Radiotherapy with apatinib for recurrence of malignant phyllodes tumor of the breast
A case report
Hong Wu, MMa, Lei Li, MMa, Jing Yang, MMa, Chen Guo, MMa, Weiming Zhang, MMa, Hui Wang, MMb,*

Abstract
Rationale: Malignant phyllodes tumors of the breast are rare, and there are currently no guidelines and a large number of clinical trials to guide the treatment of recurrence tumor. Here we reported a case of radiotherapy with apatinib for the treatment of recurrent malignant phyllodes tumor of the breast.

Patient concerns: A 58-year-old patient with massive breast mass was admitted to our hospital. Two months after surgical treatment, the tumor recurred in the chest wall scar.

Diagnoses: The histopathologic diagnoses was right breast malignant phyllodes tumor with chondrosarcomas and osteosarcomas in some areas.

Interventions: The patient was first treated with surgery. Malignant phyllodes tumor recurred in the chest wall two months after surgery and was treated with radiotherapy and apatinib.

Outcomes: With surgery, radiotherapy and apatinib treatment, the patient still died within several months.

Lessons: Apatinib and radiotherapy failed to obtain good therapeutic effect in the recurrence of breast malignant phyllodes tumor in this case.

Abbreviations: PT = phyllodes tumor, RT = radiation therapy.

Keywords: apatinib, breast, case report, phyllodes tumor

1. Introduction
Phyllodes tumors are rare fibroepithelial neoplasms breast tumors and are found in account for only 0.3 to 0.5% of all breast tumors.[1] The WHO classify Phyllodes tumors as benign, borderline, and malignant that base on stromal patterns of cellularity, nuclear atypia, mitotic activity, heterologous stromal differentiation, Phyllodes tumors, stromal hypercellularity and tumor margin appearance.[2] The majority of phyllodes tumors occur in women between 35 and 55.[3] The pathogenesis of general phyllodes tumors has the following several kinds: endocrine hormone disorder, fibrous adenoma on the basis of progress, race and reproductive lactation and other factors.[4,3]

Surgical treatment is preferred for malignant phyllodes breast tumor. However, there are few reports on the sensitivity of radiochemotherapy and other drugs after tumor recurrence.

In this report, we present a rare case of malignant phyllodes tumor that developed on the basis of fibroadenoma and treated it with surgery, radiotherapy and apatinib. But the patient’s condition continued to deteriorate rapidly and eventually died within several months.

When the patient’s disease worsened, informed written consent was obtained from the patient for publication of this case report.

2. Case presentation
A 58-year-old female patient was admitted to our hospital in September, 2018. But the history of breast related diseases started eight years ago. In October 2010, the patient had a painless mass about 0.5 cm in the upper quadrant of the right breast. Standard mammography examination indicated cystic changes in double breast and nodules in the right breast. The patient underwent a minimally invasive resection of the tumor. Postoperative pathology indicated breast hyperplasia and fibroadenoma. In July 2012, the patient’s right breast mass recurred. Right breast mass resection was performed again, and the postoperative pathology was still fibroadenoma of breast.

The recurrence of the right breast mass occurred in June 2013. At that time, the size of the tumor was about 1 × 1 cm, but the patient chose not to have surgery. Five years later, in September 2018, the mass of the right breast increased to about 15 × 10 cm. The pain in the right breast was obvious. The volume of the right breast increased significantly, with high skin tension, local redness and obvious tenderness, occupying most of the breast. Magnetic resonance examination of the breast suggested space-
occupying lesions in the right breast, which was considered as breast cancer [BI-RADS category 5] with enlarged lymph nodes in the right axilla (Fig. 1). The patient underwent right breast mass biopsy under ultrasound guidance. Postoperative pathology indicated a right breast phyllodes tumor. Then, the patient underwent surgical treatment, and the surgery was as follows: right breast phyllodes tumor expanded resection + axillary lymph node dissection + free DIEP skin flap repair + fibrous vascular anastomosis x 4 + umbilical angioplasty. The histopathologic findings: a right breast malignant phyllodes tumor with chondrosarcomas and osteosarcomas in some areas. No tumor was found in the nipple, incised line and marked incised margin. Immunohistochemistry: CK-,CKT-,Vimentin+. No metastatic tumor was found in the right axillary lymph node (0/27).

The patient rested for 2 months after surgery. Then the patient was found to have a 1 x 1 cm nodule in the surgical scar on the right chest wall. The skin at the nodule is reddened without tenderness. Computed tomography (CT) imaging of the chest revealed a small tissue density mass in the right chest wall (Fig. 2). The pathological results of nodular puncture showed malignant tumor, which tended to be phyllodes tumor. The oncologist gave radiotherapy to the right chest with the recurrent nodule. The prescription dose was PTV 60Gy/30 fractions. Because of the patient refused chemotherapy, she was treated with apatinib. The apatinib dose applied was 0.5g per day continuously.

Half month after radiotherapy, the patient presented lumbo-sacral pain. PET-CT showed that the patient had multiple bones metastasis (Fig. 3A). The retraction of the tumor in the radiotherapy area was not obvious (Fig. 3B). Oncologists recommend systemic chemotherapy and radiation therapy for metastatic lesions. The patient refused other treatments and continued to take apatinib. A month later (in March 2019), the patient had frequent seizures at home, combined with headache and mental disorders. In the end, we speculated that she died of brain metastases, brain hernia.

3. Discussion
Phyllodes tumor (PT) of the breast is a rare fibroepithelial neoplasm, accounting for 0.3% to 1% of all breast tumors. Pathology shows continuity from benign to malignant. Approximately 85% to 90% of phyllodes tumors are benign and 10% to 15% are malignant. Pathologically, these tumors are characterized by mildly increased stromal cellularity and nuclear atypia. Benign PT is difficult to distinguish from fibroadenoma of the breast. Malignant PT is characterized by...
marked stromal cellularity and nuclear pleomorphism, stromal overgrowth. The presence of heterologous sarcomatous elements (liposarcoma, chondrosarcoma, and osteosarcoma) can be a diagnosis of malignant phyllodes tumor. In this case, the patient developed benign PT into malignant PT over a period of years.

The main characteristics of malignant PT are local recurrence and progression. Surgical excision is an important treatment for PT. Breast-conserving surgery with appropriate margins (≥1 cm) is the preferred primary therapy for PT in the absence of metastatic disease. In the research of Adam et al., they concluded that the surgical margin should be at least 5 mm whatever the grade of PT. Moderate to severe nuclear stromal pleomorphism identified a subgroup of grade 1 PT with a higher rate of recurrence. In this case, due to the large breast tumor, the patient underwent extensive mastectomy and axillary lymph node resection. Currently, there are no clear guidelines for the postoperative adjuvant treatment of PT and no prospective randomized studies are available. The study by Kim et al. found that although patients with more adverse prognostic factors underwent postoperative radiation therapy (RT), RT groups were not inferior to non-RT group on cancer specific survival regardless of surgery. One meta-analysis described that

![Figure 3. Positron emission tomography imaging findings. A, Positron emission tomography images showing multiple bones metastasis. B, The local activity of the recurrent tumor of chest wall existing after radiotherapy.](image-url)
patients treated with postoperative RT had a lower relative risk of local recurrence than those not receiving postoperative RT, even after margin-negative wide local excision.\[^{[14]}\] According to the dose effect curve of tumor, NSD, TDF and other formulas, the relationship between radiotherapy dose and tumor control probability can be explained. Tumor control probability is also related to tumor sensitivity, tumor size and many other factors. Generally, when conventional radiotherapy regimen (2 Gy once a day, 5 days a week) is applied, the dose control rate of radiotherapy for subclinical lesions is 45 to 50 Gy, while the dose for residual or macroscopic tumors is 60 to 80 Gy. Because the patient had recurrence of chest wall (macroscopic tumor), conventional radiotherapy dose of 60 Gy was finally adopted.

As we mentioned above the presence of heterologous sarcomatous elements (liposarcoma, chondrosarcoma, and osteosarcoma) can be diagnosed as malignant PT. The patient’s postoperative pathology revealed a malignant phyllodes tumor of the breast. The patient herself refused radiotherapy for the treatment of this disease were not effective in this case.

**Author contributions**

**Conceptualization:** Lei Li.

**Data curation:** Chen Guo.

**Formal analysis:** Lei Li.

**Investigation:** Jing Yang.

**Methodology:** Hui Wang.

**Project administration:** Weiming Zhang.

**Software:** Chen Guo.

**Supervision:** Hui Wang.

**Writing – original draft:** Hong Wu.

**Writing – review & editing:** Hong Wu.

Hui Wang orcid: 0000-0001-5055-5491.

**References**

\[^{[1]}\] Rowell MD, Perry RR, Hsu JG, et al. Phyllodes tumors. Am J Surg 1993;165:376–9.

\[^{[2]}\] Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, Vande vijver MJ. WHO Classification of tumours of the breast. 4th edZurich: international agency for research on cancer (IARC); 2012:143–7.

\[^{[3]}\] Parker SJ, Harries SA. Phyllodes tumors. Postgrad Med J 2001;77:428–35.

\[^{[4]}\] Nieto Parra JA, Dominguez AD, Vieite MB, et al. Malignant phyllodes tumor of the breast with liposarcomatous differentiation. Solution to case 40. Radiologia 2012;54:190–2.

\[^{[5]}\] Kuroda N, Sugimoto T, Ueda S, et al. Malignant phyllodes tumor of the breast with expression of osteonectin and vinculin. Pathol Int 2001;51:277–82.

\[^{[6]}\] Rosen PP. Rosen’s Breast Pathology. 3rd edPhiladelphia: Lippincott Williams and Wilkins; 2009. 187–229.

\[^{[7]}\] Jones AM, Mitter R, Poulsom R, et al. mRNA expression profiling of phyllodes tumours of the breast: identification of genes important in the development of borderline and malignant phyllodes tumours. J Pathol 2008;216:408–17.

\[^{[8]}\] Chaney AW, Pollack A, McNees MD, et al. Primary treatment of cystosarcoma phyllodes of the breast. Cancer 2000;88:1502–11.

\[^{[9]}\] Adam M-J, Bendifallah S, Kalhorpour N, et al. Time to revise classification of phyllodes tumors of breast? results of a French multicentric study. Eur J Surg Oncol 2018;8:1010–6.

\[^{[10]}\] Yi-Jun K, Kyubo K. Radiation therapy for malignant phyllodes tumor of the breast: an analysis of SEER data. Breast 2017;32:26–32.

\[^{[11]}\] Zeng S, Zhang X, Yang D, et al. Effects of adjuvant radiotherapy on borderline and malignant phyllodes tumors: a systematic review and metaanalysis. Mol Clin Oncol 2015;3:66–71.

\[^{[12]}\] van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379:1879–86.

\[^{[13]}\] Hukkan DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol 2005;23:1011–27.

\[^{[14]}\] Liu K, Ren K, Huang Y, et al. Apatinib promotes autophagy and apoptosis through VEGFR2/STAT3/BCL-2 signaling in osteosarcoma. Cell Death Dis 2017;8:3015.

\[^{[15]}\] Zheng B, Ren T, Huang Y, et al. Apatinib inhibits migration and invasion as well as PD-L1 expression in osteosarcoma by targeting STAT3. Biochem Biophys Res Commun 2018;495:1695–701.

\[^{[16]}\] Zhu B, Li J, Xie Q, et al. Efficacy and safety of apatinib monotherapy in advanced bone and soft tissue sarcoma: an observational study. Cancer Biol Ther 2018;19:198–204.