



Original Contribution

Differences in immunohistochemistry utilization by general and breast subspecialty pathologists at a large academic institution

Margaret L. Compton^{a,*}, Melissa Hogan^b, Emily S. Reisenbichler^{b,c}^a Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, 1161 21st Avenue South, MCN CC3322, Nashville, TN 37232-2561, United States of America^b Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, United States of America^c Department of Pathology, Yale-New Haven Health System, United States of America

A B S T R A C T

Objectives: Immunohistochemistry (IHC) can be a useful adjunct in diagnostic breast pathology, but best practices have not been clearly established. We sought to compare the patterns of p63 utilization between general pathologists (GP) and subspecialized breast pathologists (BP), analyze diagnostic discrepancy rates, and identify types of lesions requiring immunohistochemistry.

Methods: The pathology database was searched over 6-year period to identify breast needle core biopsy cases utilizing p63 and subsequent excision results.

Results: P63 was ordered more frequently by BP (2.3% of cores) compared to GP (1.1% of cores, $p = 0.0005$). The most frequent utilization of p63 by GP for benign lesions (44.0%) followed by invasive carcinomas (36.0%) while BP most frequently ordered p63 on invasive carcinomas (49.5%) and DCIS (26.6%).

Conclusions: While IHC use may be thought to be most helpful to those with less experience or knowledge in breast pathology, these results suggest that utilization is increased with subspecialty training.

1. Objective

In recent years, many large academic centers have transitioned to a subspecialty sign out model for anatomic pathology. The proposed advantages to a subspecialized system include decreased turnaround time, decreased use of immunohistochemistry (IHC), improved resident education, improved communication with subspecialized clinical teams, and standardization of pathology reports [1–5]. However, only some of these advantages have been borne out in practice. While utilization studies have demonstrated an overall decreased rate of diagnostic discrepancies, there was no difference in turnaround time or in rates of extramural consultation after transition to a subspecialty signout model [5,6]. Furthermore, the effect of subspecialization on rates of IHC usage demonstrate mixed results, with some authors finding increased utilization with subspecialization and others finding a reduction in IHC ordering [7–12].

The impact of subspecialization on IHC usage in diagnostic breast pathology has not previously been studied. While hematoxylin and eosin (H&E) morphology is the gold standard for diagnostic breast pathology, immunohistochemistry (IHC) can be employed to aid in diagnostically challenging cases. Myoepithelial markers, including p63, calponin, and smooth muscle actin, may be particularly helpful in distinguishing invasive carcinoma from ductal carcinoma in situ (DCIS) and benign mimics of invasion [13,14]. However, there are several

disadvantages to the routine use of IHC, including increased cost, longer turnaround time, and misinterpretation of the immunostain (for example, a proliferative lesion with attenuation of the basal cell layer). We hypothesized that those less familiar with breast pathology may utilize IHC more frequently than those with subspecialty breast training, as they may want to increase diagnostic certainty and may not be aware of the interpretive pitfalls of individual IHC antibodies. We sought to compare p63 use in breast biopsies by general and breast pathologists, with an emphasis on which specific types of lesions required IHC for diagnosis.

2. Methods

The study site is a National Comprehensive Cancer Network affiliate, holds a certificate from the National Accreditation Program for Breast Centers (NAPBC), and is designated as a Breast Imaging Center of Excellence. In January 2012, the department of surgical pathology began to transition to a subspecialized signout system for breast pathology. After obtaining institutional review board approval, consecutive breast needle core biopsies obtained between July 1, 2008 and June 30, 2015 were identified through a search of the laboratory information system (Cerner, Copath). The pathology reports were reviewed for each case, and the pathologist rendering the diagnosis was noted. Pathologists were classified as either a subspecialized breast

* Corresponding author.

E-mail address: Margaret.L.Compton@vumc.org (M.L. Compton).

Table 1

Specific diagnoses within each diagnostic category. Within the benign diagnostic category, some biopsies fall under multiple subcategories (e.g. atypical ductal hyperplasia involving a papilloma).

Biopsy diagnosis	General pathologists	Breast pathologists
Invasive mammary carcinoma	9	52
No special type	6	51
Tubular	3	1
DCIS	1	21
Conventional	0	9
Involving sclerosing adenosis	1	4
Involving a papilloma	0	7
Involving a radial scar	0	1
Other malignant	4	4
Metastasis	1	1
Sarcoma	2	1
Malignant phyllodes		1
Metaplastic carcinoma	1	1
Benign	11	28
Myofibroblastoma/myofibroblastic proliferation	1	1
Fibroepithelial lesion	3	5
Adenosis/sclerosing adenosis	3	7
Radial scar/complex sclerosing lesion	1	4
Papilloma	0	7
Fibromatosis	1	1
Fat Necrosis	2	1
Collagenous spherulosis	0	1
Atypical ductal hyperplasia	1	5
Atrophy	0	1

pathologist or as general pathologist. Breast pathologists were defined as 1.) anyone with formal subspecialty training in breast pathology or 2.) senior faculty members without specific fellowship training who have shown expertise in diagnostic breast pathology with extensive publication within the subspecialty for at least 10 years. At the time of our study, the available myoepithelial markers at our institution were p63 and smooth muscle actin. Most pathologists at our institution used p63 as the sole myoepithelial marker, and rarely used it in a panel with smooth muscle actin. Smooth muscle actin was not used as an individual marker. Therefore, to compare rates of immunohistochemical usage, we chose to study p63 ordering practices. The use of p63 was documented for each case. For purposes of statistical analysis, diagnoses were categorized as invasive mammary carcinoma (IMC), “other” malignancies, ductal carcinoma in situ (DCIS), and benign lesions. The specific diagnostic entities in each category are summarized in Table 1. Clinical and radiologic information was collected for each case. When available, pathology reports for follow-up excision specimens were also reviewed. A search was also performed to identify all cases that had a corrected or amended report. Statistical analysis was performed using Fisher’s exact test.

3. Results

A total of 6671 breast needle core biopsies were reviewed during the study period and p63 was ordered on 130 cases (1.9%). Over the study period, there were five breast pathologists and 12 general pathologists who signed out breast needle core biopsies. p63 was ordered more frequently by breast pathologists (2.3% of cores) compared to general pathologists (1.1% of cores, $p = 0.0005$). Results are summarized in Table 2. There was substantial individual variation in ordering practices among individual pathologists, with rates among breast pathologists ranging from 0.82% to 4.5%, and rates among general pathologists ranging from 0% to 3.7%.

The most frequent utilization of p63 by general pathologists was on benign lesions (44%) followed by invasive carcinomas (36%) while

Table 2

Summary of needle core biopsy diagnoses as reviewed by general pathologists and breast pathologists. Abbreviation: DCIS, Ductal Carcinoma in Situ; IMC, Invasive Mammary Carcinoma.

Summary of needle core biopsies	General pathologists	Breast pathologists	P value
All cores reviewed	2158	4513	
All p63 ordered	25 (1.1%)	105 (2.3%)	$p = 0.0005^*$
Biopsy Diagnosis:			
DCIS	1 (4%)	21 (20%)	0.0736
IMC	9 (36%)	52 (49.5%)	0.2685
Other malignant	4 (16%)	4 (3.8%)	0.044*
Benign	11 (44%)	28 (26.6%)	0.0963

breast pathologists most frequently ordered p63 on invasive carcinomas (49.5%) followed by benign lesions (26.6%). Although breast pathologists ordered p63 on a higher overall percentage of cases, there was no statistically significant difference in the distribution of ordering patterns based on the type of pathology present, except for a higher percentage of “other” malignancies, evaluated by general pathologists (16% versus 3.8% for breast pathologists).

Of the 130 cases with p63 immunohistochemistry, follow-up excision data were available for 95 patients (73.1% of total cases, 87.9% of malignant cases, 38.5% of benign cases). There was no significant difference in biopsy/excision concordance rates between breast pathologists and general pathologists (81.0% versus 88.0%, $p = 0.41$). The discordant cases are summarized in Table 3. The most frequent reason for discordance was due to sampling. 10 cases (7.7%) were negative for carcinoma on biopsy, but had an unsampled invasive component on excision, while 7 cases (5.3%) had invasive tumor on biopsy, but no residual tumor on excision. One case had unsampled DCIS within the excision specimen. Another reason for discordant biopsy/excision diagnoses was the ability to further classify tumors once more tissue was available (17.4%, $n = 4$). Examples of tumor types in this category included malignant phyllodes tumor (biopsy diagnosis: fibroblastic proliferation), metaplastic carcinoma (malignant spindle cell neoplasm), secretory carcinoma (invasive mammary carcinoma with apocrine features) and low grade metaplastic carcinoma (low grade spindle cell lesion with fat necrosis).

Two corrected biopsy reports were issued during the study period, both of which were on cases signed out by breast subspecialized pathologists. One case was on a biopsy on which p63 immunohistochemistry was performed. The presence of invasive carcinoma initially could not be definitively determined on biopsy due to crush artifact; however, on retrospective review of the biopsy in conjunction with the excision specimen, it was felt that invasive carcinoma was present on the initial biopsy specimen. The other corrected report was on a case that did not have p63 immunohistochemistry, in which a correction was issued to revise the combined histologic grade of an invasive mammary carcinoma after consensus review of the case. There was no clinical impact from either discrepancy, since appropriate surgical management and sentinel lymph node sampling was performed in both cases.

4. Conclusions

We demonstrate that, contrary to our initial assumption, subspecialized breast pathologists have a higher rate of p63 utilization when compared to general pathologists (2.3% of cores versus 1.1% of cores, $p = 0.0005$). We also show that, although not statistically significant, breast pathologists tended to order p63 more frequently on invasive carcinomas, while general pathologists used p63 more frequently on benign lesions. Finally, despite differences in IHC utilization, there was not a significant difference in biopsy/excision

Table 3
Non-concordant biopsy/resection specimens. Abbreviations: DCIS, Ductal Carcinoma in Situ.

	General pathologist (n = 3)	Breast pathologist (n = 20)
Further classification of lesion	1	3
No residual invasive carcinoma in excision	2	5
Invasive component only present on excision	–	10
Invasive carcinoma present on excision, identified retrospectively on biopsy	–	1
DCIS only present on excision	–	1

concordance rates between breast pathologists and general pathologists.

There are inherent limitations to our study due to the retrospective design, chief among which is that there is no way to ascertain the thought process that each pathologist went through when deciding to order immunohistochemistry on a given case. While it appeared that the most p63 was most frequently used for establishing the presence or absence of a basal layer, p63 was also used for other applications, including for metaplastic carcinomas and for establishing tissue of origin and/or differentiation for malignancies that were not of breast epithelial origin. Another potential use of immunohistochemistry may be as an educational tool for a more experienced pathologist to highlight features to residents or fellows; therefore, there may be the potential that pathologists who are working with trainees may order more stains than those without a trainee. In our institution, all biopsies are pre-viewed by surgical pathology fellows, so we do not feel that trainee involvement is a significant source of bias in our study since both general and breast pathologists would always be working with a trainee, except in rare cases of trainee illness or other miscellaneous absences. Furthermore, additional stains that are ordered for purely educational purposes are coded separately from immunostains ordered for diagnostic purposes, and therefore would not be captured by our laboratory information system search. Another potential limitation is that, because less than half of the patients with benign diagnoses on core biopsy underwent subsequent excision, it is not possible to evaluate diagnostic accuracy on these specimens with regard to underdiagnosis of malignancy by comparison to the excision specimen. However, given that there have been no corrected reports issued for these patients in the subsequent four years or more since the initial biopsy, we feel as though we can reliably exclude underdiagnosis in these cases.

Despite the above limitations, the results of our study demonstrate that there is individual variability in IHC utilization, with breast subspecialized pathologists using p63 immunohistochemistry at a rate of three times that of their general pathology colleagues. We have also seen an overall trend in increasing p63 utilization at our institution, as demonstrated in Fig. 1. Besides variations in individual practice habits, there are several possible reasons that breast pathologists may be more likely than general pathologists to utilize immunohistochemistry in their practices. Subspecialty trained pathologists may be more aware of benign mimics of breast cancer and seek to exclude these diagnoses. In addition, there may be more realization of the importance of recognizing a component of DCIS for the purpose of excluding non-invasive areas when analyzing hormone receptor and HER2 status. Concern for litigation may also prompt the use of immunohistochemistry. Although pathologists are rarely named in breast cancer litigation suits and the overall rates of breast pathology malpractice claims have declined almost six-fold from 1995 to 2010, 60% of subspecialty trained breast pathologists reported ordering additional IHC tests due to litigation concerns [15–17].

Previous studies comparing IHC utilization patterns in different organ systems among expert and general pathologists have demonstrated variable and, in some cases, conflicting results. For evaluation of cervical biopsies, one series found that subspecialty trained cytopathologists and gynecologic pathologists used p16 more frequently than non-subspecialized pathologists, and had better cytohistologic

concordance [9]. Another study found that, while pathologists with more years of practice experience ordered fewer stains on gynecologic specimens, subspecialty training in gynecologic pathology did not have an impact on the rate of IHC utilization [7]. For prostate biopsies, Al Diffalha et al. found that subspecialized genitourinary pathologists had higher rates of immunohistochemistry usage, whereas in their series Flourde et al found that genitourinary pathologists ordered significantly fewer immunostains on prostate biopsies than did general pathologists [11,12]. Practice setting also appears to play a role in immunohistochemistry utilization, with significantly higher rates in commercial labs and private groups as compared to academic medical centers [18]. However, there is even significant variation within similar settings: in an analysis of immunohistochemical usage on gynecologic specimens at two academic medical centers, the rate at one academic medical center was almost twice that of the other academic medical center [8]. Overall, practice habits regarding the use of immunohistochemistry appear to be highly variable, with factors such as pathologist experience, subspecialty training, and practice setting potentially exerting an influence on individual practice habits.

There are some notable disadvantages to overutilization of immunohistochemistry, specifically an increase in cost and turn-around time and the potential for technical issues and misinterpretation. A specific pitfall in breast pathology is the reduction or loss of myoepithelial marker expression in benign sclerosing lesions and high grade DCIS, which may lead to a misdiagnosis of invasive carcinoma [19]. Another potential disadvantage is that, in a subset of cases, the diagnostic breast biopsy contains the largest extent of invasive or in-situ carcinoma, making it vital to preserve tissue for hormone receptor testing, HER2 analysis, and potential molecular testing [20,21]. In our study, we have 7 cases in which there was no residual invasive carcinoma present in the excision specimen, but we did not find that the use of p63 depleted diagnostic tissue and precluded ancillary testing, as only one case of microinvasive carcinoma did not have adequate tumor cells for ancillary testing. Despite potential disadvantages, immunohistochemistry can be a very helpful adjunct in challenging cases. Additional immunohistochemistry may change the diagnosis in between 11 and 18.3% of cases and, when compared to other diagnostic medical tests, immunohistochemistry has a very favorable cost/benefit ratio [10,22–23]. Given the wide variability in practice habits between different pathologists, further study may be required to help determine evidence based guidelines for when immunohistochemistry is appropriate.

In summary, we found that subspecialty trained breast pathologists ordered p63 on breast core biopsies more frequently than general pathologists. Breast pathologists appeared to use IHC more often in the evaluation of invasive carcinomas, whereas general pathologists used p63 more frequently on benign lesions. Due to the low overall rates of discrepancy, immunohistochemical utilization and subspecialty training did not appear to have an overall impact on diagnostic accuracy. However, given the variability in practice habits, further study of IHC ordering practices may be required in order to establish evidence based best practice guidelines.

Funding sources

None.

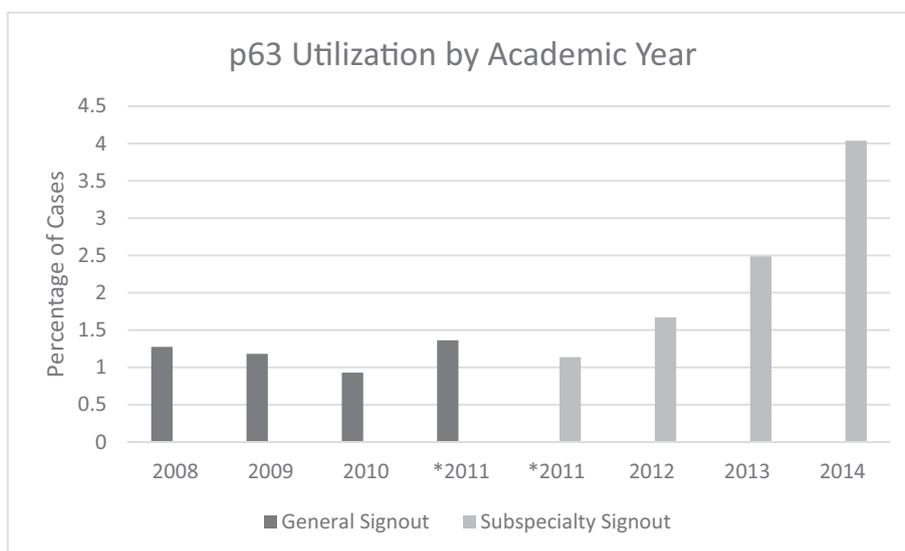


Fig. 1. Trend of p63 utilization by academic year. *Note that the academic year starting in 2011 is divided into pre- and post-subspecialization groups, as the institution transitioned to subspecialty biopsy signout midway through the academic year.

Declaration of competing interest

None.

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