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Ductal carcinoma in-situ arising within benign phyllodes tumours

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ABSTRACT

Ductal carcinoma in situ arising within a benign phyllodes tumour is a rare neoplasm of the breast. We present a case of a 19-year-old woman who had a right breast lump for six months with the above diagnosis together with a mini-review of the literature. Ultrasound revealed a 5-cm breast lump and core biopsy revealed ductal carcinoma in situ. She underwent wide local excision of the breast lump with clear margins. Final histology confirmed ductal carcinoma in situ within a fibroepithelial lesion consistent with a benign phyllodes tumour. To our knowledge, this is the youngest case of ductal carcinoma in situ arising in a phyllodes tumour to have been reported so far.

KEYWORDS

DCIS – Phyllodes tumour – Breast cancer – Carcinoma in situ – Fibroepithelial tumours

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Introduction

Phyllodes tumours are fibroepithelial breast tumours; they account for less than 1% of all breast neoplasms.[1] Phyllodes tumours have characteristic epithelial components arranged in clefts, surrounded by a mesenchymal component organised in a leaflike pattern.[2] Although malignant transformation of the stromal component can occur, a carcinoma arising from the epithelial component is only rarely reported. To date, 41 cases of breast cancer arising from phyllodes tumours have been reported, of which 19 were reported to be ductal carcinoma in situ (DCIS). We present a review and a case discussion of a 19-year-old woman diagnosed with DCIS arising from a phyllodes tumours, the youngest case to date, who was successfully managed with oncoplastic breast conserving surgery.

Case history

A 19-year-old single nulliparous woman presented with six months' history of a rapidly enlarging right breast lump. Family history was significant for an aunt with breast cancer at the age of 60 years. On clinical examination, the mass measured 5 cm and was firm, non-tender, mobile and well defined in the upper outer quadrant of the right breast. There were no skin or nipple changes. Examination of the left breast was normal. There were no palpable axillary lymph nodes. Ultrasonography of the right breast revealed a heterogeneous vascular mass with fairly well circumscribed margins in the right breast at 9–10 o'clock 5 cm from nipple, measuring 5 x 2.8 x 5.1 cm (Fig 1). An ultrasound-guided biopsy was performed in view of clinical suspicion and histology showed a low to intermediate grade DCIS. Bilateral mammograms subsequently performed showed a mass with partially obscured borders in the right upper outer quadrant, with a couple of scattered specks of benign coarse calcifications in right breast (Fig 2). There were no other suspicious lesions in either breast. Considering the patient's age, size of lesion and histology, she was counselled for mastectomy with implant reconstruction. She declined mastectomy and subsequently underwent a wide local excision and sentinel lymph node biopsy via an inframammary fold incision. The usual practice in our centre is to excise breast tissue down to the pectoral fascia. Intraoperative frozen section of two sentinel axillary lymph nodes was negative for malignancy. Parenchymal flaps were mobilised to close the defect. Histopathological examination showed a well-circumscribed fibroepithelial lesion consistent with a benign phyllodes tumours with diffuse involvement of the ductal epithelial component by multiple foci of low to intermediate nuclear grade DCIS (Figs 3 and 4). The fibroepithelial lesion showed focal leaf-like architectural pattern. The epithelial component also displayed features of columnar cell change and usual type ductal hyperplasia. There was no definite evidence of invasive carcinoma. All resection margins were free of malignancy with nearest 0.1 cm from posterior margin. After discussion with the radiation oncologist, in view of the substantial risk considering her age, it was decided to omit adjuvant radiotherapy, accepting that there will be higher risks of local recurrence. She was subsequently

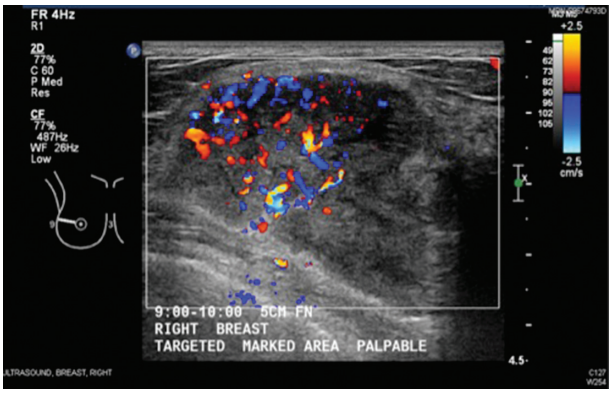

Figure 1 Ultrasound scan of the right breast revealing a heterogeneous vascular mass with fairly well-circumscribed margins in the right breast

started on chemoprevention with tamoxifen. Surveillance ultrasound performed this February revealed no recurrence or new lesions. All genetic screening for hereditary breast cancer syndromes including *BRCA1*, *BRCA2* and *PTEN* were negative.

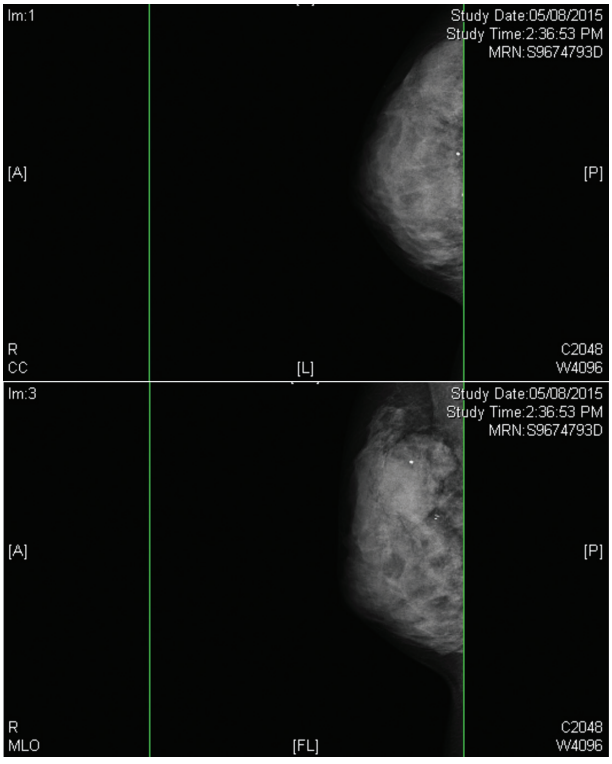

Figure 2 Bilateral mammography showing a mass with partially obscured borders in the right upper outer quadrant with couple of scattered specks of benign coarse calcifications in right breast

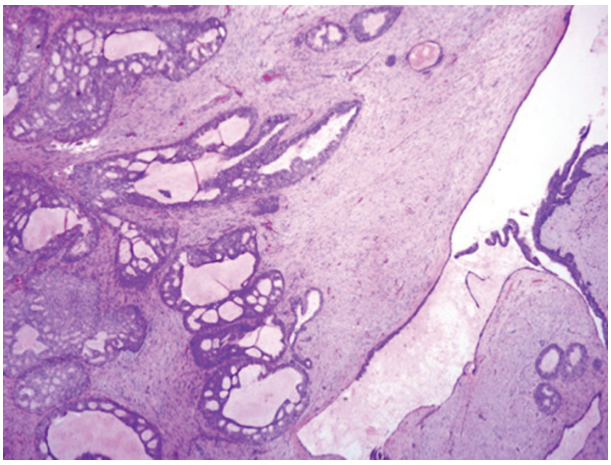

Figure 3 Fibroepithelial tumour with focal leaf-like architecture. There is secondary involvement of the ductal epithelial component by foci of ductal carcinoma in-situ (40 x magnification)

Discussion

Phyllodes tumours are graded according to their stromal characteristics, namely benign, borderline or malignant,[3] with recurrences occurring at a rate of 17%, 25% and 27%, respectively.[4] The classification is based on histological characteristics of the phyllodes tumours and is used to prognosticate their clinical course. Most series-reported benign phyllodes represented 50–70% of phyllodes tumours.[1,3] DCIS or invasive breast carcinomas can occur in conjunction with phyllodes tumours, but are very uncommon, occurring in only about 1% of patients with phyllodes tumours.[5]

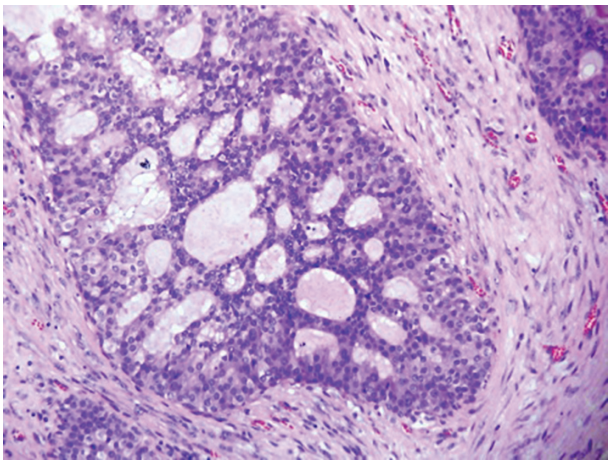

Figure 4 Secondary involvement of the ductal epithelial component of the fibroepithelial tumour by foci of ductal carcinoma in-situ (40 x magnification)

Table 1 Published data on carcinomas arising within phyllodes tumours.

Authors	Year	Age (years)	Surgery	Phyllodes grade	Size	Epithelial type	Size	Axillary lymph node involvement
Norris *et al.*	1967	–	–	–	–	Invasive carcinoma (two cases)	–	–
Cornog *et al.*	1971	–	–	–	–	Squamous cell carcinoma	–	–
Pietruska *et al.*	1978	45	–	–	5.5	Invasive carcinoma	–	Negative
Seemayer *et al.*	1975	27	Mastectomy	Malignant	6.0	Ductal carcinoma in situ	Focal	–
Bassermann *et al.*	1980	–	–	–	–	Squamous cell carcinoma	–	–
Leong *et al.*	1980	49	Local excision	Benign	6	Lobular carcinoma in situ	–	–
Leong *et al.*	1980	51	Mastectomy	Benign	4	Invasive ductal carcinoma	–	Negative
Klausner *et al.*	1983	60	Mastectomy	Malignant	4	Invasive ductal carcinoma	–	Negative
Cole-Beuglet *et al.*	1983	60	Local excision	Benign	3	Invasive ductal carcinoma	Focal	Negative
Cole-Beuglet *et al.*	1983	55	Local excision	Benign	3.5	Ductal carcinoma in situ + lobular carcinoma in situ	–	–
Hunger *et al.*	1984	57	Mastectomy	Malignant	15.5	Squamous cell carcinoma	–	–
Ishida *et al.*	1984	41	Mastectomy	Benign	5.6	Invasive ductal carcinoma	Focal	Negative
Grove *et al.*	1986	71	Mastectomy	Benign	19.0	Ductal carcinoma in situ	2	Negative
Ward *et al.*	1986	55	Mastectomy	Benign	4.0	Lobular carcinoma in situ	Focal	–
Knudsen *et al.*	1987	71	Mastectomy	Benign	7.0	Ductal carcinoma in situ + lobular carcinoma in situ	Multi-focal	Negative
Yasumura *et al.*	1988	47	Mastectomy	Benign	13.0	Invasive ductal carcinoma	Focal	Negative
De Rosa *et al.*	1989	77	Mastectomy	Benign	5.0	Ductal carcinoma in situ	0.3	Negative
Schwickerath *et al.*	1992	47	Mastectomy	Malignant	2.0	Ductal carcinoma in situ	–	Negative
Padmanabhan *et al.*	1997	47	Mastectomy	Malignant	7.5	Lobular carcinoma in situ	Focal	Negative
Naresh	1997	51	Local excision	Borderline	14.0	Ductal carcinoma in situ	Focal	–
Nishimura *et al.*	1998	80	Local excision	Malignant	10.5	Ductal carcinoma in situ	–	–
Alo *et al.*.	2001	39	Mastectomy	Malignant	9.0	Ductal carcinoma in situ	–	–
Kodama *et al.*	2003	47	Mastectomy	Benign	17.0	Invasive lobular carcinoma	Focal	Negative
Parfitt *et al.*	2004	26	Local excision	Benign	3.3	Ductal carcinoma in situ and invasive carcinoma (no special type)	–	Positive (4/13)
Lim *et al.*	2005	45	Mastectomy	Malignant	12.0	Ductal carcinoma in situ	0.6	–
Tokudome *et al.*	2005	59	Mastectomy	–	3.5	Invasive carcinoma	Negative	–
Ramdass *et al.*	2006	69	–	Benign	–	Squamous cell carcinoma	–	–
Nomura *et al.*	2006	75	Mastectomy	Malignant	3.5	Ductal carcinoma in situ	–	–
Sugie *et al.*	2007	54	Mastectomy	Malignant	8.0	Squamous cell carcinoma	–	Negative
Korula *et al.*	2008	51	Mastectomy	Malignant	21.0	Ductal carcinoma in situ and invasive ductal carcinoma	–	Positive (2/12)
Yamaguchi *et al.*	2008	54	Mastectomy	Benign	15.0	Ductal carcinoma in situ	Focal	–
Macher-Goeppinger *et al.*	2010	70	Mastectomy	Malignant	6.0	Invasive ductal carcinoma	2.5	Negative
Kuo *et al.*	2010	24	Mastectomy	Borderline	–	Ductal carcinoma in situ and invasive ductal carcinoma	–	Positive (1/2)

Table 1 Published data on carcinomas arising within phyllodes tumours.

Authors	Year	Age (years)	Surgery	Phyllodes grade	Size	Epithelial type	Size	Axillary lymph node involvement
Nio *et al.*	2010	53	Local excision	Benign	3.5	Ductal carcinoma in situ	0.5	–
Yoshinori Nio *et al.*	2011	53	Local excision	Benign	3.5	Ductal carcinoma in situ	Focal	–
Gina Shirah *et al.*	2011	49	Local excision	Benign	5.0	Lobular carcinoma in situ and invasive lobular carcinoma	0.2	–
Prithwijit Ghosh *et al.*	2015	42	Local excision	Benign	2.2	Ductal carcinoma in situ	–	–
Sharat *et al.*	2015	23	Local excision	Benign	5.0	Ductal carcinoma in situ	Focal	–
Nancy *et al.*	2017	70	Local excision	Beenign	2.3	Ductal carcinoma in situ and invasive ductal carcinoma	0.5	Negative

A literature search of PubMed was conducted using the keywords: 'breast cancer', 'phyllodes tumor', 'carcinoma in situ', 'cystosarcoma phyllodes' and 'DCIS'. Only 41 cases of carcinoma arising in patients with phyllodes tumours (Table 1) were identified, of which 19 were DCIS.[5–40]

Of the 19 cases with DCIS, all were female, with ages ranging from 23 to 80 years. To our knowledge, our case is the youngest patient to have been diagnosed with DCIS within a phyllodes tumour. Four cases had concomitant invasive components,[26,32,35] while two other cases had concomitant LCIS.[12,17] Six arose from malignant phyllodes tumours, two from borderline phyllodes tumours and ten from benign phyllodes tumours. However, among the ten cases, only six had pure DCIS from benign phyllodes tumours, ours being the seventh case to be reported in the English literature.[5,15,19,33,36,39]

The size of the phyllodes tumours ranged widely between 2.0 cm and 21.0 cm, suggesting that DCIS can occur in any palpable phyllodes tumour. Eight cases underwent wide local excision while the rest underwent total mastectomy.

Apart from four cases of DCIS with invasive components, the remainder of the patients with DCIS had negative lymph node involvement or did not undergo axillary lymph nodal sampling or dissection. Three cases reported with positive axillary lymph node involvement had invasive carcinomas.

Stromal overgrowth has been reported with rapidly enlarging phyllodes tumours; epithelial hyperplasia has also been reported to occur in as high as 74% of phyllodes tumours.[41] The best-practice diagnostic guidelines published by the Cancer Reform Strategy Breast Cancer Working Group does not recommend biopsy in women younger than 25 years of age with ultrasound showing typical features of fibroadenoma.[42] In this patient, however, the clinically rapidly enlarging size and heterogenicity of the lesion on ultrasound were suspicious, hence a biopsy was performed.

Standard treatment for phyllodes tumours involves surgical resection with no need for axillary sampling or dissection. However, adjuvant therapy may be indicated for patients with epithelial malignant change, be it radiotherapy, chemotherapy or endocrine therapy. Patients with DCIS who have had breast-conserving surgery are typically offered adjuvant radiotherapy to reduce local recurrence rates. Young age at diagnosis has been reported to be an independent predictor for local recurrence even after controlling for factors such as tumour size, presence of comedonecrosis and clinical presentation.[43,44]

A local study by Tan *et al*. showed a local recurrence rate of 10.9% for benign phyllodes tumours with no distant metastases.[45] From this study, the predicted recurrence-free survival from the normogram is more than 0.95 at 10 years for our patient. According to another validated normogram published in the *Journal of Clinical Oncology* in 2010 for the Western population, the ipsilateral breast tumour recurrence rate is about 0.2 at 10 years.[46] Based on the University of South California/Van Nuys Prognostic Index, our patient had intermediate-risk DCIS. A 2008 study by Di Saverio showed a 10-year disease-free survival of 86.8% for patients who underwent radiotherapy and 78.5% for those who did not, although this was not significant.[47] Interestingly, a more recent study by Kim *et al*. showed that patients with intermediate risk DCIS who did not undergo radiotherapy had no recurrence.[48] Fortunately, a 2015 analysis assessing 20-year mortality outcomes in patients with DCIS demonstrated no survival benefit to radiation, although it did reduce local recurrence risks significantly.[49] Radiation-related risks of thyroid, breast, brain, skin cancers, as well as leukaemia in children have been demonstrated in a linear dose–response relationship, with risks of cancer greatest for those exposed early in life, and these risks appear to persist throughout life.[50] In the Childhood Cancer Survivor Study group, the odds ratio for breast cancer increased linearly with radiation dose, with 11-fold increase for local breast doses of approximately 40 Gy relative to no radiation.[51] A dose–response relationship was also observed by Rubino, who showed that risk of post-radiation sarcoma in breast cancer patients was

30.6 times higher for doses of more than 44 Gy compared with those of less than 15 Gy.[52] However, boost radiation has also been reported by the Rare Cancer Network study to decrease local recurrence rates, particularly in young women less than 45 years of age with DCIS, with 10-year local relapse-free survival of 86% with boost radiation and 72% without.[53] In our case, the patient received chemoprevention with tamoxifen and is still on regular follow-up.

Conclusion

In conclusion, we present a rare case of DCIS arising within benign phyllodes tumor, which is the youngest reported to date. Adjuvant therapy needs to be further investigated and this group of patients should be followed up long-term given their higher rates of local recurrence.

References

1. Tan PH, T.G., Lee A, Simpson JF, Hanby AM, Fibroepithelial Tumours. In: Lakhani SR, Ellis IO, Schnitt SJ *et al.*, *WHO Classification of Tumours of the Breast*. 4th ed. Geneva: WHO; 2012. pp. 142–147.
2. Moinfar F.Biphasic tumors. In: *Essentials of Diagnostic Breast Pathology: A Practical Approach*, Heidelberg: Springer; 2007. pp. 320–350.
3. Rosen PP. *Rosen's Breast Pathology*. 2nd ed. Philadelphia, PA: Lippincott-Raven, 2001. p. 325–364.
4. Tavassoli FA. *Tumours of the Breast and Female Genital Organs. Pathology and genetics of tumours of the digestive system*. World Health Organization Classification of Tumours. Lyon: IARC Press; 2003. pp. 99–103.
5. Norris HJ, Taylor HB. Relationship of histologic features to behavior of cystosarcoma phyllodes. Analysis of ninety-four cases. *Cancer* 1967; **20(12)**: 2,090–2,099.
6. Cornog JL, Mobini J, Steiger E, Enterline HT. Squamous carcinoma of the breast.*Am J Clin Pathol* 1971; **55(4)**: 410–417.
7. Pietruszka M, Barnes L. Cystosarcoma phyllodes: a clinicopathologic analysis of 42 cases.*Cancer* 1978; **41(5)**: 1,974–1,983.
8. Seemayer TA, Tremblay G, Shibata H. The unique association of mammary stromal sarcoma with intraductal carcinoma.*Cancer* 1975; **36(2)**: 599–605.
9. Bassermann R, Eiermann W. [Cystosarcoma phylloides of the breast and bilateral breast cancer. Case report]. *Pathologe* 1980; **1(3)**: 155–158.
10. Leong AS, Meredith DJ. Tubular carcinoma developing within a recurring cystosarcoma phyllodes of the breast. *Cancer* 1980; **46(8)**: 1,863–1,867.
11. Klausner JM, Lelcuk S, Ilia B *et al*. Breast carcinoma originating in cystosarcoma phyllodes.*Clin Oncol* 1983; **9(1)**: 71–74.
12. Cole-Beuglet C, Soriano R, Kurtz AB *et al*. Ultrasound, x-ray mammography, and histopathology of cystosarcoma phylloides. *Radiology* 1983; **146(2)**: 481–486.
13. Hunger E, Turk R, Wurster K. [Malignant cystosarcoma phylloides and squamous cell carcinoma of the breast. A rare tumor combination]. *Geburtshilfe Frauenheilkd* 1984; **44(10)**: 640–642.
14. Ishida T, Izuo M, Kawai T. Breast carcinoma arising in cystosarcoma phyllodes: report of a case with a review of the literature. *Jpn J Clin Oncol* 1984; **14(1)**: 99–106.
15. Grove A, Deibjerg Kristensen L. Intraductal carcinoma within a phyllodes tumor of the breast: a case report. *Tumori* 1986; **72(2)**: 187–190.
16. Ward RM, Evans HL. Cystosarcoma phyllodes. A clinicopathologic study of 26 cases. *Cancer* 1986; **58(10)**: 2,282–2,289.
17. Knudsen PJ, Ostergaard J. Cystosarcoma phylloides with lobular and ductal carcinoma in situ. *Arch Pathol Lab Med* 1987; **111(9)**: 873–875.
18. Yasumura T, Matsui S, Hamajima T *et al*. Infiltrating ductal carcinoma developing within cystosarcoma phyllodes: a case report. *Jpn J Surg* 1988; **18 (3)**: 326–329.
19. de Rosa G, Ferrara G, Goglia P *et al*. In situ and microinvasive carcinoma with squamoid differentiation arising in a phyllodes tumor: report of a case. *Tumori* 1989; **75(5)**: 514–517.
20. Schwickerath J, Blessing MH, Wolff F. [A rare clinical manifestation of a combination tumor of cystosarcoma phylloides malignum and an intraductal cancer]. *Geburtshilfe Frauenheilkd* 1992; **52(9)**: 557–559.
21. Padmanabhan V, Dahlstrom JE, Chong GC, Bennett G. Phyllodes tumor with lobular carcinoma in situ and liposarcomatous stroma. *Pathology* 1997; **29(2)**: 224–226.
22. Deodhar K., Baraniya JB, Naresh KN *et al*. Cancerization of phyllodes tumour. *Histopathology* 1997; **30(1)**: 98–99.
23. Nishimura R, Hasebe T, Imoto S, Mukai K. Malignant phyllodes tumour with a noninvasive ductal carcinoma component. *Virchows Arch* 1998; **432(1)**: 89–93.
24. Alò PL, Andreano T, Monaco S *et al*. [Malignant phyllode tumor of the breast with features of intraductal carcinoma]. *Pathologica* 2001; **93(2)**: 124–127.
25. Kodama T, Kameyama K, Mukai M *et al*. Invasive lobular carcinoma arising in phyllodes tumor of the breast. *Virchows Arch* 2003; **442(6)**: 614–616.
26. Parfitt JR, Armstrong C, O'malley F *et al*. In-situ and invasive carcinoma within a phyllodes tumor associated with lymph node metastases. *World J Surg Oncol* 2004; **2**: 46.
27. Lim SM, Tan PH. Ductal carcinoma in situ within phyllodes tumour: a rare occurrence. *Pathology* 2005; **37(5)**: 393–396.
28. Tokudome N, Sakamoto G, Sakai T *et al*. A case of carcinosarcoma of the breast.*Breast Cancer* 2005; **12(2)**: 149–153.
29. Ramdass MJ, Dindyal S. Phyllodes breast tumour showing invasive squamous-cell carcinoma with invasive ductal, clear-cell, secretory, and squamous components. *Lancet Oncol* 2006; **7(10)**: 880.
30. Nomura M, Inoue Y, Fujita S *et al*. A case of noninvasive ductal carcinoma arising in malignant phyllodes tumor. *Breast Cancer* 2006; **13(1)**: 89–94.
31. Sugie T, Takeuchi E, Kunishima F *et al*. A case of ductal carcinoma with squamous differentiation in malignant phyllodes tumor. *Breast Cancer* 2007; **14 (3)**: 327–332.
32. Korula A, Varghese J, Thomas M *et al*. Malignant phyllodes tumour with intraductal and invasive carcinoma and lymph node metastasis. *Singapore Med J* 2008; **49(11)**: e318–e321.
33. Yamaguchi R, Tanaka M, Kishimoto Y *et al*. Ductal carcinoma in situ arising in a benign phyllodes tumor: report of a case. *Surg Today* 2008; **38(1)**: 42–45.
34. Macher-Goeppinger S, Marme F, Goeppert B *et al*. Invasive ductal breast cancer within a malignant phyllodes tumor: case report and assessment of clonality. *Hum Pathol* 2010; **41(2)**: 293–296.
35. Kuo YJ, Ho DM, Tsai YF, Hsu CY. Invasive ductal carcinoma arising in phyllodes tumor with isolated tumor cells in sentinel lymph node. *J Chin Med Assoc* 2010; **73(11)**: 602–604.
36. Nio Y, Iguchi C, Tsuboi K, Maruyama R. Ductal carcinoma in situ arising within a benign phyllodes tumor: A case report with a review of the literature. *Oncol Lett* 2011; **2(2)**: 223–228.
37. Shirah GR, Lau SK, Jayaram L *et al*. Invasive lobular carcinoma and lobular carcinoma in situ in a phyllodes tumor. *Breast J* 2011; **17(3)**: 307–309.
38. Ghosh P, Saha K. Ductal carcinoma in situ in a benign phyllodes tumor of breast: A rare presentation. *J Nat Sci Biol Med* 2014; **5(2)**: 470–472.
39. Chopra S, Muralikrishnan V, Brotto M. Youngest case of ductal carcinoma in situ arising within a benign phyllodes tumour: A case report. *Int J Surg Case Rep* 2016; **24**: 67–69.
40. Panko N, Jebran AA, Gomberawalla A, Connolly M. Invasive ductal carcinoma within a benign phyllodes tumor. *Am J Case Rep* 2017; **18**: 813–816.
41. Tan PH, Jayabaskar T, Chuah KL *et al*. Phyllodes tumors of the breast: the role of pathologic parameters.*Am J Clin Pathol* 2005; **123(4)**: 529–540.
42. Willett AM, Michell MJ, Lee MJR, eds. *Best Practice Diagnostic Guidelines for Patients Presenting with Breast Symptoms*. London: Department of Health; 2010.
43. Kong I, Narod SA, Taylor C *et al*. Age at diagnosis predicts local recurrence in women treated with breast-conserving surgery and postoperative radiation therapy for ductal carcinoma in situ: a population-based outcomes analysis. *Curr Oncol* 2014; **21(1)**: e96–e104.
44. Wapnir IL, Dignam JJ, Fisher B *et al*. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst* 2011; **103(6)**: 478–488.
45. Tan PH, Thike AA, Tan WJ *et al*. Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. *J Clin Pathol* 2012; **65(1)**: 69–76.
46. Rudloff U, Jacks LM, Goldberg JI *et al*. Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ. *J Clin Oncol* 2010; **28(23)**: 3,762–3,769.
47. Di Saverio, S., et al., 259 Patients with DCIS of the breast applying USC/Van Nuys prognostic index: a retrospective review with long term follow up. *Breast Cancer Res Treat* 2008. **109(3)**: 405–16.

48. Kim T, Catena F, Santini D *et al.* Is radiotherapy necessary for intermediate risk ductal carcinoma in situ after breast conserving surgery? *Springerplus* 2014; **3**: 405–416.
49. Narod SA, Iqbal J, Giannakeas V *et al.* Breast cancer mortality after a diagnosis of ductal carcinoma in situ. *JAMA Oncol* 2015; **1(7)**: 888–896.
50. Kleinerman RA. Cancer risks following diagnostic and therapeutic radiation exposure in children. *Pediatr Radiol* 2006; **36(Suppl 2)**: 121–125.
51. Inskip PD, Robison LL, Stovall M *et al.* Radiation dose and breast cancer risk in the childhood cancer survivor study. *J Clin Oncol* 2009; **27(24)**: 3,901–3,907.
52. Rubino C, Shamsaldin A, L↓ MG *et al.* Radiation dose and risk of soft tissue and bone sarcoma after breast cancer treatment. *Breast Cancer Res Treat* 2005; **89(3)**: 277–288.
53. Omlin A, Amichetti M, Azria D *et al.* Boost radiotherapy in young women with ductal carcinoma in situ: a multicentre, retrospective study of the Rare Cancer Network. *Lancet Oncol* 2006; **7(8)**: 652–656.