

Prognostic Factors in Phyllodes Tumor of the Breast: Are Immunohistochemical Biomarkers Useful?

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Fibroadenoma and phyllodes tumor of the breast are both fibroepithelial tumors.¹ Phyllodes tumor is an uncommon breast neoplasm constituting only 0.3 to 1.0% of all breast tumors. The median and mean age is about 45 years, about 15 years older than the median age of patients with fibroadenomas. Phyllodes tumors are rare in children and adolescents, and most lesion diagnosed as such in this age group are juvenile fibroadenomas. Phyllodes tumor can display locally destructive growth and can even metastasize. Phyllodes tumors are distinguished from fibroadenomas by their increased stromal cellularity and their leaflike architecture. Mostly, the stroma from fibroadenomas was polyclonal and the stroma of phyllodes tumors was monoclonal by PCR-based clonality assay.²

Phyllodes tumors present a morphologic continuum. At present, there is no consensus about the morphological criteria to classify the phyllodes tumor. Many authors divide phyllodes tumor into three types: benign phyllodes tumor, phyllodes tumor of uncertain malignant potential (borderline malignancy), and malignant phyllodes tumor. Others prefer to divide into benign and malignant tumor without borderline category. Histopathologic features reported to be of value in predicting metastasis are high mitotic count (usually defined as > 5 mitoses per 10 high power fields), stromal overgrowth (> one 40x field that is pure stroma without epithelial elements), severe nuclear pleomorphism and infiltrating margins. The histopathologic distinction in the morphologic continuum of phyllodes tumor is sometimes difficult and arbitrary. Immunohistochemistry, flow cytometric and molecular analysis have been utilized to better predict the clinical behavior of phyllodes tumors.³⁻⁸

In this issue, Dr. Chan Yu-Jan and coauthors⁸ performed an immunohistochemical analysis using antibodies to p53 and Ki-67 protein on patients with phyllodes tumor. This is probably the first study in Taiwan using

biomarkers to correlate with pathology and to predict the clinical behavior of phyllodes tumor. The cases were composed of 50 benign and 13 malignant tumors. The patients ranged from 14 to 69 years old, and the tumors ranged from 1.0 to 25 cm in size. Thirty benign tumors were treated by excision, and the others were treated by simple mastectomy. One malignant tumor was treated by excision, 5 were by simple mastectomy and the others were by modified radical mastectomy. The follow-up period ranged from 1 month to 15 years. No patient died in the follow-up period, but 7 patients had recurrent tumors. According to this paper, p53 protein expression > 10% was seen in 10% and 69% of benign and malignant phyllodes tumors, respectively ($p < 0.005$). Ki-67 antigen expression was also correlated with the histological grading, that is, 85% malignant tumors but only 16% benign tumor showed increased Ki-67 antigen > 10% ($p < 0.005$). Increased p53 and Ki-67 immunoreactivity was present in malignant phyllodes tumors in contrast to benign phyllodes tumors. Although different criteria for morphological classification and immunohistochemistry were used, several published series also showed that expression of Ki-67 antigen and/or p53 protein were correlated with histological grading of phyllodes tumor.³⁻⁷ p53 and Ki-67 expression may be useful adjuncts in the diagnosis of malignancy in difficult cases or when only a limited tissue sample is available. Progression from benign to malignant phyllodes tumor was reported to be associated with a significant increase in the accumulation of p53, and it was caused by an underlying missense mutation in exon 7.⁶

In this issue, Chan *et al.*⁸ report that benign phyllodes tumor with Ki-67 > 10% had a higher frequency of recurrence than those with Ki-67 < 10%. Patients with benign phyllodes tumor having a Ki-67 > 10% need to be treated and followed up properly to avoid recurrence and malignant transformation. However, all 7 tumors with recur-

rence were histologically benign and received surgical excision initially. None of the morphologically malignant phyllodes tumors with increased p53 and Ki-67 expression recurred in the follow-up period. In those patients with malignant phyllodes tumors, all except 1 received simple mastectomy or modified radical mastectomy initially. This indicated that an inadequate excision without free tumor margin might also play an important role in recurrence. Unfortunately, no data regarding the status of section margin in this paper was available to evaluate its significance. In most series of phyllodes tumor, the incidence of recurrence is related to the width of the tumor margin^{9,10} and stromal overgrowth. The value of p53 and Ki-67 expression in predicting the clinical behavior of phyllodes tumor is controversial. Some investigators reported that p53 and Ki-67 expression were independent prognostic parameters for disease-free survival and overall survival.⁴ But, others reported p53 or Ki-67 expression did not predict recurrence or clinical behavior.^{3,7} In addition to histological grade, status of section margin, and expression of p53 and Ki-67, S-phase fraction (SPF) by flowcytometry has also been reported to be an independent prognostic factor by multivariate analysis.⁴

The principle of therapy in the treatment of both benign and malignant phyllodes tumor is complete excision to prevent local recurrence. Mastectomy is necessary only when there is a large tumor and free margin cannot be achieved without it. The role of radiotherapy and chemotherapy is not established and has not been studied in randomized trials due to the rarity of phyllodes tumor. Local failure in patients with margin-negative phyllodes tumor was low.⁹ Recurrences of benign phyllodes tumors are generally morphologically benign phyllodes tumors, but occasionally a benign phyllodes tumor may dedifferentiate to an malignant phyllodes tumor. Fewer than 1 % of malignant phyllodes tumors give rise to axillary lymph node metastases, so axillary node dissection is not indicated for malignant phyllodes tumors. No study data support the use of adjuvant radiotherapy for patients with adequately resected phyllodes tumor. Patients with stromal overgrowth, particularly when the tumor size was > 5 cm, were found to have a

high rate of distant failure; such patients merit consideration of a trial that examines the efficacy of systemic therapy.⁹

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