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High-Risk Breast Lesions

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Abstract

It is well known that certain types of pre-malignant lesions can predispose some women to increased risk of breast cancer. These certain types of pre-malignant lesions are generally classified as high-risk breast lesions. These lesions become invasive cancers in about 15% of patients and hence the management and treatment of these lesions warrant a significant discussion. There are several categories of these lesions, to include atypical hyperplasia of the breast (atypical ductal hyperplasia and atypical lobular hyperplasia); carcinoma in situ (ductal carcinoma in situ and lobular carcinoma in situ); columnar cell pre-malignant lesions; lobular intraepithelial neoplasia (LIN III); radial scar/complex sclerosing lesion; sclerosing adenosis and papillary lesions of the breast. These lesions are morphologically, radiologically, histologically and clinically heterogeneous and early identification can help to prevent progression to invasive cancers. The management of these lesions has been debated internationally for years by experts as to the best treatment modality with surgical excision of the lesion often not considered necessary. It is thus important to evaluate each patient on an individual case-by-case basis. The characteristics of these high-risk breast lesions are further discussed in this chapter.

Keywords: breast cancer, in-situ carcinoma, atypical hyperplasia, pre-malignant, breast lesions, mammogram, breast ultrasound

1. Introduction

Breast cancer is the most common cancer diagnosed in women worldwide [1]. It is the fifth most common cause of death from cancer worldwide but is the second most common cause of death in developed countries [1]. The mortality rates up to 5 years after diagnosis is higher in the less developed countries compared to more developed countries specifically in Europe and North America [1]. Breast lesions can be divided into benign or non-proliferative, high risk or pre-malignant and invasive or infiltrating breast lesions [2]. Benign or non-proliferative

breast lesions are non-cancerous breast lesions that can occur in any anatomical structure of the breast and can present symptomatically or as an incidental finding on imaging or histological findings [3]. Types of benign breast lesions include mammary duct ectasia, mastitis, fat necrosis, benign cysts, breast abscess, epithelial-related calcifications, non-sclerosing adenosis, benign intraductal papilloma, breast haematoma, lipoma, fibroadenoma, periductal fibrosis and gynaecomastia (in men) [3]. Invasive breast cancers are a group of heterogeneous malignant breast lesions that originate from breast epithelial cells and invade surrounding breast tissue as well as having the potential to metastasise via lymphatics and blood to distant sites [4]. Invasive or infiltrating breast cancers tend to commonly involve the ducts and lobules of the breast [4]. These include the invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC), which comprise of around 80 and 10% of the total invasive carcinoma types respectively [2]. The other less common types of invasive breast carcinomas (~10% of all breast cancers) include medullary, mucinous, tubular, inflammatory, papillary, adenoid cystic, apocrine, lymphoma, sarcoma, phyllodes and Paget's disease of the nipple [2].

This chapter will primarily focus on high-risk or pre-malignant breast lesions. High-risk or pre-malignant breast lesions are breast lesions that have the potential to become malignant but the risk and time to progression is variable in each lesion [5]. These lesions are usually asymptomatic and are detected incidentally on breast imaging in the majority of cases [6]. Some of the more proliferative lesions (e.g. DCIS) may present with symptoms [6]. Types of high-risk breast lesions include atypical ductal hyperplasia (ADH), atypical columnar cell hyperplasia/columnar alteration with prominent apical snouts and secretions (CAPSS), ductal carcinoma in situ (DCIS), atypical lobular hyperplasia (ALH), lobular intraepithelial neoplasia (LIN III), lobular carcinoma in situ (LCIS), radial scar/complex sclerosing lesion, sclerosing adenosis, papillary lesions of the breast and flat epithelial atypia [5, 7].

In an attempt to classify breast lesions to determine the lesions that have a high relative risk of becoming malignant, Page categorised breast lesions based on morphological features into four categories [20]. The first category included non-proliferative lesions (no increased risk) such as florid adenosis, apocrine change, mild epithelial hyperplasia of usual type and duct ectasia [20]. The second category included epithelial proliferative lesions without atypia (1.5–2 times increased risk) such as moderate/florid hyperplasia of usual type or papillomatosis [20]. The third category consists of atypical hyperplastic lesions (4–5 times increased risk) such as ADH and ALH [20]. Finally the fourth category is lesions considered to be carcinoma in situ and high-risk lesions (8–10 times increased risk), which include DCIS and LCIS [20]. This criterion is still referred to by pathologists to classify breast lesions based on their histology.

2. Types of high-risk breast lesions

2.1. Atypical hyperplasia of the breast (ADH and ALH)

2.1.1. Atypical ductal hyperplasia (ADH)

Atypical ductal hyperplasia (ADH) is a pre-malignant lesion of the breast that carries a four to five times increased risk of developing carcinoma of the breast in the general population [8].

Several previous studies showed that the cumulative risk for developing invasive breast cancer is approximately 13% over a duration of up to 25 years post diagnosis of ADH [9–11]. This risk is doubled in women with a family history of breast cancer in a first-degree relative [8]. Over half of the breast cancers that develop from ADH are moderate or high grade and usually involve the ducts on histology [11]. Of the invasive breast cancers, 25% tend to be node-positive and over 80% being oestrogen receptor (ER) positive [11]. These cancers are also more likely to develop on the same breast that had ADH as opposed to the contralateral side [11]. Menopausal status of patients with ADH was also considered in determining the risk of developing invasive cancer. Some authors report that the risk is greater in premenopausal women with atypical hyperplasia [12]; while others suggested that this may only be relevant in ALH but not in ADH and that this risk was modified once the patient approaches menopause [13]. A more recent study done in 2017 showed a reduction of the cumulative risk to two times the risk of developing invasive breast cancer 10 years after the diagnosis of ADH [14]. This study was performed on a cohort of 955,331 women of which 2785 were diagnosed with ADH following either a core needle biopsy (CNB) or excisional breast biopsy (EBB) [14]. The results from this study showed a reduction in the risk of developing invasive breast cancer at 10 years following an ADH diagnosis to 5.7–6.7% [14].

It has been shown that ADH and DCIS have very similar characteristics histologically. Often it has been difficult to distinguish between ADH and DCIS especially on smaller tissue samples such as those obtained from fine needle aspiration cytology (FNAC) or core needle biopsy (CNB) [15]. Hence, the most accurate method for diagnosis is by excisional biopsy of the entire lesion [15]. ADH is described histologically as lesions with structurally complex patterns formed from the expansion and filling of breast ducts with the proliferation of monotonous epithelial cells and the presence of secondary lumens [16]. Its features are very similar to DCIS on radiological investigation and can be difficult to distinguish using imaging and CNB only [16]. On mammography, a cluster of calcifications may represent ADH [17]. Atypical hyperplasia diagnosis is confirmed in up to 10% of all the CNB performed on these calcifications [17]. Its features are similar to DCIS on ultrasonography and appears as a mildly hypoechoic microlobulated mass with normal acoustic transmission [18]. There is also a higher rate for an inaccurate diagnosis by using only an ultrasound-guided CNB instead of an excisional biopsy [19]. Studies have shown that more than half of the ADH diagnosed using this technique yielded a malignant pathology on surgical excision [19].

Page had previously categorised breast lesions based on morphological features into four categories based on the risk of developing malignancy [20]. To assess if these categories of diagnosing pre-malignant breast lesions are reproducible, a study was performed evaluating the inter-observer variation in the diagnosis of various pre-malignant ductal breast lesions including non-atypical ductal hyperplasia, ADH and DCIS [21]. Pathologists in the study followed strictly to Page's standardised criteria [20]. The study concluded that there were no significant inter-observer differences in forming the diagnosis of these lesions and if adhered to, the standardised diagnosis criteria can be a useful tool [20, 21]. However, despite these classifications, some pathologists argue that the interpretation of ADH and DCIS lesions are still subjective as histologically these lesion are very similar despite being quantitatively different as ADH involve less than two ducts in the breast [22].

ADH is usually diagnosed with a CNB; however, due to the small quantity of samples obtained, a DCIS or invasive carcinoma are unable to be excluded as previous studies have shown that ADH may exist alongside DCIS and invasive cancer [23]. A study done by Gadzala et al. confirmed this notion as they found in 36 patients that had a diagnosis of ADH on stereotactic CNB, 17 patients (47%) were confirmed to have DCIS or IDC after EBB was performed [23]. Therefore, excisional breast biopsy (EBB) was found to be the best option to confirm the ADH diagnosis and outrule ductal carcinoma [23]. In contrary, some researchers believed that it was unwarranted to perform EBB when the more improved techniques of CNB used larger gauge needles (9-, 11- or 14-gauge) and has the potential to diagnose as well as treat ADH without the need for EBB [24]. They suggested that ADH with fewer than three foci and the complete removal of calcifications on biopsy was adequate and prevented the need for EBB in some patients, which has some cosmetic deformity consequences as well as the unnecessary risk of undergoing a surgical procedure [24]. Nevertheless, the clinical recommendation for the definitive management of ADH still remains as EBB despite the improved CNB techniques as the percentage of underestimation of cancer after an ADH diagnosis can carry a risk of over 10% [11, 15].

2.1.2. Atypical lobular hyperplasia (ALH)

Another type of atypia that can be found in the breast is atypical lobular hyperplasia (ALH). Similar to ADH, its risk of developing future breast cancer is high (4–5 increased risk compared to women with no atypia), hence ALH is also categorised as a pre-malignant breast cancer [8]. Page et al. had previously reported that the high risk may be due to the involvement of ducts in some ALH lesions; however, if there is no ductal involvement, the risk is reduced to 2.7 [25]. The risk of developing breast cancer with a prior ALH lesion is higher in pre and perimenopausal women (aged 46–55) and reduced in the postmenopausal cohort, conversely, menopausal status has no bearing on ADH risk of breast cancer as both pre and post menopausal women have similar risk scores [13]. The cumulative risk for developing invasive breast cancer is approximately 18% over a duration of up to 25 years post the diagnosis of ALH, which is higher than the risk seen with ADH [9–11]. Previous studies have also shown that ALH tend to develop into moderate or high grade breast cancers and has an increased risk when associated with a strong positive family history of breast cancer as similarly observed in patients with ADH diagnosis [11]. ALH has not only been associated with the occurrence of future ipsilateral breast cancer but also with contralateral breast cancers [26].

ALH is usually asymptomatic and may be found incidentally using breast imaging; however, the majority of ALH are found as an association to mass lesions like fibroadenomas, radial scars, ADH, intraductal papillomas, pleomorphic LCIS or DCIS following a CNB [26]. If seen solitarily, these lesions appear as clustered calcifications and can be difficult to diagnose using the imaging modality alone as its characteristics on a mammogram are similar to other pre-malignant breast conditions [26].

ALH and LCIS have morphologically similar findings and have been termed collectively as lobular neoplasia (LN); however, they differ primarily based on the filling of the lobular unit and the degree of proliferation [27]. The histology of ALH obtained from either a CNB

or EBB (if associated to another mass lesion) shows the filling of the acini in the lobular unit with monotonous, small, round, cuboidal or polygonal cells with a loss of acinar lumens [16]. The diagnosis of ALH can be obtained following Page's criteria based on the morphology of breast lesions [20]. ALH falls into the third category, which also consists of ADH [20].

Multiple studies have been carried out to determine the most suitable management option for ALH. The diagnosis of ALH was made using stereotactic CNB or EBB if another pre-malignant lesion was present [16]. The perplexing issue with ALH is whether the need for management via a surgical excision is justified when it presents on its own in a CNB specimen or if it presents alongside a benign lesion on an EBB sample. The management of ALH diagnosed on CNB has remained controversial as there are conflicting opinions. A study performed by Bauer et al. divided the diagnosis of LN observed into three groups coexisting with other breast pathologies, which comprised of DCIS or invasive cancer (Group 1), ADH, phyllodes tumour, radial scar or intraductal papilloma (Group 2) and benign fibrocystic changes (Group 3) [28]. They concluded that LN in the absence of breast cancer or pre-malignant conditions (Group 1 and 2) do not need EBB [28]. Other authors had similar recommendations as patients with ALH alone or in association with benign breast disease were not associated with breast carcinoma (<8% associated with cancer) and were not deemed high risk; hence, the residual microcalcifications did not require a further EBB [29]. In addition to this, it was suggested that if strict radiographic-pathologic correlation and histologic criteria are adhered to, then the patients who do not require EBB, should be closely monitored with regular clinical follow-up and breast imaging (mammogram, ultrasound, MRI breast) [26, 30]. Another study contradicted this recommendation as they found that 17% of the patients with LN developed either DCIS or invasive carcinoma [31]. Of the ALH cohort of 20 patients, 2 developed DCIS, hence only the LCIS cohort developed invasive carcinoma [31]. Nevertheless, the group suggested that due to the high percentage of patients with cancer after the diagnosis of LN, an EBB is warranted [31]. Supporting this recommendation, other studies performed using CNB also found that LN lesions had a higher risk for developing breast cancer and an underestimation of 8–19% if CNB alone was performed without a completion EBB [32, 33]. To further stratify the exact criteria of ALH or LCIS (LN lesions) that warranted surgical excision, histologic findings of these lesions with more than 1 lobule per core involvement were considered to be diffuse lobular neoplasia while those with 1 or less lobules affected in each core (focal lobular neoplasia) did not require full excision [34]. In summary, ADH and ALH are radiologically difficult to diagnose as they have features similar to DCIS and LCIS respectively and thus are best diagnosed and managed by excisional breast biopsy (EBB).

2.2. Carcinoma in situ of the breast (DCIS and LCIS)

2.2.1. Ductal carcinoma in situ (DCIS)

Ductal carcinoma in situ (DCIS) are pre-malignant breast lesions that can present both symptomatically and asymptotically as an incidental finding on breast imaging. It accounts for up to 30% of breast cancer lesions detected on mammography [35]. These numbers have risen significantly following the introduction of screening mammography as compared to previous diagnosis of DCIS, which comprised of only 0.8–5% of all breast cancers primarily diagnosed

clinically due to symptomatic DCIS [6, 35]. It represents a premalignant proliferation of malignant epithelial cells in the lumen of the breast ducts that have not invaded the basement membrane and retains its myoepithelium layer [36]. DCIS may present with symptoms of a palpable breast lump, nipple changes and discharge or asymptotically for smaller sized lesions seen on mammography, which has been associated with a higher risk for the development of invasive carcinoma and treatment failure [6, 37]. The risk of invasive cancer in patients diagnosed with DCIS on CNB is 11-fold and vary from 17 to 50% depending on the type of DCIS lesion as the invasive cancers tends to occur in the same location as the DCIS lesion [38, 39]. DCIS is associated with similar risk factors to that of invasive breast cancer such as increasing age (peak at postmenopausal age), family history of breast cancer, nulliparity or late first pregnancy after the age of 30 and the use of hormone replacement therapy [40].

Radiologic findings account for the majority of DCIS detection. The majority of DCIS lesions appear as microcalcifications on mammography [41]. However, they can also present as circumscribed masses or focal nodular patterns [41]. Screening mammography has led to the early diagnosis and investigation of breast cancer lesions. The early implementation of the appropriate management of breast cancer has reduced mortality rates by 30% [42]. This is relevant in the case of DCIS lesions as a large percentage of the higher grade lesions have potential to become invasive and early diagnosis and management is key to reduce this risk [42]. A focused ultrasound can also be carried out once a lesion is detected on mammography to further evaluate the characteristics of the lesion and can aid in the CNB of the lesion [43]. Typical findings representing DCIS on ultrasound include features of a microlobulated irregular mass with no acoustic shadowing [43].

As mentioned previously, DCIS and ADH have similar morphology [15]. However, DCIS lesions are more proliferative and can be diagnosed based on CNB [44]. DCIS are localised lesions that usually present in one quadrant of the breast and can be as large as 5 cm in size [44]. It can be classified based on its size, nuclear grade, architectural subtype and the presence of necrosis following the 2009 College of American Pathologists/American Society of Clinical Oncology protocol [45]. The nuclear grades are subdivided into low (Grade I), intermediate (Grade II) or high grade (Grade III) [45]. High grade DCIS is comprised of proliferative large pleomorphic cells with abundant normal and abnormal mitoses [36]. Intermediate grade DCIS have similar characteristics of both high and low grade DCIS with an intermediate degree of pleomorphism [36]. They tend to present more commonly as a solid cribriform pattern [36]. Low grade DCIS has small cells that are in a uniform pattern [36]. Architectural subtypes include comedo, Paget's disease of the nipple, cribriform, micropapillary, papillary and solid patterns (listed in increasing order towards a higher grade subtype of DCIS) [45]. DCIS lesions were also found to have varying risk of developing invasive breast cancer based on genetic alterations and receptor status of the lesion with a majority of lesions exhibiting ER positivity on immunohistochemistry staining [37, 44]. Palpable DCIS lesions were more commonly associated with negative ER and PR status, which confirms its association to a higher grade DCIS and leading to more aggressive phenotype compared to DCIS found incidentally on screening [37].

As with other pre-malignant disease of the breast, the diagnosis of DCIS warrants further management with either surgery and/or other adjuvant treatments due to its nature to progress to

invasive malignancy [46]. Multiple trials have been carried out to determine the effectiveness of these treatments in the prevention of recurrence after DCIS diagnosis [46]. The options for the surgical management of DCIS consist of mastectomy of the affected breast or breast conserving surgery such as wide local excision (WLE) [46]. Suitability for either type of surgery is based on the grade of the lesion and presence of microinvasion, the patient's age at diagnosis and pre-existing co-morbidities (life expectancy) as these may influence the decision to perform a more definitive surgery like mastectomy instead of WLE due to the risk of having to re-excise the margins and the chance of local recurrence [46]. Rutter et al. reported on the increasing use of mastectomy as a treatment of DCIS especially in patients with higher grade DCIS and younger age [47]. This was due to the increased risk of recurrence and development of invasive breast cancer. Other authors have reported the effectiveness of nipple-sparing mastectomy in comparison with mastectomy whereby the probability of local recurrence was similar and low in the case of DCIS treatment [48]. However, these results were not similarly replicated favourably when the breast conserving treatment of DCIS was used as a solitary treatment modality. The RTOG 9804 trial was conducted to evaluate the effectiveness of breast conserving surgery (BCS) with or without adjuvant radiotherapy in patients diagnosed with low or intermediate risk DCIS on CNB [49]. Results showed a low risk for recurrence with BCS alone at 6.7%; however, this was significantly lower in the adjuvant radiotherapy arm at 0.9% recurrence risk [49]. This opened up the possibility of DCIS subtype with good prognosis to be considered for BCS treatment alone without further adjuvant therapy; however, the authors concluded that a longer follow-up time of more than 7 years was required to give more reproducible results as the BCS and adjuvant radiotherapy cohort had much better response [49]. In contrary to this, other studies have not yielded promising results as patients treated with BCS alone had recurrence rates of approximately 14–16%, despite the stratification of patients into the low risk DCIS category [50, 51]. Conflicting evidence has been reported regarding the need for sentinel lymph node biopsy (SLNB) in the treatment of DCIS. Some studies suggest that SLNB should not be part of the standard surgical treatment of all subtypes of DCIS as the percentage of positive SLNB range from 1 to 22% with majority of the studies reporting a lower percentage of positive findings, hence rendering it unnecessary [52]. Furthermore, some authors argue that performing a SLNB in these patients could disrupt the diagnosis of future lymphatic spread in the case where invasive carcinoma occurs [53]. The general consensus surrounding the addition of SLNB as part of the surgical treatment of DCIS is to be only reserved for those lesions with high grade of DCIS exhibiting microinvasion, large lesions of more than 5 cm in size, lesions treated with mastectomy and DCIS subtypes with high risk of developing invasive cancer [52, 53].

2.2.2. Lobular carcinoma in situ (LCIS)

Lobular carcinoma in situ (LCIS) is similar in histology to ALH; however, it is more extensive and proliferative compared to ALH [27]. It is on the higher spectrum of lobular neoplasia (LN) [27]. LCIS lesions are usually diagnosed incidentally via breast imaging such as through mammographic screening or are detected incidentally as part of a CNB or an EBB for another breast lesion diagnosis [54]. LCIS is a pre-malignant lesion that has a 15% risk of developing subsequent invasive carcinoma (IDC and ILC) on the ipsilateral breast, as well as a 9% risk

of developing invasive carcinoma on the contralateral breast (mostly ILC) [27, 55, 56]. Its estimated incidence is varied between 0.5 and 3.8% as it is most often overlapped with other premalignant or invasive lesions in the breast [57–59]. The risk of DCIS or invasive carcinoma after the diagnosis of LCIS is 17% at 15 years post diagnosis of LCIS with a relative risk of 8–10 [59]. Similarly to ALH, LCIS may be affected by menopausal status. Its incidence was observed to be higher in premenopausal women with only 10% incidence in postmenopausal women, suggesting it may be affected by reproductive history such as age at the birth of first child and ovarian function status [8, 60].

Due to the majority of LCIS being detected incidentally on CNB, it is difficult to characterise its possible findings on breast imaging. A retrospective study evaluated the appearance of LCIS on breast imaging after the diagnosis was confirmed on CNB in an attempt to define the characteristics of LCIS [61]. They described the mammographic findings of LCIS as micro calcifications [61]. Choi et al. used ultrasound imaging to characterise the feature of LCIS and described it as ill-defined, asymmetrical, elongated or round lesions with hypoechogenicity [62].

Histological findings of LCIS are well defined on CNB. LCIS morphology consists of type A and B cells [27]. The type A cells have a smaller sized nuclei compared to the larger and more pleomorphic type B cells that are usually polygonal, cuboidal or round shaped [27]. These cells fill and expand more than half of the acini in the lobular unit with loss of central lumina, which differentiates it from the features of ALH [27, 61]. There has been an ongoing debate whether CNB is sufficient to diagnose LCIS without further EBB. Murray et al. performed a prospective study that investigated the underdiagnoses rate of LN (LCIS and ALH) in samples obtained from their institution over 5 years [63]. When there was radiologic and histologic discordance, 50% of samples diagnosed as LCIS by CNB turned out to be DCIS on EBB [63]. However, when there is radiologic and histologic concordance, there were no underdiagnosed LCIS lesions by CNB [63]. They compared their results with previous studies and discovered that the underdiagnoses risk of DCIS or invasive carcinoma in samples that had radiologic and histologic discordance is significant in ~38–67% of CNB samples diagnosed as LCIS [63].

The management of LCIS is another controversial issue due to its low incidence and lack of distinguishing mammographic findings, as well as its incidental co-diagnosis with other breast lesions such as DCIS and IDC [58, 59]. Conflicting opinions have risen with some indicating that surgical excision is unnecessary, while others disagree and recommend the excision of LCIS is crucial to prevent future development of invasive carcinoma. Nagi et al. agreed with the recommendation that type A cell LCIS lesions should be treated conservatively. The reasoning is that the cohort of patients with this type of lesion, who did not have surgical excision, did not develop progressive disease up to 8 years of follow-up [26]. The authors rationale was that as long as strict criteria were followed histologically and close monitoring were performed radiologically, surgical excision did not provide further benefit in these type A lesions [26]. The type B cell LCIS lesions have poorer prognosis compared to type A, hence will require surgical excision [26]. Similar to the management of ALH, lesions diagnosed, as LCIS also did not require surgical excision unless associated or is adjacent to other co-existing more aggressive premalignant or malignant breast lesions or in the case where there is discordance between radiologic and histologic diagnosis [28]. In more aggressive forms of LCIS

that can present in the contralateral breast, some studies have recommended the option to manage LCIS by bilateral prophylactic mastectomies as part of a risk reduction surgery [64]. However, the decision to follow through with these surgeries required meticulous discussion with a multidisciplinary team (MDT) to assess the patient's risk of future carcinoma and the best management plan for the patient [64].

2.3. Columnar cell pre-malignant lesions of the breast

Types of columnar cell pre-malignant lesions of the breast include columnar alteration with prominent apical snouts and secretions (CAPSS; also known as columnar cell lesions; CCL) and flat epithelial atypia (FEA; also known as CCL with atypia) [65]. Fraser et al. described a type of breast lesion that had similar features on imaging to ADH and DCIS [66]. Although the lesion on imaging did not appear benign, it could not be classified specifically as either ADH or DCIS on histology as it lacked some features that can confirm these diagnoses [66]. These spectra of lesions were described as architecturally complex lesions that exhibited columnar epithelial cells with prominent apical cytoplasmic snouts and intraluminal secretions, which may or may not have nuclear atypia lining the terminal duct lobular unit (TDLU) [66]. This group of lesions were therefore named as columnar alteration with prominent apical snouts and secretions (CAPSS) [66]. CAPSS lesions lie on a spectrum depending on the atypia of the cells and were routinely diagnosed on ultrasound-guided CNB [67]. Studies have shown that CAPSS lesions with atypia closely resembled DCIS and had a higher risk of association with invasive cancer when compared to CAPSS lesions without atypia [67]. CAPSS and FEA lesions are described as clustered microcalcifications that may have amorphous or fine pleomorphic features located in the TDLU on mammography [68]. Again, these features are similar to other pre-malignant disease such as ADH and DCIS, hence it is difficult to diagnose without a CNB [68]. FEAs are observed histologically as dilated basophilic acini, which consists of layers of cuboidal to columnar epithelial cells with low-grade atypia on cytology and distended TDLUs [65, 69].

The presence of CAPSS in the breast was found to increase the risk of breast cancer due to its co-occurrence with other proliferative breast lesions such as DCIS [70]. However, these lesions independently did not confer a high risk of developing breast cancer [71]. FEAs have also been associated with an approximately 20% risk of developing breast cancer and a high underestimation rate for malignancy when diagnosed on CNB due to its similar co-existence with other pre-malignant lesions such as ADH and DCIS [72].

The suggested clinical recommendation for the management of columnar cell pre-malignant lesions of the breast is EBB for both CAPSS and FEA based on radiographic and histologic correlations [67, 72, 73].

2.4. Papillary lesions of the breast

Papillary lesions of the breast are composed of benign and malignant types. The papillomatosis of the breast and atypical papilloma lesions may be considered premalignant due to its association to the development of breast cancer [74]. Pre-malignant papilloma lesions can be

associated with calcifications on mammogram and appear as a homogeneous solid or intracystic lesion that is complex on ultrasound [74]. Clinically, patients with this disease may present with symptomatic findings such as a breast mass or nipple discharge [74]. Histologically, breast papilloma is described as clusters of epithelium in the ducts that develop into branching papillae, which protrude into the lumen [75]. Due to the varying spectrum of pathological findings seen in the papilloma disease of the breast, it is difficult to distinguish between true benign and malignant or premalignant lesions. Multiple studies have shown that the diagnostic technique using either FNA or CNB may be inaccurate as benign findings were often either co-existing with premalignant lesions or were underestimated [75, 76]. The suggested management of breast papillomas diagnosed on FNA or CNB is for active surveillance if there is no atypia and no discordance between imaging and histologic findings [74]. When there is doubt on biopsy or the presence of high-risk papilloma lesions then an EBB is warranted [74].

2.5. Radial scar/complex sclerosing lesion

A radial scar or complex sclerosing lesions of the breast are considered to be pre-malignant breast lesions due to its common association with other more proliferative lesions leading to its increase in breast cancer risk [77]. On mammography, a radial scar/complex sclerosing lesion is described as the presence of radiolucency in the centre of the lesion with spicules that are longer compared to malignant lesions. There is also the presence of radiating radiolucent linear structures and the absence of macrocalcifications [77]. Histologically, radial scars have a fibroelastic core with entrapped ducts and variable surrounding benign epithelial features; however, it can also be associated with atypia usually at the edges of the lesion [78]. The term radial scars was given to lesions smaller than or equal to 1 cm while the term complex sclerosing lesions is larger than 1 cm [78]. There have been various opinions among pathologists and surgeons regarding the most appropriate management of radial scars. Some suggest that a large gauge CNB was adequate to sample radial scars and there was no need for EBB as long as there is no atypia and the radiology and histology correlate [79]. However, other authors still classify radial lesions as high-risk lesions and EBB is the recommend management [79].

3. Adjuvant therapies for the treatment of high-risk breast disease

Adjuvant therapies have been considered in an attempt to reduce the risk of breast cancer following the diagnosis of a pre-malignant breast lesion via CNB or EBB. Several trials have been conducted to determine if adjuvant radiotherapy and/or endocrine therapy may be useful as a measure to reduce this risk [80].

Trials involving the use of adjuvant radiotherapy were performed on pre-malignant carcinoma in situ lesions, predominantly, DCIS. Adjuvant radiotherapy used in a study involving patients with BCS following a DCIS diagnosis, yielded promising results as there was a significant risk reduction compared to the control group especially in the postmenopausal patient cohort [81]. A meta-analysis carried out by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) evaluating the results from four randomised clinical trials

involving adjuvant radiotherapy in the management of DCIS showed that radiotherapy after BCS was successful in reducing the absolute risk of developing ipsilateral DCIS recurrence and invasive breast cancer development by 15% in the 10 year follow-up duration [80]. As similarly seen in the previous study, a greater risk reduction was seen in postmenopausal women and that radiotherapy did not have a significant effect on the contralateral breast or on distant metastatic occurrence [80]. This led to the suggestion that the patients receiving adjuvant radiotherapy as part of the BCS treatment of DCIS should be further stratified to avoid unnecessary exposure to radiotherapy, which carries its own risks [80]. The EORTC 10853 Randomised Phase III Trial further confirmed the benefit of adjuvant radiotherapy as it reduced the risk of any local recurrences after an EBB of DCIS by almost half (48%) after a 15 year follow-up [82]. The treatment of LCIS with adjuvant radiotherapy has not been explored to the same extent as DCIS lesions. A small study carried out with 25 patients treated for LCIS lesions with lumpectomy and radiotherapy reported promising findings as only 1 patient had a local recurrence after a median follow-up of 153 months [83].

Apart from radiotherapy, multiple studies have been performed to explore the effects of oral selective oestrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) as part of a preventative measure to reduce the risk of developing breast carcinoma as well as an adjuvant treatment following EBB or BCS of DCIS lesions [84–86]. The randomised International Breast Cancer Intervention Study (IBIS-I) trial was not aimed specifically at women with a known diagnosis of DCIS but was targeted for women with an increased risk for the development of DCIS and invasive breast cancer [85]. The trial reported the benefit of prophylactic tamoxifen in high-risk women leading to a 34% reduced risk of developing invasive cancer [85]. The benefit of tamoxifen was also found to outweigh the risk in this subset of high-risk patients [85]. Although this study was not investigating the adjuvant treatment of DCIS, however, the rationale of this study can still apply to the management of this disease. Most patients have a high risk of developing invasive cancer after a DCIS diagnosis and may benefit from adjuvant treatment with selective oestrogen receptor modulators because of the ER positive nature of DCIS. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 and B-24 randomised clinical trials were performed to determine the effectiveness of lumpectomy alone as a surgical treatment of DCIS compared to lumpectomy with adjuvant radiotherapy or tamoxifen therapy [86]. The trial focussed on the long-term prognosis of DCIS with these various treatment combinations and the risk of ipsilateral invasive breast cancer recurrence [86]. The trial reported that the cumulative incidence of ipsilateral invasive breast cancer recurrence (15 year follow-up) was 19.4% for lumpectomy only compared to 8.9% for lumpectomy plus adjuvant radiotherapy while the incidence was 10.0% in the lumpectomy plus radiotherapy combination treatment group compared to 8.5% for the combination treatment of lumpectomy plus adjuvant radiotherapy and tamoxifen [86]. Radiotherapy and tamoxifen therapy were concluded to be effective as adjuvant treatments to lumpectomy to reduce the risk of tumour recurrence [86]. Another prospective cohort study carried out by Thompson et al. over a follow-up period of 62 months reported similar findings to Wapnir et al. with a reduction of risk in developing DCIS recurrence or ipsilateral breast cancer in patients given adjuvant therapy combination with radiotherapy and tamoxifen after BCS [87].

4. Conclusion

High-risk breast lesions vary in the degree of risk of developing either in situ carcinoma or invasive carcinoma. Multi-observer disparities in histology reporting had previously been a concern; however, standardised criteria have been developed to overcome this issue. There is a general consensus that radiologic and histologic concordance is important to formulate an accurate diagnosis to help direct the appropriate treatment regime. The management of high-risk breast lesions is rather confusing and needs to be determined by the risk of developing invasive breast cancer. Risk reduction strategies for these high-risk breast lesions described in this chapter vary from active surveillance to surgical excision in form of an excisional biopsy or a mastectomy with or without adjuvant therapies. These strategies are largely influenced by the patient and the clinicians' decisions.

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