

Breast malignant phyllodes tumor with rare pelvic metastases and long-term overall survival

A case report and literature review

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Abstract

Background: Malignant phyllodes tumor (PT) is a rare fibro epithelial neoplasm of the breast, which is poor prognosis due to high risk of recurrence and distant metastasis.

Methods: We report a case of malignant PT. It had recurred locally five times, and the sixth relapse was occurred 54 months after first diagnosis, presenting a huge pelvic mass (14 cm × 11 cm) by CT scan. Histopathological examination has demonstrated a metastatic phyllodes tumor. After postoperative chemotherapy treatment, a longer survival has been achieved, which is more than 72 months.

Results: Our case report describes a breast PT with several local recurrences and a rare metastasis (pelvic cavity), but long-term overall survival was achieved after surgery and chemotherapy.

Conclusion: We conclude that trustworthy prognosticators that identify patients with excessive potential of aggressive clinical course should be explored. Moreover, proper treatment could prolong overall survival of metastatic PT patients.

Abbreviations: HPF = (high power field), PT = phyllodes tumor.

Keywords: case report, long-term survival, malignant phyllodes tumor, pelvic metastases

1. Introduction

Phyllodes tumors (PTs) are unique neoplastic lesions that are comprised of both stromal and epithelial components, and they account for 0.3% to 1% of breast tumors in women.^[1] PTs are subdivided into benign, borderline, and malignant categories

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JS and SZ contributed equally to this study.

The authors obtained written consent of the patient to describe her illness and publish this case report.

Ethics committee approval is not included as it is commonly accepted that case reports do not require such approval. In our work, we did not use patient data that would allow identifying her. Patient agreed to all above diagnostic tests and treatment that was used.

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according to histologic features.^[1] Approximately 25% of PTs are considered malignancy,^[2] and 20% to 50% of malignant PTs give rise to metastasis.^[3–6] Most of the cases, malignant PTs metastasize to lung, pleura, bone and soft tissue,^[6–8] rare metastatic sites were reported including liver,^[9,10] brain,^[11–13] heart,^[10] mesentery,^[14] spleen,^[10,11] kidney, adrenals, cervical,^[10] pancreas,^[9] uterus, thyroid,^[11] skin.^[14] Recurrence or metastasis of breast PTs predicts a shorter survival time, <1 year.^[5] Here, we present a case of a female breast malignant PT patient with local recurrences and subsequent metastasis to the pelvic cavity and bone; in the end, the patient was expired after 72 months of follow-up.

2. Case report

A 30-year-old female patient was admitted to the hospital complaining of a mass in her left breast for 3 months. No significant signs were observed in her past medical and family history. Physical examination revealed a mass (5 cm × 5 cm) with a clear border in the left breast. Then, the patient underwent partial mastectomy and histopathological examination revealed malignant PT.

The patient had 5 recurrences in situ later and detailed descriptions were shown in Table 1. Additionally, axillary lymph node dissection was performed in the third relapse because of axillary lymph node metastasis. In the following months, the patient was chosen to a routine follow-up procedure.

Unexpectedly, 54 months after diagnosis, the patient came to our hospital complaining of abdominal distension. Computerized tomography (CT) scan of abdominal and pelvic revealed a colossal, lobulated, and well-defined mass in the pelvic, 14 × 11 cm in size (Fig. 1A). The pelvic mass was suspected as a metastasis of breast PT. Furthermore, ¹⁸F-FDG positron emission tomogra-

Table 1**Timeline.**

Time	Description	Treatment
2010.04	Diagnosis of primary malignant phyllodes tumor	Partial mastectomy
2011.08	Local recurrence	Mastectomy
2012.11	The second local recurrence	Chest wall tumor resection
2013.07	The third local recurrence with axillary metastasis	Axillary tumor resection and axillary lymph node dissection
2013.12	The fourth local recurrence	Chest wall tumor resection
2014.07	The fifth local recurrence	Chest wall tumor resection
2014.09	Detection of pelvic and bone metastasis	Pelvic tumorectomy
2014.10		beginning the chemotherapy
2015.07	Recurrence of pelvic mass	Recurrent lesions resection
2015.11	The second recurrence of pelvic mass	Recurrent lesions resection
2016.03	The patient expired	

phy and computed tomography (FDG-PET/CT) were conducted and showed a tremendous mass with high metabolism in the pelvic cavity (Fig. 2A and B). Also, there was evidence of a thoracic vertebra and rib metastasis (Fig. 2C–F). The patient was referred to our department and the pelvic tumorectomy was carried out. Intraoperative frozen section revealed the presence of malignant spindle tumor cells. Then, panhysterectomy was continually performed. Postoperative histopathologic examination demonstrated metastatic malignant PT (Fig. 3). Through Immunohistochemical staining, SMA, CD34 were positive and desmin, CD117, EMA, ER, PR, S-100, Bcl-2, NF, GFAP, and DOG-1 were negative. Postoperative CT scan showed clean excision of pelvic metastatic tumor without residue (Fig. 1B).

The patient received 4 courses of postoperative chemotherapy (doxorubicin hydrochloride 40 mg/m² on days 1–5, Ifosfamide 2

g/m² on days 1–5, per 21 days). Then, only doxorubicin hydrochloride (40 mg/m² on days 1, per 21 day) was given for 3 courses later because of intolerable nausea and vomiting. Evaluating curative effect after the accomplishment of chemotherapy was stable disease (SD, Fig. 1C). The patient did not receive radiotherapy. Subsequently, the patient experienced pelvic metastases twice 3 months or 7 months after the chemotherapy (Fig. 1D and F). All of the metastatic lesions were palliative treated by operation (Fig. 1E).

The patient died 72 months after diagnosis of PT.

3. Discussion

The malignant PT which has a high tendency toward local recurrence and distant metastasis is uncommon in the breast. Distant metastasis developed at different time after the first diagnosis of breast PT. The average time to metastasis was 15 to 26 months,^[15] however, the patient in our case occurred metastasis 54 months after diagnosis. Most distant metastasis of malignant PTs present in lungs, pleura, bone, and soft tissue (Table 2). Rare metastatic sites have also been showed in Table 3. However, metastasis to pelvic cavity described in this case was not included based on our knowledge.

Operation is the basic treatment of breast PT regardless of the nature of the tumor. Wide local excision with negative margins of 1 to 2 cm is recommended. If negative margins cannot be obtained, then simple mastectomy is preferred. The efficacy between wide local excision and mastectomy is indistinct.^[16] Although the possibility of local recurrence declined in patients who underwent mastectomy, overall survival did not improve when perform mastectomy.^[17,18] It was unnecessary to carry out axillary lymph node dissection with breast PT if no clinically evident involvement of axillary nodes.^[18] Despite clean tumor resection and negative margin, local recurrence can hardly be avoided. The risk of relapse in malignant PTs was significantly greater than benign tumors.^[19] In this case, the patient was performed partial mastectomy after initial diagnosis as PT. Consistent with the literatures reported, the patient relapsed after 17 months, subsequently, the patient experienced other 4 times local recurrence.

Whether chemotherapy could improve disease-free survival (DFS) or overall survival (OS) for PT of the breast is controversial.^[20,21] There are no randomized clinical trials proving the effectiveness of chemotherapy in malignant PT. Morales-Vazquez suggested that adjuvant chemotherapy did not improve the 5-year recurrence-free survival in patients with breast malignant PTs after surgical resection.^[21] However, in the

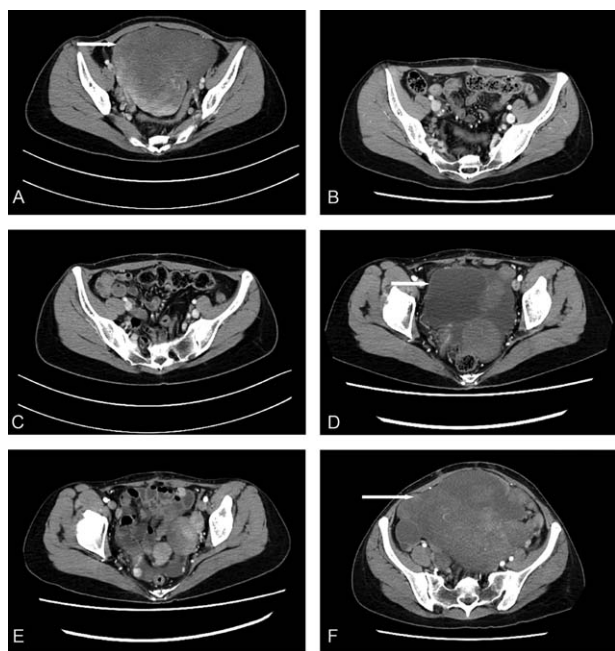


Figure 1. CT scan showed an inhomogeneous density mass with clear border in the pelvic cavity (white arrow) (A). After pelvic tumorectomy, CT scan showed no residual tumor in the pelvic cavity (B). No recurrent lesions were detected in the CT scan after chemotherapy (C). Multiple fusion lesions were found in the pelvic cavity 3 months after chemotherapy (white arrow) (D). The recurrent lesion had shrunk to a small area with obvious enhancement after surgical treatment (E). CT scan displayed that ill-defined lesions increased (white arrow) (F). CT=computed tomography.

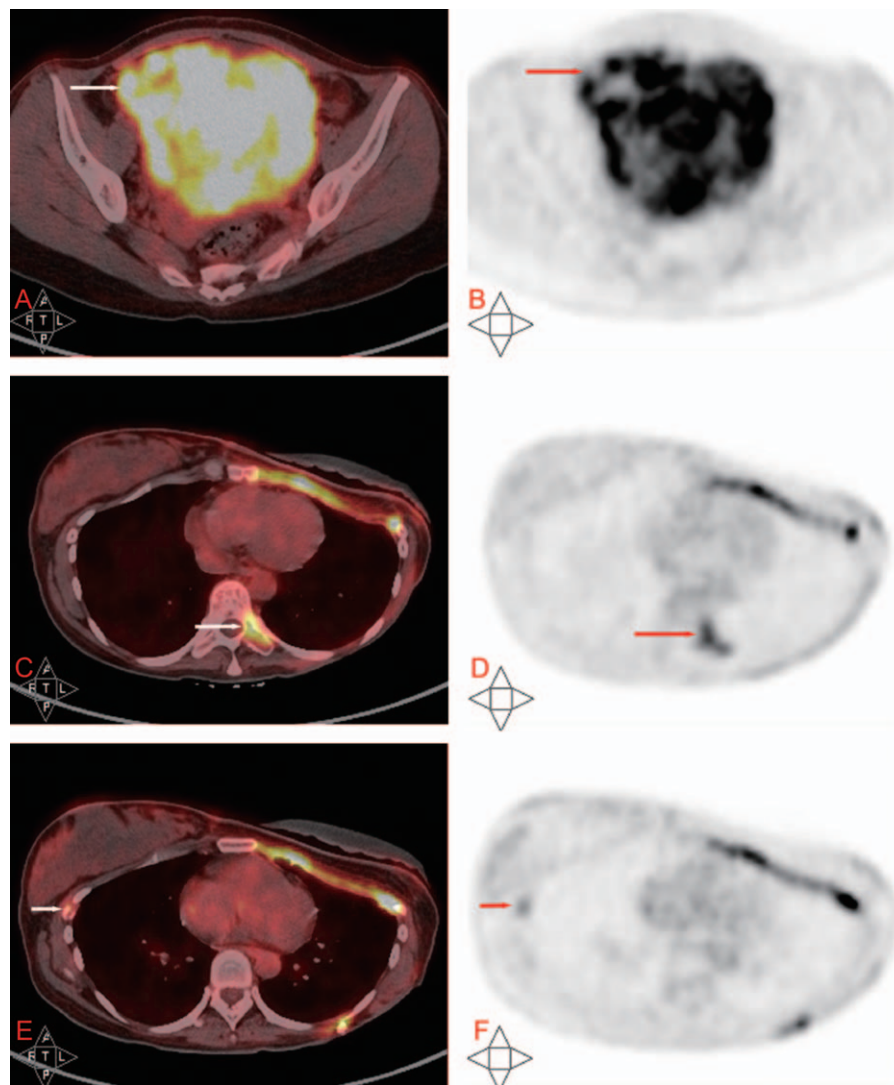


Figure 2. PET-CT obtained at baseline showed distant metastases involving the pelvic cavity (A, B), thoracic vertebra (C, D), and rib (E, F) (arrow). PET-CT = ^{18}F -FDG positron emission tomography-computed tomography.

patients with metastasis PT, chemotherapy should be considered the optimal treatment.^[22] Hawkins presented a case which received combination chemotherapy as soon as metastasis appeared had 61 months disease-free survival, which was longer than other available literatures.^[20] Radiotherapy plays a major role in the prevention of postoperative recurrence of several solid tumors. While currently, there is no consensus on the role of radiotherapy in malignant PT.^[23] Pandey et al^[24] and Belkacemi et al^[25] suggested that adjuvant radiotherapy after surgery had no significant impact on disease-free survival or overall survival. In the report from the Surveillance Epidemiology and End Results (SEER) Program on 821 malignant PTs, radiotherapy plus surgery predicted for worse cancer-specific survival compared with surgery alone.^[16]

Local recurrence is a risk factor of tumor distant metastasis. Most distant metastasis of breast PT took place after local recurrence.^[9,26] However, other investigators did not observe the association between local recurrence and systemic spread.^[24] Moreover, local recurrence can be salvaged by secondary surgery.^[25] Whether the local recurrence is a predictive factor for metastasis of breast PT is still elusive.^[5] A study suggested that

tumor size tended to be an independently predictive factor for local recurrence.^[9] Strong CEA expression in the epithelia correlated with local recurrence of PT of the breast, therefore, suitable to predict the clinical course of the disease.^[27] In addition, genetic abnormalities were pointed out to be responsible for recurrences of PT, especially 1q gain mapped to 1q21–23 region and 3p loss mapped to the FHIT gene in the 3p12–14 region.^[28] Tumor distant metastasis is the main cause of survival threatening. As long as the breast PT progresses to distant metastasis, its prognosis is unfavorable, and median survival ranges from 5 to 24 months.^[4,6,15,29] Our described patient gave rise to metastases after 54 months of first diagnosis and then died after 72 months. Microscopically, histology features of malignant PT are clear stromal cellular atypia, marked stromal overgrowth, infiltrating tumor margins, and $>10/10$ HPF of mitotic activity. Stromal cellularity, stromal overgrowth, tumor margin, and mitotic activity were all significantly correlated with distant metastases.^[17] It has been noted that 87.5% of PTs which had a characterization of mitotic activity greater than 15/10 HPF finally metastasized.^[30] MiR-21 played a crucial role in the molecular pathogenesis of PT metastasis. It induced myofibroblast

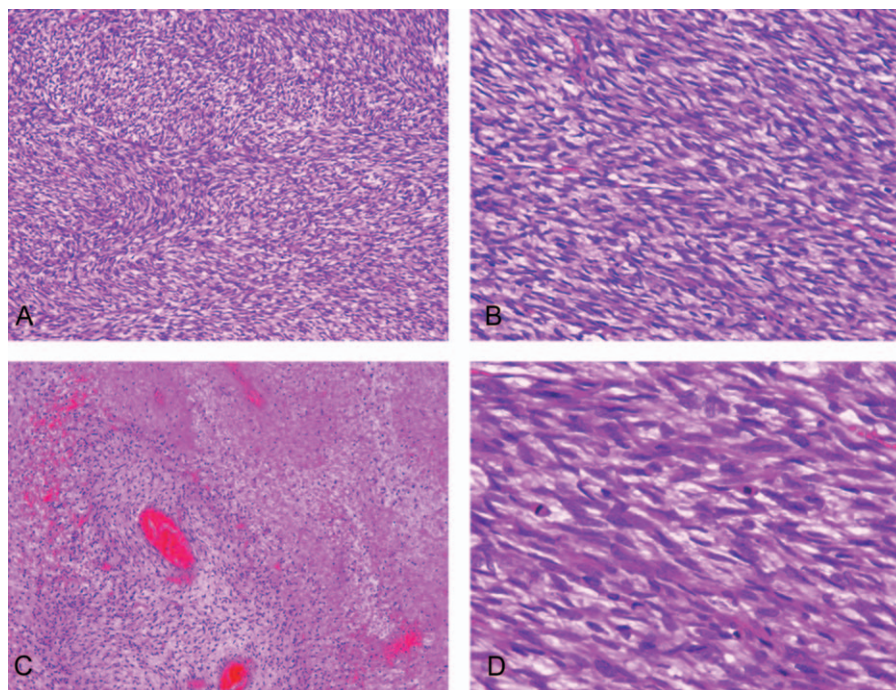


Figure 3. Histopathological examination with hematoxylin and eosin stain showed spindle cell tumor of the pelvic cavity. Microscopically, the tumor consisted of an epithelial and a cellular stromal component (A × 100, B × 200). Massive necrosis was also observed in the tumor (C × 40). The nuclei exhibited moderate atypia (D × 400).

Table 2
Reported common metastatic sites for phyllodes tumor.

Metastatic sites	Percentage
Lung ^[6,9,10,13,35]	41.7–91.0%
Pleura ^[6,9,14]	11.1–67.0%
Bone ^[6,9,10,13]	20.0–44.0%
Soft tissue ^[9,14]	37.5–58.3%
Thoracic cavity ^[9]	33.3%
Viscera ^[14]	15.0%
Gastrointestinal tract ^[36]	<1.0%

differentiation, subsequently regulated migration, and promoted metastasis.^[31] Autophagy-related protein LC3A expression in the stromal component of PT was significantly associated with distant metastasis.^[32] Metastatic PTs had a remarkably higher stromal CD10 expression, and cases with negative CD10 expression did not metastasize.^[33,34] High expression of CD10, as a metalloprotease, might increase the potential of metastasis by providing tumors with the capacity of invading vessel walls.^[33] However, these markers are still not powerful prediction in clinical practice.^[27,28,34] It is important to identify

Table 3
Clinical characteristics, pathological findings, and follow-up of 20 patients with phyllodes tumor metastasize to rare sites.

Author	Year	Age	Tumor size (cm)	Mitosis activity per 10HPF	Site of DM	Follow-up time (months)
Wei et al ^[9]	2014	24	4	/	Soft tissue, thoracic cavity	76.5
Wei et al ^[9]	2014	38	6	/	Soft tissue, thoracic cavity	55.6
Wei et al ^[9]	2014	46	2	/	Soft tissue, thoracic cavity	32.9
Wei et al ^[9]	2014	42	18	/	Soft tissue, thoracic cavity, bone	35.7
Wei et al ^[9]	2014	68	2	/	Lung, bone, pleura, liver	32.1
Wei et al ^[9]	2014	31	7	/	Lung, bone, pleura, soft tissue, liver	17.8
Norris and Taylor ^[10]	1967	49	12	/	Lung, bone, liver, adrenal	/
Wei et al ^[9]	2014	53	7	/	Pancreas	41.1
Norris and Taylor ^[10]	1967	28	4	13	Lung, heart	/
Norris and Taylor ^[10]	1967	58	5	30	Lung, bone, heart, spleen, kidney, mesentery	/
Norris and Taylor ^[10]	1967	80	12	10	Cervix	/
Rhodes et al ^[12]	1978	54	25	10	Brain	/
Rhodes et al ^[12]	1978	48	23	Rare	Brain	48
Ramakant et al ^[13]	2013	/	/	/	Brain	3
Ward and Evans ^[11]	1986	63	5	>20	Brain	13
Ward and Evans ^[11]	1986	38	/	5	Lung, gastrointestinal tract, spleen, thyroid	7
Ward and Evans ^[11]	1986	43	18	>20	Gastrointestinal tract, uterus	32
Asoglu et al ^[36]	2006	31	15	/	Gastrointestinal tract	12
Karczmarek-Borowska et al ^[37]	2015	41	/	13–15	Lung, bone, liver, kidney	18
Present case	2016	30	5	10	Pelvic cavity, bone, axilla	72

DM = distant metastasis, HPF = high power field.

some reliable factors to predict recurrence of PT and manage patients in early period.

4. Conclusion

Current case represented a malignant breast PT with local recurrences and an extraordinary localization of metastasis (pelvic cavity), but the patient possessed of long-term survival following operation and chemotherapy. From the case report of our study, we proposed that reliable predictive factors should be explored to identify patients at high risk of local recurrence and distant metastasis. Although breast PTs have unfavorable prognosis, there is no standardized therapeutic strategy for it, so there is urgent need to perform well-designed prospective studies for investigating the roles of different strategies in treatment of breast PT.

References

- [1] International Agency for Research on Cancer, Lakhani SR. *Cancer IAFRo, Organization WHWHO Classification of Tumours of the Breast*. 2012.
- [2] Mangi AA, Smith BL, Gadd MA, et al. Surgical management of phyllodes tumors. *Arch Surg* 1999;134:487–92.
- [3] Lakhani S, Ellis I, Schnitee S, et al. *World Health Organisation Classification of Tumors of the Breast*. 2012;Lyon, France:International Agency for Research on Cancer (IARC), 142–147.
- [4] Reinfuss M, Mitus J, Duda K, et al. The treatment and prognosis of patients with phyllodes tumor of the breast: An analysis of 170 cases. *Cancer* 1996;77:910–6.
- [5] Abdalla H, Sakr M. Predictive factors of local recurrence and survival following primary surgical treatment of phyllodes tumors of the breast. *J Egypt Natl Canc Inst* 2006;18:125–33.
- [6] Kapisir I, Nasiri N, A'Hern R, et al. Outcome and predictive factors of local recurrence and distant metastases following primary surgical treatment of high-grade malignant phyllodes tumours of the breast. *Eur J Surg Oncol* 2001;27:723–30.
- [7] Fou A, Schnabel FR, Hamele-Bena D, et al. Long-term outcomes of malignant phyllodes tumors patients: an institutional experience. *Am J Surg* 2006;192:492–5.
- [8] Kim S, Kim JY, Kim do H, et al. Analysis of phyllodes tumor recurrence according to the histologic grade. *Breast Cancer Res Treat* 2013;141:353–63.
- [9] Wei J, Tan YT, Cai YC, et al. Predictive factors for the local recurrence and distant metastasis of phyllodes tumors of the breast: a retrospective analysis of 192 cases at a single center. *Chin J Cancer* 2014;33:492–500.
- [10] Norris HJ, Taylor HB. Relationship of histologic features to behavior of cystosarcoma phylloides. Analysis of ninety-four cases. *Cancer* 1967;20:2090–9.
- [11] Ward RM, Evans HL. Cystosarcoma phylloides. A clinicopathologic study of 26 cases. *Cancer* 1986;58:2282–9.
- [12] Rhodes RH, Frankel KA, Davis RL, et al. Metastatic cystosarcoma phylloides. A report of 2 cases presenting with neurological symptoms. *Cancer* 1978;41:1179–87.
- [13] Ramakant P, Chakravarthy S, Cherian JA, et al. Challenges in management of phyllodes tumors of the breast: a retrospective analysis of 150 patients. *Indian J Cancer* 2013;50:345–8.
- [14] Hawkins RE, Schofield JB, Fisher C, et al. The clinical and histologic criteria that predict metastases from cystosarcoma phylloides. *Cancer* 1992;69:141–7.
- [15] Barth RJ, Wells WA, Mitchell SE, et al. A prospective, multi-institutional study of adjuvant radiotherapy after resection of malignant phyllodes tumors. *Ann Surg Oncol* 2009;16:2288–94.
- [16] Macdonald OK, Lee CM, Tward JD, et al. Malignant phyllodes tumor of the female breast: association of primary therapy with cause-specific survival from the Surveillance, Epidemiology, and End Results (SEER) program. *Cancer* 2006;107:2127–33.
- [17] Chen WH, Cheng SP, Tzen CY, et al. Surgical treatment of phyllodes tumors of the breast: retrospective review of 172 cases. *J Surg Oncol* 2005;91:185–94.
- [18] Salvadori B, Cusumano F, Bo RD, et al. Surgical treatment of phyllodes tumors of the breast. *Cancer* 1989;63:2532–6.
- [19] Barth RJJr. Histologic features predict local recurrence after breast conserving therapy of phyllodes tumors. *Breast Cancer Res Treat* 1999;57:291–5.
- [20] Hawkins R, Schofield J, Wiltshaw E, et al. Chemotherapy for metastatic cystosarcoma phylloides: ifosfamide is an active drug. *Cancer* 1992;69:2271–5.
- [21] Morales-Vásquez F, Gonzalez-Angulo AM, Broglio K, et al. Adjuvant chemotherapy with doxorubicin and dacarbazine has no effect in recurrence-free survival of malignant phyllodes tumors of the breast. *Breast J* 2007;13:551–6.
- [22] Mitus JW, Blecharz P, Walasek T, et al. Treatment of patients with distant metastases from phyllodes tumor of the breast. *World J Surg* 2016;40:323–8.
- [23] Khosravi-Shahi P. Management of non metastatic phyllodes tumors of the breast: review of the literature. *Surg Oncol* 2011;20:e143–8.
- [24] Pandey M, Mathew A, Kattoor J, et al. Malignant phyllodes tumor. *Breast J* 2001;7:411–6.
- [25] Belkacemi Y, Bousquet G, Marsiglia H, et al. Phyllodes tumor of the breast. *Int J Radiat Oncol Biol Phys* 2008;70:492–500.
- [26] Moffat CJC, Pinder SE, Dixon AR, et al. Phyllodes tumours of the breast: a clinicopathological review of thirty-two cases. *Histopathology* 1995;27:205–18.
- [27] Alberti O, Brentani MM, Goes JCS, et al. Carcinoembryonic antigen. A possible predictor of recurrence in cystosarcoma phylloides. *Cancer* 1986;57:1042–5.
- [28] Tse GM, Niu Y, Shi HJ. Phyllodes tumor of the breast: an update. *Breast Cancer* 2010;17:29–34.
- [29] de Roos WK, Kaye P, Dent DM. Factors leading to local recurrence or death after surgical resection of phyllodes tumours of the breast. *Brit J Surg* 1999;86:396–9.
- [30] Grimes MM. Cystosarcoma phylloides of the breast: histologic features, flow cytometric analysis, and clinical correlations. *Mod Pathol* 1992;5:232–9.
- [31] Gong C, Nie Y, Qu S, et al. miR-21 induces myofibroblast differentiation and promotes the malignant progression of breast phyllodes tumors. *Cancer Res* 2014;74:4341–52.
- [32] Kim SK, Jung WH, Koo JS. Expression of autophagy-related proteins in phyllodes tumor. *Int J Clin Exp Pathol* 2013;6:2145–56. 09/15.
- [33] Al-Masri M, Darwazeh G, Sawalhi S, et al. Phyllodes tumor of the breast: role of CD10 in predicting metastasis. *Ann Surg Oncol* 2012;19:1181–4.
- [34] Tariq MU, Haroon S, Kayani N. Role of CD10 immunohistochemical expression in predicting aggressive behavior of phylloides tumors. *Asian Pac J Cancer Prev* 2015;16:3147–52.
- [35] Cohn-Cedermark G, Rutqvist LE, Rosendahl I, et al. Prognostic factors in cystosarcoma phylloides. A clinicopathologic study of 77 patients. *Cancer* 1991;68:2017–22.
- [36] Asoglu O, Karanlik H, Barbaros U, et al. Malignant phyllode tumor metastatic to the duodenum. *World J Gastroenterol* 2006;12: 1649–51.
- [37] Karczmarek-Borowska B, Bukala A, Syrek-Kaplita K, et al. A rare case of breast malignant phyllodes tumor with metastases to the kidney: case report. *Medicine* 2015;94:e1312.