28. Aasmunstad TA, Haugen OA. DNA ploidy in intraductal breast carcinoma. *Eur J Cancer* 1990, **26**, 956–959.
29. Meyer MS. Cell kinetics of histological variants of in situ breast carcinoma. *Breast Cancer Res Treat* 1986, **7**, 171–180.
30. Silverstein MJ, Rossser RJ, Gierson ED, *et al.* Axillary lymph node dissection for intraductal breast cancer—is it indicated? *Cancer* 1987, **59**, 1819–1824.
31. Carter D, Smith RL. Carcinoma *in situ* of the breast. *Cancer* 1977, **40**, 1189–1193.
32. Ashikari R, Huvos AG, Snyder RE. Prospective study of non infiltrating carcinoma of the breast. *Cancer* 1977, **39**, 435–439.
33. Rosen PP. Axillary lymph node metastases in patients with occult noninvasive breast carcinoma. *Cancer* 1980, **46**, 1298–1306.
34. Rosen PP, Senie R, Schottenfeld D, Ashikari R. Non invasive breast carcinoma. Frequency of unsuspected invasion and implications for treatment. *Ann Surg* 1979, **189**, 377–382.
35. Fentiman IS. Radiosensitivity of *in situ* carcinoma of the breast. *Lancet* 1985, **ii**, 443–444.
36. Gump FE, Jicha DL, Ozello L. Ductal carcinoma *in situ* (DCIS): a revised concept. *Surgery* 1987, **102**, 790–795.
37. Fentiman IS, Fagg N, Millis RR. *In situ* ductal carcinoma of the breast: implications of disease pattern and treatment. *Eur J Surg Oncol* 1986, **12**, 261–266.
38. Kinne DW, Petrek JA, Osborne MP, Fracchia AA, De Palo AA, Rosen PP. Breast carcinoma *in situ*. *Arch Surg* 1989, **124**, 33–36.

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Which Therapy for Unexpected Phyllode Tumour of the Breast?

Stefano Zurrida, Cesare Bartoli, Viviana Galimberti, Paolo Squicciarini, Vincenzo Delledonne, Paolo Veronesi, Aldo Bono, Giuseppe de Palo and Bruno Salvadori

216 consecutive female patients with histologically confirmed phyllode tumour, the largest series yet reported, were operated on from 1970 to 1989 at our institute and followed-up for a mean period of 118 months. The type of surgery in relation to tumour histotype and natural history were investigated in order to identify the best treatment for this rare breast neoplasm when found unexpectedly at the final histological examination. For the 140 benign tumours, 55 enucleations, 52 enucleoresections, 29 wide resections and 4 mastectomies were performed; the 30 malignant lesions were treated with 3 enucleations, 7 enucleoresections, 9 wide resections and 11 mastectomies; the 46 borderline cases received 11 enucleations, 12 enucleoresections, 18 wide resections and 5 mastectomies. 28 underwent radical surgery following histological diagnosis. There were 27 relapses: 11 (7.9%) in benign, 7 (23.3%) in malignant and 9 (19.6%) in borderline cases. The average disease-free intervals were 32 months for benign, 22 months for malignant and 18 months for borderline phyllode tumours. It is concluded that a wide resection in healthy tissue is indispensable for malignant and borderline phyllode tumours, while, where benign phyllode tumour is encountered unexpectedly, even if a limited resection was performed, a wait-and-see policy is justified.
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INTRODUCTION

THE 1982 WHO classification of breast tumours [1] attempted to resolve the long-standing controversy regarding the terminology of the breast condition which Muller first identified as "cystosarcoma phylloide" in 1838 [2]. Numerous other terms have been used since then causing considerable confusion [3]. Accepting that the best appellation for the condition is phyllode tumour, we note that it includes three distinct histotypes: benign, the form first described by Muller, malignant and borderline. Distinguishing these is far from simple and we are indebted to the studies of Norris and Taylor [4] and later Azzopardi [5] for establishing the morphological criteria by which they may be differentiated: character of margins, character of associated connective tissue development, mitotic activity and cellular atypia. In view of the uncertainties concerning the natural history of this rare neoplasm, it is not surprising that the most appropriate surgical treatment remains to be established. Dyer *et al.* [6] and Thomas *et al.* [7] state that phyllode tumour constitutes less than 1% of all tumours of the female breast; and McDaniel and Crichlow's 1989 review noted that only about 700 cases have been described in the literature [8].

The series of 216 consecutive cases of phyllode tumour reported here is the largest thus far studied and therefore provides a clear indication of the most effective treatment for the condition when definitive histological analysis demonstrates its presence after surgery.

Correspondence to S. Zurrida.
S. Zurrida and V. Galimberti are at the Division of Surgical Oncology "B"; C. Bartoli and G. de Palo are at the Division of Clinical Oncology and Outpatient Clinic; P. Squicciarini, V. Delledonne and B. Salvadori are at the Division of Surgical Oncology "C" Istituto Nazionale Tumori, via Giacomo Venezian, and 20133 Milano; P. Veronesi is at the II Division of Surgery Ospedale San Raffaele, Milano; and A. Bono is at the Division of Medical Oncology Ospedale Niguarda Cà Granda, Milano, Italy.
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Table 1. Type of surgery by histotype

	Benign	Malignant	Border-line	Total (%)
Enucleation	55	3	11	69 (32)
Enucleoresection	52	7	12	71 (32.8)
Wide resection	29	9	18	56 (26)
Mastectomy	3	8	3	14 (6.5)
Subcutaneous mastectomy	1	3	2	6 (2.7)

Type of surgery: enucleation is intracapsular removal of the nodule: the capsule is opened and the nodule freed by running a finger between the inner wall of the mammary capsule and the nodule. Enucleoresection is enucleation as far as possible as just described, with removal by resection of some healthy glandular tissue attached to the nodule. Wide resection is removal of the nodule by resection surrounding healthy glandular tissue containing the capsule, without direct surgical exposure of the nodule.

Table 2. Surgery performed by clinical size of the three histotypes of phyllode tumour

	Enucleation	Enucleo-resection	Wide resection	Mastectomy
Benign (mm)				
≤25	24	18	6	—
>25 <50	23	24	12	—
≥50	8	10	11	4
Malignant (mm)				
≤25	2	—	—	—
>25 <50	—	3	2	2
≥50	1	4	7	9
Border-line (mm)				
≤25	5	2	—	—
>25 <50	5	3	6	—
≥50	1	7	12	5

PATIENTS AND METHODS

216 female patients with phyllode tumour of the breast, operated on at the Istituto Nazionale Tumori, Milan, from January 1970 to December 1989 were assessed retrospectively. Figure 1 shows the patients according to age group and histology of the neoplasm; the youngest patient was 9 years old, 160 (74.1%) were premenopausal and 56 (25.9%) were postmenopausal. Clinical and/or X-ray preoperative diagnoses were adenofibroma (72, 33.3%), adenosis (25, 11.6%) and phyllode tumour (46, 21.3%), with malignancy or suspected malignancy in 73 cases (33.8%). 126 cases were treated as outpatients, 90 were admitted. The types of surgery employed are shown in Table 1 grouped according to histotype. Phyllode tumour has two components: epithelium and connective tissue stroma; the former is not particularly proliferative and resembles that of fibroadenoma; the latter may vary markedly even within a single neoplasm. The character of the stroma distinguishes phyllode tumour from fibroadenoma: in the latter it displays greater cellularity and cell activity.

We followed Azzopardi [5] in classifying the lesions as benign, malignant or borderline; assignment was based on (a) whether tumour margins were clearly demarcated or infiltrating, (b) the cellularity of the connective tissue component (high in the malignant and borderline forms), (c) cellular atypia and (d) mitosis rate. Regarding the latter, Azzopardi states that three or more mitoses per 10 HPF (×400) is a probable indicator of malignancy. However this figure has been questioned by Pietruszka and Barnes [12] who consider tumours with 0–4 mitoses per 10 HPF as benign, 5–9 mitoses per 10 HPF as probably malignant, and 10 ore more as malignant.

Inevitably some cases show intermediate histological features and the WHO [1] recommends these be classified as borderline.

27 patients (12.5%) had a previous adenofibroma and 7 (3.2%) a previous homolateral or controlateral phyllode tumour, all removed and histologically ascertained. Mean follow up was 116 months (range 24–326). 3 patients were lost to follow-up soon after their operation, while 6 were lost later. Of the latter, 2 had benign phyllode tumours removed 70 and 96 months before, 2 had malignant lesions removed 55 and 87 months before and 2 had border-line tumours removed 12 and 73 months previously: they were free of disease at their last check up.

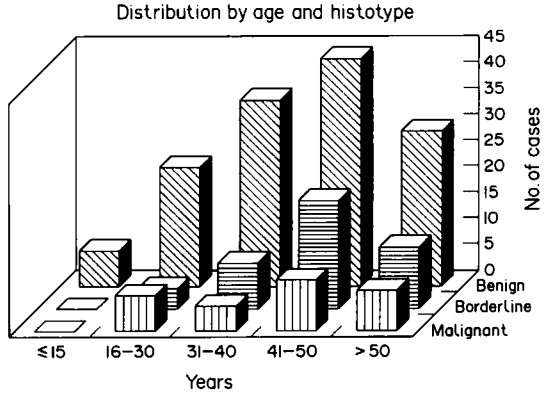

Fig. 1.

RESULTS

The three histological types were compared with the macroscopic dimensions of the lesions and the type of surgery performed (Table 2). Differences between clinical estimate of tumour size and actual size were insignificant. There was no significant correlation between type of growth and histotype, although malignant and borderline lesions tended to be larger (Table 3).

A second, more radical, intervention was performed in 28 cases following definitive histological diagnosis.

In 6 histologically benign cases, 2 enucleations and 4 enucleoresections were enlarged to wide exeresis; none of these have experienced relapses.

8 ascertained malignant cases were radicalised: 6 enucleoresec-

Table 3. Histotype by histological size of the tumour

	≤25 mm	>25 <50 mm	≥50 mm	Total
Benign	44 (31.4)	64 (45.7)	32 (22.9)	140
Malignant	4 (13.3)	7 (23.3)	19 (63.4)	30
Border-line	8 (17.4)	11 (23.9)	27 (58.7)	46
Total	56	82	78	216

(%)

Table 4. Type of primary surgery by histotype in the 27 local recurrences

	Benign	Malignant	Border-line	Total
Enucleation	5	1	1	7
Enucleoresection	5	—	4	9
Wide resection	1	3	4	8
Simple mastectomy	—	1	—	1
Subcutaneous mastectomy	—	2	—	2

tions were radicalised to 1 wide resection, 3 subcutaneous mastectomies and 2 simple mastectomies; a wide resection was extended to a simple mastectomy and a subcutaneous mastectomy enlarged to a simple mastectomy. This last case developed a local recurrence after 38 months. None of the 3 malignant cases in which we performed an enucleation was radicalised: one of these developed a local recurrence 4 months later.

Of the 23 borderline cases undergoing limited surgery (11 enucleation and 12 enucleoresection), 9 enucleations were radicalised (in one of these residual neoplasm was found) and one recurred locally; of the 2 enucleations not radicalised, 1 recurred locally and 1 did not recur. Of the 12 enucleoresections, 5 underwent radical surgery to wide resections (in one of these residual neoplasm was found); 1 developed a recurrence 16 months later. Of 7 non-radicalised borderline, 3 recurred 14, 25 and 25 months later. Table 4 shows recurrences according to histotype and surgery, while Table 5 lists them according to macroscopic diameter of neoplasm. The histological diagnoses of the 11 recurrences of the benign phyllode tumours were benign 7 cases, borderline 3 cases, and malignant 1 case. Of 7 recurrences in malignant phyllode tumours, 5 were still malignant, 1 borderline and 1 LCIS in phyllode tumour. The 9 recurrences of borderline phyllode tumour were borderline 7 cases, benign 1 and malignant 1. The interval between removal of primary tumour and recurrence is on average 32 months (range 5–95) for benign phyllode, 22 months (range 1–72) for malignant phyllode and 18 months (6–39) for borderline.

DISCUSSION

On physical examination phyllode tumour presents as a variable diameter neoformation. It may have arisen recently (within a few months) or have been present for many years [9, 10]. Although many patients report rapid growth, this is not always the case [11]. Phyllode tumour exhibits considerable inter case variability and may also vary from zone to zone in a single tumour. The lesion is always mobile with respect to the gland and does not have the infiltrative character of a carcinoma.

Table 5. Local recurrences by histotype and macroscopical size

	≤25 mm	>25 <50 mm	≥50 mm
Benign	2	3	6
Malignant	2	1	4
Border-line	1	1	7
Total	5	5	17

Table 6. Correlation between preoperative and histological diagnosis

	140 Benign	30 Malignant	46 Border-line
Clinical diagnosis			
Benignity	102 (72.8)	16 (53.3)	30 (65.2)
Malignant	11 (7.9)	11 (36.7)	11 (23.9)
Suspicious	27 (19.3)	3 (10)	5 (10.9)
X-ray diagnosis*	65 Benign	14 Malignant	20 Border-line
Benignity	50 (77)	7 (50)	—
Malignant	2 (3)	5 (35.7)	8 (40)
Suspicious	8 (12.3)	—	12 (60)
Not adequate	5 (7.7)	2 (14.3)	—

*Performed in 99 patients.
(%)

By physical examination alone it is often possible to distinguish phyllode tumour from the more common mammary carcinoma.

In the past the diagnosis of phyllode tumour presented few problems: it was a large, plurilobed mass with an elastic parenchymatous consistency, altering breast profile and giving rise to the characteristic skin vein reticulum. Today, however, because women are more aware of breast cancer and of the need for early diagnosis, the clinician is increasingly confronted with phyllode tumours of small size [9, 12] which are difficult to distinguish from fibroadenomas. The fact that the latter typically occur in young patients (20–30 age range), while phyllode tumour has its maximum incidence (82%) in the 30–60 age group [20], is an important aid to differential diagnosis.

Instrumental techniques are of secondary importance in phyllode tumour diagnosis; mammography and ultrasound can only give a general indication of malignancy [13]. Breast X-rays were performed in 99 cases in our series, while we lack experience in the application of ultrasound to diagnose these tumours.

Cytological examination by fine needle aspiration biopsy (FNAB) was performed in 59 cases and it was possible to rule out the presence of malignant cells in all cases, but in 3 instances only was phyllode tumour confirmed. Table 6 shows the clinical and radiological diagnoses in relation to the histological diagnoses.

At this point the nature of the problem facing the surgeon who discovers phyllode tumour after the diagnostic removal of a recently appeared or changed lump, becomes clear. Until quite recently total breast removal plus axillary lymph node dissection was considered the treatment of choice [14]. Other authorities, however, advise radical mastectomy only where the lesion was so extended locally as to justify removal of certainly healthy tissue [4, 10, 15–17]. It goes without saying that if the tumour is malignant or borderline, resection should include wide tracts of healthy tissue, and if the exploratory operation was limited radical surgery should be undertaken. In such cases the character of the definitive surgery must depend essentially on the dimensions of the lesion and size of the breast. If the breast is large enough a massive tumour may be radically excised by conservative surgery. In our series 41.7% (5/12) of malignant or border-line phyllode tumours recurred due to insufficiently radical surgery and 23.9% (11/46) recurred because the tumour was larger than 50 mm. Removal of axillary lymph nodes is not indicated except when they are clinically suspect; the tumour metastases mainly via the circulation to lungs or liver. Norris and Taylor [4] report only 1 case of nodal metastases in 24

"radical" mastectomies. In none of our cases were nodal metastases detected clinically at the moment of diagnosis, and none developed them subsequently. The question remains: what is the best approach when the phyllode tumour is histologically benign? The question is particularly important since even this histotype is known to recur [12, 14, 18, 19]. In our series the risk of recurrence of the benign form was relatively small (11/140 = 7.9%); in 9 of these (81%) tumour diameter was greater than 2.5 cm (Table 5). When this form does recur, recall that the life of the patient is no case at risk, while wide surgery can only diminish the chances of recurrences, not eliminate them [14]. One asks oneself whether all unexpected phyllode tumours that are shown to be benign should be followed by a second wider resection in healthy glandular tissue. If we had followed this policy we would have submitted 90.7% of our cases to useless surgery (a point also made by Bartoli *et al.* [20]), since 97/107 patients did not develop recurrences.

Macroscopic examination of the removed nodule during the operating can strongly suggest the presence of phyllode tumour: meaty consistency, grey–red colour, sometimes with fibro-gelatinous or haemorrhagic areas and, in larger tumours cystic gelatinous or fluid-filled cavities containing vegetating growths. Such occurrences are an immediate indication for more extensive surgery. Occasionally the histological character of the recurring lesion is different to that of the primary. Such cases could be secondary rather than genuine local recurrences. Benign phyllode tumours very rarely become malignant [21, 22]. It would appear that these patients have a predisposition for developing a second neoplasm: 3.3% of our series re-presented phyllode tumour in the same or controlateral breast and 12.5% developed fibroadenoma. The single patient of our series who had a benign phyllode tumour followed 42 months later by a tumour of malignant histotype may not have had a recurrence but a second neoplasm; she remains free of disease 123 months after the second operation.

It is emphasised in conclusion that all nodules of the breast appearing after the age of 30, even if clinically apparently benign (fibroadenoma), must be removed for histological examination. Nodules in younger women must also be removed if they change size, consistency or form.

1. WHO. Histological typing of breast tumors. *Tumouri* 1982, **60**, 181.
2. Muller J. Uber den feineran Bau and die Forman der Krankhaften Geschwilste. Berlin: G. Reiner, 1938.
3. Fiks A. Cystosarcoma phyllodes of the mammary gland — Muller's tumor. *Virchows Arch* 1981, **392**, 1–6.
4. Norris HJ, Taylor HB. Relationship of histologic features to behaviour of cystosarcoma phyllodes. *Cancer* 1967, **20**, 2090–2099.
5. Azzopardi JG. Sarcoma of the breast. In: Bennington J ed, *Problems in Breast Pathology*. Vol. II, *Major Problems in Pathology*. Philadelphia, WB Saunders Co. 1979, 355–359.
6. Dyer NH, Bridges EI, Taylor RS. Cystosarcoma phyllodes. *Br J Surg* 1966, **53**, 450–455.
7. Thomas AMK, Ashworth BM, Blake P. Regression of recurrent cystosarcoma phyllodes tumor after neutron therapy with development of benign calcification. *Br J Rad* 1984, **57**, 926–929.
8. McDaniel MD, Crichlow RW. Cystosarcoma phyllodes. In: Strombek SO, Rosato FE. *Surgery of the Breast*. New York, Thienne Inc, 1986, 151–152.
9. Lester J, Stout AP. Cystosarcoma phyllodes. *Cancer* 1954, **7**, 335.
10. McDivitt RW, Urban JA, Farrow JH. Cystosarcoma phyllodes. *Johns Hopkins Med J* 1967, **120**, 33.
11. McDaniel MD, Crichlow RW. *Disease of the Breast*. Philadelphia, WB Saunders Co. 1979, 151.
12. Pietruszka M, Barnes L. Cystosarcoma phyllodes: a clinicopathologic analysis of 42 cases. *Cancer* 1978, **41**, 1974.
13. Cole-Beuglet C, Kurtz AB, Meyer JE, *et al.* Ultrasound, X-ray mammography and histopathology of cystosarcoma phyllodes. *Radiology* 1983, **146**, 481.
14. Hajdu SI, Espinosa MM, Robbins GF. Recurrent cystosarcoma phyllodes: a clinicopathologic study of 32 cases. *Cancer* 1976, **38**, 1402 14.
15. Cooper WG, Ackerman LV. Cystosarcoma phyllodes with a consideration of its more malignant variant. *Surg Gynecol Obstet* 1943, 77, 279.
16. Blumencranz PW, Gray GF. Cystosarcoma phyllodes: clinical and pathological study. *NY State J Med* 1978, **78**, 623.
17. Oberman HA. Cystosarcoma phyllodes: a clinicopathologic study of hypercellular periductal stromal neoplasm of the breast. *Cancer* 1965, **18**, 697.
18. Haagensen CD. *Disease of the Breast*. Third Edition, Philadelphia, WB Saunders Co. 1986.
19. Salvadori B, Cusumano F, Del Bo R, *et al.* Surgical treatment of phyllodes tumours of the breast. *Cancer* 1989, **63**, 2532.
20. Bartoli C, Zurrida S, Veronesi P, *et al.* Small sized phyllodes tumor of the breast. *Eur J Surg Oncol* 1990, **16**, 215–219.
21. Petrek JA. Cystosarcoma phyllodes. In Harris JR, Hellman S, Hendersen IC, Kinne DIV, eds. *Breast Disease*. Philadelphia, JB Lippincott Co 1987, 583–589.
22. Treves N, Sunderland DA. Cystosarcoma phyllodes of the breast: a malignant and benign tumor; a clinicopathological study of seventy-seven cases. *Cancer* 1951, **4**, 1286–1332.