RESEARCH ARTICLE

Role of CD10 Immunohistochemical Expression in Predicting Aggressive Behavior of Phylloides Tumors

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Abstract

Background: Phylloides tumors are rare breast neoplasms with a variable clinical course depending on the tumor category. Along with histologic features, the role of immunohistochemical staining has been studied in predicting their behavior. Objectives: Our aim was to evaluate the role of CD 10 immunohistochemical staining in predicting survival, recurrence and metastasis in phylloides tumor. We also evaluated correlations of other clinicopathological features with overall and disease-free survival. Materials and Methods: CD10 expression was studied in 82 phylloides tumors divided into recurrent/metastatic and non-recurrent/non-metastatic cohorts. The Chi-square test was applied to determine the significance of differences in CD10 expression between outcome cohorts. Uni and multivariate survival analyses were also performed using log-rank test and Cox regression hazard models. Results: All 3 metastatic cases, 5 out of 6 (83.3%) recurrent cases and 37out of 73 (50.7%) non-recurrent and non-metastatic cases expressed significant (2+ or 3+) staining for CD10. This expression significantly varied between outcome cohorts (p<0.03). Tumor category and histological features including mitotic count and necrosis correlated significantly with recurrence and metastasis. A significant decrease in overall and disease free survival was seen with CD10 positivity, malignant category, increased mitoses and necrosis. Neither CD10 expression nor any other clinicopathologic feature proved to be an independent prognostic indicator in multivariate analysis. Conclusions: CD10 immunohistochemical staining can be used as a predictive tool for phylloides tumor but this expression should be interpreted in conjunction with tumor category.

Keywords: CD10 - phylloides tumor - benign - malignant - recurrence - metastasis - immunohistochemistry

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Introduction

Breast cancer is the most common malignancy in females globally and the incidence is higher in Pakistan as compared to neighboring countries and rest of the world (Moore et al., 2009; Shaukat et al., 2013; Asif et al., 2014). Phylloides tumor (PT) is a fibroepithelial neoplasm which characteristically exhibit proliferation of stromal component accompanied by compression of breast ducts and impart typical leaf life appearance (Noguchi et al., 1993; Tan et al., 2013). PT accounts for less than 1% of all breast neoplasm and like others, inherit the recurrent and metastatic potential (Rowell et al., 1993; Barth, 1999; Asoglu et al., 2004; Khurshid et al., 2006; Khurshid et al., 2013). Prediction of possible behavior and outcome of the disease helps oncologist to choose the most suitable treatment modality. Complete surgical resection with safe margins is the mainstay of treatment for all PTs and malignant PTs may require frequent follow-up visits and additional radiotherapy and/ or chemotherapy (Burton et al., 1989, Hawkins et al., 1992; Barth, 1999; Khosravi-Shah, 2011).

On the basis of a constellation of histological features, these tumors are classified into benign, borderline and malignant categories (Tan et al., 2013). Malignant PTs have the highest recurrence (36-65%) and metastatic frequency (35%) and benign PTs have the lowest recurrence (8-21%) and metastatic (7%) frequency (Rowell et al., 1993; Asoglu et al., 2004). The histological features used to characterize PTs do not hold an individual predictive value. Few researchers have evaluated the role of immunohistochemistry (IHC) in predicting the recurrence and metastasis of PTs. Immunohistochemical markers such as Ki-67, p53, CD 31, CD34, CD 117, vimentin, actin, VEGF and EGFR have been evaluated for their possible predictive but none has yet demonstrated a significant role (Millar et al., 1999; Chen et al., 2000; Ortega et al., 2001; Tse et al., 2001; 2003; 2004; 2005; 2009; Tan et al., 2005).

CD 10 is a matrix metalloprotease which plays an important role in stromal differentiation and tumor invasion. It has an established diagnostic role in a variety of tumors especially follicular lymphomas, Burkitt's lymphomas and endometrial stromal tumors (Stein et al., 1984; Gregory et al., 1987; Chu et al., 2001). Expression of CD10 has been demonstrated in a number of other

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non-hematopoietic neoplasms as well as in normal myoepithelial cells of breast (Chu et al., 2000; Moritani et al., 2002). CD10 has also been evaluated in different categories PTs and increased immunohistochemical expression in observed with increasing tumor category (Tse et al., 2005; Tsai et al., 2006; Al-Masri et al., 2012; Hussin et al., 2013). The role of CD10 has been evaluated in predicting possible outcome of PTs and no study has described any correlation of recurrence with CD10 immunohistochemical expresssion. Two studies have described significantly increased expression in metastatic cases (Tsai et al., 2006; Al-Masri et al., 2012). As the studies conducted so far are few in number, therefore, validation with further studies on a larger number of cases is required.

The aim our study was to evaluate the role of CD 10 immunohistochemical stain and clinicopathological features in predicting the survival, recurrence and metastasis in phylloides tumors.

Materials and Methods

The study was approved by institutional "Ethical Review Committee". We retrieved 82 cases of Phylloides Tumor from the surgical pathology database of Section of Histopathology, Aga Khan University Hospital for cases reported between January 2006 and March 2014 through "Integrated Laboratory Management System (ILMS)" software. We included the excisional biopsy, wide local excision, mastectomy and modified radical mastectomy (MRM) specimen. Trucut biopsies, incisional biopsies and blocks received (from outside) for second opinion were not included. Moreover, specimen with clear margins i.e presence of normal breast tissue around the entire periphery of tumor, were included. Verbal informed consent and follow up information regarding recurrence and metastasis was obtained from the patients via telephonic conversation on their contact numbers mentioned at the requisition slips. Pathology reports and slides of the cases were reviewed and data regarding the patient's age, and pathological features such as tumor size, tumor borders, resection margin status, stromal cellularity, stromal overgrowth, nuclear atypia, necrosis, heterologous element, mitotic counts and distance from resection margin was obtained. These cases were divided into three categories including benign, borderline, and malignant according to WHO criteria (Tan et al., 2013).

Representative block of the tumor with maximum cellularity and internal control of myoepithelial cells was selected for prospective staining with CD10 immunohistochemical staining. In recurrent cases, blocks of initial tumor were selected. Immunohistochemical staining was performed on the selected slides (as per kit manufactuer's instructions) by a technologist, utilizing commercially available monoclonal (ready to use) CD10 antibody (code 56C6, Dako) on automated immunostainer. Immunostaining was then be assessed by at least two pathologists. The percentage of stromal cells staining positive was scored from 0% to 100%. Staining intensity was scored as 0, 1+, 2+ and 3+ (no staining, weak, moderate and strong staining, respectively). IHC was considered positive for CD10 if more than 20% stromal cells exhibit moderate (+2) to strong (+3) expression (Tsai WC et al., 2006).

Statistical analysis

Pearson Chi-Square test was applied to examine the correlation of CD10 expression and clinicopathological features with recurrence and metastasis. Disease-free survival (DFS) and overall survival (OS) periods were calculated from the dates of pathologic diagnosis to the dates of recurrence or metastasis and death, respectively. Univariate survival curves were plotted using the Kaplan-Meier method, and statistical differences were determined by using the log-rank test. Multivariate analysis was performed using the stepwise backward LR Cox regression hazards model. A p value of less than .05 was considered significant.

Results

All of the 82 retrieved cases were females. Out of these, 60 (73.2%) were breast lumps (excisional biopsy and wide local excision specimen), followed by 9 (11%) simple mastectomy specimen, 12 (14.6%) were MRM specimen and 01 breast lump with axillary lymph nodes. Age of presentation ranged from 16-69 years with mean age of 37.2±11.9 SD. When stratified in age groups, 25 (30.5%) cases were 30 years or below, majority 48 (58.5%) were between 31 to 50 years and 9 (11.8%) were above 50 years of age. Tumor size ranged from 2.2 to 23 cm with average tumor size of 8.5±5.1cm SD. When stratified into groups, 28 (34.1%) cases were below 5cm, 29 (35.4%) cases were between 5-10 cm and 25 (30.5%) were above 10cm in size. Skin ulceration was observed in 04 (4.9%) cases. Distance from tumor margin ranged from 4-50mm with median of 1mm. 46 (56.1%) cases had safe (≥1cm) margin while 36 (43.9%) cases has <1 cm but clear margin. When categorized according to WHO criteria, 26 (31.7%) cases were benign, 25 (30.5%) were borderline and 31 (37.8%) were malignant. Positive (2+ or 3+) staining for CD10 immunohistochemical stain was observed in 46 (54.1%) cases (Figure 1A-D). Out of 6 (7.3%) recurrent cases, 4 cases were malignant and 2 cases were borderline. All of 3 (3.7%) cases with lymph node metastasis were malignant. Out of 8 (9.8%) cases which died of disease, 7 were malignant and 1 was borderline. In addition to surgical treatment, 3 malignant cases received chemotherapy, 3 malignant and 1 borderline cases received radiotherapy and 1 malignant case received both chemotherapy and radiotherapy. Follow up duration and Disease free survival (DFS) ranged from 1-88 months (median=32months and 29.3months respectively).

When separately analyzed, rate of recurrence and metastasis increased with tumor category but statistical significance was not observed. However, when collectively analyzed as a cohort, combined recurrence and metastatic rate increased significantly with tumor category (p=0.021). Death rate also correlated significantly with tumor category (p=0.008). OS and DFS insignificantly decreased with tumor category.

Similarly, when CD10 expression was separately

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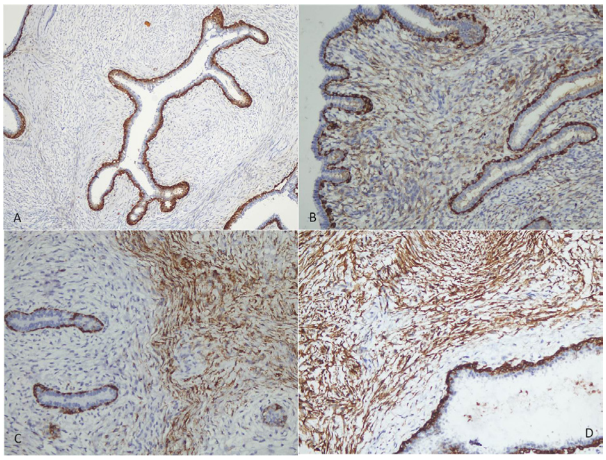

Figure 1. A) No Staining (0) in Benign Phylloides Tumor. CD10 stain highlights a continuous layer of Myoepithelial cells (Internal Control). **B)** Weak (1+) staining in borderline phlloides tumor. Stromal cells fiantly stain with CD10 stain. The intensity is much weaker than myoepithlial cells; **C)** Moderate (2+) staining in borderline phylloides tumor. Stromal cells strongly stain with CD10 stain but the intensity is slightly weaker than myoepithlial cells; **D)** Strong (3+) staining in malignant phylloides tumor. Stromal cells strongly stain with CD10 stain. The intensity is similar to the staining intensity of myoepithlial cells

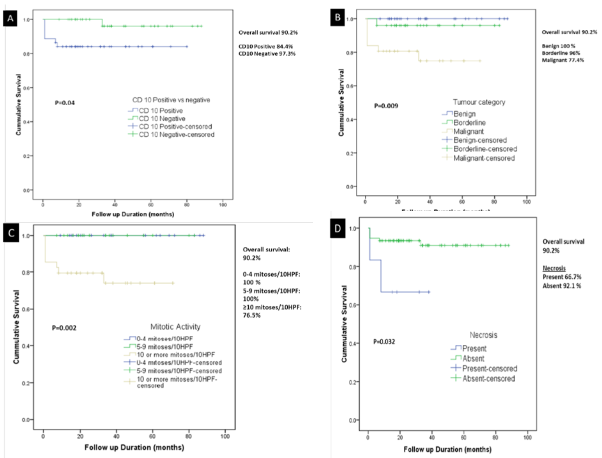

Figure 2. Kaplan-Meier Curves for Overall Survival (OS) showing significant reduction with **A)** CD10 positivity (Log-Rank significance=0.04), **B)** Malignant tumor category (Log-Rank significance=0.009), **C)** Mitotic count ≥10/10HPF (Log-Rank significance=0.002) and D) Necrosis (Log-Rank significance=0.032)

analyzed in cases with recurrence and metastasis statistical difference was not observed. However, when collective cohort of recurrent and metastatic cases was analyzed, statistical significance was observed (p=0.03) (Table 1). We also correlated clinicpathologic and histological features with recurrence and metastasis and found positive correlation of mitotic count and necrosis with recurrence and metastasis.

Tumor categories were also showed an association with a combined increase in recurrence and metastatic rate (p=0.021). Among histological features, mitotic activity and necrosis demonstrated positive correlation with recurrence and metastasis (p=0.008 and p=0.016 respectively). Stromal atypia, stromal cellularity, tumors margins, sarcomatous component, patient's age, tumor size and clear (<1cm) margins were not significantly correlated with these adverse events (Table 2).

Overall survival (OS) and DFS (DFS) significantly varied with significant CD10 staining (p=0.04 & p=0.018), malignant tumor category (p=0.009 & p=0.02),

Table 1. Comparison of CD10 Immunohistochemical Staining between Outcome Cohorts (n=82)

Outcome Cohorts	CD 10 Positive	CD 10 Negative	P value
Recurrent	05 (83.3%)	01 (16.7%)	0.152
Non-recurrent	36 (52.6%)	40 (47.3%)	
Metastatic	3	0	0.160
Non-metastatic	42 (52.3%)	37 (47.7%)	
Combined cohort			
·Recurrent or metastatic	08 (88.9%)	01 (11.1%)	0.030
·Non-recurrent and non-metastatic	37 (50.7%)	36 (49.3%)	
Dead	07 (87.5%)	01 (12.5%)	0.08
Alive	38 (51.4%)	36 (48.6%)	

Table 2. Comparison of Clinicopathologic and Histolological Features with Poor Outcome (Recurrence and Metastasis) (n=82)

Clinical & Histolo-gical features	Non-recurrent &Non-metastatic	Recurrent or Metastatic	p value
Age groups			
30 years or below	22 (30.1%)	03 (33.3%)	0.464
31 to 50 years	44 (60.3%)	04 (44.4%)	
51 years or above	07 (9.6%)	02 (22.2%)	
Tumor size (groups)			
Below 5 cm	26 (35.6%)	02 (22.2%)	0.223
5 to 10 cm	27 (37%)	02 (22.2%)	
Above 10 cm	20 (27.4%)	05 (55.6%)	
Tumor category			
Benign	26 (35.6%)	-	0.021
Borderline	23 (31.5%)	02 (22.2%)	
Malignant	24 (32.9%)	07 (77.8%)	
Stromal Atypia			
Mild	33 (45.2%)	01 (11.1%)	0.08
Moderate	17 (23.3%)	02 (22.2%)	
Marked	23 (31.5%)	06 (66.7%)	
Stromal Cellularity			
Mild	22(30.1%)		0.073
Moderate	27 (37%)	03 (33.3%)	
Marked	24(32.9%)	06 (66.7%)	
Tumor Borders			
Pushing	47 (64.4%)	03 (33.3%)	0.077
Infiltrative	26 (35.6%)	06 (66.7%)	
Mitotic Count			
0-4 / 10HPF	27 (37%)		0.008
5-9 / 10HPF	20 (27.4%)	01 (11.1%)	
>10 /10HPF	26 (35.6%)	08 (88.9%)	
Necrosis			
Present	03 (2.6%)	03 (33.3%)	0.016
Absent	70 (95.9%)	06 (66.7%)	
Skin ulceration			
Present	02 (2.7%)	02 (22.2%)	0.168
Absent	71 (97.3%)	07 (77.8%)	
Sarcomatous component	1	1	0.209
Tumor margin distance	Non-recurrent	Recurrent	
<1cm	01 (16.7%)	35 (46.1%)	0.168
≥1cm	05 (83.3%)	41 (53.9%)	

Table 3. Mean Follow Up Durations and Disease-free Survival Durations of Factors with Significant Difference. (n=82)

	Follow up duration (months)	p value (Log-Rank test)	Disease-free Duration (months)	p value (Log-Rank test)
CD 10 staining				
Positive	28.4	0.04	28.2 (1-80)	0.018
Negative	40.3		37.8 (2-88)	
Tumor category				
Benign	40.3	0.009	36.8	0.02
Borderline	33.6		33.9	
Malignant	28.5		27.3	
Mitotic Count				
0-4 / 10HPF	39.8	0.002	36.4	0.008
5-9 / 10HPF	33.7		33.1	
>10 /10HPF	29		28.6	
Necrosis				
Present	18.7	0.032	16	p<0.0001
Absent	35		33.6	

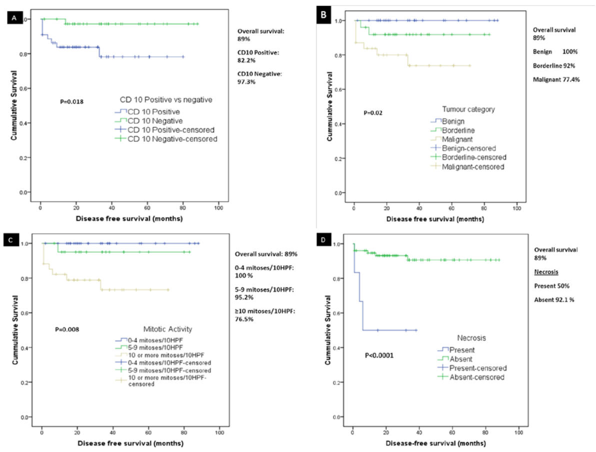

Figure 3. Kaplan-Meier Curves for Disease-freel Survival (DFS) showing significant reduction with **A)** CD10 positivity (Log-Rank significance=0.018), **B)** Malignant tumor category (Log-Rank significance=0.02), **C)** Mitotic count ≥10/10HPF (Log-Rank significance=0.008) and **D)** Necrosis (Log-Rank significance<0.0001)

increased mitotic activity (p=0.002 & p=0.008) and necrosis (p=0.032 & p<0.0001) (Figures 2 and 3). Cases with safe margins of ≥1 cm did not have significantly increased recurrence free survival in comparison to the cases with clear but <1cm surgical margin (p=0.52). The differences in overall follow up durations and disease free durations of these factors are summarized in Table 3. When multivariate analysis was done using Cox regression hazards model neither CD10 expression nor any of the clinicopathologic features showed significance independently (not shown in table).

Discussion

CD10 immunohistochemical staining is specific to myoepithelial cells as this staining is neither shared by other stromal components nor by epithelial components (Gillette et al., 1990; Guelstein et al., 1993). Hence, it is efficiently used as internal control. In English literature, so far 4 studies have been conducted to evaluate the role of CD10 in predicting recurrence and/or metastasis of phylloides tumors. In the earliest study, Tse et al. (2005) evaluated 14 recurrent and 2 metastatic cases in a cohort of 181 phylloides tumors. He performed CD10 staining on both initial as well as second (recurrent/metastatic) cases and did not find any association of staining pattern with recurrence or metastasis. Tsai et al. (2006) selected a small cohort of 22 phylloides tumor with 6 recurrent and 3 metastatic cases. He evaluated CD10, ASMA and Vimentin immunohistochemical stains and did not report any association of these with recurrence or metastasis. Al Marsi et al. (2012), in his study of CD10 expression in 46 cases, observed metastasis in 6 cases which positively correlated with increased immunohistochemical staining. Hussin et al. (2013) also failed to prove any association of CD10 immunoexpression with recurrence in their 9 recurrent cases out of total 61 cases. Our findings are also in concordance with the other studies as we do not find association with recurrence (p=0.152) or metastasis (p=0.16) separately. However, when we combine these cases with features of adverse behavior, we find a positive correlation (p=0.03). In our opinion, both recurrence and metastasis are indicators of poor behavior and association of CD10 expression with this cohort should be interpreted as association with poor behavior i.e either recurrence or metastasis. Moreover, death rate which is another indicator of poor behavior, was also associated with increased CD10 expression (p=0.008).

Among various other immunohistochemical markers like Ki-67, p53, CD 31, CD34, CD 117, vimentin, actin, VEGF and EGFR which have been evaluated in phylloides tumor, only Tan PH et al. (2005) has described a significant association of CD117 staining with recurrence.

Tan PH et al. (2005), in her another study of phylloides tumor, have evaluated the predictive role of histologic parameters in detail and found stromal atypia, stromal cellularity, tumor margins and necrosis to be significant. According to Al Marsi et al. (2012), tumor size and tumor grade was also significantly correlated with metastasis. We also analyzed clinicopathologic and histologic features and observed tumor category, mitotic activity and necrosis to correlate with recurrence and metastasis.

Complete excision of with wide margins is the mainstay of treatment for phylloides tumor. The recurrent rate for negative margins is 10% while it is 18% for excision with positive margins (31). Except for Tan PH et al (2005), we did not find any study which mentioned the margin status in recurrent cases at the time of initial excision. As tumor margin status is the sole predictor of recurrence, in other studies, the assessment of other features in recurrent cases could have been affected by this confounding factor. The strength of our study lies in avoiding this confounding factor by selecting cases with clear margin (at least 4mm) of clearance. When analyzed, 5 (10.9%) out of 41 cases with safe margins (>1cm) showed recurrence while only 1 (2.8%) out of 35 cases with clear but <1cm margin showed recurrence. The difference in recurrence rates of these two groups and recurrence free survival did not differed significantly (p=0.223 and p=0.52).

Although CD10 positivity, malignant tumor category, increased mitoses and necrosis showed a significant reduction in overall survival and disease-free survival but these did not showed independent significance in multivariate analysis.

In conclusion, we conclude that CD10 immunohistochemical staining can help to predict poor behavior of phylloides tumor in terms of recurrence and metastasis but this expression should be interpreted in conjunction with tumor category and other histological features especially mitotic activity and necrosis. Groups with clear tumor margins of greater than or equal/less than 1 cm do not differ significantly in their recurrence rates. The results of this study will help oncologists in predicting the possible outcome and deciding the treatment plans accordingly such as more frequent follow-up visits, radiotherapy and chemotherapy which might increase the recurrence-free and metastasis-free survival.

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References

Asif HM, Sultana S, Akhtar N, Rehman JU, Rehman RU (2014). Prevalence, risk factors and disease knowledge of breast cancer in Pakistan. *Asian Pac J Cancer Prev*, **15**, 4411-6.

Asoglu O, Ugurlu MM, Blanchard K, et al (2004). Risk factors for recurrence and death after primary surgical treatment of malignant phyllodes tumors. *Ann Surg Oncol*, **11**, 1011-7.

Al-Masri M, Darwazeh G, Sawalhi S, et al (2012). Phyllodes Tumor of the Breast: Role of CD10 in predicting metastasis. *Ann Surg Oncol*, **19**, 1181-4.

Barth RJ Jr (1999). Histologic features predict local recurrence after breast conserving therapy of phyllodes tumors. *Breast Cancer Res Treat*, **57**, 291-5.

Barth RJ Jr, Wells WA, Mitchell SE, Cole BF (2009). A prospective, multi-institutional study of adjuvant radiotherapy after resection of malignant phyllodes tumors. *Ann Surg Oncol*, **16**, 2288-94.

Burton GV, Hart LL, Leight GS, et al (1989). Cystosarcoma phyllodes. Effective therapy with cisplatin and etoposide chemotherapy. *Cancer*, **63**, 2088-92.

Chen CM, Chen CJ, Chang CL, et al (2000). CD34, CD117 and actin expression in phyllodes tumor of the breast. *J Surg Res*, **94**, 84-91.

Chu P, Arber DA (2000). Paraffin section detection of CD10 in 505 non hematopoietic neoplasms. *Am J Clin Pathol*, **113**, 374-82.

Chu PG, Arber DA, Weiss LM, Chang KL (2001). Utility of CD10 in distinguishing between endometrial stromal sarcoma and uterine smooth muscle tumours: an immunohistochemical comparison of 34 cases. *Mod Pathol*, **14**, 465-471.

Gillette CE, Bobrow LG, Millis RR (1990) S100 protein in human mammary tissue: Immunoreactivity in breast carcinoma, including Paget's disease of the nipple and value as a marker of myoepithelial cells. *J Pathol*, **160**, 19-24.

Gregory CD, Tursz T, Edwards CF, et al (1987). Identification of a subset of normal B cells with a Burkitt's lymphoma (BL)-like phenotype. *J Immunol*, **139**, 313-8.

Guelstein VI, Tchypysheva TA, Ermilova VD, Ljubimov AV (1993) Myoepithelial and basement membrane antigen and malignant human breast tumors. *Int J Cancer*, **53**, 269-77.

Hawkins RE, Schofield JB, Wiltshaw E, et al (1992). Ifosfamide is an active drug for chemotherapy of metastatic cystosarcoma phyllodes. *Cancer*, **69**, 2271-5.

Hussin H, Pailoor J, Cheng PS (2013). The role of CD10 immunohistochemistry in the grading of phyllodes tumor of the breast. *J Interdiscipl Histopathol*, **1**, 195-203.

Khosravi-Shahi P (2011). Management of non-metastatic phyllodes tumors of the breast: review of the literature. *Surg Oncol*, **20**, 143-8.

Khurshid A, Kayani N, Bhurgri Y (2006). Phylloides tumors in adolescent girls and young women in Pakistan. *Asian Pac J Cancer Prev*, **7**, 563-6.

Khurshid A, Faridi N, Arif AM, Naqvi H, Tahir M (2013). Breast lesions in adolescents and young women in Pakistan-a 5 year study of significance of early recognition. *Asian Pac J Cancer Prev*, **14**, 3465-7.

Millar EK, Beretov J, Marr P, et al (1999). Malignant phyllodes tumours of the breast display increased stromal p53 protein expression. *Histopathology*, **34**, 491-6.

Moore MA, AriyaratneY, Badar F, et al (2009). Cancer epidemiology in South Asia past, present and future. *Asian Pac J Cancer Prev*, **10**, 49-67.

Moritani S, Kushima R, Sugihara H, et al (2002). Availability of CD10 immunohistochemistry as a marker of breast myoepithelial cells on paraffin sections. *Mod Pathol*, **15**, 397-405.

Noguchi S, Motomura S, Inaji H, Imaoka S, Koyama H (1993). Clonal analysis of fibroadenoma and phyllodes tumor of the breast. *Cancer Res*, **53**, 4071-4.

Ortega E, Aranda FI, Chulia MT, et al (2001). Phyllodes tumor of the breast with actin inclusions in stromal cells: diagnosis by fine-needle aspiration cytology. *Diagn Cytopathol*, **25**, 115-7.

Rowell MD, Perry RR, Hsiu JG, Barranco SC (1993). Phyllodes tumors. *Am J Surg*, **165**, 376-9.

Shaukat U, Ismail M, Mehmood N (2013). Epidemiology, major risk factors and genetic predisposition for breast cancer in the Pakistani population. *Asian Pac J Cancer Prev*, **14**, 625-9.

Stein H, Lennert K, Feller AC, Mason DY (1984). Immunohistological analysis of human lymphoma: correlation of histological and immunological categories. *Adv Cancer Res*, **42**, 67-147.

Tan PH, Jayabaskar T, Chuah KL, et al (2005). Phyllodes tumors of the breast: the role of pathologic parameters. *Am J Clin Pathol*, **123**, 529-40.

Tan PH, Jayabaskar T, Yip G, et al (2005). P53 and c-kit (CD117) protein expression as prognostic indicators in breast phyllodes tumors: a tissue microarray study. *Mod Pathol*, **18**, 1527-34.

Tan PH, Tse GM, Lee A (2013). WHO classification of Tumors of the Breast (4th edn). IARC Press, Lyon, France pp 142-7.

Tsai WC, Jin JS, Yu JC, Sheu LF (2006). CD10, actin, and vimentin expression in breast phyllodes tumors correlates with tumor grades of the WHO grading system. *Int J Surg Pathol*, **14**, 127-31.

Tse GM, Lui PC, Scolyer RA, et al (2003). Tumour angiogenesis and p53 protein expression in mammary phyllodes tumours. *Mod Pathol*, **16**, 1007-13.

Tse GMK, Lui PCW, Lee CS, et al (2004). Stromal expression of vascular endoethelial growth factor correlates with tumor grade and microvessel density in mammary phyllodes tumors: a multicenter study of 185 cases. *Hum Pathol*, **35**, 1053-7.

Tse GM, Tan PH (2005). Recent advances in the pathology of fibroepithelial tumors of the breast. *Curr Diagn Pathol*, **11**, 426-34.

Tse GM, Tsang AK, Putti TC, et al (2005). Stromal CD10 expression in mammary fibroadenomas and phyllodes tumours. *J Clin Pathol*, **58**, 185-9.

Tse GMK, Lui PC, Vong JS, et al (2009). Increased epidermal growth factor receptor (EGFR) expression in malignant mammary phyllodes tumors. *Breast Cancer Res Treat*, **114**, 441-8.

Yang X, Kandil D, Cosar EF, Khan A (2014). Fibroepithelial tumors of the breast: pathologic and immunohistochemical features and molecular mechanisms. *Arch Pathol Lab Med*, **138**, 25-36.