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REVIEW

Management of Intraductal Papilloma of the Breast Diagnosed on Core Needle Biopsy: Latest Controversies

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Abstract

Intraductal papillomas (IDPs), including central papilloma and peripheral papilloma, are common in the female population. Due to the lack of specific clinical manifestations of IDPs, it is easy to misdiagnose or miss diagnose. The difficulty of differential diagnosis using imaging techniques also contributes to these conditions. Histopathology is the gold standard for the diagnosis of IDPs while the possibility of under sample exists in the percutaneous biopsy. There have been some debates about how to treat asymptomatic IDPs without atypia diagnosed on core needle biopsy (CNB), especially when the upgrade rate to carcinoma is considered. This article concludes that further surgery is recommended for IDPs without atypia diagnosed on CNB who have high-risk factors, while appropriate imaging follow-up may be suitable for those without risk factors.

Keywords Intraductal papilloma · Manifestation · Imaging · Preoperative biopsy · Treatment · Core needle biopsy

Introduction

An intraductal papilloma (IDP) is a benign growth that arises from the milk duct epithelium and is defined as a proliferative epithelial lesion with a fibrovascular core (Hodorowicz-Zaniewska et al. 2019a, b; Fadzli et al. 2021). It is affecting two to three percent of the female population and accounting for about 10 percent of all benign breast hyperplasia, with the most common age between 35–55 years old (Wei 2016; Tsilimigras et al. 2017; Boufelli et al. 2018). Most papillary neoplasms of the breast occur in women, but men can also be affected (Zhong et al. 2020). The characteristics of the epithelium determine whether a papillary neoplasm is benign, atypical, or carcinoma. IDP is split into two types: first central papilloma (large-duct papilloma), which typically involves a single lesion around the nipple, and second peripheral papilloma (small-duct papilloma), which typically involves multiple lesions (Murad et al. 1981; Lewis et al. 2006). Previous findings pointed out that the risk of breast cancer (BC) from peripheral IDPs might be higher than that of central IDPs (Ohuchi et al. 1984; Lewis et al. 2006; Eiada et al. 2012). What's more, there is a higher risk of carcinogenesis when epithelial atypical proliferation lies both inside and outside the papilloma (Maxwell 2009). Considering the possibility of accompanying malignant, the diagnosis of IDP is crucial while imaging is hard to rely on because of the overlapping radiologic findings (Choi et al. 2006).

Therefore, the prediction of malignancy based on preoperative biopsy is important and can guide further treatment. There is a consensus that IDPs with atypical ductal hyperplasia (ADH) diagnosed on core needle biopsy (CNB) should be excised (McGhan et al. 2012; Wen and Cheng 2013), but the management of IDPs without atypia diagnosed on CNB is under debate, vacillating between close imaging follow-up and invasive surgical procedures. A recent consensus conference recommended that papillary lesions diagnosed on CNB be excised by vacuum-assisted biopsy (VAB) in preference to open surgery (Rageth et al. 2019). While most facilities no longer remove asymptomatic radiology–pathology concordant IDPs without atypia but instead monitor them using sonographic imaging because of their low upgrading rate to malignancy (Patterson et al. 2014; Yamaguchi et al. 2015; Hong et al. 2016; Han et al. 2018; Genco et al. 2020).

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This article reviews the clinical manifestations, diagnosis, and treatment of IDPs from the perspective of recent research advances, and discusses the existing controversies in the management of IDPs diagnosed on CNB in the hope of providing an overview of IDPs and possibly bringing practical suggestions to the diagnosis and treatment of IDPs (Fig. 1).

Clinical Manifestations

Nipple discharge is the most common clinical manifestation in perimenopausal and postmenopausal women between the ages of 40–50 which can be seen in 60–80% of patients with IDPs (Brookes and Bourke 2008; Wei 2016). The performance of pathologic nipple discharge tends to be unilateral, from a single duct orifice, spontaneous, and serous or bloody while physiologic nipple discharge tends to be bilateral, from multiple duct orifices, and white, green, or yellow in color (Alcock and Layer 2010). Some patients only show discharge after squeezing or colliding the breast, and the discharge duct orifice is fixed. In clinical practice, if press lightly the nipple-areola area in sequence, the discharge duct orifice will be found when the discharge is visible.

Breast mass, another major papilloma symptom, is uncommon in clinical practice. Benign masses typically are small in size, mobile, have discrete, well-defined margins, and soft or rubbery in texture (Expert Panel on Breast Imaging et al. 2017b). Most IDPs are asymptomatic, especially small ones, it is usually not until nipple discharge occurs can the disease be found (Li and Kirk 2022). Due to the lack of specific clinical manifestations of IDPs, it is easy to misdiagnose or miss diagnose (Zervoudis et al. 2010).

Almost 90% of IDPs are central, with a single nidus located in the lactiferous duct, which usually occur in elderly women and manifest serous or bloody nipple discharge (Al

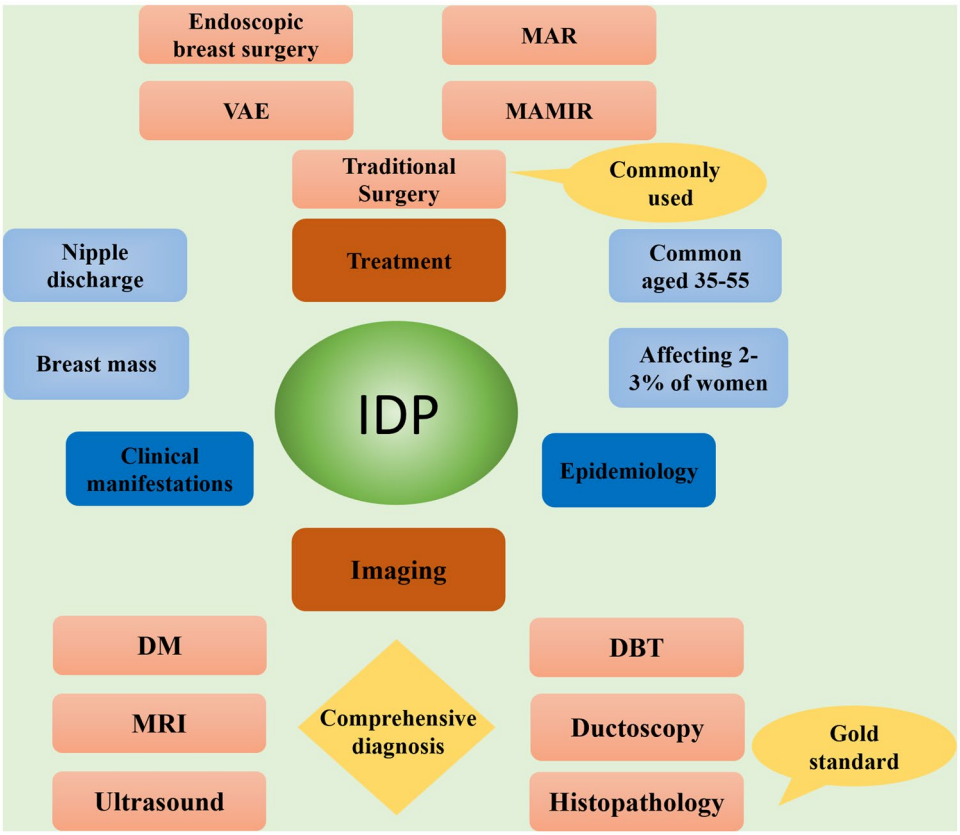

Fig. 1 Overview of the IDP. An IDP is a benign growth which is affecting 2–3% of the female population and the most common age is between 35–55 years old. Nipple discharge is the most common manifestation of IDPs with breast mass follows. Imaging techniques used in diagnosing IDPs commonly include DM, DBT, ultrasound, MRI, and ductoscopy which show advantages of noninvasive and convenient while they present limitations in some degree. Histopathology is usually the gold standard for the diagnosis of IDPs. In addition to traditional surgery which is commonly used, other techniques such as VAE, endoscopic breast surgery, MAR, and MAMIR are playing an important role in removing IDPs. *IDP* intraductal papilloma, *DM* digital mammography, *DBT* digital breast tomosynthesis, *MRI* magnetic resonance imaging, *VAE* vacuum-assisted excision, *MAR* mammography-assisted resection, *MAMIR* mammotome-assisted minimally invasive resection

Sarakbi et al. 2006). Peripheral IDPs are rare and usually develop in young women with commonly multiple, occasionally bilateral presentations. They may appear as palpable masses, although they are usually clinically silent and discovered by chance during routine imaging exams (Ganesan et al. 2006).

Imaging Techniques

Imaging techniques, which commonly include digital mammography (DM), digital breast tomosynthesis (DBT), ultrasound (US), magnetic resonance imaging (MRI), and fiberoptic ductoscopy (FDS), show advantages of noninvasive and convenient, and are widely used in diagnosing IDPs, though they present limitations in some degree (Table 1). DM or DBT is generally used routinely for patients over 40 years old with a palpable lump as the initial imaging assessment; while US is for patients younger than 30 years old; for women aged 30 to 39 years, either DM or DBT or US can be used for initial evaluation (Expert Panel on Breast Imaging et al. 2017b). Galactography is not recommended as a diagnostic method because it lacks high-level research evidence (Ahn et al. 2018).

Digital Mammography

Since IDPs are usually small in volume and light in density, it is difficult to find positive results in DM. When an IDP (diameter greater than two centimeters) is large enough to be seen, it can appear as a round or oval mass with a well-circumscribed or indistinct margin, and may occasionally accompany it by calcifications which is similar to papillary carcinoma (Woods et al. 1992; Muttarak et al. 2008; Li and Kirk 2022). Some specific features on DM have been suggested inclined to malignancy which include pleomorphic calcifications and architectural distortion (Eiada et al. 2012; Jagmohan et al. 2013). As a routine examination for IDPs, DM is always combined with other imaging examinations and is generally used routinely for patients over 40 years old with a palpable lump as the initial imaging assessment (Expert Panel on Breast Imaging et al. 2017b).

Contrasted-enhanced mammography (CEM), which is commercially introduced in 2011 (Jochelson and Lobbes 2021), has emerged as a viable alternative to contrast-enhanced magnetic resonance imaging (CE-MRI) which uses iodinated contrast materials for the visualization of breast neovascularity (Patel et al. 2018). It has the advantage of demonstrating both anatomic changes and local changes in breast perfusion, presumably caused by tumor angiogenesis, especially in dense breasts which may not be seen by DM or DBT (Barra et al. 2018; Jochelson and Lobbes 2021). The most substantial limitation of CEM is the possibility of contrast material reactions (Zanardo et al. 2019). What's more, lesions close to the chest wall or in the medial part of the breast may be overlooked in CEM (Lalji et al. 2016).

Digital Breast Tomosynthesis

DBT, which allows the creation and viewing of thin-section reconstructed images, may decrease the lesion-masking effect of overlapping normal tissue and improve noncalcified lesions imaging (Noroozian et al. 2012; Skaane et al. 2012; Zuley et al. 2014), thus could be useful in the setting of nipple discharge evaluation (Expert Panel on Breast Imaging et al. 2017a). DBT imaging improves the visualization of subtle signs, which may be useful in IDPs, and determinates lesions found on DM more accurately as either more suspicious of malignancy or benign (Bansal and Young 2015). But it has limited accuracy in women with dense breasts (Patel et al. 2018).

Ultrasound

US is the main imaging method for IDPs and is preferred as the investigation for women younger than 30 years old because they tend to have denser breast tissue, which is associated with decreased mammographic sensitivity (Checka et al. 2012). US is also useful in the second-look examination after a negative finding or a finding not unequivocally characterized as benign on DM or DBT in women over 40 years old with a palpable mass because of its ability in detecting small lesions (Durfee et al. 2000; Expert Panel on Breast Imaging et al. 2017b). It also has the advantages of no damage, no pain, repeatable inspection, efficiency, economy, and ease of use.

IDPs tend to be round or oval, hypoechoic in echo texture, and parallel in orientation to the chest wall enhanced by US (Kim et al. 2008). Sometimes a dilated duct with a solid mass within may be detected (Fadzli et al. 2021). Because of the non-specific ultrasonographic features, it is difficult to distinguish malignant papillary breast lesions from benign ones, while the combination of multiple technologies can greatly improve diagnostic accuracy (Niu et al. 2021). For example, US can be combined with elastography technology to display the location, size, shape, internal echo, and blood supply status of IDPs more intuitively, as well as information on the interval relationship between the lesion and the duct and the hardness of the lesion (Fig. 2).

Contrast-enhanced ultrasound (CEUS) can better reflect the contour, continuity, course, and branch of blood vessels. Some studies found that benign papillomas and atypical or malignant papillomas are significantly different in some

Table 1 Advantages and disadvantages between different imaging techniques

Imaging techniques	Advantages	Disadvantages	References
DM	Routine examination; used for differential diagnosis (generally used for patients over 40 years old with palpable masses)	Only when the IDP (diameter > 2 cm) is large enough to be seen; lack of specificity in the diagnosis	Woods et al. (1992), Muttarak et al. (2008), Expert Panel on Breast Imaging et al. (2017b), Li and Kirk (2022)
DBT	Useful in the setting of nipple discharge evaluation; better visualization of subtle signs; more accurate than DM	Limited accuracy in women with dense breasts; not commonly used clinically	Bansal and Young (2015), Expert Panel on Breast Imaging et al. (2017a), Patel et al. (2018)
US	The main imaging method for IDPs; can be used as a second-look examination after DM or DBT; capacity of finding tiny lesions	Low in specificity and sensitivity	Durfee et al. (2000), Checka et al. (2012), Expert Panel on Breast Imaging et al. (2017b), Niu et al. (2021)
MRI	High sensitivity in diagnosing IDPs; better show the IDP and its surrounding environment; higher PPV and NPV in detection of abnormal lesions in patients with pathologic nipple discharge than DM and US	Lacking in the specificity of diagnosis of IDPs and is difficult to characterize whether the lesions tend to be malignant or benign	Morrogh et al. (2007), Ballesio et al. (2008), Son et al. (2009), Zhu et al. (2012); Wang et al. (2015)
FDS	The first choice for diagnosis of IDPs with nipple discharge; early detection of small IDPs; better preoperative reference (cytological investigation of duct flushing fluid and suspicious lesion biopsies)	The operation requirement is high and cannot be used in small duct	Kapenhas-Valdes et al. (2008), Dooley (2009), Kamali et al. (2010), Fisher and Margenthaler (2011), Gui et al. (2018)

DM digital mammography, *IDP* intraductal papilloma, *DBT* digital breast tomosynthesis, *US* ultrasound, *MRI* magnetic resonance imaging, *PPV* positive predictive value, *NPV* negative predictive value, *FDS* fiberoptic ductoscopy

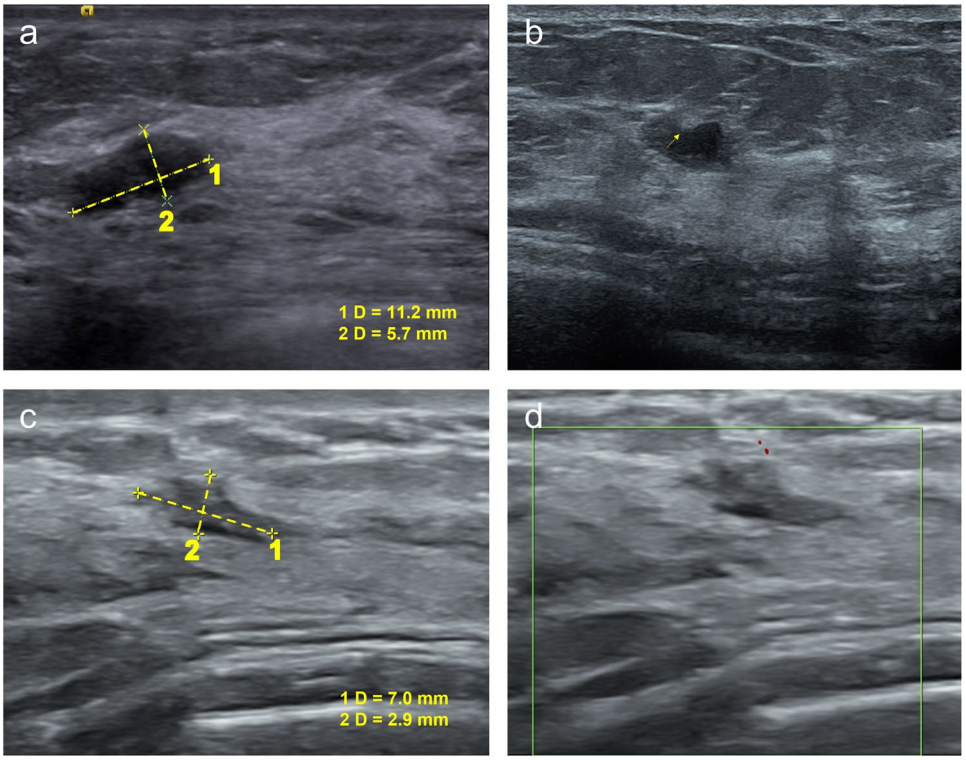

Fig. 2 Three groups papillary lesions including solid type (**a**), intracapsular type (**b**) and intraductal type (**c**), pathologically confirmed to be intraductal papillomas on conventional US. The doppler image (**d**) of the intraductal type papilloma (**c**) revealed peripheral but no internal vascularity

patterns, which included irregular enhancement, heterogeneous enhancement, enlargement of scope, perfusion defect, presence of vascularity, and absence of dilated ducts (Zhao et al. 2010, 2017; Niu et al. 2021; Fadzli et al. 2021). What's more, real-time contrast echocardiography can make a better diagnosis and improve accuracy for some small, low-echoic solid masses, or some masses that cannot be judged as cystic solid masses (Kettenbach et al. 2005).

Magnetic Resonance Imaging

Breast MRI, especially CE-MRI, has high sensitivity in diagnosing IDPs and does not reduce the diagnostic accuracy rate due to the complexity of disease types. Because of its high resolution of soft tissues, both the IDP and its surrounding environment can be excellently visualized in MRI, besides, pathology can be shown in good details (Ballesio et al. 2008; Son et al. 2009).

IDPs can perform themself in mass-like or non-mass-like types on MRI. To be specific, the characteristic shapes of mass lesions consist of round, lobulated, burr-like masses while the non-mass lesions have various shapes such as ductal, segmental, regional, and multiple mass-like. After being strengthened, the enhancement patterns can be homogeneous enhancement, heterogeneous enhancement, rim enhancement, clustered ring enhancement, and focal nodulary-punctate (Hao et al. 2019). Because an IDP can manifest itself in both benign and malignant forms, MRI is ineffective in diagnosing and characterizing it (Zhu et al. 2012; Wang et al. 2015). Radiologists tend to prefer MRI over ductography in the evaluation of nipple discharge when DM and US are negative for the higher positive predictive value (PPV) and negative predictive value (NPV) in the detection of abnormal lesions in patients with pathologic nipple discharge (Morrogh et al. 2007) (Fig. 3).

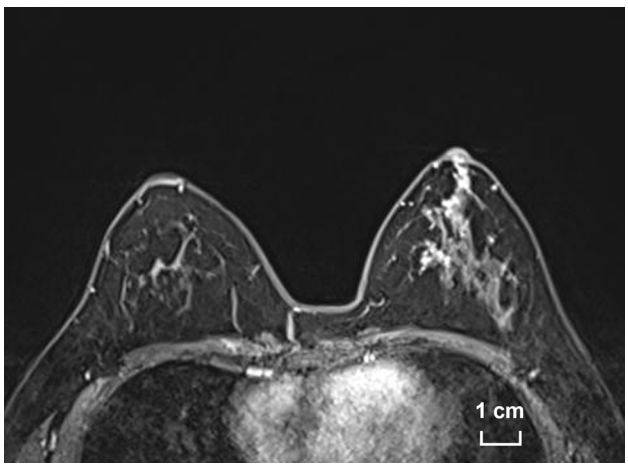

Fig. 3 Axial contrast-enhanced magnetic resonance image of the left breast demonstrates dilated ducts with punctate enhancement around

Fiberoptic Ductoscopy

FDS is very accurate in the diagnosis of IDPs with PPV and NPV of at least 90% (Gui et al. 2018). The greatest advantage lies in the early detection of small IDPs (Kamali et al. 2010; Fisher and Margenthaler 2011). Both duct ectasia and IDP are commonly recognized in FDS (Gui et al. 2018). By observing the characteristics of the lesions, cytological investigation of duct flushing fluid, and suspicious lesion biopsies, doctors can have better preoperative references. However, it is available at only a few centers because surgeons need to be experienced in this technique (Kapenhas-Valdes et al. 2008; Dooley 2009).

Preoperative Biopsy

Histopathology is usually the gold standard for the diagnosis of breast diseases concerning the limitations of imaging techniques, so as in IDPs. If a suspicious mass has been identified on imaging, a biopsy is necessary. Cytological examination of nipple discharge exfoliation can be used if the patient has nipple discharge; if not, imaging techniques can also be used, while histopathology is required for a definitive diagnosis. IDPs diagnosed by preoperative biopsy which mainly include fine needle aspiration biopsy (FNAB), CNB, and VAB, can be diagnosed in more depth as ADH, ductal carcinoma in situ (DCIS), or BC after surgery (Eiada et al. 2012). Progress in the pathology-morphology diagnosis of the breasts, especially immunohistochemistry, allows for a more precise differentiation between various papillary growths (Agoumi et al. 2016). Image-guided biopsy has the advantage of biopsy accuracy and the ability to place a biopsy marker clip (Expert Panel on Breast Imaging et al. 2017b).

CNB is the most commonly used biopsy method before surgery and has a diagnosis precision of 93.2%, which can diagnose most papillary lesions (Wang et al. 2017). Vacuum-assisted CNB is particularly useful in ensuring complete sampling of small IDPs, in addition, if the process of removing IDPs is enough, it can be therapeutic and may lead to a permanent cessation of nipple discharge in 90 to 97.2% of patients (Dennis et al. 2000). While the underestimation rate of atypical ductal or lobular cells is approximately 14% and DCIS or BC is approximately 13% (Li et al. 2020a, b). On one hand, because the CNB sample only contains a tiny portion of the lesion, malignant tumors adjacent to IDPs or within IDPs may be missed, on the other hand, the normal myoepithelial layer cannot be seen in small CNB samples (Rosen et al. 2002).

FNAB is an effective and less painful procedure for the evaluation of patients with palpable masses under US guidance, for the small diameter of the needle allows a more flexible sampling procedure. Jamidi et al. reported that reduced cellular cohesion, epithelial structures with solid and cribriform patterns, atypical cellular cytomorphologic features, neuroendocrine features, the presence of neutrophils (background and infiltrating), and hemorrhage indicated malignant lesions in FNAB (Jamidi et al. 2021). While series of studies indicate that CNB is superior to FNAB in terms of sensitivity, specificity, and correct histological grading of palpable masses (Homesh et al. 2005; Garg et al. 2007).

VAB is better than CNB and FNAB because it obtains more tissue samples for pathological analysis and is closer to a surgical biopsy which has a diagnosis precision up to 98–100%, while the damage of surrounding tissues and the fragmentation of material add uncertainty to the histological evaluation of both the lesion and its margin (Nakano et al. 2007). However, recent studies showed that if the lesion is completely or mostly removed during VAB, the overall diagnostic underestimation rate of invasive cancer among DCIS patients is significantly lower compared to those showing mammographically documented residual lesions following VAB (Nicosia et al. 2022, 2021a). What's more, patients with a diagnosis of ADH on VAB have relatively lower upgrade rates to DCIS or invasive carcinoma considering the following parameters: breast imaging reporting and data system (BI-RADS) $\leq$ 4a; size of the lesion $\leq$ 15 mm; age of the patients $<$ 50 years; in presence of ADH only in samples with microcalcifications (Nicosia et al. 2021b). These could be used for identifying patients with low risk of upstaging to infiltrating carcinomas and thus avoiding overtreatment (Table 2).

Because of the resemblance of structure between benign and malignant lesions, it is necessary to evaluate the sample's representativeness and have sufficient clinical-pathological correlation analysis. Assessing the presence and distribution of the myoepithelial cells (MECs) in IDPs is also important for differential diagnosis (Stefanou et al. 2004; Collins et al. 2006; Vielh 2021). For example, estrogen receptors (ER), and basal cytokeratins (CK5, CK5/6, CK14, and 34βE12) can be used to assess the presence and extent of ductal epithelial atypia in IDPs (Grin et al. 2009; Tse et al. 2009, 2014; Agoumi et al. 2016).

Treatment

Although an IDP is a benign tumor, it is frequently recommended for surgery due to the difficulty in diagnosing it, the risk of atypia, and their morphologic resemblance to malignant lesions like low-grade papillary ductal carcinoma in situ, encapsulated papillary carcinoma, or solid papillary carcinoma (Wen and Cheng 2013). The surgery is based on

Table 2 Advantages and disadvantages of different preoperative biopsy

Preoperative biopsy	Advantages	Disadvantages	References
FNAB	The small diameter of the needle allows a more flexible sampling procedure; less painful and more economic than CNB	Requires expert sampling techniques; inferior to CNB in terms of sensitivity, specificity, and correct histological grading of palpable masses	Homesh et al. (2005), Garg et al. (2007), Eiada et al. (2012), Jamidi et al. (2021)
CNB	The most commonly used biopsy before surgery; provides larger tissue sample than FNAB; can be therapeutic if the process of removing the IDP is enough	Artifactual distortion of the tissue, misplaced epithelial cells and small size of the sample can create diagnostic difficulty; may displace a small mobile mass in a single pass and miss the target	Dennis et al. (2000), Rosen et al. (2002), Wang et al. (2017), Bennett and Saboo (2019), Li et al. (2020a, b)
VAB	Similar to surgical biopsy in terms of tissue volume and have the highest diagnostic accuracy among three biopsy techniques; not only for diagnosis but also a therapeutic tool	Unable to determine the histologic evaluation of resection margins because of fractured tissues	Nakano et al. (2007), Jaffer et al. (2009), Rageth et al. (2016), Surg (2016), Hodorowicz-Zaniewska et al. (2019a, b), Nicosia et al. (2022), Nicosia et al. (2021a,b)

FNAB fine needle aspiration biopsy, *CNB* core needle biopsy, *IDP* intraductal papilloma, *VAB* vacuum-assisted biopsy

the principle of complete excision while preserving as many healthy glands as possible (Tran et al. 2017). If excision is not complete, there will be a greater recurrence rate and a certain probability of carcinogenicity.

Patients who were suspicious of IDPs, with an accompanying sanguineous nipple discharge used to have a mastectomy (Hodorowicz-Zaniewska et al. 2019a, b), but now with the development of imaging and minimally invasive surgery, surgical approaches are becoming less invasive. In addition to traditional surgery, other techniques such as vacuum-assisted excision (VAE), endoscopic breast surgery, mammography-assisted resection (MAR), and mammotome-assisted minimally invasive resection (MAMIR) are playing an important role in removing most IDPs (Wei et al. 2009), while there are still some limitations for multiple IDPs (Ling et al. 2009). Among them, endoscopic papilloma resection is still in exploration and has not been widely used in clinical practice. This type of operation has the characteristics of less damage, less pain, and almost no scars, but is only suitable for patients with nipple discharge. Bender et al. followed up 22 patients with nipple discharge who successfully underwent endoscopic papilloma resection for 2 to 22 months, and the result showed that 21 patients had no recurrence symptoms of nipple discharge (Bender et al. 2009). VAE is a common minimally invasive technique in clinical practice with the advantages of being thorough, simple, and intuitive, but it is currently rarely used in the treatment of IDPs. It is also suitable for patients without nipple discharge, which makes up for the deficiency of ductoscopy. According to certain research, VAE cannot completely replace traditional surgery because it eliminates too little tissues, resulting in a significant risk of remaining lesions (Maxwell 2009). MAMIR is a new minimally invasive surgery which can not only accurately locate the breast mass, but also remove multiple masses in one operation, resulting in less trauma, faster recovery, and better cosmetic results. It is reported that the accuracy and sensitivity of ultrasound-guided MAMIR to remove suspicious breast lesions are high (Meloni et al. 2001). But for patients with multiple lesions, this needs to be carefully selected because of the possibility of recurrence.

Controversies

In the last decade, whether implementing surgery on patients with IDPs without ductal atypia diagnosed on CNB has been the subject of intense investigation. According to current recommendations, IDPs with atypia diagnosed on CNB need to be excused because of their high association with malignancy (Menes et al. 2014; Shiino et al. 2015). While for IDPs with no abnormalities, the management vacillates between close imaging follow-up and invasive surgical procedures. Considering even with developed imaging techniques and

improved biopsy techniques, the lesions may still be undersampled at CNB (Bennett and Saboo 2019), and there is a risk of missing atypical or even malignant tumors, particularly in resection margins, therefore open surgical biopsy is regularly suggested (Rageth et al. 2016; Surg 2016). The current underestimation of BC at CNB ranges from zero point four to four percent (Kiran et al. 2018; Grimm et al. 2018; Gruzinova et al. 2020). On the other hand, an open incisional biopsy can confirm the diagnosis, guide subsequent treatment and prevent some patients from further surgery. At the same time, it is more aggressive and may cause chronic pain, anxiety, and depression (Spivey et al. 2018). Some studies suggested that VAB can be considered as a treatment option, but a five-year-follow-up is required (Jaffer et al. 2009; Rageth et al. 2016; Surg 2016; Hodorowicz-Zaniewska et al. 2019a, b).

This article concludes some cases undergo a higher risk of malignant transformation or BC underestimation and in such situations, resections may be recommended:

1. Older populations, especially populations that age > 50 years old. McGhan et al. (2012) found that age > 50 years was associated with a higher rate of upstaging in patients diagnosed with ADH on CNB while age < 50 years with focal atypia only, and no residual calcifications post-biopsy may avoid excisional biopsy. Foley and colleagues showed that older age was independently associated with malignancy, and that the odds ratio was equal to 1.07 for each year increases in age (Foley et al. 2015). Hodorowicz-Zaniewska et al. detected an increased risk for underestimation in older populations, which is consistent with the later reports (Rasmussen et al. 2018; Hodorowicz-Zaniewska et al. 2019a, b; Chen et al. 2019; Yu et al. 2019).
2. The presence of concurrent contralateral BC, multifocality. Han et al. (2018) found the presence of concurrent contralateral breast cancer, the presence of symptoms, and multifocality were factors significantly associated with upgrading to malignancy in patients who were diagnosed as benign IDP without atypia on CNB.
3. Clinical symptoms (nipple discharge and/or a palpable mass). Shouhed et al. showed a clinically palpable mass was a significant predictor of upstaging to malignancy (Shouhed et al. 2012). The risk factors for the upgrade in IDPs were evaluated and diagnosed by percutaneous biopsy, and it was found that the clinical presentation with bloody nipple discharge or palpable mass was significantly associated with the upgrade (Ahn et al. 2018).
4. The large size of the lesion (greater than one to one point five centimeters). Hong et al. reported that lesion size greater than one centimeter was significantly associated with an upgrade to malignancy (Hong et al. 2016). Similarly, Ahn et al. (2018) showed that size on imaging greater than or equal to one point five centimeters is an independent predictor of malignancy and Genco et al. (2020) demonstrated that IDP size greater than or equal to one centimeter was the only statistically significant factor for the upgrade on surgical excision. On the other hand, studies found that IDP less than or equal to one centimeter were significantly more likely to remain benign on surgical excision (Shouhed et al. 2012; Abbassi-Rahbar et al. 2021).
5. Peripheral location. Researchers found that peripheral lesions were more likely to upgrade than central lesions (Kil et al. 2008; Ahn et al. 2018; Chen et al. 2019).
6. A not circumscribed margin in imaging. It was demonstrated that benign papillary lesions had a circumscribed margin compared to malignant and high-risk lesions (Kim et al. 2008; Shin et al. 2008; Kuzmiak et al. 2014).
7. Patients with high BI-RADS classification/scores, ultrasound abnormality (at least 4c) and mammographic distortion, masses, and microcalcification. Kim et al. (2016) suggested that IDP patients could be stratified into a low risk for upgrade group if there was imaging-pathologic concordance and using BI-RADS with the risk of the upgrade being one point four to one point eight percent for BI-RADS 3 and BI-RADS 4a. Another study found similar results that BI-RADS ≥ 4b was significantly associated with the upgrade of IDPs diagnosed by percutaneous biopsy (Ahn et al. 2018). Shouhed et al. (2012) found that mammograms in patients with benign papillary lesions demonstrated significantly more masses than in patients with atypia or malignancy. Li and co-workers retrospectively reviewed 4,450 IDPs with surgical excision in Chinese women and showed that IDPs with malignancy had significant correlations with clinical manifestations such as nipple discharge, a palpable breast mass, ultrasound abnormality (BI-RADS 4c and 5), mammographic distortion, and microcalcification upon DM (Li et al. 2020a, b).
8. The small diameter of the needle (12–16G). McGhan et al. (2012) found that smaller needle diameter (12–16G), and length of biopsy core less than two centimeters were factors associated with higher rates of upstaging in patients diagnosed with ADH on CNB. Meanwhile, a study showed an IDP sampled by a 12G or larger needle, greater than or equal to seven cores, or > 96 mm^2 retained its benign features upon excision (Shamonki et al. 2013).

Table 3 Risk factors for IDP patients that may result in misdiagnosis of malignancy on CNB or transformation to BC

Risk factors
Older populations, especially populations that age > 50 years old (McGhan et al. 2012; Foley et al. 2015; Rasmussen et al. 2018; Hodorowicz-Zaniewska et al. 2019a, b; Chen et al. 2019; Yu et al. 2019)
Menopausal status and family history of BC (Laval et al. 2015; Kiran et al. 2018)
The presence of concurrent contralateral BC (Han et al. 2018)
Clinical symptoms (nipple discharge and/or a palpable mass) (Shouhed et al. 2012; Han et al. 2018; Ahn et al. 2018; Li et al. 2020a, b)
The large size of the lesion (> 1–1.5 cm) (Shouhed et al. 2012; Hong et al. 2016; Ahn et al. 2018; Genco et al. 2020; Abbassi-Rahbar et al. 2021)
The peripheral location of the lesion (Kil et al. 2008; Ahn et al.2018; Chen et al. 2019)
Multifocality lesions (Han et al. 2018)
A not circumscribed margin in imaging (Kim et al. 2008; Shin et al. 2008; Kuzmiak et al. 2014)
Patients with high BI-RADS classification/scores, ultrasound abnormality (at least 4c) and mammographic distortion, masses and microcalcification (Shouhed et al. 2012; Kim et al. 2016; Ahn et al. 2018; Li et al. 2020a, b)
The small diameter of the needle (12–16G) (McGhan et al. 2012; Shamonki et al. 2013)

IDP intraductal papilloma, *CNB* core needle biopsy, *BC* breast cancer, *BI-RADS* breast imaging reporting and data system

Besides, menopausal status and family history of BC are predictors of malignant tumors (Laval et al. 2015; Kiran et al. 2018) (Table 3).

On the other hand, some studies showed that occasional IDPs smaller than two millimeters do not need to be removed and benign IDPs without atypia do not require resections when there are no palpable masses or imaging/pathological discrepancies (Jaffer et al. 2013; Nakhlis et al. 2015). A recent multi-institutional prospective study holds the same view, which recently reported a low rate (less than two percent) of upgrade to carcinoma at excision of asymptomatic and concordant IDPs (Nakhlis et al. 2021). According to the findings of these investigations, most facilities no longer remove asymptomatic radiology–pathology concordant IDPs without atypia but instead monitor them using sonographic imaging (Jaffer et al. 2013; Hong et al. 2016; Genco et al. 2020).

Conclusion

With the advancement of inspection techniques and minimally invasive operations, both the diagnosis and treatment of IDPs are constantly updated. However, the etiology and pathogenesis of IDPs are still unclear, and non-uniform definitions and diagnostic criteria result in the inability to standardize the diagnosis and treatment. IDPs are now facing the risk of malignant transformation, underdiagnosis, improper treatment, and the possibility of recurrence, yet our suggestions might be used to facilitate a more precise treatment (Fig. 4).

Pathologists must be familiar with the diagnosis of IDPs without atypia and its differential diagnoses, as well as the need to assess ductal epithelial atypia in a papilloma with the aid of immunohistochemical markers in challenging cases, as the management of asymptomatic IDPs without atypia diagnosed at radiology pathology concordant core biopsy, is shifting towards imaging follow-up without immediate surgical excision. Further treatment should be made with caution in cases where there is a high risk of malignant transformation or BC underestimate.

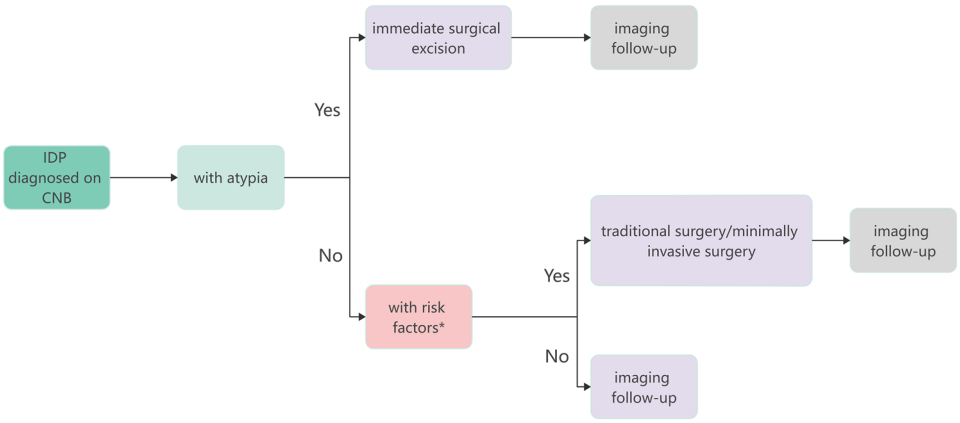

Fig. 4 Treatment determinants on patients with IDP diagnosed on CNB. IDPs with atypia diagnosed on CNB need to be completely excused because of their high association with malignancy and an imaging follow-up is required. While for IDPs with no abnormalities diagnosed on CNB, on one hand, if patients undergo risk factors (*1. Older populations, especially populations that age > 50 years old. 2. The presence of concurrent contralateral BC, multifocality. 3. Clinical symptoms (nipple discharge and/or a palpable mass). 4. The large size of the lesion (> 1–1.5 cm). 5. Peripheral location. 6. A not circumscribed margin in imaging. 7. Patients with high breast imaging reporting and data system classification/scores, ultrasound abnormality (at least 4c) and mammographic distortion, masses, and microcalcification. 8. The small diameter of the needle (12–16G). 9. Menopausal status. 10. Family history of BC), we suggest either traditional surgery or minimally invasive surgery should be considered, if not, close imaging follow-up instead of invasive surgical procedures may be considered. *IDP* intraductal papilloma, *CNB* core needle biopsy, *BC* breast cancer

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Data availability Data are available upon request from the authors.

Declarations

Conflict of interest The authors claim no conflicts of interests.

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