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Prognostic factors of breast phyllodes tumors

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Summary. Background. Phyllodes tumor (PT) is a relatively rare breast tumor, accounting for <1% of all breast tumors.

Main body. Adjuvant therapy with chemotherapy or radiation therapy, other than surgical excision, has not been established yet. PT, similar to other breast tumors, is classified as benign, borderline, and malignant according to the World Health Organization classification system, depending on stromal cellularity, stromal atypia, mitotic activity, stromal overgrowth, and tumor border. However, this histological grading system cannot effectively or fully reflect the clinical prognosis of PT. Several studies have investigated prognostic factors for PT as some PTs recur or metastasize to distant sites, and thus, prediction of prognosis is clinically imperative.

Conclusion. This review discusses clinicopathological factors, immunohistochemical markers, and molecular factors that have been investigated in previous studies to have an impact on the clinical prognosis of PT.

Key words: Breast, Prognosis, Phyllodes tumor

Background

Phyllodes tumor (PT) of the breast is a relatively rare tumor, accounting for less than 1% of all breast tumors (Rosen et al., 2014). Histologically, it is a fibroepithelial neoplasm composed of an epithelial component of luminal and myoepithelial cells and a stromal component of myofibroblast cells. Like other tumors of the breast, PT is classified as benign, borderline, and malignant according to the World Health Organization (WHO) classification system, depending on the histologic features (World Health Organization and International Agency for Research on Cancer, 2020). PT is usually benign; however, local recurrence rates range from 17% to 27% depending on the histologic grade, and distant metastasis occurs in 22% of malignant PTs (World Health Organization and International Agency for Research on Cancer, 2020). Histologic grade of PT is a sum of several of histologic features, such as stromal cellularity, stromal atypia, mitotic activity, stromal overgrowth, and tumor border. Such histologic grade of PT is correlated with prognosis, but precise prediction of clinical prognosis for individual patients is limited (Lenhard et al., 2008; Karim et al., 2009; Tan et al., 2012). Therefore, there have been several studies that aimed at investigating prognostic factors that can predict clinical prognosis for PT. Clinicopathologic parameters, immunohistochemical markers, and molecular and genomic characteristics can generally help predict clinical prognosis for tumors. This review is focused on clinicopathologic factors, biomarkers evaluated by immunohistochemistry (IHC), and genomic/molecular characteristics that have been investigated to have an impact on clinical prognosis of PT.

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Factors for assessing prognosis of breast PT

Local recurrence (LR), distant metastasis (DM), disease-free survival (DFS), and overall survival (OS) are frequently used for predicting prognoses for a majority of tumor types. Several studies have used these variables to investigate prognostic factors for PT; and factors that have an impact on these variables are clinicopathologic factors, biomarkers evaluated by IHC, and genomic/molecular factors.

Clinicopathologic factors

Surgical resection margin

Tumor extension on the surgical resection margin is an important prognostic factor for tumors in general, and especially so for PT for the following reasons. First, PTs are frequently marginally excised at the first attempt of surgical excision because they clinically, radiologically, and histologically present as benign tumors (Liberman et al., 1996; Chao et al., 2002; Abe et al., 2011). Second, unlike breast cancers, effectiveness of chemotherapy as adjuvant treatment for PT has not been established yet, and radiotherapy is reported to be only partly effective under limited conditions (Zeng et al., 2015; Chao et al., 2019). Therefore, appropriate surgical interventions are

Table 1. Summary of clinical studies presenting surgical resection margin status as a significant prognostic factor in phyllodes tumors.

Patient group	Geographical region	Surgical procedure	Definition of margin status	Statistical significant result for SRM
605 PT -440 benign -111 borderline -54 malignant	Asian	n/a	Complete: surrounding rim of non-lesional breast tissue Focal involvement: tumor extended in only one focus to the inked margin Diffuse involvement: breached by tumor in more than one focus	RFS: HR (95% CI) 7.14 (4.07-12.52), p<0.001
290 PT -181 benign -76 borderline -33 malignant	Asian	Mastectomy:36 BCS:233	Clear margin: no tumor cells found at the painted margin	LR: p<0.00; TR: p=0.005; RFS: log-rank 8.582, p = 0.003 LRFS: log-rank 15.294, p < 0.001; LR: HR 4.673, p = 0.003
188 MPT	Asian	Lumpectomy: 92 Wide excision: 45 Mastectomy: 51	Surgical margin distance <1cm versus ≥1cm	SRM ≥1cm -UA: Recurrence: HR (95% CI) 0.17 (0.09-0.35), p<0.001 -MA: Recurrence: HR (95% CI) 0.28 (0.13-0.61), p=0.001
57 PT -37 benign -12 borderline -8 malignant	Asian	Lumpectomy: 15 Wide excision: 24 Mastectomy: 11 Mastectomy with ND: 7	Positive margin: tumor cells present at SRM; Close margin: tumor cells present < 1 cm from SRM; Clear margin: tumor cells present >1 cm from SRM	Close/positive RM -RFS: HR (95% CI) 3.796 (0.800-5.179), p<0.001
192 PT -80 benign -63 borderline -49 malignant	Asian	Excision: 41 WLE: 104 Mastectomy: 47	Positive margin: tumor cells present at SRM; Close margin: tumor cells present < 1 cm from SRM; Clear margin: tumor cells present >1 cm from SRM	LR: p<0.001; DM: p=0.002; UA: LRFS (p<0.001), DMFS (p=0.002), OS (p=0.001); MA -LRFS: HR (95%CI) 4.530 (2.589-7.928), p<0.001 -DMFS: HR (95%CI) 2.581 (1.223-5.451), p=0.013 -OS: HR (95%CI) 2.507 (1.157-5.431), p=0.020
164 PT -82 benign -42 borderline -40 malignant	Asian	Local or wide excision: 148 Mastectomy: 16	Positive margin: tumor cells present at SRM; Negative margin: divided based on the size of the resection margin: 0.1 mm, 1.0 mm, and 1.0 cm	Positive RM -LR: p=0.040 (UA), p=0.029 (MA)
40 PT -31 low -3 intermediate -3 high	USA	Simple excision:18 WLE: 13 Mastectomy: 10	Positive margin: tumor cells present at SRM Narrow margin: tumor cells present < 1 cm from SRM	Positive RM - LR: p<0.05 Narrow margin - LR: p<0.05
172 PT -131 benign -12 borderline -29 malignant	Asian	Local excision: 71 Wide excision: 55 Mastectomy:46	Positive margin: tumor cells present at SRM	Positive RM -LR: p=0.00018
182 PT -138 benign -13 borderline -31 malignant	Asian	BCS: 132 Mastectomy: 50	Positive margin: tumor cells present at SRM	Positive RM MA -LR: HR (95%CI) 8.0 (2.8-23.0), p<0.001
9234 PT -5693 benign -1813 borderline -1720 malignant	Worldwide	BCS: 2926 Mastectomy: 631 N/A:	Different definition due to multiple studies in meta-analysis	Positive RM -LR (OR 3.32; 95% CI 2.18-5.06; HR, 5.00; 95% CI 3.09-8.10) -LR for malignant PT (OR 6.85; 95% CI 1.58-29.64)
50 PT -3 borderline -16 low -31 high	USA	WLE: 22 Mastectomy: 28	SRM: <1cm versus ≥1cm	Surgical RM <1cm -LR: p=0.0120 -OS: p=0.0302
45 PT -31 benign -5 borderline -9 malignant	Asian	BCS: 42 Mastectomy: 3	Positive margin: tumor cells present at SRM	Positive RM -LR: p=0.0034 MA -LR (HR, 0.086; 95% CI, 0.01-0.743; p= 0.026)
30 PT -16 benign -8 borderline -6 malignant	USA	N/A	Not described	Positive RM -LR: p=0.02
193 PT -145 benign -33 borderline -15 malignant	Asian	Local excision: 143 Wide excision: 39 Mastectomy:11	Positive margin: tumor cells present at SRM or within a 1-mm safety margin of SRM	Positive RM -DFS in malignant PT: p<0.001

PT, phyllodes tumor; ND, node dissection; WLE, wide local excision; BCS, breast conserving surgery; SRM, surgical resection margin; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; LR, local recurrence; TR, tumor recurrence; LRFS, local recurrence-free survival; UA, univariate analysis; MA, multivariate analysis; RM, resection margin; DM, distant metastasis; DMFS, distant metastasis-free survival; OS, overall survival; OR, odd ratio; DFS, disease-free survival.

very important in PT, and several studies suggest surgical resection margin status as a significant prognostic factor (Mangi et al., 1999; Chaney et al., 2000; Asoglu et al., 2004; Chen et al., 2005; Cheng et al., 2006; Taira et al., 2007; Jang et al., 2012; Tan et al., 2012; Wei et al., 2014; Li et al., 2019, 2021; Lu et al., 2019; Ravindhran and Rajan, 2021; Toussaint et al., 2021) (Table 1). Positive surgical resection margin correlates with LR (Asoglu et al., 2004; Cheng et al., 2006; Esposito et al., 2006; Taira et al., 2007; Jang et al., 2012; Li et al., 2019; Lu et al., 2019; Toussaint et al., 2021), DFS (Tan et al., 2012; Wei et al., 2014; Li et al., 2021; Ravindhran and Rajan, 2021), and OS (Wei et al., 2014). When assessing surgical resection margin for PT, the width of tumor-free margin or definition of free resection margin needs to be considered first. The appropriate surgical excision for PT has been defined as securing wide tumor-free margin, but there is no consensus guideline on the precise width of tumor-free margin or definition of free resection margin. As for invasive carcinomas of the breast, positive resection margin is defined as presence of tumor at inked margin; for ductal carcinoma in situ, free resection margin is defined as tumor-free distance width >2 mm. In contrast, surgical margin status for PT is variously described as positive, close, wide, and negative. The definition of negative resection margin is variable in studies; some define negative resection margin as no tumor on the inked margin, while others define negative resection margin as no tumor within >10 mm from inked margin. The definition of close margin also varies from 0.1 mm to <3 mm, and that of positive resection margin ranges from presence of tumor on the inked margin to presence of tumor within <10-20 mm from the inked margin (Reinfuss et al., 1996; Barth, 1999; Mangi et al., 1999; Chaney et al., 2000; Chen et al., 2005; Cheng et al., 2006; Jang et al., 2012; Lin et al., 2013; Mituś et al., 2014; Onkendi et al., 2014; Yom et al., 2015). In practice, the precise assessment of resection margin status for PT is difficult because many factors, such as irregular tumor margin, multifocal presence of the tumor, problems with inking the margin, and issues with adequacy in tumor sampling need to be considered. Histologic grade is the second factor to be considered. Studies have reported that the impact of surgical resection margin status on clinical prognosis varies according to the histologic grade. In case of benign PT, positive resection margin does not have any effect on LR (Tan et al., 2006; Teo et al., 2012; Kim et al., 2013; Lu et al., 2019). This conclusion is based on the results of a large meta-analysis study that showed only a tendency for increased LR in benign PTs with positive resection margin (OR 3.95; 95% CI 0.58-26.76) (Lu et al., 2019). In this meta-analysis study, when analyzed for all PTs in a total of 24 studies showing surgical resection margin status, positive resection margin was a significant risk factor of LR (OR 3.32; 95% CI 2.18-5.06; HR, 5.00; 95% CI 3.09-8.10). However, in the results of meta-analysis of six studies that reported LR rate in benign PT, positive resection margin was not a significant risk factor for LR (Lu et al., 2019). In addition, in a retrospective study on PTs with local recurrence, 46% of those with uninvolved margins showed LR, and there were cases with involved margins that showed no LR during the follow-up period (Tan et al., 2006). Patients with benign PTs who showed LR all underwent local excision, and the rate of LR was not correlated with surgical margin status (Kim et al., 2013). In one retrospective study involving patients less than 25 years old who were diagnosed with PT, those who underwent simple enucleation and were diagnosed with benign PT showed no LR during the mean and median follow-up period of 47.6 and 29.5 months irrespective of surgical margin status (Teo et al., 2012). whereas positive resection margin has a significant impact on LR in malignant PT (Kim et al., 2013; Lu et al., 2019; Li et al., 2021). Therefore, ensuring an adequate resection margin at surgical excision is crucial for high grade PT. However, considering the limited number of research studies, differences in definition of resection margin status, and different geographic distribution of the patients that may affect the conclusion that the surgical resection margin status does not significantly affect LR in benign PT, further studies to redefine the adequate resection margin in benign PT and analysis for cost-effectiveness in re-surgery for patients with positive resection margin in benign PT are needed.

Other clinicohistologic factors

The WHO system is the most representative grading system for PT that incorporates various factors, such as stromal cellularity, stromal atypia, mitosis, stromal overgrowth, and tumor margin. These variables have been reported to correlate with clinical prognosis of PT in various studies (Asoglu et al., 2004; Roa et al., 2006; Taira et al., 2007; Tan et al., 2012; Lin et al., 2013; Sawalhi and Al-Shatti, 2013; Onkendi et al., 2014; Wei et al., 2014; Zhou et al., 2018; Li et al., 2019; Lu et al., 2019; Di Liso et al., 2020; Ravindhran and Rajan, 2021). The other histological features related to prognosis of PT include large tumor size (Asoglu et al., 2004; Roa et al., 2006; Onkendi et al., 2014; Wei et al., 2014; Di Liso et al., 2020; Koh et al., 2018), tumor necrosis (Li et al., 2019; Lu et al., 2019), malignant heterologous element (Koh et al., 2018; Di Liso et al., 2020; Li et al., 2021), and neutrophil-to-lymphocyte ratio (Ravindhran and Rajan, 2021). These histologic features have varied effects on prognostic parameters of PT. For example, mitosis and stromal atypia are correlated with LR, but not with DM or OS, whereas tumor necrosis and stromal overgrowth are correlated with LR, DM, and OS.

The type of surgical procedure comprising vacuum-assisted biopsy, local excision, wide excision, and mastectomy is one of the clinical factors that correlate with prognosis in PT. When analyzed by excluding histologic grade, the possibility of LR does not increase more in breast conservation surgery than in mastectomy

(Lu et al., 2019); however, the result is different when histologic grade is added in the analysis. In the case of benign PT, the type of surgical procedure did not have any effect on LR (Ben Hassouna et al., 2006; Kim et al., 2013; Park et al., 2019). However, in the case of borderline PT, patients who underwent mastectomy showed longer DFS (Ben Hassouna et al., 2006; Belkacémi et al., 2008; Lim et al., 2021), and those who underwent local excision with safety margin <5 mm had increased LR compared to those who underwent mastectomy (Kim et al., 2013). In the case of malignant PT, patients who underwent mastectomy showed improved LR-free survival (Asoglu et al., 2004; Ben Hassouna et al., 2006; Neron et al., 2020; Lim et al., 2021) and DFS (Ben Hassouna et al., 2006; Belkacémi et al., 2008). In addition, patient age correlated with LR (Ben Hassouna et al., 2006; Wei et al., 2014; Choi et al., 2019; Ditsatham and Chongruksut, 2019; Spanheimer et al., 2019) and DM (Pezner et al., 2008; Rodrigues et al., 2018; Neron et al., 2020). Younger age was correlated with predictive factors for lower rates of LRFS [hazard ratio (HR)=3.045, p=0.005] in multivariate analysis (Wei et al., 2014), and age<35 years (Choi et al., 2019), age<40 years (Spanheimer et al., 2019), and age<45 years (Ditsatham and Chongruksut, 2019) showed correlation with increased LR risk (p=0.001, 0.020, and 0.015, respectively). Age≥50 years was correlated with decreased MFS [HR 2.14 (1.03-3.81), p=0.038] (Neron

Table 2. Summary of studies that developed and/or validated nomograms for predicting prognosis of breast phyllodes tumors.

Patients group/nation	Parameters included	Scoring system	Used statistical method	Prognostic factor predicted or validated
605 PT/ Singapore -440 benign -111 borderline -54 malignant	Atypia Mitoses Overgrowth Surgical margins (AMOS criteria)	Total score range: 0-100 -atypia: 0-21 -mitosis: 0-25 -overgrowth: 0-14 -surgical margin: 0-40	-Reduced model selection by the Akaike's information criterion -C-indices and likelihood ratio analysis	-Nomogram with a higher C-index predict RFS at 1, 3, 5 and 10 years better than total histological score *Nomogram: HR=1.05, 95% CI (1.04 to 1.06), p<0.001, c-index= 0.79 *Histologic score: HR=1.27, 95% CI (1.15 to 1.40), p<0.001, c-index= 0.65
43 PT/ Japan -29 benign -11 borderline -3 malignant	Atypia Mitoses Overgrowth Surgical margins (AMOS criteria)	Total score range: 0-100 -atypia: 0-21 -mitosis: 0-25 -overgrowth: 0-14 -surgical margin: 0-40	-Reduced model selection by the Akaike's information criterion -C-indices and likelihood ratio analysis	Univariate Cox regression -high nomogram score: decreased RFS [HR=1.11, 95% CI (1.02 to 1.20), p=0.0005, c-index= 0.904]
34 PT/ Australia -13 benign -14 borderline -2 malignant -5 N/A	Atypia Mitoses Overgrowth Surgical margins (AMOS criteria)	Total score range: 0-100 -atypia: 0-21 -mitosis: 0-25 -overgrowth: 0-14 -surgical margin: 0-40	-Reduced model selection by the Akaike's information criterion -C-indices and likelihood ratio analysis	Univariate Cox regression -high nomogram score: increased risk of developing relapse [HR=1.15, 95% CI (1.02 to 1.30), p=0.0006, c-index= 0.933]
259 PT/ Singapore -196 benign -27 borderline -17 malignant	Atypia Mitoses Overgrowth Surgical margins (AMOS criteria)	Total score range: 0-100 -atypia: 0-21 -mitosis: 0-25 -overgrowth: 0-14 -surgical margin: 0-40	-Reduced model selection by the Akaike's information criterion -C-indices and likelihood ratio analysis	Univariate Cox regression -high nomogram score: decreased RFS [HR=1.07, 95% CI (1.04 to 1.11), p<0.0001]
404 PT/ China -168 benign -184 borderline -52 malignant	FA surgery history Surgery method Residual tumor Mitosis Cellularity Tumor margin	Total score range: 0-350 -FA surgery history: 0-30 -Surgery method: 0-100 -Residual tumor: 0-65 -Mitosis: 0-50 -Cellularity: 0-80 -Tumor margin: 0-50	-Based on the results of multivariate Cox analysis using the regression Modeling Strategies package -Harrell's concordance index (C-index)	The nomogram with a higher C-index predicts for 1-, 3-, and 5-year RFS (C-index = 0.835, SE = 0.050)
334 PT/ China -224 benign -91 borderline -19 malignant	Surgical margin Mitosis Tumor border	Total score range: 0-22 -Surgical margin: 0-8 -Mitosis: 0-10 -Tumor border: 0-7	-Based on the results of multivariate Cox analysis using the Akaike's information criterion and ROC analysis -C-index (Begg's method)	Nomogram predicts 1-, 3-, and 5-year RFS: c-index 0.71 (95% CI, 0.67-0.75)
182 PT/ China -61 benign -73 borderline -48 malignant	FH of tumor Lobulation Cystic component Signal on FS T2WI Internal enhancement	Total score range: 0-300 -FH of tumor: 0-100 -Lobulation: 0-60 -Cystic component: 0-60 -Signal on FS T2WI: 0-60 -Internal enhancement: 0-70	-Stepwise multivariate logistic regression analysis -Hosmer-Lemeshow goodness-of-fit test -ROC curve and DCA used	-Nomogram estimate non-benign PT risk: AUC of the nomogram 0.795 (95% CI: 0.639, 0.835) -p-value of the Hosmer-Lemeshow goodness-of-fit test: 0.907

PT, phyllodes tumor; FA, fibroadenoma; FH, family history; FS T2WI, fat saturated T2 weighted imaging; ROC, receiver operating characteristic; DCA, decision curve analysis; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; AUC, area under the ROC curve.

et al., 2020), and advanced age at diagnosis was correlated with increased DM (p=0.010) (Rodrigues et al., 2018).

As various clinicopathologic parameters affect prognosis of PT, a nomogram has been developed for risk assessment and prediction of LR by selecting the most important clinicopathological factors and adding weight to them (Tan et al., 2012; Nishimura et al., 2014; Chng et al., 2016; Zhou et al., 2018; Chao et al., 2020; Ma et al., 2021). Nomograms developed to date have differences in the parameters that are incorporated, scoring system, and predicted factors (Table 2). Factors used in nomograms vary between nomogram systems, but the most representative Singapore nomogram evaluates AMOS criteria consisting of cellular atypia, mitosis, stromal overgrowth, and surgical margin (Tan et al., 2012). The other nomograms include clinicopathological parameters, such as history of fibroadenoma surgery, surgical method, residual tumor, tumor border, and family history of tumor (Zhou et al., 2018; Chao et al., 2020; Ma et al., 2021), or radiologic factors, such as lobulation, cystic component, signal on FS T2WI, and internal enhancement (Ma et al., 2021). The limitations of these nomograms are: 1) a limited number of patients involved in the development of the nomogram (range: 182-605), especially those with malignant PT with poor prognosis (range: 19-54); 2) no validation studies other than the Singapore nomogram (Nishimura et al., 2014; Chng et al., 2016, 2018); 3) inadequate statistical analyses because of low recurrence rates in patients involved in the development of the nomogram due to the inherent low overall recurrence rates (10-21%) in PT (Tan et al., 2005a; World Health Organization and International Agency for Research on Cancer., 2020); and 4) a limitation in decision making for treatment due to the fact that nomograms developed till now are effective in prediction of RFS, but not specific for LR or DM.

Immunohistochemical markers

The clinicopathologic parameters have limitations in predicting precise prognosis for PT; thus, necessitating the search for additional prognostic markers. IHC is the most widely used method for assessing prognostic markers in most tumors, and most immunohistochemical markers for PT are those related to tumorigenesis and/or tumor progression. The immunohistochemical markers whose increased expression correlates with a higher histologic grade of PT include ALDH1 (Zhang et al., 2016), actin (Chen et al., 2000), B7-H3 (Kim et al., 2018), CD10 (Kulkarni et al., 2017), c-Myc (Sawyer et al., 2003), endothelin1 (Tse et al., 2007), EGFR (Kersting et al., 2006; Tse et al., 2009; Takizawa et al., 2016), IMP3 (Takizawa et al., 2016), EZH2 (Zhang et al., 2016), HIF-1α (Kuijper et al., 2005b), MMP-14 (Kim et al., 2012), Ki-67 (Kleer et al., 2001; Erhan et al., 2002; Shpitz et al., 2002; Kuijper et al., 2005a; Esposito et al., 2006; Kersting et al., 2006; Giri, 2009; Shubham et al., 2019; Mohd Ali et al., 2020), p16 (Karim et al., 2010), p53 (Feakins et al., 1999; Kuenen-Boumeester et al., 1999; Millar et al., 1999; Gatalica et al., 2001; Kleer et al., 2001; Erhan et al., 2002; Shpitz et al., 2002; Tse et al., 2002; Tan et al., 2005b; Esposito et al., 2006; Giri, 2009; Korcheva et al., 2011; Shubham et al., 2019; Mohd Ali et al., 2020), pH3 (Korcheva et al., 2011), heparin sulfate (10E4) (Koo et al., 2006), Twist (Kwon et al., 2012), HMGA2 (Kwon et al., 2012), TGF-beta (Kwon et al., 2012), S100A4 (Kwon et al., 2012), CXCR4 (Kwon et al., 2012), CD117 (c-kit) (Chen et al., 2000; Sawyer et al., 2003; Tse et al., 2004b; Esposito et al., 2006; Noronha et al., 2011), VEGF (Tse et al., 2004a), SPARC (Kim et al., 2017), KRT15 (Chong et al., 2012), TCN1 (Chong et al., 2012), HOXB13 (Chong et al., 2012), PAX3 (Jones et al., 2008a), SIX1 (Jones et al., 2008a), TGFB2 (Jones et al., 2008a), HMGA2 (Jones et al., 2008a), and TERT (Tsang et al., 2018). The expression of CD34 (Chen et al., 2000; Noronha et al., 2011) and epithelial endothelin 1 (Esposito et al., 2006) decreases with reduction in histologic grade of PT. Markers associated with increased local recurrence or distant metastasis are MMP-14 (Kim et al., 2012), cytoplasmic epithelial E-cadherin (Tsang et al., 2012), CD117 (c-kit) (Tan et al., 2005b), α-SMA (Gong et al., 2014), and CD10 (Al-Masri et al., 2012; Tariq et al., 2015). Stromal PDGFRβ positivity and co-positivity of epithelial PDGF/stromal PDGFRβ correlate with increased disease-related death (Feakins et al., 2000); and HIF-1α overexpression (Kuijper et al., 2005b), stromal YAP/stromal pYAP expression (Kim et al., 2014), IMP3/EGFR overexpression (Takizawa et al., 2016), cytoplasmic epithelial E-cadherin expression (Tsang et al., 2012), p53 expression (Yonemori et al., 2006), Ki-67 labeling index (LI) (Niezabitowski et al., 2001), TWIST (Kwon et al., 2012), TERT (Tsang et al., 2018), and ALDH1A1 (Chougule et al., 2016) correlate with decreased DFS. Stromal pYAP (Kim et al., 2014), p53 expression (Yonemori et al., 2006), c-kit (Chougule et al., 2016), Ki-67 LI (Niezabitowski et al., 2001), and TWIST (Kwon et al., 2012) correlate with shorter OS. Ki-67 LI has a cutoff value of 11.2% in classifying patients with PT into low-risk and high-risk groups (Niezabitowski et al., 2001; Yonemori et al., 2006).

IHC can assess protein expression via antigen-antibody reaction in formalin-fixed paraffin-embedded tissue. The accuracy and reliability of IHC have been continuously improving with advances in antibody production, automation in staining, and standardization of method. Therefore, IHC is the most preferred method for evaluating prognostic and/or predictive markers for various tumor types. Furthermore, companion diagnostics by IHC have been used in clinical practice for certain tumor types and their biomarkers. However, IHC also has a few limitations and considerations. First, antibodies against the same molecule can provide different results depending on the clone, manufacturing company, and methodology. Second, researchers can use different cutoff values for the same antibody. Table 3

Table 3. Summary of studies investigating p53 immunohistochemical staining in phyllodes tumors.

Patient group	p53 antibody	IHC method	p53 expression interpretation method	Significant result for p53 IHC result
30 PT -16 benign -8 borderline -6 malignant	DO-7, Ventana	Ventana BenchMark automatic staining system	Combined immunoreactive score: the product of the intensity score and the proportion score; -Intensity score: 3+, strong; 2+, moderate; 1+, weak; 0, no staining; -Proportion score: 0, 4% or less; 1, 5% to 33%; 2, 34% to 66%; 3, 66% or more	p53 expression score -Benign VS Non-benign: p<0.001 -Benign VS Borderline: p<0.001 -Benign VS Malignant: p=0.003
21 PT -12 benign -9 malignant	DO-7, 1:100, Dako, Carpinteria, CA	Manual avidin-biotin peroxidase complex method	Positive % = the number of p53-positive nuclei / total number of stromal nuclei ->30%: high-level p53 expression -1-30%: low-level expression -<1%: negative	No p53 expression in benign PT High-level expression in 55% of malignant PT p53 expression associated with stromal overgrowth, cellular atypia, and infiltrating tumor margin
20 PT -7 benign -7 low-grade -6 high-grade	DO-7, Novocastra, Newcastle-upon-Tyne, UK	Elite avidin-biotin-peroxidase kit (Vector, Burlingame, CA)	Focally positive: unequivocal nuclear staining in 10%- 50% of the tumor cells Diffusely positive: unequivocal nuclear staining in more than 50% of the tumor cells	p53 expression in benign PT: 29% p53 expression in malignant PT: 54%
24 PT -12 benign -6 borderline -6 malignant	N/A	N/A	Positive: defined as unequivocal staining of 10% or more cells	p53 expression positive rate -Benign VS Non-benign: p=0.0093 -Benign VS Borderline: p=0.0450
25 PT -13 benign -12 malignant	DO-7, Novocastra	Automatic immunostainer (Ventana Medical Systems, Tucson, AZ)	Positive % = the number of p53-positive cell / total number of examined cell (200)	p53 expression percentage -Benign VS Non-benign: p=0.002
31 PT -12 benign -10 borderline -9 malignant	DO-7, Ventana	Ventana Benchmark, or XT instruments (Ventana, Tucson, AZ)	Evaluation of stain intensity (0-negative, 1+, 2+, 3+) and percentage of cells labeled	p53 expression percentage -Benign (mean;22%) VS Malignant (mean;48%): p<0.05
335 PT -250 benign -54 borderline -31 malignant	DO-7, Dako, 1:70 dilution	Dako Autostainer	Positive: defined as unequivocal staining regardless of intensity and proportion of cells stained -Intensity score: 3+, strong; 2+, moderate; 1+, weak; 0, no staining	Stromal p53 positive rate and intensity increase as PT grade increase (p=0.004, and p=0.002, respectively); Stromal p53 positivity: correlated with luminal epithelial and myoepithelial p53 immunoexpression (p<0.001)
143 PT -87 benign -37 borderline -19 malignant	DO-7, Novocastra, UK	Manual avidin-biotin peroxidase complex method	p53 staining score; -0: No staining; -1: < 33% of the stromal cell nuclei stained weakly; -2: 34-67% of cell nuclei stained with weak to moderate staining intensity; -3: >67% cells displayed moderate to strong nuclear staining	p53 staining score - significantly different among PT grade (p<0.001) -associated with the mitotic count (p=0.0309)
57 PT -27 benign -17 borderline -13 malignant	DO-7, Dako, 1:100 dilution	Manual avidin-biotin peroxidase complex method	Positive % = the number of p53-positive nuclei / total number of stromal nuclei Intensity grade; -0: no staining; -1: staining visible only at x400; -2: staining visible at x100; -3: staining visible at x25 Epithelial staining interpretation; -High level p53 expression:>30%; -Low level p53 expression: 1-30%; -Negative: <1%	Stromal p53 positivity: correlated with -tumor grade (p=0.001) -stromal overgrowth (p=0.0003), -stromal pleomorphism (p=0.006) -high mitosis (p=0.05)
15 PT -9 benign -6 malignant	DO-7, Novocastra, Newcastle-upon-Tyne, UK	N/A	Evaluation of stain intensity and proportion -0: No expression; -1+: less than 33% cell nuclei stained with weak staining intensity -2+: 34-67% cell nuclei stained with weak to moderate staining intensity; -3+: more than 67% cells displayed moderate to strong nuclear immunostaining	Malignant PT -Increased p53 expression compared to benign PT -Characteristic p53 expression in areas of periepithelial stromal condensation
19 PT -10 benign -8 borderline -1 malignant	-1801, Oncoscience, Cambridge, MA, USA.; working dilution 1/500 -DO-1, Santa Cruz Biotechnology, Santa Cruz, CA, U.S.A.; working dilution 1/100	Manual avidin-biotin peroxidase complex method	Counting the number of positive cells in a total of 300 cells in three different areas of the tumor Negative: No immunostaining expression	1801 p53 antibody -p53 overexpression in 4 PT (1 benign, 2 borderline, and 1 malignant) DO-1 p53 antibody -p53 overexpression in 1 PT (1 malignant)
57 PT -42 benign -9 borderline -6 malignant	DO-7, Dako, 1:100 dilution	Manual avidin-biotin peroxidase complex method	Mild (0-50%) Moderate (51-80%) Marked (more than 80%)	p53 expression positive rate -histologic grade (p<0.001)

PT, phyllodes tumor.

shows that although p53 had been consistently investigated in various studies on phyllodes tumors, each study used different antibody clones, employed different methods of immunohistochemistry, and applied different modes of detection. For example, p53 antibody has different clones, such as DO-7, DO-1, and 1810, and it can be stained either manually or by autostainers from different manufacturers (Table 2). Interpretation of p53 staining results is also variable across studies; basically, staining intensity and proportion of positively stained tumor cells are evaluated in combination, but some studies evaluated either staining intensity or proportion of positive cells only. Different cutoff values can be used and staining results can be variably described as follows: 1) positive and negative; 2) four tiers of grades 0, 1, 2, and 3; and 3) low and high (Table 3).

Genomic and molecular factors

Breast PT is a fibroepithelial tumor sharing certain histologic features with fibroadenoma. Histological differentiation between fibroadenoma and benign PT can sometimes be very difficult because they both contain an epithelial component and stromal component. Fibroadenoma more often shows pericanalicular pattern rather than intracanalicular pattern when compared to PT, but it is not an absolute criterion. Stromal atypia and mitosis are rarer in fibroadenoma, but this is also subjective. With respect to stromal cellularity, benign PT shows relatively uniform stromal cellularity with slightly more increased stromal cellularity in areas adjacent to the epithelial components. It is especially difficult to differentiate the cellular fibroadenoma from benign PT because the former exhibits increased stromal cellularity and mitosis. Such difficulties in histological differentiation between fibroadenoma and benign PT have led to molecular studies on fibroepithelial tumors.

Advances in molecular methodologies and techniques have helped identify new molecular characteristics of tumors, including PT. Novel genomic and molecular alterations identified in PT have provided information on tumorigenesis and tumor progression mechanism (Tan et al., 2015; Chang et al., 2020). The following genomic and molecular alterations are found in PT: 1) frequent mutations in MED12 and RARA in fibroadenoma and PT, and they are involved in fibroepithelial tumorigenesis; 2) frequent mutations in FLNA, SETD2, KMT2D, BCOR, and MAP3K1 in PT rather than in fibroadenoma, suggesting their role in PT development; and 3) mutations in cancer-driver genes, such as NF1, RB1, TP53, PIK3CA, ERBB4, and EGFR are primarily found in borderline and malignant PT, and not in fibroadenoma and benign PT, suggesting their role in malignant transformation. These genomic and molecular factors affect the prognosis of PT, including TP53 (Vorotnikov et al., 2020), MED12 (Ng et al., 2015), miR-21 (Gong et al., 2014), MDM4 (Tan et al., 2014), RAF1 (Tan et al., 2014), EGFR (Tan et al., 2014), PDZD2 (Tan et al., 2014), CDKN2A (Tan et al., 2014), and MACROD2 (Tan et al., 2014) (Table 4). Genes whose mutation rates increase with an increase in histological grade of PT are FLNA (Md Nasir et al., 2019), RB1 (Cani et al., 2015; Tan et al., 2015; Piscuoglio et al., 2016; Md Nasir et al., 2019), TP53 (Md Nasir et al., 2019), and TERT promoter (Piscuoglio et al., 2016; Tsang et al., 2018). The genomic features related to tumor recurrence in PT include amplifications in MDM4, RAF1, EGFR, PDZD2, CDKN2A and MACROD2 (Tan et al., 2014), mutations in TP53 (Vorotnikov et al., 2020), upregulation of miR-21 (Gong et al., 2014), and no mutation in MED12 (Ng et al., 2015). Mutations in MED12 are associated with improved DFS (Ng et al., 2015). Concordant with the nomogram developed by incorporating several clinicopathologic parameters that affect prognosis of PT, a gene panel of 16 genes that are frequently mutated in PT has been selected (Chang et al., 2020). This gene panel has been useful in differentiating fibroadenoma from PT, and in determining the histologic grade of PT; however, it has been ineffective in predicting prognosis in PT (Chang et al., 2020).

Conclusion

Various clinicopathologic factors, IHC biomarkers, and genomic/molecular factors have been suggested as prognostic factors for PT, but none of them have been clinically used, except the WHO histologic grade. The most important reason for this is the conflicting results in studies. For instance, some studies have reported surgical resection margin status as a significant prognostic factor (Mangi et al., 1999; Chaney et al., 2000; Asoglu et al., 2004; Chen et al., 2005; Cheng et al., 2006; Taira et al., 2007; Jang et al., 2012; Tan et al., 2012; Wei et al., 2014; Lu et al., 2019; Li et al., 2019, 2021; Ravindhran and Rajan, 2021; Toussaint et al., 2021), whereas others have refuted it as a significant prognostic factor (Mokbel et al., 1999; Barrio et al., 2007; Lenhard et al., 2008; Abusalem and Al-Masri, 2011; Tsang et al., 2012; Kim et al., 2013; Sawalhi and Al-Shatti, 2013; Yom et al., 2015; Park et al., 2019; Noordman et al., 2020; Lim et al., 2021). Some studies have reported that p53 and c-kit are related to prognosis in PT (Niezabitowski et al., 2001; Tan et al., 2005b; Yonemori et al., 2006; Chougule et al., 2016), but others have reported that they have no correlation with prognosis (Feakins et al., 1999; Esposito et al., 2006). In the case of molecular markers, a study has found that mutations in MER12 in PT are related to prognosis (Ng et al., 2015), whereas another study has reported the contrary (Laé et al., 2016). These conflicting results on the same factors can be attributed to differences in race of patients. Patients with PT are known to show clinical differences according to race. The overall incidence of PT is higher in the Asian population than in the Western population (Asian 3.83%, Western 0.5-2.5%) (Chua et al., 1988). Moreover, age at diagnosis is younger in Asian population than that in Western population (Asian,

Table 4. Summary of molecular studies investigating molecular and genomic features as prognostic factors in phyllodes tumors.

Patient group	Gene or molecule	Molecular study method	Significant findings	Significant result for prognostic factor
76 PT - 53 non-malignant - 23 malignant	*TP53*	N/A	-LOH for VNTR1 and R72P loci in TP53: 14.4% of PT *No LOH in non-malignant PT *LOH in malignant PT: 47.8% -Somatic mutations in TP53 gene in malignant PT: 34.7%	-Somatic mutations in TP53 gene and LOH in VNTR1 and R72P loci: correlated with malignant recurrence (p<0.05); -LOH in TP53 gene locus VNTR1 in malignant PT: correlated with distant metastasis (p<0.05); -Shorter RFS in LOH in VNTR1 and R72P loci and somatic mutations in TP53 (78.0±8.8% vs 95.7±4.3%); -Shorter OS in malignant PT with LOH in VNTR1 locus (87.0±7.1% vs 95.7±4.3%)
112 PT -66 benign -32 borderline -14 malignant	*MED12*	Illumina MiSeq next-generation sequencing platform	MED12 mutations (missense, splice site, indel); -65.1% benign; -65.6% borderline -42.8% malignant	PT with MED12 mutations -improved disease-free survivals (HR 9.99, 95% CI 1.55 - 64.42, p=0.015)
268 PT -167 benign -36 borderline -65 malignant	*miR-21*	-in situ hybridization -miRNA assay -qRT-PCR	-The microarray expression of miR-21: significantly upregulated by 4.3-, 11.1-, and 20.6-fold in benign, borderline, and malignant PT (p<0.001); -miRNA locked nucleic acid ISH; * moderate or strong miR-21 staining in borderline or malignant PT; * only minimal cytoplasmic staining in benign PT; - The expression of miR-21: associated with higher tumor grade, mitotic activity, and stromal overgrowth (p < 0.001)	-The value of miR-21 for predicting recurrence (ROC curve): (recurrence/metastasis, AUC, 0.92/0.87; 95% CI, 0.87-0.96/0.79-0.94); -The expression of miR-21: more abundant in PT with local recurrence and distal metastasis (p< 0.001); -Shorter OS in high miR-21 expression than low expression (p<0.001) -High miR-21 expression in multivariate Cox regression analysis; * independent prognostic predictors for LRFS (p=0.002) and OS (p=0.017)
20 PT -7 benign -7 borderline -6 malignant	*MDM4; RAF1* *EGFR* *PDZD2* *CDKN2A*	Affymetrix OncoScan™ FFPE Express molecular inversion probe microarray platform	No mutations identified in all PT samples	-MDM4, RAF1, EGFR and PDZD2 high level amplification: observed exclusively in PT with recurrence/death; -Homozygous deletion in CDKN2A and MACROD2: detected exclusively in PT with recurrence/death
493 PT -322 benign -117 borderline -54 malignant	*TERT promoter* *FLNA* *TP53* *RB1*	QIAseq Targeted DNA Custom Panel (Qiagen)	-MED12 mutation: significantly decreased with increasing PT grade (p = 0.0006) -PTEN aberration between borderline and malignant PT: 1% versus 11%, p = 0.0043	-Higher number of genetic aberrations observed with increasing PT grade; *TERT promoter (32%/61%/46%, p < 0.0001); *FLNA (13%/22%/19%, p = 0.0289); *TP53 (3%/9%/17%, p = 0.0003) *RB1 (3%/7%/11%, p = 0.0297)
22 PT -10 benign -8 borderline -4 malignant	*MED12, RARA; FLNA, SETD2, KMT2D, BCOR MAP3K1, NF1, RB1, TP53, PIK3CA, EGFR ERBB4*	-TruSeq Paired-End Genomic DNA kit (Illumina) -TruSeq Exome Enrichment kit (Illumina) -Illumina HiSeq 2000 instrument	-MED12 (73%) and RARA (32%) mutations frequently observed in both FA and PT -Mutations in FLNA, SETD2, KMT2D, BCOR and MAP3K1 in PT	-Mutations in NF1, RB1, TP53, PIK3CA, ERBB4 and EGFR in borderline and malignant PT
15 PT -5 benign -5 borderline -5 malignant	*MER12* *TP53* *RB1* *NF1* *IGF1R* *EGFR*	multiplexed PCR-based NGS (Ion Torrent Personal Genome Machine)	-MED12 mutation in 67% of PT -The number of high level CNA: increased in malignant PT (p = 0.002) *median 0; range, 0-2 in benign *median 0; range, 0-0 in borderline *median 2; range, 2-6 in malignant -High level CNA exclusively confined to malignant PT	-loss-of-function alterations of TP53, RB1 and NF1 occurred exclusively in malignant PT -Amplification of IGF1R and EGFR in malignant PT
76 PT -40 benign -14 borderline -22 malignant	*MED12* *TP53* *SETD2* *EGFR* *TERT promoter* *TERT*	massively parallel sequencing using the MSK-IMPACT sequencing assay	-MED12 mutation in 56% of PT -Mutation in the TERT promoter in 52% and TERT gene amplification in 4% of PT -The frequency of TERT alterations: significantly increased with increasing PT grade (18%/57%/68%, p<0.01)	Mutation of cancer genes (TP53, RB1, SETD2 and EGFR): exclusively detected in borderline and malignant PT
96 PT -57 benign -25 borderline -14 malignant	*TERT promoter*	Sanger sequencing method	-TERT promoter mutation in 27.1% of PT *21.1% benign *40.0% borderline *28.5% malignant -TERT promoter mutation: associated with stromal overgrowth (p = 0.032)	-TERT promoter mutation: associated with high stromal TERT expression (p=0.042) -PT with high stromal TERT: significantly associated with early relapse in PT with positive surgical margin (p = 0.025)

PT, phyllodes tumor; ISH, in situ hybridization; FFPE, formalin-fixed, paraffin-embedded; LOH, loss of heterozygosity; CNA, copy-number alterations; HR, hazard ratio; CI, confidence interval; ROC, receiver operating characteristic; AUC, area under the ROC curve; OS, overall survival; LRFS, local recurrence-free survival.

25-30 years; Western, 40 years) (Chua et al., 1988). In Asia, adolescent patients (aged <20 years) account for 50% to 33% of the entire population with PT (Chua et al., 1988). Additionally, Asian patients are reported to have higher tumor recurrence rates than non-Asian patients (Karim et al., 2009). Hispanic women have a higher incidence of borderline and malignant PT than Caucasian and Black women ($p<0.01$). Tumors in Hispanic patients are larger ($p=0.01$) and have higher mitotic rates ($p=0.004$) than those in Caucasian and Black women (Pimiento et al., 2011). Furthermore, Black patients have a higher incidence of borderline and malignant PT and a higher rate of local recurrence than non-Black patients (Johnson et al., 2021). Patients with malignant PT show differences in age at diagnosis, tumor size, and prognosis according to their race (Moten and Goldberg, 2019). Therefore, significant prognostic factors differ depending on the race as tumor biology and behavior of PT varies according to race.

Another reason for the conflicting results on prognostic factors for PT is intratumoral heterogeneity. PT shows intratumoral heterogeneity in histologic and molecular features (Jones et al., 2008b; Liu et al., 2016; Tan et al., 2020). PT also shows immunohistochemical heterogeneity in areas with histologic heterogeneity (Fig. 1). Therefore, these heterogeneities lead to conflicting results in evaluation of prognostic factors; hence, tissue selection is a critical issue in the assessment. This tissue selection is especially important in borderline and malignant PT because the tumor size increases as histologic grade gets higher.

Analysis by artificial intelligence (AI) is an alternative to overcome these limitations. The emergence of digital pathology has enabled digitalization of pathology slides, and the use of machine learning and/or deep learning with AI is actively progressing. The use of AI in digital pathology for tumor studies ranges from histologic diagnosis to tumor classification and prediction of prognosis (Niazi et al., 2019; Homeyer et al., 2021). Additionally, AI in digital pathology has been applied to breast cancer diagnosis, classification, and prognosis prediction (Robertson et al., 2018; Chang and Mrkonjic, 2020; Ibrahim et al., 2020); thus, application of AI to the histologic diagnosis, classification, and prediction of tumor behavior for PT needs to be studied.

Under the current circumstances of conflicting results regarding various prognostic factors of PT, the best practice in pathologic reporting of PT would be to state the histologic grade according to the WHO grading system and describe stromal cellularity, stromal atypia, mitosis, stromal overgrowth, and resection margin status of the tumor along with tumor size, presence of tumor necrosis, and presence of malignant heterologous element. We also recommend including the safety margin of surgical resection margins in the report. Immunohistochemical marker studies and/or molecular studies in PT still remain optional, however, it is best recommended to reach a consensus on the choice of markers and methods through a multidisciplinary approach in each institution.

In summary, research on various clinicopathologic factors, immunohistochemical factors, and molecular/genomic features for the prediction of prognosis in PT are continuing. Several significant factors have been found, and nomograms are being developed by incorporating them; however, a lower incidence rate than that of breast cancers, differences in clinical characteristics according to race, conflicting results in the same tumor due to intratumoral heterogeneity, and absence of standardized assessment method have led to the limited use of these features in clinical practice. Therefore, it is necessary to overcome these limitations in the future by including various clinicopathologic factors, immunohistochemical factors, and molecular/genomic features with AI-based machine learning and/or

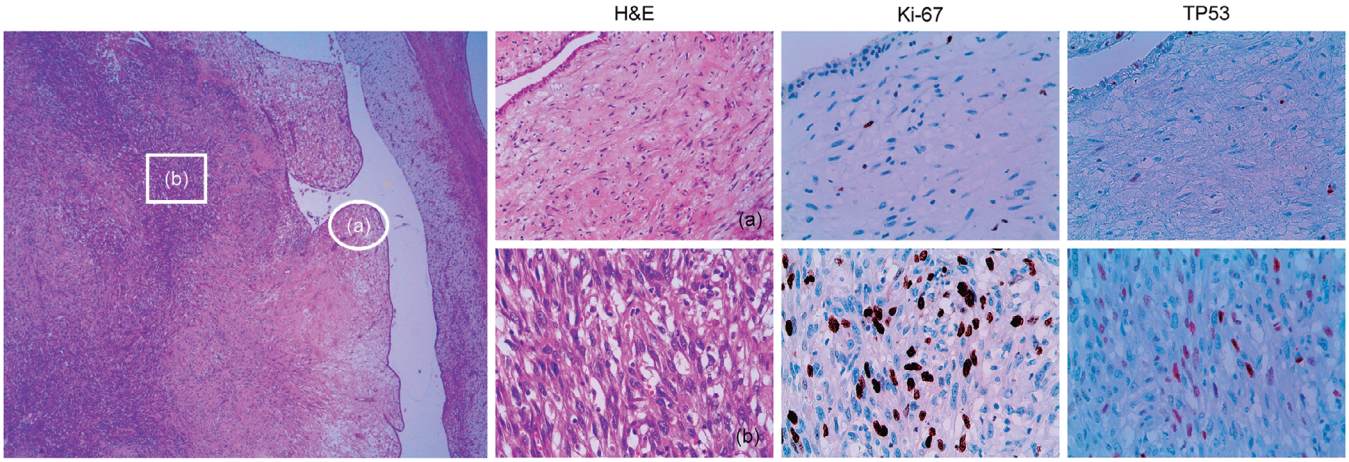

Fig. 1. Heterogeneity of immunohistochemical markers in breast phyllodes tumor. In low power view, breast phyllodes tumor shows histological heterogeneity with low-grade features **(a)** and high-grade features **(b)** in the same tumor. The phyllodes tumor also shows immunohistochemical heterogeneity, with more tumor cells staining positive to Ki-67 and p53 in areas of high grade than in areas of low grade features.

deep learning.

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