and reported in a collaborative fashion, noting the benefit of a review from second pair of experienced eyes. Our results support the use of second review to ensure inclusion of CAP-required data elements in pathology reports.

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KEY WORDS: **breast pathology; quality; second opinion; error**

INTRODUCTION

Accurate histologic assessment is the foundation on which treatment decisions are made and therapeutic responses measured. When patients seek a second opinion or transfer of their care, the pathology report is an essential element of their continuum of care. In the early 1990 s, the Association of Directors of Anatomic and Surgical Pathology (ADASP) recommended routine review of outside pathologic interpretation when patients are referred to another institution for further treatment [1]. Despite this call, no consensus has emerged for the adoption of a mandatory second review policy, and debate remains regarding the value of such a practice; some studies have suggested that only selective review is necessary, for cases with high-risk of diagnostic error (e.g., tumors of certain anatomic sites such as the ovary, soft tissue, and lymph nodes) [2].

In a survey published in 2000, only 50% of 126 participating hospitals, mostly academic health centers, had a mandatory second review policy [3]. Various factors are thought to be responsible for institutions' reluctance to adopt a mandatory policy, including workload constraints, the financial cost of a second opinion, challenges in doctor-patient communication, and potential treatment delays [4–7].

It has been routine practice to review the histopathologic material accompanying all patients referred to our tertiary care center. The review is carried out by a pathologist with subspecialty expertise prior to the clinician developing a treatment plan and initiating therapy. Recently we have demonstrated the value that is added by providing precise pathologic diagnoses to clinicians formulating evidence-based treatment plans [8].

The aim of this retrospective study was to determine the rate of concordance in all referral pathology reviewed by a breast pathologist with subspecialty expertise.

MATERIALS

The pathology database at The University of Texas MD Anderson Cancer Center was searched for all referred patients seeking a medical second opinion to the Breast center whose specimens were received during calendar year 2010. Consultation cases, defined as cases for which the primary pathologist was seeking an "expert" opinion before rendering the final diagnosis, were excluded from the study. The referral basis included community hospitals, commercial laboratories and academic centers. One pathologist with breast sub-specialty expertise compared scanned copies of contributors' pathology reports with reports issued at our institution, all of which were prepared by the subspecialist breast pathology group. The subspecialty breast pathologists in our group number 12, are fellowship trained, and have been in practice from 5 to

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Precis: There is a significant rate of discrepancy (11.47%) comparing outside pathology reports of patients with breast diseases seeking a second opinion or transfer of care. Second review of breast pathology is a quality and patient safety mechanism that reduces error, not only in the setting of complicated/unusual cases, but also through capturing uncomplicated but simply overlooked diagnostic errors.

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30 years. Whenever a discrepancy with the original pathology report was identified, the report and slides were reviewed by a second pathologist (in essence a third review) for confirmation of the changed diagnosis.

The variables reviewed in this retrospective comparison were histologic classification; tumor grade, necrosis, size, and margin; lymphatic/vascular invasion, dermal involvement, and biomarker profile (estrogen receptor [ER], progesterone receptor [PR], and Her-2). Each variable was classified as "agree," "disagree," "missing information," or "not applicable." Cases with a discrepancy considered to be clinically significant, defined as those with a direct impact on management, were further analyzed. These included cases with a "significant" difference in histologic classification, a difference in tumor size enough to change the T-status in the TNM staging system (excluding T1 subcategories), or a difference in margin status, identification of lymphatic/vascular invasion (in resection specimens), dermal involvement, or biomarker profile.

The College of American Pathologists (CAP) produces and regularly updates protocols (including checklists) for pathologists to use as a resource to aid in effective reporting of cancer surgical pathology findings necessary to provide quality patient care [9]. The American College of Surgeons Commission on Cancer (ACoS-CoC) has mandated that pathologists at CoC-approved programs include scientifically validated or regularly used data elements (SVDE) in their surgical pathology reports on cancer specimens. As a secondary objective of this study, we assessed compliance with CAP required data elements in reports submitted to our institution.

RESULTS

Of a total of 1,970 cases reviewed, there was concordance, or lack of a significant discrepancy in 88.53%. A "significant" discrepancy, defined as a disagreement that affected patient care, was noted in 226 cases (11.47%), of which histologic classification (66 cases: 33.5%) and biomarker reporting (50 cases; 25%) accounted for the majority of changed diagnoses (Table I).

Four hundred and eighteen cases were missing at least one CAP-required data element (Table I). CAP protocol compliance was evaluated based on the 1,323 resection specimens and 31.6% of cases were missing at least one CAP required data element.

Histologic Diagnosis

Histologic classification was changed in 82 cases as a result of the second review; of these, the change was considered to be clinically significant in 66 (3.35% of all cases). Changes in this group were categorized as "upgraded diagnoses" (N = 31), "downgraded diagnoses" (N = 20), or a "change in histologic classification" (N = 31) (Tables II–IV). The most problematic diagnostic categories were classification of intraductal lesions including atypical hyperplasia, lobular carcinoma, metaplastic carcinoma, and phyllodes tumors.

TABLE I. Categories of Discrepancy/Missing Information in 1970 Patients With Breast Pathology Observed After Second Review of Original Pathology

Variable	Number missing (N = 418)	Number discrepant (N = 226)
Histologic diagnosis	N/A	66
Tumor grade	82	13
Immunohistochemical analysis	N/A	50
Lymphatic/vascular invasion	141	31
Tumor margin	36	46
Tumor size	40	18
Dermal involvement	119	2

TABLE II. Breast Pathology Cases Upgraded Upon Second Review

Change Upon Second Review	Number (N = 31)
Benign changed to atypical ductal hyperplasia	9
Atypical ductal hyperplasia changed to ductal carcinoma in situ	6
Benign changed to ductal carcinoma in situ	2
Benign changed to lobular carcinoma in situ	2
Focal invasive carcinoma in mastectomy specimens overlooked	2
Benign phyllodes tumor changed to phyllodes tumor of "undetermined malignant potential"	2
Atypical lobular hyperplasia changed to pleomorphic lobular carcinoma in situ	1
Residual post-therapy invasive carcinoma overlooked	1
Residual ductal carcinoma in situ in re-excision specimen overlooked	1
Second focus of invasive ductal carcinoma in mastectomy specimen overlooked	1
Invasive carcinoma in breast parenchyma changed to metastasis to lymph node	1
Micrometastasis to lymph node missed (made the disease node positive)	1
Metastasis in 2/7 lymph nodes missed	1
Benign papilloma changed to atypical papillary proliferation	1

Tumor Grade

Tumor grade was missing in 82 cases, and a two-fold difference in grade (i.e., a change from low to high grade, or high to low grade) was identified in 13 cases.

Tumor Size

Size of the lesion had not been reported in 40 surgical resection cases (size mentioned in the gross description portion of the report was considered adequate). In 18 cases, the tumor size was increased on the basis of accurate measurement of the lesion on the provided glass slides, which in four cases resulted in a change in T-status of the tumor (excluding T1 subcategories). The accuracy of size measurement of large lesions, where gross description as opposed to microscopic measurement is the primary source of reliable information, cannot be evaluated during second review of cases in a referral setting (i.e., when there is no access to radiographic findings, gross pictures, or the residual gross specimen).

Margin Status

Margin status had not been reported in 36 surgical resection cases and, in an additional 46 cases, there was a discrepancy between the margin status in the original report and the second review. What should be considered an "adequate" margin is a very controversial subject in breast tumor pathology and there is no consensus on what constitutes an optimal negative margin. At our institution, in the majority of cases, a minimum margin of 0.2 cm is required for ductal carcinoma in situ lesions to be considered "adequately" excised. However, even among our treating physicians, "adequacy" criteria can vary by patient, clinical setting, and planned adjuvant therapies. For the purpose of this review, we considered tumor margins of less than 0.2 cm as positive, since the majority of patients whose tumor has a margin less than 2 mm undergo re-excision at our institution.

A lack of agreement regarding what represents an "adequate" margin also pertains to invasive carcinoma. For the purpose of this review, we considered tumor "at ink" as positive margin, and required that an exact measurement of distance be provided on all margins of less than 1.0 cm.

In other words, a close (less than 1.0 cm) margin that had not been specified more precisely was considered lacking information.

Lymphatic/Vascular Invasion

The presence or absence of lymphatic/vascular invasion had not been mentioned in 141 resection cases, and a discrepancy was noted in an additional 31 node negative cases. All discrepancies related to lymph/vascular space invasion were interpreted based on the criteria established by Rosen, that is tumor cells within an endothelial lined space away from the main tumor mass that does not conform exactly to the space (thus eliminating the possibility of retraction artifact) [10].

Dermal Involvement

The presence or absence of dermal involvement had not been reported in the report in 119 relevant cases. However, in only two cases was a discrepancy noted from what was documented in the outside report.

Biomarker Profile

Biomarker profile followed histologic diagnosis as the second most common area with significant discrepancy (50 cases; 25%) between initial and second review pathology reports (Table V). In 19 patients ER status changed from negative to positive and for five patients, ER status changed from positive to negative. For 20 patients progesterone hormone receptor status changed from PR negative to PR positive, and in 12 patients PR status changed from positive to negative. Notably, changes in the degree of positivity were not considered "significant" (low positive vs. positive), and in the PR group, only in cases wherein the patient's tumor was changed from "hormonal receptor negative" (i.e., ER−/PR−) to "hormonal receptor positive" (i.e., ER−/PR+) was the discrepancy counted as "significant". Disagreement in interpretation of ER immunostains (24 cases) represented almost half (48%) of discrepancies in this group. In 20% of discrepant cases, (those with additional material) the change in interpretation was confirmed by repeat immunohistochemical staining performed at our institution. In cases with immunohistochemical differences in Her2 interpretation (from negative including 0, 1+ to positive 3+) subsequent fluorescent in situ hybridization studies performed at our institution on three cases with discrepant Her2/neu immunostain interpretation were confirmatory. In the fourth case, additional material was not available for testing.

These results of changing the contributor's diagnosis are significantly higher than the rate of outside pathologists changing MD Anderson Cancer Center (MDACC) pathologists' diagnosis. In comparison, our pathology department sent out 240 cases for second opinion in 2011. These were cases for which the patient's care has been transferred to another facility or if the patient has requested a second opinion. There was a significant change in diagnosis in 1/240 or (0.4%) of MDACC pathology cases re-reviewed by an outside pathologist. This difference may be secondary to the practice of sub-specialty sign out by our pathologists. There is likely a benefit of redundancy, which is a benefit of review of a high volume of a particular pathologic entity that facilitates accurate pathologic diagnoses. An internal audit of our pathology reports at the same time showed that 90% of breast pathology reports included all of the data elements recommended by the CAP.

DISCUSSION

We identified a significant rate of discrepancy (11.47%) comparing outside pathology reports of patients with breast diseases seeking a second opinion or transfer of care to those issued by our breast pathology group during a 1-year period. A high rate (31.6%) of incomplete compliance with inclusion of CAP requirements was also observed in reports submitted for review during the same time period.

The number of varied therapeutic modalities available to the patient with breast cancer, including different surgical approach (segmental resection vs. variations of total mastectomy) and radiotherapeutic (partial breast vs. total irradiation) and systemic adjuvant therapy regimens (chemotherapy, hormonal therapy, and targeted therapy), mandates correct interpretation of histopathologic features that can be used in designing the optimum treatment strategy for each patient. The fact that more and more clinical/therapeutic decisions are being based upon the presence or absence of various pathologic parameters emphasizes the necessity for thoroughness and accuracy of pathology reports, not only from the academic standpoint but also from the perspective of comprehensive patient care.

The observed 31% rate of missing some type of SVDE in resection specimens is concerning, especially considering that these are cases that had been referred to our institution for treatment purposes because of either patient preference or unavailability of certain therapeutic modalities at the referring institution. Importantly, there was not a significant difference in the number of errors or omissions observed in reports originating from either community based hospitals or commercial laboratories. Among cases with missing information, those with missing information regarding the presence or absence of lymphatic/vascular invasion represented the largest group (141 cases). This number is particularly relevant, since many breast cancer patients are referred to centers for the purpose of receiving radiation and/or chemotherapy. As the presence or absence of lymphatic/vascular invasion (especially in young patients and patients with small tumors and negative lymph nodes) is a major determining factor in planning patients' therapeutic treatment and options for immediate reconstruction, it is of most importance that this variable be included in reports detailing the surgical resection.

Due to the many different tumors types encountered in surgical pathology practice and because the amount of information required in pathology reports is often extensive, it is very difficult for pathologists to consistently remember all of the information required for each case [11–14]. Even though detailed checklists are available through the CAP web site, and the ACS-CoC has mandated that pathology reports at ASC-CoC—approved cancer programs include all SVDEs in reports, is the use of pathology checklists is still not universally adopted in the evaluation of carcinoma. Second review of a patient's outside pathology by another pathologist is rational and wise when major therapeutic interventions are planned based on the interpretation of tissue [8,15]. Our finding of a relatively high number of reports with at least one missing CAP-required data element highlights the importance of standardization of pathology reports by adhering to CAP requirements. This can be achieved by adopting the synoptic reporting policy, a strategy that has been proven to be effective in several studies [13,16].

Our finding of a 11% rate of "significant" discrepancy between the original report and the second review at our institution is similar to rates reported in the literature. In a recent study, Price et al. [17] reported an 11% rate of discrepancy with "high or medium" clinical impact in pathology reports of 100 randomly selected breast cancer patients, defined as changes with a potential to lead to a change in the "intent of treatment," "treatment modality," "type or duration of treatment within a modality," or "the emphasis placed on a recommended modality [17]." The similarity of discrepancy rates between this study and ours is most likely attributable to the fact that both studies were performed in major referral centers with high volume of cancer patients, who often have more complicated pathology reports than the general referral patient population [6]. Pathologist practice patterns at referral cancer centers benefit from redundancy, the pathologist is provided the opportunity to review many examples of complicated cancer pathology in their daily routine practice.

Although numerous publications show the clinical benefits of implementing a pathology second review program when patients are referred for treatment from a different institution and despite the recommendations of the ADASP, second review by no means an uniformly adopted practice. The low, but persistent rate of interobserver

variation (diagnostic discrepancy) resulting in a clinically significant impact on patient care favors its routine use, and several large studies of interinstitutional pathology consultations in general pathology have reported major discordance rates of 1.4–9.0% [6,8,17–19].

Certain areas of breast pathology, specifically ductal proliferative lesions, are well known to be associated with a high rate of interobserver variability [20–21], and therefore it is not surprising that this group of lesions represented the single most common diagnostic category of discrepancy in our study. One also would expect relatively rare breast entities such as squamous cell carcinoma, primary sarcomas, or phyllodes tumors to represent hot spots for discrepancies. However, our study also revealed significant discrepancies in several unexpected groups of lesions, including mucinous carcinomas, metaplastic carcinomas, and atypical vascular lesions (Table III). These changes in diagnoses frequently resulted in different treatment regimens. Moreover, less common (in the context of known breast cancer) but histologically recognizable lesions with well-defined criteria, such as metastatic neuroendocrine tumor from a gastrointestinal primary, were surprisingly included in our cohort of patients with misdiagnosed disease likely due to interpretation or cognitive error.

Another major group of discrepant diagnoses (such as stromal invasion or positive lymph nodes) was considered to result from the original pathologist overlooking the diagnostic area (errors in oversight) (Figs. 1–3). As opposed to the areas of discrepancy described previously (which are considered to be either inherently very subjective and therefore prone to discordance, or rare and therefore likely to be misdiagnosed), errors in oversight can happen in any practice setting and by any pathologist, with or without expertise in the field of breast pathology. In fact second review of cases by a pathologist in the very same working group has been reported to catch such errors [22–24], but adoption of a policy requiring review of every single case by two pathologists is not practical or recommended in routine practice [25]. Considering these potential problems, it appears reasonable to at least review cases that have been referred from another institution most likely because of clinical complexity or necessity of some sort of major therapeutic procedure.

Fifty patients in this current study had a clinically significant change in biomarker expression profile from hormone receptor positive to negative or the converse or presence of Her2 over expression to absence of Her2 over expression. The implications of this change are most serious, as therapeutic decisions often rest on biomarker expression profiles. Plausible explanations of immunohistochemcial discrepancies include not following adequate staining protocols or using appropriate scoring systems. It is likely that prognostic and predictive immunohistochemical errors will decrease as labs follow proficiency testing recommended for both the IHC lab as well as individual pathologists [26–28].

Routine second review of pathology material is costly in terms of pathologist time, and few insurance policies pay for pathology second opinions. However, studies have shown that it can reduce healthcare costs by preventing inappropriate therapy [24–25], especially when subspecialist pathologists who have more experience in recognizing/categorizing disease entities are responsible for reviewing the cases. If reviewing all cases were not feasible in a busy referral setting because of logistical or financial constraints, it would be very beneficial to review cases in at least certain subgroups of patients in which second review has a higher likelihood of resulting in a significant change in therapy. A policy of selective review of cases before recommending a final treatment plan has been proven recently to be very effective in patients with node-negative breast cancer or ductal carcinoma in situ [29]. In a recent study with results similar to ours, Kennecke et al., reviewed the pathology of 405 patients with node negative breast cancer, documented pathology changes in 20% (81 patients). The most frequent changed elements in the study were tumor grade (40%), and lymphovascular

TABLE III. Breast Pathology Cases Downgraded Upon Second Review

Breast Pathology cases Downgraded Upon Second Review	Number (N = 20)
Ductal carcinoma in situ changed to atypical ductal hyperplasia	5
Atypical ductal hyperplasia changed to fibrocystic changes	4
Invasive ductal carcinoma changed to ductal carcinoma in situ	2
Lobular carcinoma in situ changed to benign breast	1
Phyllodes tumor changed to fibroadenoma (on resection)	1
Adenomyoepithelioma changed to sclerosingadenosis	1
Metastasis in lymph node changed to parenchymal breast carcinoma	1
Metastasis in axillary soft tissue changed to parenchymal breast carcinoma	1
Micrometastasis changed to isolated tumor cells (made the disease node negative)	1
Residual carcinoma in mastectomy specimen changed to benign breast tissue	1
"Angiosarcomatous" component in metaplastic carcinoma changed to benign vessels	1
"Extensive myxoidliposarcomatous" component in malignant phyllodes tumor changed to myxoid stromal overgrowth	1

TABLE IV. Subset of Breast Pathology Cases With a Significant Change Within the Category of Histological Diagnosis

Change on Second Review	Number (N = 15)
Invasive ductal carcinoma changed to metaplastic carcinoma	3
Phyllodes tumor changed to metaplastic carcinoma	2
Mucinous carcinoma changed to high-grade invasive ductal carcinoma	2
Inflammatory myofibroblastic tumor changed to low-grade primary sarcoma	1
Invasive ductal carcinoma changed to invasive squamous cell carcinoma	1
Telangiectasia changed to atypical vascular proliferation	1
Recurrent invasive ductal carcinoma changed to myoepithelioma "of probably adnexal origin"	1
Benign fibrosis changed to metaplastic carcinoma	1
Metastatic breast carcinoma changed to mediastinal cyst	1
Metastatic breast carcinoma changed to metastatic low-grade neuroendocrine tumor to the mesentery	1
Invasive ductal carcinoma with focal adenoid cystic carcinoma pattern changed to lobular carcinoma in situ involving fibroadenoma with foci of collagenous spherulosis	1

TABLE V. Subset of Cases With a Significant Change in Diagnosis in the Category of Biomarker Profile[a]

Biomarker Expression	Number of Patients	NumberConfirmed onRepeat IHC[b]/FISH
ER− to ER+	19	
ER+ to ER−	5	8
PR− to PR+	20	
PR+ to PR−	12	4
Her 2− to Her 2+	1	1
Her2+ to Her 2−	3	2

[a]Some cases had more than one discordance in biomarker expression.
[b]IHC, Immunohistochemical analysis; FISH, fluorescent in situ hybridization; ER, estrogen receptor; PR, progesterone receptor; + positive; − negative.

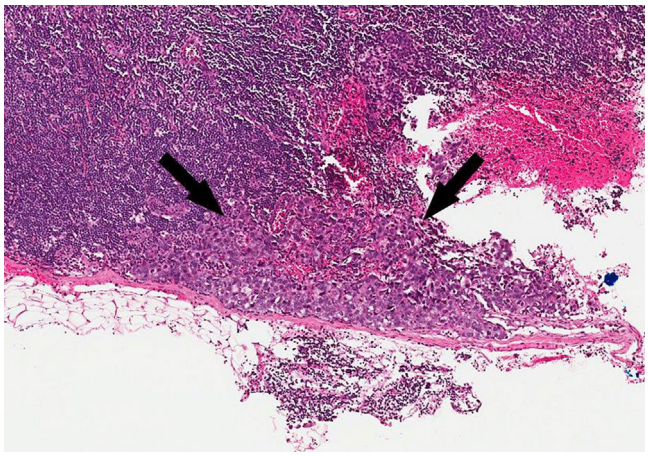

Fig. 1. Metastatic carcinoma to an axillary lymph node, identified in second review. H &E × 40.

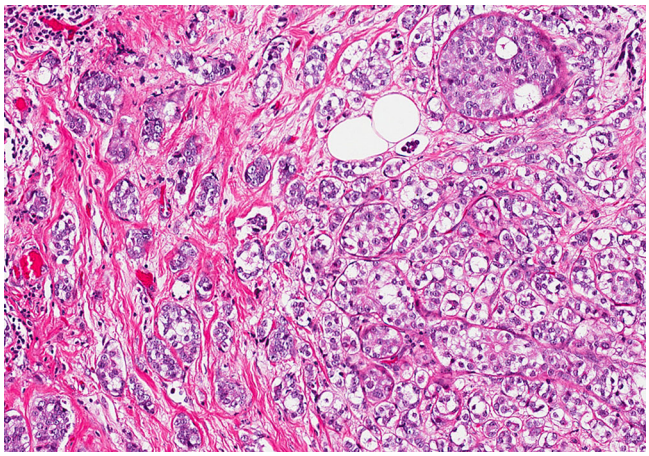

Fig. 2. Invasive ductal carcinoma originally diagnosed as DCIS. H &E × 40.

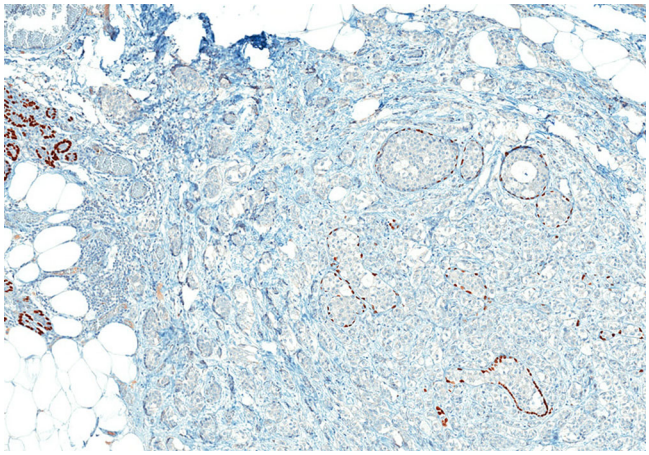

Fig. 3. Invasive ductal carcinoma originally diagnosed as DCIS. P63 immunohistochemical stain shows preservation of myoepithelial cells around DCIS and absence of myoepithelial cell staining in the invasive component.

(26%), nodal (15%), and margin (12%) status. With results similar to the current study, the authors found that the change in diagnoses resulted in treatment modifications in a subset of their patients [29].

Overall, several studies have shown that even though the cost of second review can be substantial, it is still relatively low in comparison to the cost of inappropriate therapy and or additional diagnostic imaging the patient may unnecessarily undergo [5,7,8].

CONCLUSION

Our results confirm the importance of second review of breast pathology in a referral center setting with a high volume of cancer patients, not only in the setting of complicated/unusual cases but also through capturing uncomplicated but simply overlooked diagnostic errors. Our results also highlight the effectiveness of second review as a way of ensuring standardized inclusion of critical diagnostic information in the final pathology reports, thereby improving patient care by providing clinicians with the elements necessary to establish a course of treatment or recommend a patent for an eligible clinical trial.

Importantly, the pathologist performing the second review should report the changed findings without hubris, but as a result of a second thorough review. It is beneficial to communicate that it is not uncommon to overlook subtle findings in pathology that may alter patient care. For the patient who is not seeking transfer of care, second targeted review of unusual and borderline cases should be performed by pathologists within the same practice. We agree with the findings of Marco et al. that significant improvement in the agreement among pathologist assessing breast tissues can be achieved by careful histologic review, following standardized criteria, and observing recommendations for immunohistochemical analysis [26].

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