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Original Article

Prognosis and Clinical Outcome of Papillary Carcinoma of The Breast at A Tertiary Care Hospital

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Abstract

Objective: To determine the clinical, pathologic and prognostic features of papillary breast cancer seen at a tertiary care hospital.

Materials and Methods: A retrospective review of medical charts of patients seen during the period between January 2010 to December 2013 was performed.

Results: There were 86 patients with papillary breast cancer who underwent surgery during the period. This constituted 3% of all breast cancer patients who underwent surgery during the same period. The majority (74%) were invasive papillary cancers. Most patients were menopausal with an average age of 61 years. Most cancers were hormone-receptor positive, and HER2 negative. The average tumor size was 2 cm and only 10% had axillary node metastasis. The majority (69%) underwent mastectomy and most (60%) had hormonal therapy as the only systemic adjuvant. Under a median follow-up of 22 months (range; 1 to 53 months), there were no recurrences or deaths observed in the series.

Conclusion: Papillary breast cancer has a very good prognosis and treatment should be minimized in a similar way as a mucinous carcinoma.

Keywords: Papillary breast cancer, Papillary lesions, Prognosis

Introduction

Breast cancer is a heterogenous disease with varying morphology, behavior, and response to therapy. In 2003, the WHO defined invasive papillary carcinoma of breast as a type of invasive mammary carcinoma[1].

Papillary carcinoma of breast represents 0.5% of newly diagnosed of breast cancers[2,3,4]. The term papillary carcinoma encompasses a morphologically heterogeneous group of lesions which share growth pattern characterized by the presence of fibrovascular stalks lined by epithelial cells[4]. Malignant papillary neoplasm of the breast includes DCIS which arises in intraductal

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papilloma, papillary DCIS, intracystic (encapsulated) papillary carcinoma, solid papillary carcinoma and invasive papillary carcinoma[4-7]. All malignant papillary neoplasms of the breast lack an intact myoepithelial cell layer within the papillae, which differentiates them from intraductal papilloma.

Proposed criteria for DCIS arising in a papillary lesion include the presence of DCIS greater than 3mm in size[8], and DCIS comprising at least a third but less than 90% of the papillary lesion[7]. The area of DCIS usually composes of uniform appearing cells with low or intermediate nuclear atypia.

Papillary DCIS is characterized by the presence of fibrovascular fronds lined by neoplastic epithelium with no pre-existing benign papilloma. The lining epithelium is typically monomorphic, stratified columnar cells. Nuclei are usually of low or intermediate grade. There are no myoepithelial cells in the papillae, but this layer is retained at periphery of the involved duct.

Intracystic (encapsulated) papillary carcinoma is a solitary, centrally located malignant papillary proliferation involving a dilated duct. The duct is filled with slender fibrovascular stalks lacking myoepithelial cells. The involved duct is surrounded by a thick fibrous capsule, also without a myoepithelial cell layer, leading some investigators to propose that this lesion should be considered invasive rather than in situ. On the other hand, some consider the lesion in situ based on the presence of basement membrane (collagen type IV) and the indolent behavior of the lesion[9]. Some intracystic papillary carcinoma may be associated with an invasive component characterized by an infiltrative appearance with extension beyond the fibrous capsules and associated stromal reaction. In these cases, it is recommended that the staging should be determined based on the size of invasive component only, in order to prevent overtreatment[4-6].

Solid papillary carcinoma appears as a well circumscribed, densely cellular, expansile nodules of epithelial cells. Extra and intracellular mucin production are common, and there is an underlying fibrovascular core. Solid papillary carcinoma is often accompanied by an area of invasive carcinoma (usually mucinous or neuroendocrine-like carcinoma)[4,10,11].

The diagnosis of Invasive papillary carcinoma is extremely rare and should be reserved for infiltrating breast carcinoma exhibiting papillary morphology. This invasive lesion tends to be found in older women, typically aged 70 years or more[12]. These patients are older than those with the more common breast cancer and papillomas.

Clinically apparent papillary lesions will present with a breast lump or bloody nipple discharge. These lesions may also be asymptomatic, but detectable on screening mammography or ultrasonography. Differentiating between benign and malignant lesions via core biopsies may be difficult because the invasive part is seen at the periphery, while biopsies are targeted at the center.

On breast imaging findings, there are three basic ultrasonographic profiles: intraductal mass with or without duct dilatation; intracystic mass; and, solid pattern with an intraductal mass completely filling the duct. Papillary carcinomas are noted to have a larger solid component and spontaneous intracystic bleeding. In both benign and malignant lesions, the shape of the lesion is often round or oval, and with circumscribed margins. However, nonparallel orientation, an echogenic halo, posterior acoustic enhancement and associated microcalcification are more frequently found in malignant lesions[4]. Mammographic findings usually show a well circumscribed and homogenous mass, although sometimes the border may be obscured. Malignant and benign lesions often cannot be distinguished by the mammography.

The prevalence of malignancy on surgical excision for papillary lesions found on core needle biopsy ranges from 17 to 34%[13]. Excisional biopsy should be done for all papillary lesions diagnosed on needle biopsy due to a high upgrade rate to malignancy.

Available data suggests better outcome for papillary carcinoma compared to non-specific invasive ductal carcinoma, but treatment related information is limited. The lack of information underscores the need for treatment and outcome related studies in papillary carcinoma of the breast.

Because of its relative rarity, there is a paucity of information regarding this type of tumor. Most previous studies are based on small case series. In the present study, we reviewed 86 patients with papillary carcinoma, including both invasive and noninvasive types, in terms of clinicopathologic findings, molecular immunohistochemistry, and overall disease-related outcomes at a single institute.

Materials And Methods

Medical charts of patients diagnosed with malig-

nant papillary carcinoma of breast treated at Ramathibodi Hospital from January 2010 to December 2013 were reviewed. Patients with the diagnosis of micropapillary carcinoma or those with incomplete clinicopathologic information were excluded.

All patients underwent clinical examination and mammographic and ultrasound evaluation before the surgery. Preliminary tissue diagnosis was usually done with core needle biopsy (Ramathibodi Hospital), although a few was done via excisional biopsy (from outside institutions).

All patients received standard surgical management either with mastectomy or breast conserving surgery, and axillary management depending on nodal status.

Table 1 Summary of patient and pathological characteristics

Characteristics	Summary (n = 86 unless stated otherwise)
Age (years): mean (SD) [range]	61.7 (13.9) [31 to 90]
Core Needle Biopsy diagnosis (n = 62) (%)	
Papillary cancer	25/62 (40)
Invasive mammary cancer	11/62 (18)
Ductal carcinoma in situ	6/62 (10)
Papillary lesion with atypia	11/62 (18)
Papillary lesion	5/62 (8)
Inflammation and fibrocystic change	4/62 (6)
Initial excisional biopsy	24 (28)
Number of operations (%)	
One	54 (63)
Multiple (re-excision or mastectomy)	32 (37)
Definitive breast surgery (%)	
Mastectomy	59 (69)
Breast conserving surgery	27 (31)
Invasive papillary cancer (%)	64 (74)
Microinvasive papillary cancer	8/64 (13)
Mixed papillary cancer (%)	28 (33)
With ductal carcinoma, NOS	21/28 (75)
With mucinous carcinoma	10/28 (36)
Size of primary tumor (cm); n = 78	
Mean (SD)	2.2 (1.4)
Median (range)	2.0 (0.2 to 7.0)
Axillary nodes evaluated (%)	71 (83)
Positive axillary nodes (%)	7/71 (10)
Estrogen receptor expression (%)	
Mean (SD)	84.2 (21.8)
Median (range)	90 (0 to 100)
Progesterone receptor expression (%)	
Mean (SD)	52.2 (36.5)
Median (range)	60 (0 to 100)
Ki 67 (%); n = 80	
Mean (SD)	18.8 (15.1)
Median (range)	15 (2 to 80)
HER2/neu expression; n = 84 (%)	
0	43/84 (51)
1+	20/84 (24)
2+	19/84 (23)
3+	2/84 (2)
Triple negative cancer	2 (2)

Adjuvant treatment was given based on prognostic and predictive factors such as tumor size, estrogen receptor status, HER2 status and nodal status.

Information retrieved from medical records included patient-related data (age at diagnosis, menopausal status), tumor characteristics (size, grade, ER, PR and HER2 status with associated percentages), surgical treatment, nodal status, type of adjuvant systemic treatment, radiation therapy, date of last follow-up, and disease status or survival at last follow-up. The study protocol was approved by the Ethics Committee of Ramathibodi Hospital.

Statistical comparison between independent groups or categories was done using t-test, rank test, chi-square test, or Fisher's exact test as appropriate. The statistical software Stata v. 12 (Stata Corp., College Station, USA) was used for all analyses.

Results

Most of the patients were postmenopausal, with a median age of 61 years (range, 31 to 90 years; see Table 1). No male papillary breast cancer was seen in the period under study. The majority of papillary breast cancer was invasive (74%). There were 28 patients (33%) with mixed type carcinoma. These were either with invasive ductal (74%) or mucinous carcinoma (36%). In the present study, no co-existence between the papillary carcinoma and neuroendocrine tumor was found.

The average tumor size was 2.2 cm. The Estrogen Receptor (ER) was positive in 97% of papillary carcinomas, with an average ER expression of 84.2%. Expression of Ki67 was low, with an average of 18.8%. HER2 expression was negative (IHC 0 or 1+) in 75 % of patients, with the rest being mostly equivocal (IHC 2+; 23%). Confirmatory tests such as FISH was not done in most of these latter cases because of the small size of the tumor and treatment with Trastuzumab was not considered necessary. Only 2 invasive papillary carcinomas were found to be HER2 positive (IHC 3+) in the present study. However, these two patients had mixed invasive papillary and ductal carcinoma, so HER2 positivity could be from the invasive ductal part.

Among the 86 patients in the present study, 27 (31%) underwent breast conserving therapy (BCT), and 59 (69%) underwent mastectomy. Some patients (37%) underwent secondary surgeries because their first operations were not able to completely remove the tumor. Sentinel lymph nodes biopsy (SLNB) was performed for clinically node negative breast cancer. In 71 patients, a dual technique consisting of a blue dye and radioisotope injection was used to identify the SLN's. There were 7 patients (10%) with positive SLNB. Patients who had macrometastasis in the sentinel nodes underwent axillary node dissection, but no additional positive nodes were found in all cases. In 3 patients with micrometastasis on SLNB, axillary dissection was omitted.

Table 2 Adjuvant treatment, follow-up and outcomes of patients with papillary cancer

Treatment and outcomes	Summary (n = 85 unless stated otherwise) *
Chemotherapy; n = 84 (%)	
None	63/84 (75)
4AC	11/84 (13)
4AC+12P	1/84 (1)
6FAC	6/84 (7)
6CMF	2/84 (2)
4TC	1/84 (1)
Radiation therapy; n = 84 (%)	19/84 (23)
Hormonal treatment; n = 84 (%)	79/84 (94)
Hormonal treatment *only*; n = 84 (%)	50/84 (60)
Follow-up time (months)	
Mean (SD)	24.1 (12.7)
Median (range)	22.2 (1.0 to 52.7)
Recurrent cancer	0
Cancer-related deaths	0

* One patient was lost to follow-up

Table 3 Comparing patients with breast conserving surgery who did or did not undergo whole breast irradiation

Characteristic and Treatment	RT (n = 15)	No RT (n = 11)	*p*-value[a]
Age (years): mean (SD)	54.6 (11.1)	72.0 (16.1)	< 0.001
Size (cm): median (range)	1.9 (0.4 to 6.0)	0.8 (0.2 to 4.7)	0.312
ER expression (%): median (range)	95 (80 to 100)	90 (0 to 100)	0.133
PR expression (%): median (range)	80 (5 to 95)	30 (0 to 100)	0.215
Ki67: median (range)	20 (2 to 40)	15 (5 to 60)	0.916
HER2/neu expression: median (range)	0 (0 to 2+)	1+ (0 to 2+)	0.692
Axillary nodes evaluated (%)	13 (87)	1 (9)	< 0.001
Hormonal treatment only (%)	0	10 (91)	< 0.001

a: *p*-value according to t-test, rank test, chi-square test, or Fisher's exact test as appropriate; RT: whole breast radiation therapy

Adjuvant treatment was given based on tumor biology, staging, and surgery performed. Only 4 patients received no adjuvant treatment after surgery. Of these, 2 were lost to follow up, and the remaining 2 refused any adjuvant treatment. Chemotherapy was given based on tumor staging and biology. Anthracycline-based regimen was the main regimen in the study (as shown in the Table 2).

Hormonal treatment, either with tamoxifen or an aromatase inhibitor, was prescribed for most patients (94%) due to the vast majority having ER-positive tumor. Over half (60%) of patients received hormonal treatment as their only adjuvant treatment. Radiation therapy (RT) was provided for 19 (23%) patients, 15 of whom had undergone BCT.

Patients who underwent BCT with and without whole breast RT were compared (Table 3). RT was omitted in patients who were older and frail, some with smaller tumors, such that axillary surgery was usually omitted as well and hormonal therapy was likely given as the only adjuvant treatment.

Patients were followed every 3 to 6 months in the first 5 years. The median follow-up time was 22 months (range, 1 to 53 months). No recurrences, both local and distant, were found in any patient in the study, and no cancer related deaths were observed.

Discussion

In the present study, the proportion of papillary carcinoma was approximately 3% of all breast cancers undergoing surgery, a relatively high proportion. Similarly, although the published literature suggests true invasive papillary carcinoma to be rare (e.g., 1 to 2%), the present study found a much higher proportion of invasive papillary carcinoma. There is no clear explanation as to why this was the case, although the overdiagnosis of invasiveness is one explanation.

Nonetheless, most of the patients in the present study were predominantly post-menopausal, which was consistent with previous studies.

Papillary carcinomas in the present study were found to be mostly ER positive and HER2 negative, also consistent with previous reports. A novel finding was that IHC HER2 equivocal or positive papillary cancers were often in association or mixed with invasive ductal carcinoma.

Previous reports suggest that invasive papillary carcinomas are less aggressive, with better prognosis compared to invasive ductal carcinoma of no special type. But due to the relative rarity of this type of cancer, no clear conclusions could be found in the literature. The present study seems to show that all papillary cancers, including invasive types, have very good prognosis under the current standard treatment regimen, with no cancer recurrence or cancer-related deaths observed in all patients, although the follow-up period was rather short. A significant proportion of patients underwent BCT without whole breast irradiation, and no recurrences were detected within the follow-up period.

Other studies concluded that solid papillary carcinoma was closely related to mucinous carcinoma[14]. In the present study, the coexistence with mucinous carcinoma, for both in situ and invasive papillary cancers, was also seen. This evidence, along with the estimated low incidence of cancer recurrence and mortality, and the fact that most of the tumors were ER positive and HER2 negative, suggests that invasive papillary carcinoma of the breast has a very good to excellent prognosis, similar to that of mucinous carcinoma. This leads to the recommendation that the treatment of most papil-

lary carcinomas of the breast could be limited to local and hormonal treatment. However, these observations require further confirmation.

Major limitations of the present study included the possibility of overdiagnosis of the invasiveness of papillary carcinoma, and the short period of follow-up. Also, treatment recommendations made have never been tested. But the present results strongly suggest very good prognosis for this type of cancer, and the idea of minimizing the use of chemotherapy or other toxic systemic treatment should be carefully considered.

Conclusion

The present study found a higher proportion of invasive papillary carcinoma of the breast compared to other studies. The prognosis of this type of breast cancer was found to be very good to excellent. It is suggested that invasive papillary carcinoma should be considered a good prognosis subtype and treatment could be minimized accordingly.

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