



Treating papillary tumors of the breast—role of adjuvant treatment—a narrative review

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Background and Objective: Papillary tumours of the breast are a rare and heterogeneous disease group. They have uncertain clinical behaviour and lack definitive treatment guidelines. Due to the paucity of data including randomized phase two and three trials, there are no clear recommendations on the use of adjuvant treatment, if any, in this diverse histology.

Methods: Articles published between January 2015 till August 2021, on the topic covering papillary lesions of the breast were retrieved from databases including PubMed, EMBASE, Scopus. Only studies published in English language were reviewed.

Key Content and Findings: Here I have tried to review the recent literature in light of the use of adjuvant treatment strategies ranging from radiation therapy (RT) to hormonal and chemotherapy in papillary tumours of the breast, stressing on de-escalation of the treatment especially with regards to the use of systemic agents. Benign papillary lesions even if they are multiple or associated with atypia require no adjuvant treatment. However, adjuvant radiotherapy should be offered to all *in-situ* lesions and invasive papillary carcinomas (IPCs). Systemic chemotherapy is reserved for lymph node-positive diseases only. Use of hormonal agents is guided by the hormone receptor status of the *in-situ* and invasive lesions.

Conclusions: De-escalation of the adjuvant treatment for papillary lesions of the breast can save the patient from additional toxicities associated with the use of adjuvant treatment especially those due to cytotoxic agents.

Keywords: Adjuvant treatment; breast; cancer; papillary

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Introduction

Papillary tumours of the breast are rare and heterogeneous lesions of the breast accounts for less than 3% of all breast tumours (1). The 5th edition of World Health Organization (WHO) Classification of Breast Tumors (2), describes these tumours in detail ranging from benign intraductal papilloma to invasive papillary carcinoma (IPC). Most of these lesions are benign and only a minority show atypical behaviour or malignant characteristics. The majority of them have overlapping histological features with low concordance in their diagnosis (3). Also, there are no pinpoint clinic-radiological characteristics attributable to these lesions. They can be central or peripheral in location and are not

always readily detectable on radiological imaging. Thus they have an uncertain clinical behaviour. It is not uncommon for these lesions to be diagnosed in asymptomatic females and/or on screening.

Usually, there is a 1.5–2 times higher incidence of future breast carcinoma as compared to the general population, in women with benign duct papilloma which increases to 4.3 times if associated with atypia (4). There is a dearth of randomized clinical data available for this disease entity. The majority of the recommendations come from case series or retrospective studies. To treat or not, to prescribe any adjuvant treatment or not are some debatable questions because of mixed results from

Table 1 Literature search strategy

Items	Specification
Date of search	09 September, 2021
Databases and other sources searched	PubMed, EMBASE, Scopus
Search terms used	“Intraductal papilloma breast”, “Ductal carcinoma <i>in situ</i> papillary breast”, “Encapsulated papillary carcinoma breast”, “Encapsulated papillary carcinoma breast with invasion”, “Solid papillary carcinoma <i>in situ</i> breast”, “Solid papillary carcinoma breast with invasion”, “Intraductal papillary adenocarcinoma breast with invasion”, “Invasive micropapillary carcinoma of breast”
Timeframe	January 2015–August 2021
Inclusion and exclusion criteria	Inclusion: (I) English language studies; (II) case series and review articles Exclusion: non-English
Selection process	Mohsin Khan did the study selection and review

the literature. Here, I have tried to review the role of adjuvant treatment if any, in these lesions. I present this article in accordance with the Narrative Review reporting checklist (available at <https://tro.amegrounps.com/article/view/10.21037/tro-22-19/rc>).

Methods

Recent articles on the topic covering papillary lesions of the breast were retrieved from databases including PubMed, EMBASE, Scopus. Due to the rarity of the disease only retrospective studies, case series or review articles were available for literature review. To be specific as for the use of adjuvant treatment is concerned only the literature published between January 2015 till August 2021 in English language only was reviewed (*Table 1*).

Results

The search strategy included the following terms: “Intraductal papilloma breast”, “Ductal carcinoma *in situ* papillary breast”, “Encapsulated papillary carcinoma breast”, “Encapsulated papillary carcinoma breast with invasion”, “Solid papillary carcinoma *in situ* breast”, “Solid papillary carcinoma breast with invasion”, “Intraductal papillary adenocarcinoma breast with invasion”, “Invasive micropapillary carcinoma of breast”. Initial search on 9 September, 2021 resulted in 746 hits with above mentioned terms. However, when search results were narrowed down to “and adjuvant treatment” Boolean function, 31 records were returned. Out of these 31 records 17 overlapping records were found. Thus for final analysis,

data from 14 records was reviewed (*Figure 1*).

Discussion

Benign breast papilloma

Benign lesions include solitary intraductal papilloma and intraductal papillomatosis. An international multicentre review of the malignancy rates of excised papillomatous lesions of the breast (4), found that the upgrade rates from benign core needle biopsy to malignancy are somewhere near 14.4% and out of these 3.7% had invasive disease. Another retrospective review by Moynihan *et al.* (5) revealed that patients with benign papilloma without atypia on core biopsy have a low risk of upgrade to malignancy, with upgrade rates to malignancy of 2.4%. With this background, it can be argued that with such low rates of upgradation these lesions can safely be followed with the watch and wait for policy. This is particularly more relevant in women less than 35 years of age group where no upgradation rates to invasive disease were found. However, authors from the International Conference on lesions of uncertain malignant potential in the breast (B3 Lesions) recommended that even in such lesions underestimation of the stage can occur with core needle biopsy, warranting the use of a vacuum-assisted biopsy (VAB) in such lesions if wait and watch policy is to be adopted (6).

Atypical lesions

Upgrade rates after surgical excision of the papillary lesion with atypia can be as high as 28% (7). Even if these

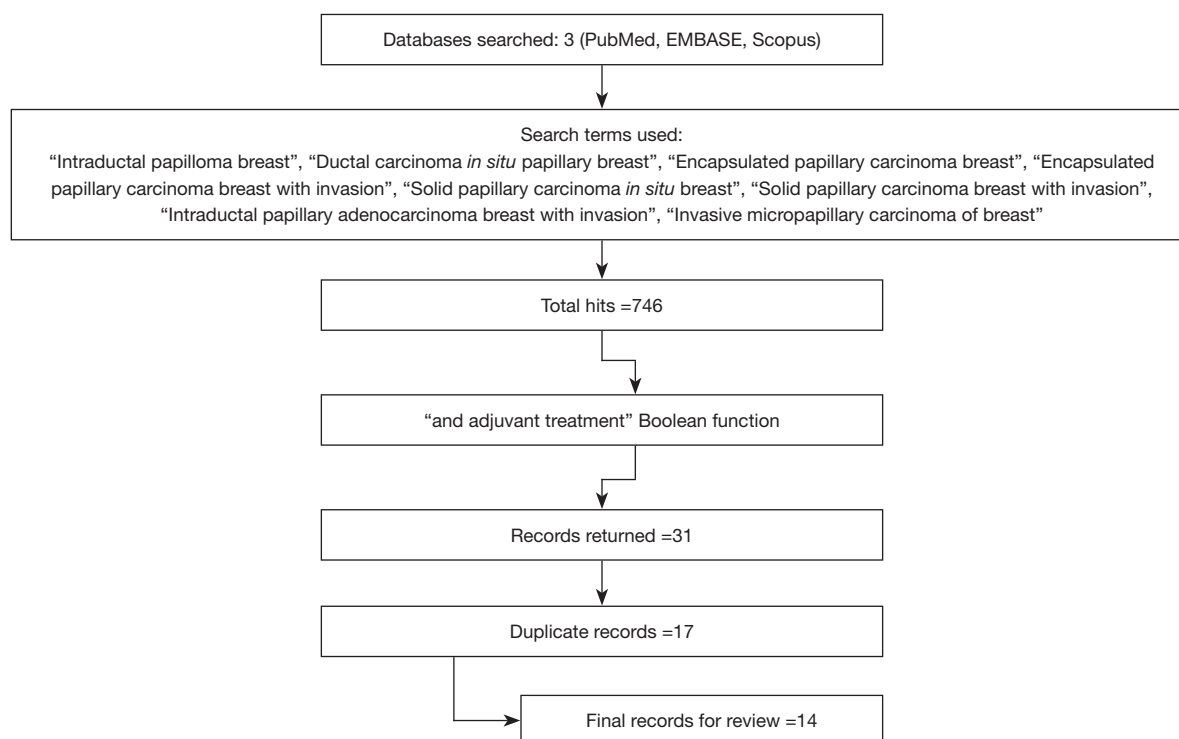


Figure 1 Search strategy for present review.

lesions are diagnosed on VAB there is a high possibility of them being malignant and therefore, surgical excision is warranted (8)

There is no role of any form of adjuvant treatment in benign papillary lesions even when associated with atypia provided they have been adequately excised. Some case reports in the literature do suggest the role of adjuvant treatment (9). However, they are single case reports especially describing multiple recurrent benign lesions. This may be due to invasive lesions masquerading as a benign prototype.

In-situ and invasive papillary lesions

Important prognosticators

Size of lesion

Usually these lesions present with small-sized tumours. Hassan *et al.* (10), in a recent analysis on the clinical presentations of these lesions reported that the median tumour size was 2 cm (range, 0.2 to 6 cm). When individual tumours were stratified according to size pure *in situ* lesions had a median size of 1.9 cm (1.2 to 4 cm), and those with associated invasion had the largest median size, 2.4 cm (0.2 to 6 cm). In a population-based study, Zheng *et al.* (11)

reported that the majority of the invasive papillary lesions presented with smaller-sized tumours as compared to their ductal counterparts.

Nodal status

Although less common, axillary lymph node metastasis has been noted even without frank invasion. However, in Surveillance, Epidemiology, and End Results (SEER) database analysis Mogal *et al.* (12) reported that out of all the patients who had axillary nodal status available only 5.5% had tumour involvement. Concerning invasive disease, another SEER data reported that the rate of lymph nodal involvement at diagnosis was lower in invasive papillary cancers (11.6%) (11). This rate was significantly less when compared to the patients with invasive ductal carcinoma (IDC).

Distant metastasis

Sedano *et al.* (13) on presenting their literature review reported the rate of distant metastasis to be around 1.9%. This was in agreement with the less than 1% rate for distant metastasis reported in the SEER data (12).

Grade (Gr)

Majority of the patients present with Gr 1 or 2 diseases. In the SEER report, nearly 81.9% of the patients presented with Gr 1 or 2 disease (12). Similarly for invasive disease,

73.8% of the patients had Gr 1 or 2 lesions in comparison to invasive ductal disease where 34.1% presented with Gr 3 disease.

Hormone receptor and HER 2 neu status

More than 90% of the *in situ* lesions express estrogen receptor/progesterone receptor (ER and/or PR) (12). Their invasive counterparts also strongly express ER and or PR (14). Occasionally, these may be human epidermal growth factor receptor 2 (Her2Neu) positive (14,15).

Ki67 and p53

These lesions have been shown to possess a low Ki67 index (less than 20) and p53 status (less than 10%) in more than two third of the patient's data as reported by Zhang *et al.* from a major Chinese cancer centre (14).

Thus, to summarize, *in-situ* as well as invasive papillary lesions usually have favourable prognosticators with small tumour size presentation, low nodal burden, well to moderately differentiated lesions, hormone receptor-positive with low proliferative indices. With this background, we now discuss the adjuvant treatment for these lesions.

Role of radiotherapy

Mogal *et al.* (12) reported that the use of radiation post-lumpectomy improved survival as compared to the use of surgery alone. In their analysis of around 2,649 patients from the SEER data having a diagnosis of intracystic papillary carcinoma, they found a statistically significant improvement in survival with $P < 0.0001$ for patients who received post-lumpectomy radiation. This stands true even on multivariate analysis. However, the authors did not find any significant difference in survival in patients who received either a lumpectomy or mastectomy.

Fakhreddine *et al.* (16) found that among 10,485 patients with invasive papillary breast carcinoma at a median follow up of 56 months, patients treated with lumpectomy combined with radiation had a superior mean overall survival as compared to those who received mastectomy alone or lumpectomy alone. Improved overall survival also correlated with lower histologic grade, lower T stage and younger age. They concluded that lumpectomy alone is not an appropriate treatment for all early-stage patients with IPC and that radiation therapy (RT) needs to be a component of adjuvant treatment.

In a recent analysis by Huang *et al.* (15) the authors while investigating the clinic-pathological characteristics between IPC and IDC of breast and their prognosis, revealed that elderly patients, advanced stage and no RT use were

associated with poor prognosis.

Thus, post-lumpectomy RT should be offered to all the patients of *in-situ* and IPC patients even in the presence of favourable prognosticators.

Role of hormonal therapy

As discussed earlier majority of the papillary tumours of the breast are hormone receptor-positive (>80%). Thus it is logical to prescribe hormonal agents in adjuvant settings. Zhang *et al.* (14) reported in their experience from a major Chinese cancer centre, that 86.5% of the patients with intra-cystic papillary carcinoma were hormone receptor-positive and nearly 84.7% received hormonal therapy. In the SEER database study too (12), 90.2% had hormone receptor-positive disease. Adjuvant hormonal therapy was frequently administered, though they did not provide exact numbers, however, they concluded that the benefit of adjuvant hormonal therapy in patients receiving radiotherapy or not was likely similar.

In another SEER investigative data in invasive papillary lesions (11), higher rates of ER/PR positivity were found in IPC tumours as compared to IDC ($P < 0.001$). This accounted for a better prognosticator in IPC tumours and benefit from hormonal therapy. In a recent trial by Huang *et al.* (15) IPC tumours were more likely to be hormone receptor-positive as compared to IDC tumours. The use of hormonal therapy in such tumours was found to be prognostic for 5-year overall survival on univariate analysis. However, such a result was not duplicated on multivariate analysis.

With this background, hormonal therapy should be considered as an adjuvant in hormone receptor-positive papillary tumours whether *in-situ* lesion post-surgery or IPCs.

Role of chemotherapy

As discussed earlier, the majority of the papillary tumours have favourable prognosticators even if associated with invasive components. Early T stage, lymph nodal negative, low grade, hormone-receptor-positive disease are the hallmarks of these lesions. With these 'ideal' findings it is imperative to hypothesise that the use of systemic chemotherapy should be very limited. Indeed, Turashvili *et al.* (17) while reporting the data on 21-gene recurrence score (RS) in these special histologic subtypes of invasive breast carcinoma noted that papillary carcinomas usually

have a low recurrence score (<18). The benefit of chemotherapy in patients with breast carcinoma of low RS is estimated to be too small to outweigh the risks of side effects.

National Cancer Comprehensive Network (NCCN) guidelines recommend the use of adjuvant hormonal therapy alone, even in lesions with T3 status provided they are node-negative or with microscopic nodal positivity (pN0 or pNi+). However, for node-positive, i.e., pN+ with at least \geq ipsilateral metastases >2 mm, the use of adjuvant chemotherapy in addition to adjuvant hormonal therapy can be considered (18).

Huang *et al.* (15) reported that stage for stage, the utilization of chemotherapy was less marked in IPCs as compared to IDCs. Adjuvant chemotherapy was used in only 16.1% of the patients diagnosed with IPC as compared to 44.9% of patients with IDC histology. 83% of patients with IDC stage 3 received chemotherapy whereas, only 45.3% with IPC received chemotherapy. Even with this less aggressive treatment, there was no significant overall survival difference between these two histo-pathologies. Thus, with the presence of papillary histology, the treatment can be de-escalated in accordance with the NCCN guidelines.

Conclusions

After the literature search and based on the results from the above-mentioned trials it can be concluded as of now that (I) there is no role of any form of adjuvant treatment in benign papillary lesions even if they are multiple or associated with atypia; (II) adjuvant radiotherapy should be offered to all *in-situ* lesions including encapsulated papillary carcinomas and solid papillary carcinomas with or without hormonal therapy based on hormonal receptor status; and (III) post resection adjuvant radiation with or without hormonal therapy should be offered in IPCs with systemic chemotherapy reserved in lymph node-positive diseases only.

However, more prospective and large-scale retrospective studies are needed in the future to further validate our conclusions and to figure out the influence of loco-regional treatments as well as systemic treatment on long-term survival.

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Footnote

Reporting Checklist: The author has completed the Narrative Review reporting checklist. Available at <https://tro.amegrouns.com/article/view/10.21037/tro-22-19/rc>

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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