Biotechnic & Histochemistry

ISSN: 1052-0295 (Print) 1473-7760 (Online) Journal homepage: https://www.tandfonline.com/loi/ibih20

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To cite this article: T. Bonacho, F. Rodrigues & J. Liberal (2019): Immunohistochemistry for diagnosis and prognosis of breast cancer: a review, Biotechnic & Histochemistry, DOI: 10.1080/10520295.2019.1651901

To link to this article: https://doi.org/10.1080/10520295.2019.1651901

Published online: 10 Sep 2019.

BIOTECHNIC & HISTOCHEMISTRY
https://doi.org/10.1080/10520295.2019.1651901

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Immunohistochemistry for diagnosis and prognosis of breast cancer: a review

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ABSTRACT

Breast cancer is the most prevalent malignant tumor and main oncologic cause of mortality in women. Although most diagnosis of breast pathology is accomplished using hematoxylin and eosin stained sections, some cases require immunohistochemistry for proper evaluation. We investigated the latter cases including distinctions between ductal and lobular carcinoma, in situ and invasive carcinoma, typical ductal hyperplasia and atypical ductal hyperplasia/ductal carcinoma in situ, papillary and spindle cell lesion assessment, metastasis evaluation, and assessment of prognostic and therapy markers. E-cadherin is used to differentiate ductal and lobular carcinoma; 34βE12, CK8, p120 catenin and β-catenin also produce consistent results. Myoepithelial cell (MEC) stains are used to evaluate in situ and invasive carcinoma; calponin, smooth muscle myosin heavy chain and p63 are sensitive/specific markers. 34βE12 and CK5/6 are positive in ductal hyperplasia, which enables its differentiation from atypical ductal hyperplasia and ductal carcinoma in situ. CK 5/6, ER and MEC markers are consistent options for evaluating papillary lesions. Spindle cell lesions can be assessed using β-catenin, SMA, CD34, p63, CKs and hormone receptors. It is important to differentiate primary carcinomas from metastases; the most commonly used markers to identify breast origin include mammaglobin, GCDFP-15, GATA3 and ER, although none of these is completely sensitive or specific. Immunohistochemistry can be used to evaluate central prognostic and predictive factors including molecular subtypes, HER2, hormone receptors, proliferation markers (Ki-67) and lymph-vascular invasion markers including ERG, CD31, CD34, factor VIII and podoplanin. Owing to the complexity of mammary lesions, diagnosis also depends on each particular situation, evaluation of cytological characteristics revealed by immunochemistry and correlation with histological findings.

KEYWORDS

Breast; cancer; diagnosis; immunohistochemistry; prognosis; review

Breast cancer is the most prevalent malignant tumor and the main oncologic cause of mortality in women in both developed and developing countries (Jemal et al. 2011). Risk factors that contribute to high incidence include unhealthy lifestyle, long time fertility, use of hormone based contraceptives, hormone replacement therapy, alcohol consumption, obesity after menopause and physical inactivity (Ghoncheh et al. 2016). Early diagnosis is vital for identifying high risk cases and providing the most appropriate treatment (Anothaisintawee et al. 2013).

Glandular and ductal breast tissue comprise three cell types: myoepithelial cells (MEC), basal cells and luminal cells. Each type expresses different protein subtypes, which are described in Table 1 (Lerwill 2004; Yeh I-T 2008; Liu 2014; Zaha 2014).

Immunohistochemistry (IHC) for diagnosis

Ductal carcinoma vs. lobular carcinoma

Most invasive and in situ ductal and lobular carcinomas are identified easily using hematoxylin and eosin (H & E) stained sections. Some cases exhibit ambiguous morphological features, however, and IHC can be helpful for classifying the cancer. Accurate pathological classification is vital from a therapeutic standpoint, because ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) are treated differently (Khazai and Rosa 2015; Peng et al. 2017).

The therapeutic goal for DCIS is to eradicate it by surgery and/or radiation, because it is a nonobligate precursor of invasive carcinoma (Gorringe et al. 2017). LCIS can be a risk factor for and a nonobligate precursor

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Table 1. Proteins expressed by different cell types in breast.

Myoepithelial cells
SMA, calponin, p63, S100, CD10, SMMHC, maspin, P-cadherin, WT1 and basal types CKs (CK5/6, CK14, CK17)
Luminal cells
CK 7, CK8, CK18, CK19, EMA, MFGM, α-lactalbumin, ER, PR
Basal cells
CK5/6, CK14, CK17

SMA, smooth muscle actin; SMMHC, smooth muscle myosin heavy chain; WT1, Wilm's tumor 1 protein; CK, cytokeratin; EMA, epithelial membrane antigen; MFGM, milk fat globule membrane antigen; ER, estrogen receptor; PR, progesterone.

of invasive carcinoma. Management is controversial and depends on the characteristics of each case, but long term clinical follow-up, with or without chemoprophylaxis, usually is recommended (Lakhani et al. 2012; Ginter and D'Alfonso 2017). Despite being biologically, pathologically and clinically different, invasive lobular and ductal carcinomas are treated similarly owing to prognostic and predictive factors (Jacobs et al. 2015).

E-cadherin is the most common marker for differentiating ductal and lobular carcinomas. For the majority of ductal carcinomas, E-cadherin exhibits membrane staining. By contrast, most lobular carcinomas exhibit complete loss of membrane E-cadherin expression (Acs et al. 2001; Dabbs et al. 2007a; Singhai et al. 2011; Li et al. 2014), although aberrant staining may be found in approximately 10–16% of cases (Lakhani et al. 2012).

For high molecular weight cytokeratin (HMWCK), 34βE12 can be used together with E-cadherin, especially in cases where E-cadherin staining is inconclusive. Bratthauer et al. (2002) reported perinuclear cytoplasmic staining in lobular neoplastic cases; immunostaining was absent or reduced in ductal neoplastic cases. Basal ductal carcinoma was the exception; this was positive for 34βE12 (Thike et al. 2010).

Despite being positive in ductal and lobular carcinomas, CK8 also can be used, because the staining pattern is different. Lehr et al. (2000) reported predominantly peripheral cytoplasmic staining in ductal carcinoma in addition to molding of adjacent tumor cells to each other to form tumor cell clusters. Perinuclear staining was observed in cases of lobular carcinoma.

p120 Catenin exhibits intense membrane staining in ductal carcinoma and strong diffuse cytoplasmic staining in lobular carcinoma (Dabbs et al. 2007a, 2007b; Li et al. 2014). β-Catenin, a membrane stain with or without cytoplasmic expression, was observed in ductal carcinoma, whereas lobular carcinoma exhibited no membrane staining and a granular cytoplasmic pattern (Dabbs et al. 2007a; Karabacak et al. 2011).

In situ carcinoma vs. invasive carcinoma

In situ carcinoma is defined as proliferation of malignant epithelial cells that are restrained by the basement membrane (Ward et al. 2015). By contrast, invasive carcinoma penetrates the basement membrane and invades the surrounding stroma (Zhao et al. 2014). Histologically, the main characteristic of invasion is the lack of MECs around the lesion (Rosen 2008). Detection of presence or absence of MECs in H & E stained sections can be challenging; therefore, IHC is a valuable tool for detecting small foci of invasion (Liu 2014). Among the MEC markers listed above, calponin, smooth muscle myosin heavy chain (SMMHC) and p63 are the most specific and sensitive. Calponin and SMMHC exhibit a linear cytoplasmic pattern with gaps in MECs in in situ carcinomas; invasive carcinomas are characterized by absence of expression for calponin and SMMHC. P63 immunostaining for in situ carcinoma is characterized by a linear dot-like nuclear pattern, focally discontinuous, in MECs; expression for p63 is absent in invasive carcinomas. The combination of calponin, SMMHC and p63 produces cytoplasmic and nuclear staining and can be a valuable option (Yeh I-T 2008; Liu 2014). These markers also can be useful for differential diagnosis of invasive carcinoma from other conditions that mimic infiltration, such as sclerosing adenosis and radial scars (Liu 2014; Zaha 2014). By contrast, other uncertain situations may occur when certain invasive carcinomas resemble carcinoma in situ, such as solid papillary and cribriform carcinomas (Lerwill 2004). Another marker, p75 neurotrophin receptor, exhibits immunoreactivity similar to SMMHC and p63; it is consistently positive for MECs (Popnikolov et al. 2005).

Usual ductal hyperplasia (UDH) vs. atypical ductal hyperplasia (ADH) and DCIS

Accurate classification of UDH (benign lesion), ADH (borderline lesion) and DCIS (pre-invasive lesion) is important, because an excision follows in ADH and DCIS cases, while clinical follow-up is suitable for patients with UDH (Zhao et al. 2014). Distinction generally can be made using H & E stained sections due to the distinct morphological features of each. UDH has greater cell heterogeneity with nuclear overlapping, indistinct cell margins and variations of cell shape and size. By contrast, ADH and DCIS exhibit a uniform cell population with distinct cell margins organized around punched out spaces (Dirbas 2011).

In cases of uncertainty, IHC can give greater emphasis to the differentiating traits.

Application of a breast marker cocktail consisting of basal cell, MEC and luminal cell markers produces a mosaic staining pattern in cases of UDH, which reflects the polymorphic proliferation characteristics of this condition. No immunostaining of basal/myoepithelial markers is observed in ADH and DCIS, because these markers exhibit clonal proliferation of luminal cells (Abdel-Fatah et al. 2008). Otterbach et al. (2000) reported that CK 5/6 produced strong expression in 87.6% of UDH cases. Lack of expression was observed in 47.4% of ADH cases, while 43.1% exhibited only a few immunopositive cells. Only 3.7% of DCIS cases exhibited CK 5/6 staining. Moinfar et al. (1999) reported a strong reaction for 34βE12 in all UDH cases by contrast to absent to weak staining in 80 and 90% of ADH and DCIS cases, respectively. Lacroix-Triki et al. (2003) reported that CK5/6 exhibits less reactivity than 34βE12 in DCIS cases; therefore, a clearer interpretation may be achieved using the latter marker for differential diagnosis.

Estrogen receptors (ER) and progesterone receptors (PR), exhibit scattered nuclear immunostaining in UDH cases, while a diffuse nuclear pattern is observed in ADH/DCIS cases (Lin et al. 2015). Martinez et al. (2016) reported that use of ER together with CK5 increased the sensitivity of the differentiation of UDH from ADH and DCIS compared to using these two markers separately.

Evaluation of papillary lesions

Fibrovascular cores that support epithelial proliferation are characteristic of papillary lesions of the breast (Rakha and Ellis 2018). This heterogeneous group of neoplasms includes benign intraductal papilloma (IDP), atypical papilloma, IDP with DCIS, papillary DCIS, papillary carcinoma variants – encapsulated papillary carcinoma (EPC) and solid papillary carcinoma (SPC). Recognition of papillary architecture generally is clear, but accurate subclassification frequently can be challenging (Jorns 2016). The most commonly used immunostains include HMWCKs (CK5/6, CK14, 34βE12), MEC markers (p63, SMMHC, SMA, CK14, CD10, S100, calponin), neuroendocrine markers (chromogranin, synaptophysin) and hormone receptors (HR) ER and PR (Otsuki et al. 2007; Kuroda et al. 2014; Tse et al. 2014; Wei 2016).

One of the difficulties with diagnosis of papillary lesions using H & E staining is discrimination of IDP from atypical papilloma. IDP is a benign, confined proliferation with fibrovascular cores surrounded by an internal myoepithelial layer and an external epithelial layer. The epithelium can exhibit UDH and/or apocrine metaplasia (Jorns 2016). There is no uniform definition for atypical papilloma. The term, atypical papilloma, generally is used when a case fails to meet DCIS criteria or to indicate the possible presence of a neoplastic component in a papilloma (Agoumi et al. 2016). Diagnostic problems may occur when there is an IDP with UDH, which may cause uncertainty in cases of atypia (Simpson et al. 2005). CK 5/6 and ER immunostaining can be used to clarify the pathology. CK 5/6 is not expressed in cases of atypia, which distinguishes it from the strong staining pattern of UDH (Nofech-mozes et al. 2008). ER exhibits a strong diffuse expression in atypical papilloma, whereas weaker staining is observed with IDP with UDH (Grin et al. 2009). One possible problem with interpretation is non-expression of CK 5/6 in IDP apocrine metaplasia, which may cause diagnostic errors (Nofech-mozes et al. 2008).

The immunostaining patterns of CK5/6 and ER are equal; for atypical papilloma and IDP with DCIS, CK5/6 is unstained and ER is stained diffusely (Ichihara et al. 2007). Therefore, discrimination of atypical papilloma from IDP with DCIS should be based on the different sizes of the lesions. Atypical papilloma usually is < 0.3 cm, while IDP with DCIS generally is > 0.3 cm. IHC can be useful by accentuating the abnormal area to help determine the size of both lesions (Lakhani et al. 2012).

A distinctive feature of IDP with DCIS is the existence of recognizable benign cells, which contrasts with the malignant epithelium throughout the papillary DCIS and papillary carcinoma lesions. MEC markers stain within the papillae and at the periphery of the lesion in IDP with DCIS cases (Jorns 2016). On the other hand, papillary DCIS exhibits only peripheral expression (Tse et al. 2007). Although considered an in situ lesion, EPC generally lacks MECs within papillae; at the periphery, they are absent in > 85% of cases (Rakha et al. 2011). Some investigators have considered EPC a subtype of invasive carcinoma with good prognosis (Grabowski et al. 2008; Rakha et al. 2012) or a lesion in transition (Hill and Yeh 2005; Esposito et al. 2009). A diffuse ER staining pattern is observed for EPC, while CK5/6 is negative (Agoumi et al. 2016). SPC also is considered an in situ lesion. Absence of MECs within papillae is characteristic of this condition; at the periphery, they are absent in > 70% of cases (Rakha and Ellis 2018). Therefore, it has been suggested that SPC also represents a subtype of invasive carcinoma with a good prognosis (Jorns 2016). CK 5/6 also is negative for SPC; the neuroendocrine markers, chromogranin and synaptophysin, frequently are positive (Rabban et al. 2006; Otsuki et al. 2007).

IDP with abundant sclerosis can appear infiltrative and may lead to false diagnosis of invasion. Because the myoepithelium usually remains in the sclerotic foci of benign cases, MEC markers can be useful for

highlighting them (Mugler et al. 2007). Similarly, these markers can be used to detect invasion or pseudo-invasion in papillary DCIS, because they are absent in cases of true invasion (Tse et al. 2007). In papillary carcinomas, however, pseudo-invasion and true invasion can be difficult to distinguish in cases of dense sclerosis, and MEC markers are not useful, because they generally are not expressed in papillary and invasive carcinomas (Mugler et al. 2007; Dewar et al. 2011; Rakha et al. 2011).

Core needle biopsy commonly is used for diagnosis of papillary lesions. Diagnostic inaccuracy may occur, however, due to insufficient sampling, sample unsuitability or unclear histopathologic characteristics (Wen and Cheng 2013). Cases identified as nonmalignant may in fact be malignant; this has been reported at a rate of 15.7% (Wen and Cheng 2013). Overestimation also may occur, although less frequently, i.e., 5–10% (Tse 2017). Because surgical excision should be performed in cases of atypia/malignancy, whereas imaging follow-up is recommended for benign lesions, an accurate distinction is mandatory (Grin et al. 2009). The combined immunoprofile of CK5-low/ER-high is consistent with atypical/malignant lesions (specificity and sensitivity, 100 and 93%, respectively). CK5-high/ER-low profile is consistent with benign cases (specificity and sensitivity, 93 and 100%, respectively). Together with the morphological features, these profiles can be helpful for interpreting papillary lesions in core needle biopsy (Grin et al. 2009).

Evaluation of spindle cell lesions

Although myoepithelial and luminal cells can exhibit spindle shapes, spindle cell lesions of the breast generally refer to mesenchymal or mesenchymal-like cells that exhibit stretched and elongated cytoplasm (Tan and Sahin 2017). Spindle cell lesions include a wide spectrum of lesions ranging from low to high grade (Magro 2017). The most common low grade lesions include fibromatosis, benign and borderline phyllodes tumor, pseudoangiomatous stromal hyperplasia (PASH) and myofibroblastoma. Spindle cell metaplastic carcinoma and malignant phyllodes tumors are the most common high grade lesions (Charu and Cimino-Mathews 2017; Tay and Tan 2017).

Limited sampling by core needle biopsy together with overlapping morphological features among some lesions can cause diagnostic difficulties. In these cases, IHC may be a valuable tool (Rakha et al. 2016). Accurate diagnosis is vital owing to different management implications; for metaplastic carcinoma, neoadjuvant chemotherapy may be used, while in other lesions, such as myofibroblastoma and malignant phyllodes tumor, neoadjuvant chemotherapy plays no significant role (Charu and Cimino-Mathews 2017).

Fibromatosis is a benign fibroblastic and myofibroblastic proliferation characterized by long intersecting fascicles of spindle cells with wavy and elongated nuclei in collagenous stroma. Although this is a locally aggressive lesion, it does not metastasize (Tan and Sahin 2017). β-Catenin exhibits nuclear reactivity in 70–80% of cases (Abdelwahab et al. 2018), but lacks specificity; phyllodes tumor and spindle cell metaplastic carcinoma also are immunoreactive for this marker (Lacroix-Triki et al. 2010). Desmin and SMA may be expressed in fibromatosis (Hicks and Lester 2016; Tan and Sahin 2017). By contrast, CD31, CD34, CD99, CD117, BCL2, p63, S100, ER and CKs usually are absent (Bhat et al. 2015; Ashoor et al. 2017; Kuba et al. 2017).

PASH is a benign proliferation of myofibroblastic cells arranged in slit-like pseudovascular spaces lined by spindle shaped myofibroblasts (Virk and Khan 2010). This lesion stains strongly for CD34 (Drinka et al. 2012), although no staining occurs for other endothelial markers including CD31, factors VIII, XIIIa, ERG and von Willebrand (Abdelrahman et al. 2015; Krawczyk et al. 2016; Rosa et al. 2017). CD34 staining can be interpreted as endothelial differentiation, which can be a potential pitfall (Cheah et al. 2016). PASH also can be positive for SMA, BCL2, calponin, CD99, vimentin, actin, PR, ER and desmin (Zámečník 2014; Abdelrahman et al. 2015; Rafeek et al. 2017; Rebutini et al. 2017), although the last two exhibit weak focal staining (Bowman et al. 2012; Rebutini et al. 2017). Reactivity for S100 and CKs is absent (Drinka et al. 2012). Differential diagnoses that can be more doubtful include angiosarcoma and myofibroblastoma. Angiosarcoma can be distinguished using endothelial markers, because staining is observed, by contrast to PASH (Rebutini et al. 2017). In addition, angiosarcoma is unstained for calponin, desmin and actin (Tan and Sahin 2017). Unlike PASH, myofibroblastoma exhibits AR staining (Aytaç et al. 2015).

Myofibroblastoma is a benign myofibroblastic proliferation with a circumscribed border whose cells may exhibit spindle shaped to epithelioid morphology. Cells are arranged in parallel short fascicles interrupted by collagen fibers (Charu and Cimino-Mathews 2017; Tay and Tan 2017). Immunomarkers include CD34, desmin, vimentin, SMA, ER, PR, androgen receptor (AR) and others that can be expressed variably including BCL2, CD99, CD10, calponin and h-caldesmon (Uchoa et al. 2010; Aytaç et al. 2015; Dekate et al. 2015; Metry et al. 2016). Epithelial membrane antigen (EMA) expression occurs occasionally, although it is focal and weak (Howitt and Fletcher 2016). No staining appears for CKs, S100, E-cadherin, human

melanoma black-45 (HMB-45) and p63 (Dekate et al. 2015; Metry et al. 2016). Myofibroblastoma variants can exhibit a predominance of epithelioid cells and a pseudoinfiltrative pattern, which, in addition to HR staining and absence of E-cadherin staining, can lead to a misdiagnosis of invasive lobular carcinoma (Jing et al. 2017). Differentiation of myofibroblastoma from leiomyoma and low-grade myofibroblastic sarcoma may be necessary. Leiomyoma generally is positive for SMA, desmin and h-caldesmon, but not for CD34, BCL2 and CD99 (Dekate et al. 2015; Kafadar et al. 2017). Absence of CD34 and desmin expression is observed in low grade myofibroblastic sarcoma (Myong and Min 2016).

Phyllodes tumor is a fibroepithelial lesion that exhibits a neoplastic stromal component organized in a leaf-like pattern, and a benign appearing epithelial component. The tumor grade, i.e., benign, borderline or malignant, is based on histologic features including cellularity and atypia of the stroma, tumor border, malignant heterologous elements and mitotic activity (Cheah et al. 2016; Charu and Cimino-Mathews 2017). CD34 and BCL-2 immunostaining is present in the stromal cells of benign and borderline tumors, which helps differentiate it from metaplastic carcinoma (negative expression) (Moore and Lee 2001; Cimino-Mathews et al. 2014). Malignant tumors tend to be less reactive for CD34 than benign/borderline tumors; staining was 57 and 100%, respectively (Cimino-Mathews et al. 2014). In addition to the use of CD34, differentiation of phyllodes tumor from metaplastic carcinoma usually can be accomplished using p63 and a CKs panel owing to the immunostaining of metaplastic carcinoma and the absence of staining in phyllodes tumor; however, malignant tumors occasionally can be positive for both (Cimino-Mathews et al. 2014). Nuclear expression of β-catenin in 94% of benign cases and 57% of borderline/malignant cases has been reported (Lacroix-Triki et al. 2010). Staining for BCL2, ER and PR was reduced in cases of malignancy compared to borderline and benign cases (Moore and Lee 2001; Tse et al. 2002). Esposito et al. (2006) reported an endothelin 1 expression rate of 17% in malignant cases; 50% and 100% were observed for borderline and benign cases, respectively. The expression rates of CD117, Ki-67, CD10, EGFR, IMP3, pH3, p21 and p53 increase progressively according to the degree of malignancy (expression rate: benign cases < borderline cases < malignant cases) (Esposito et al. 2006; Tse et al. 2009; Ibrahim 2011; Korcheva et al. 2011; Noronha et al. 2011; Bellezza et al. 2016).

Spindle cell metaplastic carcinoma must be considered in the differential diagnosis of any spindle cell lesion of the breast. A predominant spindle cell morphology occurs throughout the lesion (Tan and Sahin 2017) and the degree of cytological atypia may range from mild to prominent pleomorphism. Microscopically, spindle cell metaplastic carcinoma typically is infiltrative (Cheah et al. 2016). The spindle cell metaplastic carcinoma pattern may include short or long fascicles arranged in a storiform or herringbone fashion. A mixed pattern also can occur (Charu and Cimino-Mathews 2017). A CK panel generally is applied to assess this condition, because use of single antibodies may produce only focal staining. The most commonly used antibodies include 34βE12, CK5/6, CK14, CK17 (HMWCKs), CK19, CAM5.2 (low molecular weight cytokeratins), AE1/AE3 and MNF116 (pan-cytokeratins); pan-cytokeratins and HMWCKs are among the most sensitive (Lin et al. 2017; Rakha et al. 2017). Koker et al. (2004) reported p63 staining in 86.7% of cases; however, malignant phyllodes tumor also can be stained occasionally (Cimino-Mathews et al. 2014). Lacroix-Triki et al. (2010) reported focal nuclear staining for β-catenin in 23% of cases. Cimino-Mathews et al. (2013) reported sry-related HMG-BOX gene 10 (SOX10) protein staining in 46% of cases, while all phyllodes tumors were negative. Snail was reported to be a sensitive marker for spindle cell metaplastic carcinoma, but exhibited low specificity; staining was observed also for PASH, myofibroblastoma and phyllodes tumor (Nassar et al. 2010). Other markers also can be expressed including S100, EGFR, SMA, vimentin, CD10 and maspin (Altaf et al. 2014; Rakha et al. 2017). ER, PR, human epidermal growth factor receptor 2 (HER2), BCL2 and CD34 usually exhibit no expression (Dunne et al. 2003; Carter et al. 2006; Pezzi et al. 2007; Cimino-Mathews et al. 2014).

Assessment of metastases

It is crucial to differentiate primary carcinomas from metastases, because different clinical management is involved. Differentiation often can be accomplished by morphology; however, histologic features can be ambiguous. The patient's clinical history and comparison with previous tumor slides may be useful, but these are not always available. IHC can be decisive for assessing the origin of the tumor (Bombonati and Lerwill 2012). Because no single marker is completely specific or sensitive, a panel of antibodies is recommended (Lakhani et al. 2012).

Metastasis to breast

Extramammary metastases to breast are rare and account for approximately 0.2–2% of all malignant breast tumors (Peng et al. 2017). In 70–80% of cases, the history of

neoplasia in breast is known; however, in the remaining cases, metastasis may be the initial sign of a disseminated neoplasm and it is in this context that IHC can be particularly useful (Lakhani et al. 2012). Because lymph node evaluation and breast surgery generally are not required for metastasis, it is vital to differentiate accurately metastasis from primary breast carcinoma. Lung adenocarcinoma, ovarian and gastric carcinomas, carcinoid tumor, melanoma and prostate carcinoma are among the most common extramammary metastases to breast (Hicks and Lester 2016).

An indication that metastasis may be present is the absence of circumscribed nests of cells and lack of ER, PR and HER2 staining (Zhao et al. 2014), but most of these cases are primary breast carcinomas (Hicks and Lester 2016). Possible immunohistochemical markers used for the cases described above with the respective percentages of staining are presented in Table 2 (Busam and Jungbluth 1999; Filie et al. 2002; Tot 2002; Kidwai et al. 2003; Werling et al. 2003; Chu and Weiss 2004; Dennis et al. 2005; O'Connell et al. 2005; Tornos et al. 2005; Cheng et al. 2006; Fritzsche et al. 2007; Sasaki et al. 2007; Nonaka et al. 2008; Ohsie et al. 2008; Striebel et al. 2008; Wang et al. 2009; Bishop et al. 2010; Gomez-Fernandez et al. 2010; Yang and Nonaka 2010; Shao et al. 2012; Whithaus et al. 2012; Ellis et al. 2013; Miettinen et al. 2014; Hicks and Lester 2016; Ren et al. 2018).

Metastasis from breast

Although breast metastases may occur in several locations, bone, lung, liver and brain are the most common sites; bone is the most frequent (Hicks and Lester 2016). Common breast specific markers used to evaluate tumors from unknown primary sources include mammaglobin, gross cystic disease fluid protein 15 (GCDFP-15), ER and GATA binding protein 3 (GATA3). Because none of these markers is completely sensitive or specific, it is important to recognize that the clinical context and tumor location, as well as the use of markers specific to other organs, are key factors for interpreting these breast markers and obtaining an accurate diagnosis (Gown et al. 2016).

Different patterns of spread have been observed according to the histological and molecular subtypes. Lobular carcinomas tend to metastasize to peritoneum, retroperitoneum, bone, bone marrow, gynecologic organs and the gastrointestinal tract; ductal carcinomas are more prone to involve lung and pleura (He et al. 2014; Inoue et al. 2017; Mathew et al. 2017). Regarding molecular subtypes, HR-/HER2- profile (basal-like) is associated with

Table 2. Immunohistochemical markers used to differentiate extramammary metastases from primary breast carcinoma with the respective percentages of positivity.

	Marker	Extramammary metastases positivity (%)	Primary breast carcinoma positivity (%)
Lung adenocarcinoma	Napsin	83	0
	TTF-1	60	0
	GCDFP-15	5	62
	Mammaglobin	0	72
	ER	8	81
	GATA3	8	> 90
Ovarian carcinoma	WT1	76	2
	PAX-8	87	0
	CA 125	90	16
	GATA3	6	> 90
Gastric carcinoma	CK20	57	5
	CDX2	70	0
	GCDFP-15	0	62
	Mammaglobin	0	72
	GATA3	0	> 90
	ER	0	81
Carcinoid tumor	Synaptophysin	95	15
	Chromogranin	85	20
	GCDFP-15	5	62
	CK7	20	92
	ER	10	81
Melanoma	HMB-45	81	0
	S100	98	30
	Melan-A	81	0
	GATA3	0	> 90
	ER	0	81
	CKs	4	> 90
Prostatic carcinoma	PSA	90	23
	PAP	92	0
	GCDFP-15	10	62
	GATA3	2	> 90
	ER	11	81
	CK7	13	92

TTF-1,thyroid transcription factor-1; GCDFP-15, gross cystic disease fluid protein 15; ER, estrogen receptor; GATA3, GATA binding protein 3; WT1, Wilm's tumor 1 protein; PAX-8, paired-box gene 8; CA 125, cancer antigen 125; CDX2, homeobox protein CDX2; HMB-45, human melanoma black-45; melan-A, melanoma antigen; PSA, prostate specific antigen; PAP, prostatic acid phosphatase.

metastases to the brain and lung. Profiles of HR+/HER2- (luminal A) and HR+/HER2+ (luminal B) are related to bone metastases. Liver metastases are associated with the HR-/HER2+ profile (HER2-enriched) (Gong et al. 2017; Wu et al. 2017).

Metastasis to axillary sentinel nodes

Because it is the first to receive lymphatic drainage from a breast tumor, the sentinel lymph node (SLN) is most likely to exhibit metastasis. SLN biopsy is a specific and sensitive way to predict axillary lymph node status and an alternative, with less morbidity, to axillary dissection (Aydiner et al. 2016). Axillary lymph node status is the most significant predictor of disease-free survival and represents an integral component of the staging and treatment of breast cancer (Liu et al. 2017; Nicolini et al. 2017).

Despite several proposals, a standardized protocol for histopathological evaluation of SLN remains elusive (Charalampoudis and Markopoulos 2018). Intraoperative frozen sections currently are the accepted standard; however, these can be false negative in > 25% of cases. Therefore, generally accepted practice requires at least three H & E stained sections, which should detect most metastases, and a minimum of one IHC section for pan-cytokeratins (Van et al. 2016). IHC can be helpful for assessing a suspicious area in an H & E section, particularly for detecting micrometastases and isolated tumor cells (ITC). IHC can detect positivity in 12–29% of SLN sections that were missed by H & E; these are mostly micrometastases and ITC (Apple 2016). In addition to the use of IHC, the greater the number of sections obtained from a block and stained with H & E, the greater the chance of detecting metastases (Giobuin et al. 2011). The significance of micrometastases and ITC, however, is uncertain (Youssef et al. 2016).

Prognostic and predictive factors

Prognostic factors provide necessary information concerning the patient's probable clinical course, indicate disease-free or overall survival and suggest the biological aggressiveness of a tumor (Aydiner et al. 2016). Evaluation of predictive factors enables estimation of whether a patient will benefit from or be resistant to a certain treatment, as well as selection of specific treatments for each case, which improves the response rate and reduces toxicity owing to nonbeneficial therapies (Hicks and Lester 2016; Nicolini et al. 2017). Some factors, such as ER, PR and HER2 status, can be both prognostic and predictive (Shousha 2017).

Morphologic factors for prognosis include lymph node status, the most significant predictor of disease-free survival; poorer prognosis with each additional lymph node involved (Schwartz et al. 2014; Van et al. 2016), tumor size with direct correlation between the number of involved lymph nodes and risk of recurrence (Foulkes et al. 2010; Shahriari-Ahmadi et al. 2017), tumor histologic type and grade; well differentiated and poorly differentiated tumors exhibit favorable or less favorable prognosis, respectively (Eliyatkin et al. 2015), distant metastases, presence of lymph-vascular invasion, proliferative rate, ER, PR and HER2 status (Aydiner et al. 2016).

Patient characteristics including age, co-morbidities and menopausal status also should be considered. In addition, a combination of factors have more prognostic value than each factor individually (Hicks and Lester 2016).

Although the advances that have been made in molecular classification of breast cancer, e.g., gene expression profiling, their clinical applicability remains limited; pathologists continue to use conventional techniques such as IHC and in situ hybridization (ISH) (Rakha and Green 2017).

Hormone receptors

ER and PR evaluation is essential for all newly diagnosed cases of breast cancer, and when applicable, for recurrent/metastatic ones (Nicolini et al. 2017). Positive ER and PR expression is associated with longer disease-free status and overall survival and is an indicator of responsiveness to endocrine therapy (Ly et al. 2012; Honma et al. 2014).

HR can be informative for prognosis: it may predict a slow growing indolent tumor with later recurrence (Aydiner et al. 2016). HR are used mainly to predict endocrine therapy response, however, and particularly to identify patients with early breast cancer who might benefit from such treatments. Endocrine therapy should be considered for patients with ER-positive tumors; conversely, it is not applicable for patients with ER-negative tumors (Nicolini et al. 2017). Nevertheless, negative HR cases exhibited a better response to chemotherapy compared to positive HR cases (Early Breast Cancer Trialists' Collaborative Group 2005).

HR typically is assessed by IHC. If ≥ 1% of the tumor cell nuclei are reactive, the tumor can be considered positive **a**nd endocrine therapy may be considered (Zaha 2014). It also is important to consider staining intensity (weak, moderate, strong) in the tumor in addition to the percentage of stained cells (Hammond et al. 2010; Brouckaert et al. 2012).

HER2

HER2 overexpression, which plays an important role in sustaining several pathways for tumor growth, occurs in

15–30% of breast cancers and is associated with poor prognosis (Iqbal and Iqbal 2014). HER2 is associated with frequent lymph node metastases, high grade histopathology and high mitotic activity (Ly et al. 2012). Beyond its use for prognosis, HER2 overexpression is used to identify patients who may benefit from HER2-targeted therapies, such as trastuzumab, and to predict response to anthracycline-based chemotherapies (Gennari et al. 2008; Slamon et al. 2011). HER2-targeted therapies are applicable only in patients with HER2 overexpression in adjuvant, neoadjuvant and metastatic contexts (Slamon et al. 2001; Mass et al. 2005; Seidman et al. 2008). Similarly, anthracycline based chemotherapies are related to better outcomes in HER2-positive patients (Gennari et al. 2008). HER2 overexpression may be an indicator of resistance and lower response rates to endocrine therapies: despite some conflicting reports, an unfavorable impact on response to tamoxifen has been reported (Wright et al. 1992; Leitzel et al. 1995; Yamauchi et al. 1997; Elledge et al. 1998; Lipton et al. 2003).

IHC, fluorescence in situ hybridization (FISH) and chromogenic in situ hybridization (CISH) are among the techniques available for assessing HER2 status (Rosa et al. 2013). IHC has been widely used despite the greater precision and reproducibility with the FISH technique. IHC is a rapid assay and is less demanding technically (Press et al. 2002; Penault-Llorca et al. 2009). HercepTest™ classifications based on HER2 IHC staining are described in Table 3 (Dako 2014). Weakly positive cases require confirmation and should be re-tested using ISH (Dako 2014; Zaha 2014).

Proliferation assessment

Proliferation can be used to evaluate prognosis and treatment. In addition to mitotic index assessment using H & E staining, IHC, ISH, flow cytometry or gene expression profiling can be used (Badve and Gökmen-Polar 2016). IHC can be used to evaluate markers including Ki-67, p21, p27, cyclin-D and cyclin-E (Fayed et al. 2012; Gao et al. 2013; Xu et al. 2013; Soliman and Anis 2014).

Table 3. Classifications and immunohistochemical reactions of HER2 HercepTest™ assay (Dako 2014).

Score	HER2 classification	Staining pattern
3+	Positive	Strong complete membrane staining in > 10% of tumor cells
2+	Weakly positive	Weak to moderate complete membrane staining in > 10% of tumor cells
1+	Negative	Faint/barely perceptible, incomplete, membrane staining in > 10% of tumor cells
0+	Negative	Absence of staining, or membrane staining in < 10% of tumor cells

Ki-67, despite disadvantages including lack of standardization and poor reproducibility, is a widely used immunomarker for assessing proliferation; it is affordable and technically less demanding than gene expression profiling (Shousha 2017). The percentage of stained cells (nuclear staining) among the total number of tumor cells in the evaluated area, gives the Ki-67 index. This is used mainly to differentiate luminal A from luminal B subtypes, which may guide therapeutic management. Low proliferation is associated with the luminal A subtype, whereas the luminal B subtype is associated with higher proliferation rates (Shousha 2017). Over the years, the St. Gallen Panel has proposed criteria to define standard values: ≤ 15%, 16–30% and > 30% for low, intermediate and high rates, respectively, and cut points of Ki67 positive tumor cells of 14%, 20% and 30% to differentiate luminal A from luminal B subtypes. The Panel noted a high degree of inter-laboratory variation in Ki-67 measurement, therefore the cut points should be interpreted with consideration for local laboratory values (Goldhirsch et al. 2009, 2011, 2013; Coates et al. 2015).

Highly proliferative tumors are associated with poor prognosis, but are more likely to respond to chemotherapy (Kim et al. 2014). For low proliferating tumors, despite the lack of response to chemotherapy, low Ki-67 rates are associated with good prognosis. In highly proliferative tumors that are sensitive to therapy, high Ki-67 rates are associated with a favorable outcome, i.e., improved survival and improved chances of complete response (absence of cancerous cells in the tissue samples removed during biopsy or surgery after chemotherapy or radiation). For highly proliferative tumors that are resistant to chemotherapy, high expression of Ki-67 is associated with reduced survival and unfavorable outcome (Denkert et al. 2015).

Lymph-vascular invasion

Lymph-vascular invasion (LVI) is the first step in the spread of tumor cells; these cells can remain in the breast to form secondary invasive foci or leave through the blood or lymph vessels (Tot et al. 2014). LVI can be defined as the presence of a tumor embolus within an endothelium-lined space in the peritumor area (Agarwal et al. 2018). LVI detection is particularly valuable for node-negative patients and can be used to make decisions regarding adjuvant therapy (Shousha 2017). Several factors exhibit an increased risk of occurrence due to LVI: axillary lymph node metastases, local/distant recurrence independent of the axillary node status and metastases in additional nodes in positive sentinel node cases. Also, LVI can be associated with resistance to chemotherapy as well as with other aggressive features

including lack of HR expression, high histologic grade and high Ki-67 rate (Hicks and Lester 2016).

IHC can be used to detect LVI; IHC increases the frequency of detection compared to H & E staining. Both methods have prognostic significance (Mohammed et al. 2007). ERG, CD31, CD34, factor VIII and podoplanin are commonly used immunomarkers (Kim et al. 2013; Gujam et al. 2014; Agarwal et al. 2018). ERG, which is specific for endothelial cells, exhibits nuclear immunoreactivity in blood and lymphatic vessels. CD31 expression appears in blood vessels and is variably present in lymphatic vessels. CD34 staining occurs in blood vessels and weakly in lymphatic vessels; also, stromal cells are positive, which reduces its usefulness for distinguishing LVI from retraction artifacts. Factor VIII is expressed in both blood and lymphatic vessels; it is weaker in small vessels. Podoplanin staining is observed in lymphatic vessels, but not in blood vessels; it also is positive in MECs, so it is of little value for differentiating LVI from DCIS. It is not necessary to distinguish blood and lymphatic vessels, because both have prognostic significance (Aydiner et al. 2016; Hicks and Lester 2016; Shousha 2017).

Retraction artifacts mimic true LVI. DCIS, as LVI, form circumscribed nests of tumor cells. Retraction artifacts and DCIS are the main conditions that may resemble LVI and lead to misdiagnosis. The MEC layer can differentiate LVI from DCIS. The MEC layer can be assessed using the p63 immunomarker (Koo et al. 2010). SMMHC stains smooth muscle in the walls of blood vessels, so it should not be used to differentiate LVI from DCIS (Shousha 2017). To identify retraction artifacts, vascular markers such as podoplanin or CD31, can be used to highlight LVI (Dileep and Prasad 2018).

Molecular subtypes

Classification of tumors into molecular subtypes according to their gene expression profiles is important for prognosis and for choosing specific treatments. Classification can be done using the IHC markers, ER, PR, HER2, Ki-67, EGFR and basal CKs. The four major subtypes are luminal A, luminal B, HER2-enriched and basal-like (Eliyatkin et al. 2015).

Luminal A comprises 50–60% of breast cancers, whose profile is defined by positive ER, usually positive PR, negative HER2, low Ki-67 proliferation and low to absent basal CKs or EGFR. Prognosis is favorable; it is responsive to endocrine therapy and variably responsive to chemotherapy. Time to recurrence can be > 10 years (Yersal and Barutca 2014; Eliyatkin et al. 2015; Hicks and Lester 2016).

Fifteen to twenty percent of breast cancers have a luminal B profile, which is defined by positive ER, negative to low PR, variable HER2 expression, higher Ki-67 proliferation than luminal A and low to absent basal CKs or EGFR. Prognosis is less favorable than luminal A. HER2-targeted therapy can be used for HER2 positive cases. Luminal B profile is less responsive to endocrine therapy than luminal A and exhibits a variable, but better than luminal A, response to chemotherapy. Time to recurrence is < 10 years (Yersal and Barutca 2014; Eliyatkin et al. 2015; Badve and Gökmen-Polar 2016; Hicks and Lester 2016).

HER2-enriched subtypes represent 15–20% of breast cancers, whose profile is defined by negative ER, negative PR, positive HER2, high Ki-67 and possible presence of basal CKs or EGFR. Prognosis usually is unfavorable. This cancer is responsive to HER2-targeted therapy and to chemotherapy with anthracyclines. Time to recurrence is < 10 years (Yersal and Barutca 2014; Eliyatkin et al. 2015; Hicks and Lester 2016).

Ten to fifteen percent of breast cancers have a basal-like profile, which is defined by negative ER, PR and HER2 (triple negative), high Ki-67 proliferation and presence of basal CKs and EGFR. The prognosis is unfavorable; this cancer is responsive to endocrine or HER2-targeted therapies, and platinum group chemotherapies and PARP inhibitors can be beneficial. Because EGFR frequently is overexpressed, it also may be a potential therapeutic target. Time to recurrence is < 5 years (Yersal and Barutca 2014; Eliyatkin et al. 2015; Hicks and Lester 2016). Owing to the need to improve therapeutic outcomes and because of their immunogenic characteristics, the programmed death-ligand 1 (PD-L1) is a potential target for triple negative breast cancers. This ligand was overexpressed in approximately 20% of triple negative breast cancers, which suggests a potential role for anti-PD-L1 therapy (Mittendorf et al. 2014). Phase I clinical trials using anti-PD-L1 antibodies exhibited tumor size reduction and a positive reaction to therapy (Pusztai et al. 2016).

Conclusions

Although most diagnoses of breast pathologies can be accomplished using H & E stained sections, several types cause diagnostic problems for which IHC becomes a vital tool (Table 4). Owing to the complex nature of mammary lesions, the success of diagnosis also depends on understanding each particular situation. To avoid incorrect interpretation of immunostaining, it is mandatory to evaluate the cytological characteristics carefully and to correlate the histological findings. IHC plays a vital role for prognosis and predicting response to therapy. Despite advances in the molecular classification of breast cancer, conventional techniques, such as IHC, remain indispensable to everyday clinical practice.

Table 4. Immunomarkers for breast cancer for assessing various conditions, respective location/marking pattern, and positivity and negativity.

Marker	Staining pattern	Positive	Negative	References
34βE12	Perinuclear cytoplasmic	Lobular carcinoma	Ductal carcinoma	Bratthauer et al. 2002
	Cytoplasmic	UDH	ADH and DCIS	Moinfar et al. 1999; Lacroix-Triki et al. 2003
Actin	Spindle cells	PASH	Angiosarcoma	Rosa et al. 2017; Tan and Sahin 2017
AR	Spindle cells	Myofibroblastoma	PASH	Ibrahim and Shousha 2013; Aytaç et al. 2015
β-catenin	Membranous with/without cytoplasmic expression	Ductal carcinoma		Dabbs et al. 2007a; Karabacak et al. 2011
	Membranous negative/cytoplasmic granular	Lobular carcinoma		
	Nuclear	Fibromatosis		Abdelwahab et al. 2018
	Nuclear in stromal cells	More expressed in benign phyllodes tumor than borderline/malignant		Lacroix-Triki et al. 2010
	Nuclear	Occasionally expressed in spindle cell metaplastic carcinoma		Lacroix-Triki et al. 2010
BCL2		Usually negative in fibromatosis		Ashoor et al. 2017
	Spindle cells	PASH		Charu and Cimino-Mathews 2017
		Variably expressed in myofibroblastoma	Leiomyoma	Dekate et al. 2015; Magro 2017
	Stromal cells	Benign and borderline phyllodes tumors	Spindle cell metaplastic carcinoma	Moore and Lee 2001; Cimino-Mathews et al. 2014
	Lower expression in malignant phyllodes tumor than benign/borderline			Moore and Lee 2001
CA 125	Used to distinguish metastatic ovarian carcinoma from primary breast carcinoma			Tornos et al. 2005
Calponin	Cytoplasmic	In situ carcinoma	Invasive carcinoma	Yeh I-T 2008
	Spindle cells	PASH	Angiosarcoma	Lakhani et al. 2012; Tan and Sahin 2017
		Variably expressed in myofibroblastoma		Magro 2017
CD10	Spindle cells	Variably expressed in myofibroblastoma		Magro 2017
		Spindle cell metaplastic carcinoma		Rakha et al. 2017
	Proportional association between expression and degree in phyllodes tumor			Ibrahim 2011
CD117		Usually negative in fibromatosis		Bhat et al. 2015
	Proportional association between expression and degree in phyllodes tumor			Noronha et al. 2011
CD31		Usually negative in fibromatosis		Charu and Cimino-Mathews 2017
	Spindle cells	Angiosarcoma	PASH	Rebutini et al. 2017; Rosa et al. 2017
	Expressed in BV and variably in LV	Used to evaluate lymph-vascular invasion LVI	Retraction artifacts	Gujam et al. 2014; Shousha 2017 Dileep and Prasad 2018
CD34		Usually negative in fibromatosis		Tan and Sahin 2017
	Spindle cells	PASH		Virk and Khan 2010
		Myofibroblastoma	Leiomyoma and low-grade myofibroblastic sarcoma	Metry et al. 2016; Myong and Min 2016; Magro 2017
	Stromal cells	Benign and borderline phyllodes tumors malignant less reactive	Spindle cell metaplastic carcinoma	Moore and Lee 2001; Cimino-Mathews et al. 2014
	BV and more weakly in LV	Used to evaluate lymph-vascular invasion		Shousha 2017; Agarwal et al. 2018
CD99		Usually negative in fibromatosis		Ashoor et al. 2017
	Spindle cells	PASH		Charu and Cimino-Mathews 2017
		Variably expressed in myofibroblastoma	Leiomyoma	Dekate et al. 2015; Magro 2017
CDX2	Used to distinguish metastatic gastric carcinoma from primary breast carcinoma			Werling et al. 2003
Chromogranin	Cytoplasmic	SPC		Otsuki et al. 2007
	Used to distinguish metastatic carcinoid tumor from primary breast carcinoma			Hicks and Lester 2016

(*Continued*)

Table 4. (Continued).

Marker	Staining pattern	Positive	Negative	References
CK 5/6	Cytoplasmic	UDH	ADH and DCIS	Otterbach et al. 2000; Lacroix-Triki et al. 2003
	Cytoplasmic	IDP with UDH	Atypical papilloma	Nofech-mozes et al. 2008
			IDP with DCIS	Jorns 2016
			EPC and SPC	Rabban et al. 2006; Agoumi et al. 2016
CKs		Usually negative in fibromatosis		Tan and Sahin 2017
			PASH	Charu and Cimino-Mathews 2017
			Myofibroblastoma	Dekate et al. 2015
	Spindle cells	Spindle cell metaplastic carcinoma	Phyllodes tumor malignant may be positive	Cimino-Mathews et al. 2014
	Used to assess breast origin			Shao et al. 2012
	Used to assess metastasis in axillary sentinel nodes			Apple 2016; Van et al. 2016
CK20	Used to distinguish metastatic gastric carcinoma from primary breast carcinoma			Chu and Weiss 2004
CK7	Used to assess breast origin			Bombonati and Lerwill 2012
CK8	Peripheralpredominant cytoplasmic	Ductal carcinoma		Lehr et al. 2000
	Perinuclear	Lobular carcinoma		
Cyclin-D and Cyclin-E	Can be used to evaluate proliferation			Gao et al. 2013; Xu et al. 2013
Desmin	Cytoplasmic	May be expressed in fibromatosis		Tan and Sahin 2017
	Spindle cells	Variable positive in PASH	Angiosarcoma	Lakhani et al. 2012; Tan and Sahin 2017
		Myofibroblastoma	Low-grade myofibroblastic sarcoma	Metry et al. 2016; Myong and Min 2016
E-cadherin	Membranous	Ductal carcinoma	Lobular carcinoma	Li et al. 2014
			Myofibroblastoma	Dekate et al. 2015
EGFR	Proportional association between expression and degree in phyllodes tumor			Tse et al. 2009
	Spindle cells	Spindle cell metaplastic carcinoma		Rakha et al. 2017
	Used as a prognosis factor			Hicks and Lester 2016
EMA	Focal and weak in spindle cells	Occasionally expressed in myofibroblastoma		Howitt and Fletcher 2016
Endothelial markers	Spindle cells	Angiosarcoma	PASH although positive for CD34	Rafeek et al. 2017; Rebutini et al. 2017
Endothelin 1	Negativity related to malignant phyllodes tumor			Esposito et al. 2006
ER	Nuclear scattered	UDH		Lin et al. 2015
	Nuclear diffuse	ADH and DCIS		
	Strong diffuse	Atypical papilloma	IDP with UDH	Grin et al. 2009
	Diffuse	IDP with DCIS		Jorns 2016
	Diffuse	EPC		Agoumi et al. 2016
		Usually negative in fibromatosis		Charu and Cimino-Mathews 2017
	Focal and weak	PASH	Spindle cell metaplastic carcinoma	Carter et al. 2006; Virk and Khan 2010; Aytaç et al. 2015
	Spindle cells	Myofibroblastoma		
	Lower expression in malignant phyllodes tumor than benign/borderline			Tse et al. 2002
	Used to assess breast origin			Gown et al. 2016
	Used as a prognosis factor			Shousha 2017
ERG	Nuclear in BV and LV	Used to evaluate lymph-vascular invasion		Kim et al. 2013
Factor VIII	BV and LV	Used to evaluate lymph-vascular invasion		Gujam et al. 2014; Shousha 2017
			PASH	Rafeek et al. 2017
GATA3	Used to assess breast origin			Gown et al. 2016
GCDFP-15	Cytoplasmic	Apocrine carcinoma		Darb-Esfahani et al. 2014
	Used to assess breast origin			Gown et al. 2016
H-caldesmon	Spindle cells	Variably expressed in myofibroblastoma		Metry et al. 2016

(*Continued*)

Table 4. (Continued).

Marker	Staining pattern	Positive	Negative	References
HER2			Spindle cell metaplastic carcinoma	Carter et al. 2006
	Used as a prognosis factor			Shousha 2017
HMB-45			Myofibroblastoma	Metry et al. 2016
	Used to distinguish metastatic melanoma from primary breast carcinoma			Filie et al. 2002
IMP3	Proportional association between expression and degree in phyllodes tumor			Bellezza et al. 2016
Ki-67	Proportional association between expression and degree in phyllodes tumor			Noronha et al. 2011
	Used to evaluate proliferation			Shousha 2017
Mammaglobin	Used to assess breast origin			Gown et al. 2016
Maspin	Spindle cells	Spindle cell metaplastic carcinoma		Rakha et al. 2017
MEC markers	MEC	In situ carcinoma	Invasive carcinoma	Yeh I-T 2008
	Within the papillae and peripheral	IDP with DCIS	EPC and SPC	Tse et al. 2007; Jorns 2016
	Peripheral only	Papillary DCIS		
	MEC	IDP with abundant sclerosis	Invasion	Mugler et al. 2007
		Pseudoinvasion	Papillary DCIS invasion	Tse et al. 2007
		DCIS	LVI	Hicks and Lester 2016
		Sclerosing adenosis and radial scars	Invasive carcinoma	Liu 2014; Zaha 2014
Melan-A	Used to distinguish metastatic melanoma from primary breast carcinoma			Busam and Jungbluth 1999
Napsin	Used to distinguish metastatic lung adenocarcinoma from primary breast carcinoma			Bishop et al. 2010
p120 catenin	Membranous	Ductal carcinoma		Dabbs et al. 2007a, 2007b; Li et al. 2014
	Cytoplasmic	Lobular carcinoma		
p21	Proportional association between expression and degree in phyllodes tumor			Esposito et al. 2006
	Can be used to evaluate proliferation			Soliman and Anis 2014
p27	Can be used to evaluate proliferation			Fayed et al. 2012
p53	Proportional association between expression and degree in phyllodes tumor			Korcheva et al. 2011
p63	Nuclear	In situ carcinoma	Invasive carcinoma	Yeh I-T 2008
		Usually negative in fibromatosis		Rakha et al. 2016
			Myofibroblastoma	Charu and Cimino-Mathews 2017
	Nuclear	Spindle cell metaplastic carcinoma	Phyllodes tumor malignant may be positive	Koker et al. 2004; Cimino-Mathews et al. 2014
p75 neurotrophin receptor	Membranous and cytoplasmic	In situ carcinoma	Invasive carcinoma	Popnikolov et al. 2005
PAP	Used to distinguish metastatic prostatic carcinoma from primary breast carcinoma			Cheng et al. 2006
PAX8	Used to distinguish metastatic ovarian carcinoma from primary breast carcinoma			Nonaka et al. 2008
pH3	Proportional association between expression and degree in phyllodes tumor			Korcheva et al. 2011
Podoplanin	LV	Used to evaluate lymph-vascular invasion		Shousha 2017; Agarwal et al. 2018
		LVI	Retraction artifacts	Dileep and Prasad 2018
PR	Nuclear in stromal cells	PASH	Spindle cell metaplastic carcinoma	Virk and Khan 2010; Cimino-Mathews et al. 2014; Metry et al. 2016
	Spindle cells	Myofibroblastoma		
	Lower expression in malignant phyllodes tumor than benign/borderline			Tse et al. 2002
	Used as a prognosis factor			Shousha 2017

(*Continued*)

Table 4. (Continued).

Marker	Staining pattern	Positive	Negative	References
PSA	Used to distinguish metastatic prostatic carcinoma from primary breast carcinoma			Hicks and Lester 2016
S100		Usually negative in fibromatoses		Tan and Sahin 2017
	Spindle cells	Spindle cell metaplastic carcinoma	PASH Myofibroblastoma	Cheah et al. 2016; Metry et al. 2016; Charu and Cimino-Mathews 2017
	Used to distinguish metastatic melanoma from primary breast carcinoma			Ren et al. 2018
SMA	Cytoplasmic	May be expressed in fibromatosis		Tan and Sahin 2017
	Spindle cells	PASH		Virk and Khan 2010
		Myofibroblastoma		Metry et al. 2016
		Spindle cell metaplastic carcinoma		Rakha et al. 2017
SMMHC	Cytoplasmic	In situ carcinoma	Invasive carcinoma	Yeh I-T 2008
Snail	Sensitive for spindle cell metaplastic carcinoma but reduced specificity			Nassar et al. 2010
SOX10	Spindle cells	Variably expressed in spindle cell metaplastic carcinoma	Phyllodes tumors	Cimino-Mathews et al. 2013
Synaptophysin	Cytoplasmic	SPC		Otsuki et al. 2007
	Used to distinguish metastatic carcinoid tumor from primary breast carcinoma			Hicks and Lester 2016
TTF-1	Used to distinguish metastatic lung adenocarcinoma from primary breast carcinoma			Whithaus et al. 2012
Vimentin	Spindle cells	PASH		Virk and Khan 2010
		Myofibroblastoma		Magro 2017
		Spindle cell metaplastic carcinoma	-	Altaf et al. 2014
WT1	Used to distinguish metastatic ovarian carcinoma from primary breast carcinoma			Tornos et al. 2005

UDH, usual ductal hyperplasia; ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; PASH, pseudoangiomatous stromal hyperplasia; AR, androgen receptor; BCL2, B-cell lymphoma protein 2; CA 125, cancer antigen 125; LVI, lymph-vascular invasion; BV, blood vessels; LV, lymphatic vessels; CDX2, homeobox protein CDX2; SPC, solid papillary carcinoma; CK, cytokeratin; IDP, intraductal papilloma; EPC, encapsulated papillary carcinoma; EGFR, epidermal growth factor receptor; EMA, epithelial membrane antigen; ER, estrogen receptor; GATA3, GATA Binding Protein 3; GCDFP-15, gross cystic disease fluid protein 15; HER2, human epidermal growth factor receptor 2; HMB-45, human melanoma black-45; IMP3, insulin-like growth factor II mRNA binding protein 3; MEC, myoepithelial cell; PAP, prostatic acid phosphatase; PSA, prostate specific antigen; PAX-8, paired-box gene 8; pH3, phospho-Histone3; PR, progesterone receptor; SMA, smooth muscle actin; SMMHC, smooth muscle myosin heavy chain; Melan-A, melanoma antigen; SOX10, sry-related HMG-BOX gene 10; TTF-1, thyroid transcription factor-1; WT1, Wilm's tumor 1 protein.

Disclosure statement

No potential conflict of interest was reported by the authors.

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