

# Clinical practice guidelines for intraductal papilloma: Chinese Society of breast surgery (CSBrS) practice guidelines 2021

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Intraductal papilloma of the breast is relatively common, accounting for 5.3% of all benign breast diseases.<sup>[1]</sup> However, relapse readily occurs with pathological changes such as atypical ductal hyperplasia (ADH) and canceration, and the rate of underestimation of biopsy diagnosis is high.<sup>[2,3]</sup> Therefore, specific considerations are required for the diagnosis and treatment methods of intraductal papilloma, and some clinical problems with these methods remain controversial. To standardize the diagnosis and treatment of intraductal papilloma of the breast and provide a reference for the clinical work of breast specialists, Chinese Society of Breast Surgery has determined the key clinical issues of the clinical practice guidelines for intraductal papilloma of the breast through a literature search and expert discussion. The relevant evidence was evaluated with reference to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, and the *Clinical Practice Guidelines for Intraductal Papilloma: Chinese Society of Breast Surgery (CSBrS) practice guidelines 2021* was formulated to provide a reference for the clinical work of breast surgeons in China.

## Level of evidence and recommendation strength

### Level of evidence standard<sup>[4]</sup>

### Recommendation strength standard<sup>[4]</sup>

### Recommendation Strength Review Committee

The voting committee of this guideline comprised 76 members, including 63 (82.9%) breast surgeons, 3 (3.9%) oncologists, 4 (5.3%) radiologists, 2 (2.6%) pathologist, 2 (2.6%) radiation therapists, and 2 (2.6%) epidemiologists.

## Target audience

The target audience is clinicians specializing in breast diseases in China.

## Recommendations

### Recommendation 1: diagnostic method

Component	Level of evidence	Recommendation strength
1.1 Clinical manifestations: bloody or serous nipple discharge and/or breast mass <sup>[5]</sup>	I	A
1.2 Ultrasonography <sup>[6,7],*</sup>	II	A
1.3 Mammography <sup>[6,7],†</sup>	II	A
1.4 Ductoscopy <sup>[8,9]</sup>	I	A
1.5 Cytological examination of nipple discharge <sup>[6]</sup>	II	A
1.6 Core needle biopsy <sup>[2],‡</sup>	I	A

\* Ultrasound examination is performed to exclude other breast tumors for the central type and to locate tumor sites for the peripheral type.

† Mammography can be used as an auxiliary examination, except for other breast tumors.

‡ Core needle biopsy (CNB) has diagnostic value for the peripheral type.

### Recommendation 2: surgical indications

Component	Level of evidence	Recommendation strength
2.1 Clinically and/or pathologically diagnosed intraductal papilloma without surgical contraindications <sup>[5]</sup>	I	A

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Chinese Medical Journal 2021;134(14)

Received: 19-02-2021 Edited by: Yan-Jie Yin and Xiu-Yuan Hao

## Access this article online

### Quick Response Code:



### Website:

www.cmj.org

### DOI:

10.1097/CM9.0000000000001533

**Recommendation 3: operation mode**

	Component	Level of evidence	Recommendation strength
3.1	Open surgery <sup>[5,10],*</sup>	I	A
3.2	Vacuum-assisted breast biopsy (VABB) <sup>[5,10-12],†</sup>	I	A

\* Simple tumor resection or lobular or quadrant resection including duct excision with nipple discharge as the main manifestation. † Suitable for intraductal papilloma visible on imaging.

**Discussion**

The panel reviewed the literature and restated the standard for histological classification of breast tumors defined by the World Health Organization in 2003. According to its anatomical location and histological features, intraductal papilloma can be divided into the central and peripheral type. The central type originates from a large duct, is usually located under the areola; in contrast, the peripheral type originates from the terminal ductal-lobular unit.<sup>[13]</sup> Most cases of intraductal papilloma are of the central type. Peripheral papilloma accounts for only about 10% of cases.<sup>[14]</sup> Central intraductal papilloma mainly manifests as unilateral nipple discharge, which is often bloody or serous. In some patients, physical examination reveals palpable breast masses, most of which are located around the areola and compress the tumor area, bloody or serous liquid discharge is often present at the corresponding nipple ductal opening.<sup>[5]</sup> Peripheral intraductal papilloma is usually concealed and is characterized by nipple discharge or a breast mass that can be found by imaging examination. The typical clinical manifestation of both types is bloody or serous nipple discharge with or without a breast mass.

The most common breast imaging methods show fewer specific signs of intraductal papilloma, and the sensitivity and specificity of different imaging methods for the diagnosis of intraductal papilloma are quite different.<sup>[6-8,15-17]</sup> The sensitivity and specificity of ultrasound examination range from 67.3% to 82.9% and from 17.9% to 61.5% respectively, and the sensitivity of mammography ranges from 57.1% to 62.9%.<sup>[6,7]</sup> However, calcification can be seen in malignant transformation of intraductal papilloma, and mammography is of significance in differentiating benign from malignant lesions.<sup>[6,7]</sup> A meta-analysis of 921 cases among 10 studies showed that magnetic resonance imaging (MRI) was superior to galactography in the diagnosis of patients with negative ultrasound and mammography.<sup>[17]</sup> Ductoscopy is a highly sensitive diagnostic method for lesions in patients with nipple discharge that are not specifically found by ultrasound and mammography, especially for central intraductal lesions. One meta-analysis showed that the sensitivity and specificity of ductoscopy were 94% and 47%, respectively.<sup>[8,9]</sup> Cytological examination of nipple discharge exfoliation is also an available diagnostic method, but its sensitivity is only 22.8%; however, its specificity is as high as 85.5%.<sup>[6]</sup> According to China's national conditions and the anatomical characteristics of Chinese women's

breasts, the panel recommends ultrasound examination as the first-choice imaging examination technique, with the addition of mammography and MRI to distinguish intraductal papilloma from other types of malignant tumors when necessary. Nipple discharge is a common manifestation of central intraductal papilloma, and ductoscopy or cytological examination of nipple discharge exfoliation is recommended for a definitive diagnosis. In contrast, the main manifestation of peripheral intraductal papilloma is a breast mass. For this type of tumor, imaging examination combined with core needle biopsy/vacuum-assisted breast biopsy (CNB/VABB) is recommended to obtain a histopathological diagnosis. Because galactography lacks high-level research evidence,<sup>[18]</sup> the panel does not recommend it as a diagnostic method.

The diagnostic underestimation rates of CNB and VABB for intraductal papilloma are 15.7%–19.1% and 5.0%, respectively,<sup>[2-3,19]</sup> and both central and peripheral intraductal papillomas are at risk of malignant transformation.<sup>[1]</sup> A study of 915 patients showed that lobular resection or quadrant resection including the duct excision was the most accurate diagnostic method (sensitivity and specificity of 100%) for patients with pathological nipple discharge.<sup>[10]</sup> The panel recommends that all clinically diagnosed intraductal papillomas should be treated surgically and that the tumor should be completely removed. The First and Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions) recommended that imaging-visible papilloma should be removed by VABB and that the patient should subsequently undergo surveillance.<sup>[11]</sup> Open surgical resection is the first choice for patients with ADH.<sup>[11]</sup> Larger lesions that cannot be completely removed by VABB should be treated by open surgery.<sup>[12]</sup> According to the site of single intraductal papilloma as well as the accessibility and cost of CNB and VABB in Chinese primary hospitals, the panel equally recommends complete resection by open surgical resection and VABB for single intraductal papilloma without nipple discharge.

For central intraductal papilloma with nipple discharge, open surgery is recommended and should include lobular resection or quadrant resection including the intraductal lesion<sup>[5,10]</sup>; open surgery or CNB/VABB can be performed for peripheral intraductal papilloma.<sup>[5,10-12]</sup> When the lesions are multiple and involve the whole breast, prophylactic mastectomy or subcutaneous mastectomy with or without prosthesis reconstruction can be considered.<sup>[4]</sup> The panel believes that patients diagnosed with central or peripheral intraductal papilloma with ADH by CNB/VABB should be treated individually according to their specific conditions. If the patient has a single lesion and imaging shows that it has been completely removed, follow-up monitoring can be carried out; open extended resection is recommended in cases of uncertain complete resection.<sup>[11,12]</sup>

**Conflicts of interest**

The expert committee for these guidelines declares no conflict of interest.

These guidelines are a reference for breast disease specialists in clinical practice. However, the guidelines are not to be used as the basis for medical evaluation, and do not play an arbitrating role in the handling of any medical disputes. The guidelines are not a reference for patients or non-breast specialists. The Chinese Society of Breast Surgery assumes no responsibility for results involving the inappropriate application of these guidelines, and reserves the right to interpret and revise the guidelines.

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**How to cite this article:** Wu D, Shi AP, Song AL, Fan ZM. Clinical practice guidelines for intraductal papilloma: Chinese Society of Breast Surgery (CSBrS) practice guidelines 2021. *Chin Med J* 2021;134:1658–1660. doi: 10.1097/CM9.0000000000001533