A Retrospective Chart Review of Clinicopathological Findings from Radiological Examination, Core Biopsies and Surgical Excisions of Breast Tumours in Manitoba, Canada

by

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ABSTRACT

Breast carcinoma is the most common cancer diagnosed in Canadian women. Effective screening and early diagnosis of breast carcinoma can increase the survival of breast carcinoma patients. Diagnostic imaging and core biopsy procedures are routinely employed as pre-operative breast carcinoma diagnostic tools. The utility of imaging and core biopsy is dependent on their ability to accurately and reliably detect and characterize malignant tumours. We retrospectively reviewed 266 invasive breast carcinoma patient records in Manitoba, Canada from 2018 to 2019. The aim of the study was to evaluate the level of agreement between diagnostic findings reported from the imaging, core biopsy and surgical excision specimens of breast carcinoma. Level of suspicion on imaging and BI-RADS score were concordant with pathologic tumour type in 85-86% and 100% of cases. Imaging and pathologic tumour size and stage were significantly correlated ($R = 0.475$, $p = <0.001$) and concordant in 8% and 53% of cases, respectively. Concordance of pathologic and imaging tumour size was significantly higher in tumours ≤2 cm ($p = 0.007$). Tumour size ≤2 cm ($p = 0.014$) and IDC histologic type ($p = 0.003$) significantly increased the likelihood of tumour stage concordance. Assessment of axillary lymph node disease on imaging and pathology were significantly correlated ($p = <0.001$). Imaging accurately predicted lymph node status in 74% of patients. Agreement between lymph node status on imaging and pathology was significantly higher in tumours ≤2 cm ($p = 0.009$). CNB accurately identified breast carcinoma in 99.6% of patients. Histologic grade on CNB and surgical excision were significantly correlated ($p = <0.001$) and concordant in 62% of cases. Rate of concordance was significantly higher in grade 2 tumours ($p = <0.001$). A significant correlation ($p = <0.001$) and concordance rate of 79% were noted between histologic type reported on CNB and surgical excision. The likelihood of histologic type concordance was significantly greater in IDC tumours

than other histologic types (p = <0.001). Overall, imaging and CNB of IBC patients in Manitoba, Canada was observed to have reasonable accuracy and reliability in the detection and characterization of breast carcinoma.

KEYWORDS

Breast carcinoma; breast tumours; core biopsies; surgical excision; diagnostic imaging.

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AC	Carcinoma with apocrine differentiation
AJCC	American Joint Committee on Cancer
BI-RADS	Breast Imaging Reporting & Data System
CNB	Core needle biopsy
CPAC	Canadian Partnership Against Cancer
DCIS	Ductal carcinoma in situ
FFH	Fischer-Freeman-Halton test
FPR	False positive rate
FNR	False negative rate
IBC	Invasive breast carcinoma
ICC	Invasive cribriform carcinoma
IDC	Invasive ductal carcinoma
IDC/ILC	Invasive carcinoma with mixed ductal and lobular features
ILC	Invasive lobular carcinoma
IMC	Invasive medullary carcinoma
IMPC	Invasive micropapillary carcinoma
LCIS	Lobular carcinoma in situ
MC	Mucinous carcinoma
MCB	Metaplastic carcinoma
MRI	Magnetic resonance imaging
NME	Non-mass enhancement
NPV	Negative predictive value

PPV	Positive predictive value
SCC	Squamous cell carcinoma
SLNB	Sentinel lymph node biopsy
TC	Tubular carcinoma
TNR	True negative rate
TPR	True positive rate
UICC	Union for International Cancer Control

CHAPTER 1. INTRODUCTION

1.1. Breast carcinoma

Breast carcinoma includes a group of heterogenous malignant epithelial tumours that arise in the glandular tissue of the breast.[1,2] Approximately 1 in 8 Canadian women are diagnosed with breast carcinoma.[3] Among Canadian women, breast carcinoma is responsible for the second largest number of cancer-related deaths.[3,4,5,6,7] The incidence of breast carcinoma, 118.20 per 100,000 women, and mortality rate of breast carcinoma patients, 34.07 per 100,000 women, is significantly higher in Manitoba, Canada compared to the national averages.[3] The incidence of breast carcinoma increases exponentially in women over the age of 30 but is rare in women younger than 25 of age.[1] Moreover, Canada's ageing population continues to increase, resulting in a greater number of individuals at risk of developing breast cancer.[1,2]

1.2. Etiology and clinical features of breast carcinoma

The etiology of breast carcinoma is multifactorial.[1,2] Genetics, diet, hormones, and reproductive factors have been delineated as risk factors for breast carcinoma development.[1,2] Breast carcinoma is more common in developed Western countries where diets high in animal protein and fat, sedentary lifestyle, low parity, short lactation duration and increased age of first childbirth are prevalent.[1,2] Breast carcinoma development also appears to be associated with unopposed exogenous sex hormones, estrogen and progesterone.[1,2] This is further supported by the higher incidence of breast carcinoma in premenopausal women than postmenopausal women who lack ovarian androgen production.[1,2] Extended unopposed androgen production associated with early menarche, late menopause, postmenopausal hormone replacement therapy and nulliparity have also been linked to an increased risk of breast carcinoma.[1,2] A moderate increase

in breast carcinoma risk has been associated with smoking and alcohol consumption.[1,2] A family history of breast carcinoma has been strongly correlated to a greater risk of developing breast carcinoma.[1,2] Most notably, a significantly higher risk of breast carcinoma has been attributed to two high-penetrance genes, *BRCA1* and *BRCA2.*[1,2]

Classically, breast carcinoma presents as a palpable mass that may be associated with skin retraction, nipple discharge, nipple retraction and changes in breast shape, size or skin texture.[2] Ulceration of overlying skin may present in late stage cases.[1,2,8] Clinically observed diffuse erythema or edema of more than 1/3 of the breast skin is defined as inflammatory breast carcinoma.[1,2,8] Approximately 90% of breast carcinomas are unifocal and can present at any location within the breast tissue.[2] Breast carcinoma can invade beyond the basement membrane that typically contains epithelial cells, growing into the breast stoma. After stromal invasion, breast carcinoma has the potential to extend into vasculature, regional lymph nodes and other distant sites.[1] Bone, brain, liver and lung are the most common sites of breast carcinoma distant metastases.[2] However, breast carcinoma is rarely detected as regional lymph node or distant metastases without prior identification of a primary tumour.[1]

Breast carcinoma prognosis and management are primarily based on the following histopathological and clinical features: patient age, tumour size, stage, histologic type, grade, Ki67 value, lymph node involvement, lymphovascular invasion, margin status, hormone receptor and gene expression profiles.[2,4] Overall, the 10-year survival rate of breast carcinoma is estimated to be 80%.[2] Early stage breast carcinoma patients have a lower rate of mortality (4%) compared to late stage patients (17%).[2] In addition, the five-year survival rate of patients with localized breast carcinoma is significantly higher (>95%) than those with lymph node metastases

(85%).[2] Moreover, patients with distant metastases or inflammatory carcinoma have an inferior prognosis, with respective 5-year survival rates of <10% and 5%.

1.3. Screening and diagnosis of breast carcinoma

Breast carcinoma screening programs aim to detect early stage disease allowing for rapid intervention.[9] Moreover, effective screening and diagnosis of breast carcinoma have been observed to reduce mortality[11,12,13] and morbidity of patients.[13] Therefore, diagnostic breast imaging modalities, including mammography, US and MRI, are widely employed for pre-operative screening and diagnosis of breast carcinoma.[14,15,16,17,18]

Screening programs for breast carcinoma have been implemented in Canadian health care systems since the early 1990s.[11] For example, BreastCheck, a province-wide standardized breast carcinoma screening program in Manitoba, Canada administrated by CancerCare Manitoba (Figure 1.1), was implemented in Manitoba in 1995.[19,20] In Manitoba, asymptomatic individuals are screened mammographically every two years from the age of 50 to 74.[11,16,19,20,21] Initial screening generally includes mammography, with additional imaging modalities such as US and MRI being employed depending on the assessed risk of breast carcinoma.[19,20] In the advent of abnormal results on initial screening, patients undergo secondary diagnostic mammography or US.[19,20] If findings on secondary screening remain suspicious, a biopsy of the breast abnormality will be performed.[19] Two main types of biopsies are used: (1) US-guided CNB in the case of mass forming lesions and (2) stereotactic CNB for non-mass forming abnormalities only identified on mammography.[19,22]

The quality and efficacy of Canadian screening programs can be assessed using the following performance indicators: PPV, FPR, FNR and carcinoma detection rate.[13] PPV serves

as a measure of a screening programs accuracy in predicting the presence of malignancy.[23] CPAC recommends that breast screening programs have a PPV of ≥5% on initial screening and ≥6% on re-screening.[13] The quality of breast carcinoma screening can be estimated by the FNR and FPR of the program.[23] CPAC recommends that Canadian breast screening programs aim to have a FNR of <0.06% within 12 months of initial screening and <0.12% within 12-24 months of initial screening.[23] Presently, Canada does not have a recommended target for FPRs.[23] Other jurisdictions such as the UK, New Zealand and Australia have set recommended thresholds for the FPR of breast carcinoma screening programs which range from <0.2% to <0.34%.[23] A screening program's efficacy in the detection of breast carcinoma is reflected by the carcinoma detection rate.[23] CPAP also provides recommended target invasive carcinoma detection rate of >0.5% on initial screens and >0.37% on subsequent screens.[23] Currently, there is no recommended target in situ carcinoma detection rate for Canadian programs.[23]

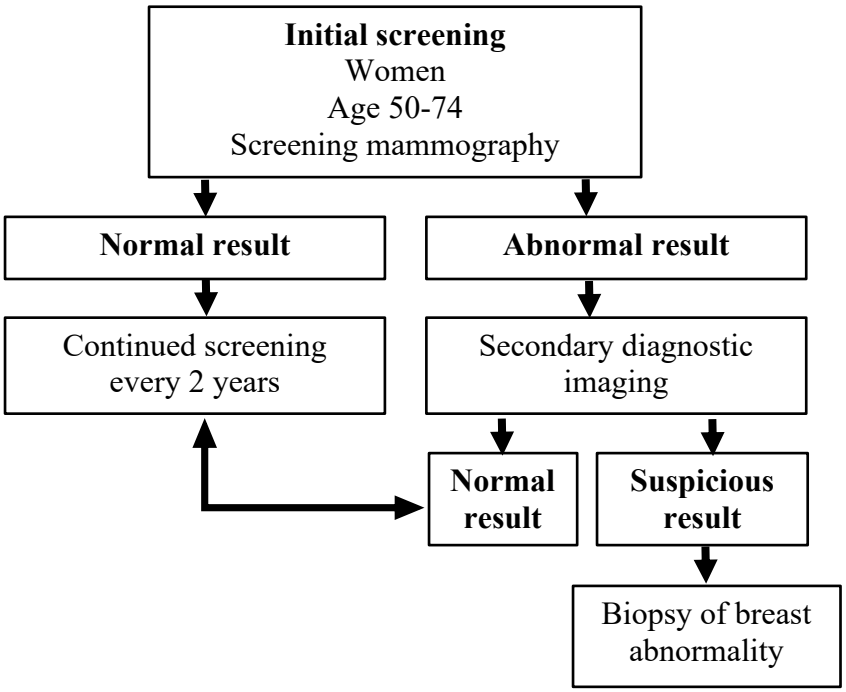

Figure 1.1 Summary of BreastCheck breast carcinoma screening program in Manitoba, Canada.

1.4. Breast imaging reporting & data system

The American College of Radiology developed BI-RADS to aid in the standardization of breast imaging interpretation and reporting.[6,8,18,24,25,26,27,28] BI-RADS includes guidelines, criterion and terminology for the classification and reporting of breast lesions.[3,8,14,18,24,25,26,27,29] BI-RADS lexicon provides more clarity in reporting, enhances communication and facilitates inter-institutional research.[25,27,29] Assessment categories for classifying the level of suspicion on imaging assessment are also provided in the BI-RADS lexicon.[21,25,27,30]

As summarized in Table 1.1, concern for malignancy from breast imaging is reported as a BI-RADS score of 0, 1, 2, 3, 4, 5 or 6.[18,31] Negative and probably benign imaging findings are assigned categories 1 to 3, whereas suspicious findings are designated as categories 4 to 6.[6,28] Category 0 indicates that imaging assessment is incomplete, and additional imaging evaluation is required.[4,25,27,27,31] Category 1 is designated to cases where patient evaluation reveals no abnormalities, and no additional imaging is required.[4,25,31] Category 2 is assigned when imaging findings indicate a benign lesion, with no possibility of suspicious or malignant lesions, and requires continued routine screening.[4,25,27,31] Category 3 consists of imaging features indicating a probably benign lesion, with a <2% risk of malignancy, requiring short term follow-up imaging.[4,21,22,25,27,31] Category 4 is assigned when imaging reveals suspicious abnormalities, with a 2-80% risk of malignancy, for which biopsy is recommended.[4,21,22,25, ,27,28,31] Category 4 is further subdivided into 4A, 4B and 4C subcategories that further stratify and predict the risk of malignancy.[21,28] Likelihood of malignancy is defined as >2% to ≤10% for category 4A, >10% to ≤50% for category 4B, and >50% to ≤95% for category 4C.[21] Category 5 is characterized as imaging features highly suggestive of a malignant lesion, with a greater than 95% perceived risk of malignancy, requiring biopsy to guide further clinical and surgical management.[4,21,22,25,27,31]

Category 6 is exclusively designated to lesions that have been histologically confirmed as malignant on biopsy.[6]

Table 1.1. Summary of BI-RADS assessment categories as described by the American College of Radiology [4,21,22,25,27,28,31]

BI-RADS category		Likelihood of malignancy	Management
0	Incomplete assessment	N/A	Additional imaging evaluation required
1	Normal	0%	Continue routine annual screening
2	Benign	0%	Continue routine annual screening
3	Probably benign	<2%	Biopsy recommended
4A	Low suspicion for malignancy	>2% to ≤10%	Biopsy recommended
4B	Moderate suspicion for malignancy	<10% to ≤50%	Biopsy recommended
4C	High suspicion for malignancy	<50% to ≤95%	Biopsy recommended
5	Malignant	>95%	Biopsy recommended
6	Biopsy proven malignancy	Proven malignancy	Staging and treatment planning

1.5. Breast mammography

Mammography involves the examination of breast tissue using x-ray imaging and it presently serves as the primary screening tool for breast carcinoma.[5,6,13,18,25,27,28,32] X-rays penetrate different tissue types at a variable rate resulting in the observation of fibrous tissue, metal and calcifications as areas of white in contrast to the grey coloured adipose tissue of the breast.[18] Mass-forming breast carcinomas will generally appear as a solid, white lesion that can be distinguished from the grey background.[18,25,27] The mass margin on mammography can

provide insight into how the lesion interacts with adjacent tissue.[18,2,27] Circumscribed margins are attributed to the expansile pattern and pushing of the surrounding tissue that is more often associated with benign lesions such as fibroadenomas or simple cysts.[18,25,27] Spiculated, angular, microlobulated or indistinct margins suggest that the lesion is invading into the adjacent tissue, a feature characteristic of carcinoma.[18,25,27]

Other commonly detected mammographic breast abnormalities include architectural distortion, asymmetry and calcifications.[17,18,25,27] Architectural distortion, a localized parenchymal texture alteration appearing as a line radiating from a central focus, is diagnosed as IBC in 33% of cases.[18] Asymmetry is defined as a focal area of increased breast parenchyma density, interspersed in the adipose tissue and lacking definitive borders on mammography.[18] Compared to architectural distortion, the risk of malignancy associated with asymmetry is markedly lower at 13%.[18] Calcifications are most accurately and sensitively detected by mammography as only calcifications >1 mm are effectively detected on other imaging modalities.[17,18] Calcifications are generally composed of radiopaque calcium phosphate and oxalate.[18] The number, size, distribution and evolution of calcifications in breast tissue are features that are used to determine the risk of underlying malignancy.[18] A large number of calcifications are associated with in situ and invasive carcinoma.[18] Malignancy is associated with small to moderate size calcifications, measuring 0.1-1.0 mm in greatest dimension.[18] Calcifications with a grouped or linear pattern are associated with in situ carcinoma.[18]

Presently, the effectiveness of mammography at reducing breast carcinoma patient mortality is still a point of contention.[33] Mammographic breast screening has been reported to contribute to the overtreatment of patients from false positive screening results.[33] Additionally, the sensitivity and effectiveness of mammography screening decline significantly in patients

with dense breast tissue.[25,27] Most notably, mammography alone fails to detect 5-15% of breast carcinomas.[2]

1.6. Breast ultrasonography

US has higher sensitivity and can better detect IBCs elusive on mammography.[1,2,18] As a result, US is most often used to screen for breast masses in patients <35 years old with dense parenchyma and as secondary imaging in older patients after mammography.[1,2,18,28,29] US can also be used to detect the presence of axillary lymph node metastases.[25,27,34] Importantly, lesion size and shape determined from US examination tend to correlate with pathologic findings.[17,18] US can also serve as a method of visualization to guide breast lesion biopsy for accurate sampling.[17,18,22,28]

US utilizes the variable refraction of soundwaves in response to different tissue types to distinguish abnormalities in the breast parenchyma.[18,25,27] The resulting echo pattern reveals features of the breast lesion such as shape, size and composition.[17,18,25,27] Simple cysts generally appear as a circumscribed lesions lacking internal echo. Debris filled cysts, benign or necrotic invasive tumours, can manifest as mixed solid and cystic lesions on US.[18,25,27] Benign lesions are often oriented parallel to the skin surface, “wider than tall”, while malignant lesions have a non-parallel orientation, “taller than wide”, on US.[18,25,27] Heterogenous masses, such as IBCs, are more likely to produce acoustic shadowing, a phenomenon wherein sound waves are reflected posteriorly, creating a darkened area behind the mass.[18,25,27] Tumour margin is assessed on US and mammography in a similar fashion.[18,25,27] In essence, homogenous, circumscribed, hypoechoic, “wider than tall” masses associated with posterior acoustic shadowing are often benign lesions.[18,25,27] Conversely, hyperechoic, “taller than wide” masses with posterior acoustic

shadowing and spiculated, microlobulated, or angular margins are more likely to be malignant tumours.[18,25,27] US findings suspicious for lymph node metastases include cortical thickening, increased transverse node diameter, and disappearance of lymph node hilum.[25,27,35,36,37,38]

1.7. Breast magnetic resonance imaging

Breast imaging can be performed with the highest sensitivity using magnetic MRI.[24,27,39] MRI can often detect lesions that have not been previously identified with other imaging modalities.[24,27,39,40] MRI-guided biopsy can also be helpful in the detection and more reliable sampling of non-mass forming lesions.[39] Additionally, MRI appears to assess neoadjuvant therapy response more effectively and detect occult primary tumours in patients that solely present with axillary node metastases.[40,41] However, MRI examination is more costly and has lower specificity than other breast imaging techniques.[27,39] Therefore, MRI is recommended as an additional breast screening modality in patients with an increased risk of carcinoma due to genetic predisposition or family history of breast carcinoma.[40,41]

MRI is a functional imaging technique wherein the variable refraction of radio waves within a magnetic field in response to different tissues generates images of breast abnormalities.[40] Breast abnormalities identified on MRI are categorized as one of the following: (1) foci, areas of enhancement <5mm; (2) masses, space-occupying lesions; or (3) NME, an area of enhancement without the presence of space-occupying lesions.[40] Foci and masses are further described by their margins, shape and internal enhancement pattern.[27,39,40] Similarly, NME is categorized based on their distribution and internal enhancement pattern.[27,39,40] Malignant tumours manifest most often as masses with irregular margin or shape, heterogenous or rim

internal enhancement patterns, or as NME with segmental distribution and clumped or clustered ring internal enhancement patterns.[27,39,40]

1.8. Breast core needle biopsy

Following the identification of suspicious abnormalities on breast imaging, standard diagnostic protocols involve the subsequent performance of breast CNB.[2,12,18,31,42,43,44,45,46,47,48,49] CNB is a minimally invasive procedure employed to obtain lesional tissue samples for preliminary histological evaluation and diagnosis.[2,12,18,21,24,31,43,44,45,46,47,48,49,50,51,52,53,54,55] Prognostic information such as histologic grade, histologic type, necrosis, lymphovascular invasion and the presence of in situ carcinoma can be identified from histologic assessment of such biopsies.[2,18,24,45,46,50,52,53,54,56] These pathologic findings can then be used to guide clinical decisions regarding patient treatment.[2,24,45,46,50,52,53,54,55,56] Breast lesions detected on imaging can also be marked with metal clips or localization wires during the biopsy procedure to facilitate lesion identification on surgical excision.[18]

Two main types of image-guided CNB are most commonly employed for breast lesion evaluation: (1) US-guided CNB and (2) stereotactic CNB. US-guided CNB is often preferred due to its minimally invasive nature, readily available equipment, real-time visualization, multi-directional sampling, low cost, lack of ionizing radiation, and ability to examine both breast and axilla.[22] However, it can only be used to sample sonographically evident abnormalities, which often does not include small masses and calcifications.[22,24,42,46] Stereotactic core biopsy involves the use of angled, stereotactic images to determine the precise location of a lesion in multiple dimensions.[22] Stereotactic guidance can be used to direct biopsy of all mammographically detected lesions but is most often used for calcification sampling.[22,24]

The frequent use of CNB has significantly reduced the number of unnecessary surgical excisions performed on benign breast lesions.[31,55] Additionally, patients benefit from the reduced tissue sampling, fewer morbidities, rapid definitive diagnoses and prognostic information associated with CNB.[18,45] Unfortunately, the procedure is associated with several complications, including pneumothorax, hematomas, infection, false-negative results, needle track seeding of tumour and infection, all of which have a very low incidence of <0.1%.[22,24,51,55,56,57] Therefore, the benefits of CNB appear to greatly outweigh the potential risks.[55,57]

Chiefly, the utility of CNB in the diagnosis of breast carcinoma is highly dependent on concordance between imaging and pathology findings.[18,22,45] Concordance is achieved when the pathologic findings on CNB are deemed to provide a reasonable explanation for the imaging features.[18] Fortunately, optimal CNB programs have been reported to have discordance rates of as low as 1-8%.[18,24] However, due to their small size, the accuracy of diagnoses made from CNB samples can be limited and often requires subsequent surgical excision of the lesions for further histological examination.[12,43,44,48,49,58]

1.9. Pathologic classification of invasive breast carcinoma

IBC is defined as an extension of neoplastic proliferations through the basement membrane, with growth in the underlying breast stroma.[1] IBC can further invade into lymphatics, vasculature and other distant sites.[1] IBC is characterized pathologically by histologic type, Nottingham histologic grade and the presence of lymphovascular invasion or in situ components.[2] Tumour size, distance from margins, tumour-infiltrating lymphocytes and changes in the adjacent stroma are other important histologic features.[2] IBC most commonly appears as a spiculated, irregular mass that may or may not be associated with reactive stroma on imaging.[1,2]

Alternatively, IBC can manifest on imaging as calcifications, architectural distortion, asymmetry or a well-circumscribed mass.[1,2] Macroscopically, IBC produces a grossly visible mass with a nodular, stellate or irregular shape.[1,2] IBC tumours are often poorly circumscribed with moderately or ill-defined borders.[1,2] The tumours are firm or hard with a gritty texture. [1,2] Microscopically, IBCs are divided into subtypes based on their histologic characteristics. [1,2] IBCs with a histologic pattern composing >89% of the tumour are assigned a special histologic type such as lobular, mucinous, mucinous cystadenocarcinoma, metaplastic, micropapillary, medullary, tubular, cribriform, or apocrine.[2] Tumours wherein this criterion is not met are labelled as invasive breast carcinoma of non-specific type or IDC.[2] The majority of these IBC histologic types have in situ counterparts that are theorized to function as early, localized precursor lesions.[1,2]

1.9.1. Invasive ductal carcinoma

IDC consists of a heterogenous group of IBCs that do not display special histologic features to allow for further morphological classification.[1,2] IDC accounts for the majority of IBCs, at approximately 75%.[45] IDC patients have been observed to have a 10-year survival rate of 65% to 78%.[2] Histological features of IDC can be varied.[2] IDC may display an infiltrative or continuous pushing border.[2] Neoplastic IDC cells may arrange in clusters, cords, or trabeculae, while some tumours produce a solid or syncytial pattern of infiltration.[2] Occasionally, glandular differentiation, targetoid features or single-file infiltration are observed.[2] IDC tumour cells will display a high degree of nuclear pleomorphism, mitotic activity, apoptosis and occasionally necrosis.[2] Stromal changes observed in IDC are highly variable, including hyalinization, scant connective tissue or cellular fibroblastic proliferation.[2] In some cases, IDC can present with a

secondary special subtype.[2] A tumour is designated as mixed if a special subtype is found to compose between 10% to 90% of the mass.[2] IDCs wherein <10% of the lesion is a special subtype are classified as IDC.[2]

In the past, IMC was recognized as an IBC subtype, however it is now classified as a special morphological pattern of IDC with medullary features.[2] These tumours is a rare morphologic type, accounting for <5% of all cases.[45,59] IDC tumours with medullary features are frequently identified on imaging and gross examination as a large, circumscribed, firm, lobulated or nodular tumour.[45,59] Medullary pattern is characterized by the following histologic features: (1) 75% compositions of solid sheets of enlarged cells with pleomorphic nuclei and prominent nucleoli, (2) high mitotic count, (3) pushing borders, and (4) moderate to high lymphoplasmacytic infiltrates.[1,45] IDC patients with medullary morphology have a relatively good prognosis and strong chemotherapy response.[1] Compared to IDC patients with other morphological patterns, those with medullary features are often younger and have been reported to have a 10-year survival rate of up to 84% and disease-free survival rate of >90%.[1,45,59] Additionally, these patients display a lower frequency of axillary lymph nodes metastases than IDC patients.[45]

1.9.2. Invasive lobular carcinoma

ILC is responsible for 5% to 15% of IBCs.[2,45] ILC often presents clinically as a poorly defined, palpable and spiculated mass or architectural distortion on imaging.[1,2,45] Grossly, ILC appears as a poorly circumscribed, irregular tumour due to its diffuse cell infiltration pattern.[1,2] Histologically, ILC is identified as a proliferation of small dyscohesive cells dispersed or arranged in single file, linear cords invading the stroma.[1,2,45] The concentric arrangement of these

infiltrating cords around normal ducts is frequently noted.[2,45] A thin rim of cytoplasm, rounded or notched ovoid nuclei, and central mucoid inclusions are characteristic features of ILC cells.[2] Presently, there is conflicting evidence as to whether prognosis differs in patients with ILC compared to those with IDC.[2]

1.9.3. Mucinous carcinoma

Approximately 2% of IBCs are reported as MC.[2,45] On imaging, MC appears as a lobulated, well-circumscribed mass or architectural distortion.[2,45] On gross evaluation, MC is a gelatinous, shiny, soft and viscous nodule with pushing borders.[1,2] MC must have a mucin component of >90%, containing clusters of neoplastic epithelial cells with low to intermediate grade nuclei suspended in the extracellular mucin pools.[2,45] Fibrous septa with capillary vessels are also present, dividing these mucin pools.[2,45] Low rates of recurrence and a high 5-year survival rate of 94% have been observed in patients with MC diagnosis.[2,45]

1.9.4. Mucinous cystadenocarcinoma

Mucinous cystadenocarcinoma is an extremely rare subtype, with only 30 total cases having been reported worldwide.[2] Clinically, mucinous cystadenocarcinoma is a palpable mass.[2,45] On imaging, mucinous cystadenocarcinoma appears as an ill-defined or well-defined lobulated, heterogeneous, hypoechoic mass.[45] Grossly, mucinous cystadenocarcinoma is a partly solid and cystic, circumscribed mass containing mucinous material.[2] Histologically, these tumours present as mucin filled cystic spaces lined with atypical columnar cells containing cytoplasmic mucin and basally located nuclei.[2] A peripheral myoepithelial layer surrounding the cystic spaces is absent in mucinous cystadenocarcinoma.[2,45] Patients with mucinous

cystadenocarcinoma have been reported to have a relatively good prognosis with a low incidence of lymph node and distant metastases.[2,45]

1.9.5. Invasive micropapillary carcinoma

IMPC accounts for 0.9% to 2% of all IBCs.[2,45] IMPC normally presents as a palpable mass clinically.[2] On imaging, IMPC appears most commonly as an ill-defined, dense and irregular mass.[2,45] On gross examination, IMPC are well-circumscribed, soft-to-moderately firm, tan-grey and possibly encapsulated tumours.[45] Histologic diagnosis of IMPC requires that >90% of the tumour is composed of clear spaces in the background of invasive neoplastic cell clusters with micropapillary architecture and reversed cell polarity.[1,2,45] The cytoplasm of IMPC cells may be dense, finely granular or eosinophilic.[2] IMPC is associated with a worse prognosis than IDC, as it has been reported to be affiliated with lymphovascular invasion and lymph node metastasis more frequently.[2] Conversely, no increased risk of recurrence or lowered survival rate has been linked to the IMPC subtype.[2]

1.9.6. Tubular carcinoma

TC is estimated to make up 1.6-2 % of all IBCs, occurring most commonly in postmenopausal women.[2,45] These tumours are often detected as small, spiculated, ill-defined or discrete masses incidentally on mammography.[2,45] Macroscopically, TC are characterized as small (<20 mm), firm-hard, pale-grey, ill-defined and spiculated tumours.[2] Microscopically, TC displays a stellate invasive border.[2,45] Angular or small ovoid to round tubules and glands within a fibrous or desmoplastic stroma are characteristic of TC.[2,45] Notably, TC tubules lack a supporting myoepithelium.[2,45] The neoplastic cells contain uniform, sparsely mitotic, small to

intermediate size nuclei and are exclusively well-differentiated (grade 1).[2,45] The prognosis of TC patients is high, with an 88% 5-year survival rate and a rare incidence of recurrence.[2]

1.9.7. Invasive cribriform carcinoma

ICC is another exclusively low-grade subtype, accounting for only 0.4% of IBC cases.[2] Clinically, ICC tumours do not display any distinct features that differentiate them from other IBC subtypes.[2,45] ICC is frequently detected incidentally and a spiculated mass with calcifications on mammography.[2] On gross examination, ICC appears as a firm, hard, spiculated mass.[2] ICC is characterized by the following histologic features: >90% of the lesion consists of epithelial cell cribriform islands, sparse mitotic activity and uniform low-grade nuclei.[2,45] The cribriform islands are located in desmoplastic stroma and composed of multiple epithelial cell layers creating secondary cuboidal and columnar cells lined with glandular structures.[2,45] Mucinous and apical secretions may also be observed.[2,45] ICC patients have an indolent course and favourable prognosis, with a 90% to 100% 10-year survival rate.[2,45]

1.9.8. Carcinoma with apocrine differentiation

AC is a rare IBC subtype, accounting for 1% of all reported cases.[2,45] The classic apocrine morphology must account for >90% of the lesion to be classified as AC.[2,45] AC presents clinically as poorly circumscribed and firm masses, sometimes with associated calcifications on mammography.[2] Grossly, AC is indistinguishable from IDC.[2] The prognosis of AC has yet to be delineated, with different studies reporting varied and contradicting findings.[2,45] Histologically, AC is characterized by large neoplastic cells, resembling apocrine sweat glands.[2] Cells display abundant eosinophilic granular cytoplasm and enlarged, round to oval nuclei with moderate

atypia and prominent nucleoli.[2] Presently, prognosis is determined using conventional prognostic factors for IBC such as type, grade, size and nodal status.[45,60]

1.9.9. Metaplastic carcinoma

MCB is relatively rare, accounting for only 0.2% to 1% of all IBC cases.[2,45] MCB is more likely to be detected at a late stage as a palpable mass.[2,45] On imaging, MCB tumours tend to be nodular, less infiltrative, associated with fewer calcifications and acoustic shadowing.[45] On gross examination, MCB can appear as a circumscribed or an irregular bordered, indistinct mass and are generally larger, ranging from 2 to >10 cm.[2] In tumours with SCC differentiation, cystic degeneration is often also observed.[2] Areas of squamous and chondroid metaplasia produce a glistening, pearly white-grey surface.[2] Conversely, a gritty and hard cut surface is associated with areas of osseus metaplasia.[2] Microscopically, the appearance of MCB is varied.[2] A diagnosis of MCB requires atypical squamous spindle cells of mesenchymal differentiation and a lack of histological features characteristic to IDC.[2,45] MCB has a 5-year survival rate of 62%.[2] MCB patients tend to have a lower frequency of lymph node metastases but a significantly worse prognosis than other IBC subtypes.[45] MCB tumours that exclusively display squamous cell morphology can be further classified as pure metaplastic SCC of the breast.[2] Pure metaplastic SCC of the breast are rare tumours, accounting for <0.1% of all IBCs.[61,62,63] Histologic diagnosis of SCC requires that >90% of the tumour displays squamous differentiation and the absence of any neoplastic ductal or mesenchymal elements.[61,62,63,64]

1.9.10. Breast carcinoma in situ

Carcinoma in situ is defined as a neoplastic proliferation of epithelial cells localized to the ductal and lobular structures of the breast, not extending beyond the basement membrane.[1] Several histologic variants of breast carcinoma in situ have been recorded, including DCIS and LCIS.[1,2]

DCIS can present clinically as a palpable mass or nipple discharge.[1,2] However, most DCIS cases, up to 85%, are detected as impalpable breast abnormalities identified as calcifications on mammography.[1,2,60] On imaging, low-grade DCIS appears as granular and amorphous patterned calcifications.[1,2] Conversely, linear, pleomorphic or branching calcifications patterns are classically associated with high-grade DCIS.[1,2] MRI and US have a low sensitivity for these characteristic features of DCIS and are therefore not generally used in DCIS screening.[2] In most cases, DCIS does not present as a macroscopically identifiable mass.[2] Extensive high-grade DICS in rare cases may produce a firm, gritty mass or multiple foci of round and pale comedonecrosis due to extensive stromal reaction or intraluminal necrosis.[2] Paget's disease of the nipple, wherein the DCIS extends into the basal layer of the epidermis of the nipple by extending from subareolar ducts and travelling along the basement membrane, can occur in cases of high-grade lesions.[1,2,8] Histologically, DCIS is characterized by the infiltration of the epidermis by single cells or clusters of large, pleomorphic high-grade neoplastic epithelial cells, which may be hyperkertotic and parakeratotic.[1,2] Survival from DCIS is high. In those over 50, the risk of death is estimated to be no greater than that of the general population.[1,2] Minimal to extensive DCIS is identified in association with IDC in 80% of patients.[2]

LCIS is characterized as a non-invasive proliferation of neoplastic dyscohesive cells arising from terminal duct lobular units.[1,2,45] Greater than 50% of terminal duct lobular units

acini are enlarged and occupied by neoplastic cells.[1,2,45] Terminal duct involvement may or may not be pagetoid.[1,2,45] LCIS often does not produce occult clinical manifestations and is most often identified incidentally on microscopic evaluation of breast biopsies, and surgical excisions performed targeting other lesions.[1,2,45,65] Individuals with LCIS have an 8 to 10-fold increased risk of subsequently developing breast carcinoma.[2,65] As a result, patients diagnosed with classic LCIS undergo active imaging surveillance.[1,2,45]

1.9.11. Histologic grading of invasive breast carcinoma

Tumour grade is a significant prognostic factor for IBC patients.[45] Poorly differentiated, high grade IBCs confer a worse prognosis than those that are well-differentiated and low-grade.[8] Presently, Nottingham histologic score is used to grade breast carcinoma.[1,2,8,45,53] As illustrated in Table 1.2, Nottingham histologic score is based on the evaluation of the following three characteristics: (1) mitotic count, (2) nuclear pleomorphism, and (3) tubular formation as a measure of glandular differentiation.[1,2,5,45,53] Each feature is independently assessed and assigned a numerical score of 1 to 3.[1,2,45]

The degree of tubule and gland formation is examined at low magnification across the entire tumour.[2,45] Only clear central lumina surrounded by polarized neoplastic cells are considered gland formation.[2] If glands compose the majority (>75%), a moderate amount (10-75%) or little to none (<10%) of the tumour, it is scored as grades 1, 2 or 3, respectively.[1,2,45]

The area of tumour with the highest degree of nuclear pleomorphism is compared to the nuclear size and shape of epithelial cells in adjacent normal breast tissue to assign a nuclear pleomorphism score.[2,45] Nucleoli size, number and irregularity of nuclear outlines can also be used to determine nuclear pleomorphism score.[2,45] Ideally, nuclear pleomorphism is scored at

40x magnification.[2,45] A score of 1 is defined as nuclei of uniform size, similar to benign epithelial cells, with very inconspicuous nucleoli, even chromatin pattern and minimal pleomorphism.[1,2,45] A score of 2 indicates nuclei 1.5 to 2 times larger than benign epithelial cells, with inconspicuous nucleoli and mild to moderate pleomorphism.[1,2,45] Score 3 is assigned to tumours with nuclei >2 times larger than benign epithelial cells, with vesicular chromatin and highly pleomorphic and prominent nucleoli.[1,2,45]

Mitotic count is evaluated by counting the number of mitotic figures present in a defined microscopic field area expressed in mm^2.[2,8,45] The accuracy of mitotic counts is highly dependent on optimal tissue fixation and section preparation.[2,45] Mitotic count score is based on the "hotspot", the tumour area with the highest frequency of mitotic figures, which is typically situated at the tumours leading edge.[2,45] Scores of 1, 2 and 3 are assigned for mitotic counts by referencing standardized thresholds that are based on the diameter of the high power field and its corresponding area.[2,45]

The scores determined for the mitotic count, nuclear pleomorphism and tubular/glandular formation are then added together to produce a total score of 3 to 9, from which the Nottingham grade is assigned.[2,8,45] A total score of 3 to 5 points is well-differentiated (grade 1), 6 to 7 points is moderately differentiated (grade 2), and 8 to 9 points is poorly differentiated (grade 3).[2,8,45]

Table 1.2. Summary of Nottingham histologic grading criteria for invasive breast carcinoma (Adapted from Kumer[1]).

Histologic feature	Score
Tubule formation	
Majority of tumour (>75%)	1
Moderate degree (10% to 75%)	2
Little to none (<10%)	3
Nuclear pleomorphism	
Small, regular uniform cell; normal cell size; uniform chromatin	1
Moderate increase in size and variability; open, vesicular nuclei with visible nucleoli	2
Marked variation, especially large and bizarre nuclei, vesicular with prominent, often multiple nucleoli	3
Mitotic counts	
≤3 mitoses per mm^2	1
4 to 7 mitoses per mm^2	2
≥8 mitoses per mm^2	3
Overall tumour grade	
Grade 1, well differentiated	3 to 5 points
Grade 2, moderately differentiated	6 to 7 points
Grade 3, poorly differentiated	8 to 9 points

1.10. Staging of invasive breast carcinoma

AJCC and UICC both provide systems for staging carcinoma of the breast.[1,8,66] The staging systems are applied to invasive and in situ breast carcinomas.[1,8,66] Tumour stage is coded into a TNM system wherein primary tumour (T), regional lymph node status (N) and presence of metastases (M) categories are assigned to the breast carcinoma.[1,8,66] Importantly, the TNM system serves as a guide for clinicians to determine prognosis and appropriate treatment strategies for patients.[1,8,45,66] Accurate staging of breast carcinomas can improve therapy selection, implementation and effectiveness.[1,8,66] It can also help reduce unnecessary surgical

procedures and permit more limited surgical management, such as breast-conserving surgery, in patients with early-stage disease.[1,8,66] Primary tumour classification is primarily based on tumour size and includes the following T categories: TX, T0, Tis, T1mi, T1a, T1b, T1c, T2, T3, T4a, T4b, T4c, and T4d.[1,8,66] Regional lymph node status classification is mainly based on the number and size of axillary lymph nodes metastases and includes the following categories: NX, N0, N0(i+), N1mi, N1a, N1b, N1c, N2a, N2b, N3a, N3b, N3c.[1,8,66] Metastatic disease classification is based on the location and size of metastatic tumour sites and includes two categories, M0(i+) and M1.[1,8,66] The criteria for each T, N, and M stage are summarized in Table 1.3 to 1.5.

Pathologic TNM stage can then be used to divide patients into AJCC Anatomic Stage Groups 0, IA, IB, IIA, IIB, IIIA, IIIB, IIIC and IV, assembled based on established survival rates.[8] Stage 0 indicates the exclusive presence of in situ disease and included Tis, N0, M0 tumours.[8] Stage IA represents T1 tumours that are node negative (T1, N0, M0 disease). Stage IB includes T0 and TI tumours associated with lymph node micrometastases (T0-1, N1mi, M0).[8] Stage IIA comprises T0 and T1 tumours with 1 to 3 lymph node metastases (T0-1, N1, M0) and node negative T2 tumours (T2, N0, M0).[8] Stage IIB encompasses both T2 tumours with 1 to 3 positive lymph nodes (T2, N1, M0) and node negative T3 tumours (T3, N0, M0).[8] Stage IIIA constitutes T3 tumours with 1 to 3 lymph node metastases (T3, N1, M0) or tumours of any T stage with 4 to 9 lymph node metastases (T0-2, N2, M0).[8] Stage IIIB is defined as T4 tumours with 1 to 9 positive lymph nodes (T4, N0-2, M0).[8] Stage IIIC represents tumours with any T stage and ≥10 lymph node metastases (T0-4, N3, M0).[8] Stage IV includes tumours of any T or N stage with distant metastases (T0-4, N0-3, M1).[8] Markedly, IBC patients can be further stratified into AJCC Prognostic Stage Groups, formed based on established patient outcomes and

prognosis.[8] AJCC Prognostic Stage Group assignment is dependent on a combination of tumour features including TNM stage, histologic grade, hormone receptor and gene expression profiles.[8]

Table 1.3. Summary of primary tumour (T) pathologic classifications of breast carcinoma from AJCC Cancer Staging Manual, 8th ed. (Adapted from Edge[8]).

T category	**T criteria**
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis(DCIS)	Ductal carcinoma in situ
Tis (Paget)	Paget disease of the nipple in the absence of associated invasive carcinoma and/or ductal carcinoma in situ
T1	Tumour ≤20 mm in greatest dimension
T1mi	Tumour ≤ 1 mm in greatest dimension
T1a	Tumour >1 mm but ≤5 mm in greatest dimension
T1b	Tumour >5 mm but ≤10 mm in greatest dimension
T1c	Tumour >10 mm but ≤20 mm in greatest dimension
T2	Tumour >20 mm but ≤50 mm in greatest dimension
T3	Tumour >50 mm in greatest dimension
T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules)
T4a	Extension to the chest wall
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria of inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma

Table 1.4. Summary of regional lymph nodes (N) pathologic classifications of breast carcinoma from AJCC Cancer Staging Manual, 8th ed. (Adapted from Edge[8]).

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis identified
N0(i+)	Isolated tumour cells only (malignant clusters no larger than 0.2 mm or less than 200 cells) in regional lymph node(s)
N1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or internal mammary nodes with micrometastases or micrometastases by SLNB
N1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
N1a	Metastases in 1-3 axillary lymph nodes, at least one large than 2.0 mm
N1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
N1c	N1a and N1b combined
N2	Metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes in the absence of axillary lymph node metastases
N2a	Metastases in 4-9 axillary lymph nodes (at least one tumour deposit larger than 2.0 mm)
N2b	Metastases in internal mammary lymph nodes with negative axillary lymph nodes
N3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular lymph nodes; or positive ipsilateral internal mammary lymph nodes with one or more positive axillary lymph nodes; or >3 axillary lymph nodes and micrometastases or micrometastases by SLNB of ipsilateral internal mammary lymph nodes
N3a	Metastases in 10 or more axillary lymph nodes (at least one tumour deposit larger than 2 mm); or metastases in the infraclavicular lymph nodes
N3b	N1a or N2a in the presence of positive internal mammary lymph nodes; pr N2a in the presence of N1b
N3c	Metastases in ipsilateral supraclavicular lymph nodes

Table 1.5. Summary of distant metastasis (M) pathologic classifications of breast carcinoma from AJCC Cancer Staging Manual, 8th ed. (Adapted from Edge[8]).

M category	M criteria
M0	No evidence of distant metastases
M0(i+)	No evidence of distant metastases in the presence of tumour cells or deposits no larger than 0.2 mm detected by microscopic or molecular techniques in nonregional nodal tissue
M1	Histologically proven metastases in distant organ; or metastases >0.2 mm in non-regional nodes

1.11. Treatment and management of invasive breast carcinoma

Treatment and surgical management of IBC patients is primarily guided by tumour size, stage, histologic type, hormone receptor status, gene expression profile and axillary lymph node status.[36,28,67,68,69] Standard treatment of localized, early stage IBC, such as Tis, N0, M0; T0-3, N1, M0; and T1-3, N0-1, M0 disease, may consist of surgery, neoadjuvant systemic therapy and adjuvant radiation therapy or systemic therapy.[7,70,71,72] Surgery generally includes either a lumpectomy or mastectomy and SLNB.[34,36,38,69,70,71,72] In the presence of positive sentinel lymph nodes, an axillary lymph node dissection will also be performed.[7,70,71] Breast-conserving lumpectomy can be used for the surgical management of localized tumours of any histologic type.[7,70,71] However, lumpectomy is contraindicated in the advent of inflammatory breast carcinoma, diffuse calcifications on imaging, multifocal and metastatic disease.[70,71]

Post-lumpectomy, patients with both node-negative and node-positive disease benefit from whole-breast radiation therapy.[7,70,71] After a mastectomy, patients with negative lymph nodes (N0) or 1 to 3 positive lymph nodes (N1) may receive radiation therapy.[7,70,71] Regional radiation therapy is recommended post-mastectomy in patients at high risk of local recurrence due to the presence of the following features: positive or ≤1 mm negative margins after resection,

>3 positive lymph nodes (N2-3), extranodal disease or primary tumours >5 cm (T3).[7,70,71] Axillary irradiation is generally used in patients with node-positive disease (N1-3) after mastectomy.[7,70,71] Radiation therapy is also recommended as treatment for patients with inoperable tumours, inflammatory breast carcinoma and metastatic disease (T4, N0-3, M0-1).[7,70,71]

Both neoadjuvant and adjuvant systemic therapy may include endocrine hormone therapy, chemotherapy or targeted molecular therapies.[7,70,71,72] Systemic therapy treatment recommendations are dependent on tumour stage, grade, histologic type, hormone receptor status, gene expression profile and patient characteristics.[7,70,71,72] For instance, hormone receptor-negative, high grade or stage tumours are often targeted with chemotherapy, whereas hormone receptor-positive breast carcinoma patients benefit from tamoxifen hormone therapy.[7,70,71,72] Similarly, ILC appears to show a diminished pathological response to neoadjuvant chemotherapy compared to IDC.[2,45] As a result, ILC patients may benefit from alternative neoadjuvant treatments such as hormone therapy.[2] In general, neoadjuvant systemic therapy is recommended for patients with operable HER2-positive or hormone receptor negative, inoperable and metastatic IBC, including T3-4, N2-3, M0-1 stage disease.[70,72]

CHAPTER 2. LITERATURE REVIEW

The utility of diagnostic imaging and BI-RADS classification as breast screening tools is dependent on their ability to accurately and reliably predict the likelihood of malignancy. BI-RADS implementation has been observed to improve the reliability of malignancy prediction on imaging for patients with breast abnormalities.[6,21,28,30,60] However, the diagnostic criteria for BI-RADS classification are comprehensive and subject to interpretation, resulting in high variability

in its application.[6,28] In the literature, imaging has been reported to have a sensitivity (TNR) for malignancy anywhere from 97.6% to 98.4%.[60,73] By comparison, discordance between diagnosis of breast abnormalities on imaging and pathology has been observed to range from 0.3% to 24.0%.[6,30,55] Meanwhile, other researchers have recorded FPRs and FNRs for breast screening, ranging from 20% to 50% and 0.8% to 15%, respectively.[5,55, ,73]

More specifically, Hu et al.[6] evaluated the degree of correlation between mammographically determined BI-RADS scores and final pathologic diagnoses of 3935 breast screening patients. BI-RADS scores on mammography accurately predicted the presence of malignant histology in 99.7% of cases.[6] Malignant tumours undetected by imaging were identified on pathologic evaluation in 0.02% of BI-RADS 1, 0.04% of BI-RADS 2 and 0.19% of BI-RADS 3 lesions.[6] Secondary imaging was found to have resulted in an increased BI-RADS score in 39 patients.[6] Similarly, Radhakrishna et al.[55] performed a retrospective chart review of 437 breast screening patients to determine concordance between imaging and pathology findings in BI-RADS category 3-5 lesions. The PPV of BI-RADS 5 for the presence of malignancy was measured as 93.25%.[55] The NPV of BI-RADS 3 for the presence of malignancy was 98.4%.[55] Overall, BI-RADS classification of breast imaging abnormalities was calculated to have a FNR of 0.8%.[55]

Equally, in the retrospective chart review of 1071 patients with breast imaging abnormalities by Duarte Filho et al.[30], BI-RADS scores were concordant with CNB findings in 94.7% of cases.[30] Most notably, the BI-RADS category assigned to breast masses accurately predicted malignancy in 75.2% of cases and benign disease in 98.8% of cases.[30] Chan et al.[73] also retrospectively examined the accuracy of breast carcinoma detection using combined US and mammography. Malignant histology was observed on the biopsy of all palpable breast masses

assigned BI-RADS 5.[73] Only 33% of masses designated as BI-RADS 4 were malignant on biopsy.[73] BI-RADS 3 lesions were reported to have malignancy on biopsy in 1.9% of cases.[73] Of the palpable breast masses deemed BI-RADS 1-2, 0.3% were found to have malignant histology on biopsy.[73] Overall, diagnostic imaging as a means of breast carcinoma detection was observed to have a sensitivity (TPR) of 97.6%, FNR of 0.3% and NPV of 99.7%.[73]

Likewise, Spinelli Varella et al.[28] performed a cross-sectional study to examine the accuracy of BI-RADS categories in distinguishing benign and malignant breast tumours. BI-RADS category 3 was found to have a NPV of 96.5%.[28] PPVs of 6.1%, 25.4%, 80.9% and 94.7% were reported for BI-RADS categories 4A, 4B, 4C and 5, respectively.[28] Overall, BI-RADS categories 3 and 5 were found to serve as reliable predictors of benign and malignant breast tumours.[28] Due to the high FPR, Spinelli Varella et al.[28] recommend that BI-RADS category 3 serve as the maximum cut-off for which imaging follow-up is the only treatment course. Moreover, any breast imaging abnormalities categorized as BI-RADS 4 or higher are recommended to undergo biopsy in order to ensure all malignancies are detected as they noted a decreased level of sensitivity for lesions assigned these BI-RADS categories.[28] Comparatively, Raza et al.[16] examined concordance between BI-RADS scoring and CNB diagnoses of IBC patients. Malignancy was identified in 0.8% of BI-RADS 3, 16.2% of BI-RADS 4 and 100% of BIRADS 5 lesions.[16] A NPV for BI-RADS 3 lesions was measured to range from 99.2% to 98.6%, whereas a 15.5% to 20.0% PPV was estimated for BI-RADS 4 lesions.[16]

The ability to further subcategorize such lesions into 4A, 4B, and 4C can help better stratify and predict the risk of malignancy in such lesions.[28] However, the subcategorization of BI-RADS 4 lesions appears to be complicated by their propensity to be complex, displaying both features of both benign and malignant lesions.[28] As a result, uniform application of BI-RADS 4

subcategories A to C has been reported to be particularly challenging, as these subcategories can be difficult to define and distinguish.[28] The nature of interval imaging characteristic of breast screening may contribute to inter-observer variability.[16] Each imaging examination produces a unique set of images allowing examiners to view different lesion features with varying clarity.[16] Increased breast tissue density has also been associated with decreased specificity of imaging for IBC diagnosis. For instance, the FPR of mammographic breast carcinoma screening tends to be higher in women aged 40-49, who generally have denser breast tissue than those over 50.[5] Overall, technical parameters, experience, training and patient characteristics contribute to variability in breast imaging interpretation.[16] As a result, Raza et al.[16] recommended a biopsy be performed on all solid masses even in the presence of benign imaging features.[16]

As previously mentioned, IBC staging and treatment are mainly based on tumour size.[36,38,67,68,69] Pathologic assessment of the excision specimen is considered the gold standard for IBC tumour size measurement and staging.[68] However, assessing patient eligibility for neoadjuvant therapies and breast conserving surgery requires the use of imaging for pre-operative tumour measurement and staging.[14,15,67,68] Moreover, neoadjuvant therapy and CNB can alter tumour size, thereby limiting the accuracy of measurement on surgical excision.[15] Discordance in the tumour size or stage reported on imaging and pathology can result in IBC patients being under or over treated by clinicians.[68] To ensure that patient management decisions are accurate and appropriate, a high degree of concordance between imaging and pathology measurement of tumour size is necessary.[14,44,67,68]

A significant correlation between imaging and pathology tumour measurement has previously been reported in the literature.[12,15,68] Hamza et al.[68] evaluated the concordance of tumour size on imaging and pathology in 406 IBC cases. A strong correlation (R = 0.61)

between imaging and pathologic tumour size was observed. Differences in tumour size were found to be within ±2mm in 40.4 % of IBC cases and within ±5mm in 66.5% of IBC cases.[68] Tumour size on imaging and pathology were noted to be exactly the same in only 9.6% of cases.[68] Fortunately, concordance between imaging and pathology tumour stage was significantly higher at 59.9%.[68] Discordance was associated with stage underestimation in 14.5% and overestimation in 25.6% of cases.[68] Similarly, Podall et al.[12] examined 213 IBC cases and identified tumour size underestimation and overestimation rates of 14% and 5% on imaging, respectively.[12] Hlawatsch et al.[77] also evaluated the level of agreement between tumour size determined on imaging and histology in 104 IBC patients. Concordance of tumour measurements, defined as a size difference within ±5mm, was reported in up to 77% of cases.

Difference in invasive growth patterns has been associated with the continued variability in tumour size determined on imaging and pathology.[14,15] For example, IDC is characterized by a circumscribed lesion and therefore tends to be easier to accurately measure on imaging.[15] Conversely, ILC is characterized by a diffuse, infiltrative growth pattern and frequent multifocality.[14,15,17] Several studies have reported a higher frequency of US and pathologic tumour size discordance in patients with ILC.[2,14,15,17] Furthermore, studies have reported significantly higher concordance rates between imaging and pathology tumour size in cases of IDC compared to other histologic types of IBC.[2,15,67,68] However, histologic type has been found to have no significant impact on the likelihood of imaging and pathologic size concordance in other studies.[14] Instead, differences in size on imaging and pathology have been postulated to be most often due to the presence of in situ disease that produces ill-defined tumour margins on imaging.[12,14] Increased tumour size has also been associated with greater discordance in tumour size determined on imaging and pathology.[12,14,68] For example, cases with a final pathologic

tumour size of ≤2 cm have been reported to be 3.9 times more likely to have concordant tumour measurement than those >2cm.[68]

The use of different imaging modalities may also be responsible for the variability in tumour measurement. Mammographic tumour size is generally measured from the longest tumour axis.[14,67] Errors in measurement on mammography may be attributed to non-parallel orientation of the longest axis and distance of the tumour in relation to the imaging detector.[67] Equally, spiculated and ill-defined lesions are often difficult to accurately measure on mammography.[67] Increased breast density has also been associated with greater discordance between mammographic and pathologic tumour size.[14] In contrast, US permits multidimensional measurement of tumours that have been observed to better correlate with pathologic tumour measurement.[67] However, other studies have identified a greater frequency of size underestimation when US alone is used for tumour measurement.[14,15]

As previously discussed, breast carcinoma patient staging, prognosis and treatment are largely dependent on the presence of lymph node metastases.[34] Presently, SLNB is widely employed as an initial screening for axillary disease to determine if axillary dissection is required.[36,38,69] Unfortunately, SLNB is an additional procedure that requires time and delays surgical excision due to the need for pathologic assessment of the specimen.[38] US can detect larger lymph node metastases, limiting the number of SLNB and allowing for pre-operative diagnoses of axillary disease.[36,38,69] However, the reliability of imaging in the assessment of axillary lymph node metastases remains controversial.[5] Among patients with histologically identified positive lymph nodes, approximately half present with clinically occult lymph node metastases detected on imaging.[5] Variation in reported accuracy and reliability of lymph node metastases detection using imaging may be attributable to differences in equipment imaging

resolution and application of criteria for classifying abnormal lymph nodes.[36,69] Additionally, pre-operative imaging often misses microscopic lymph node metastases.[34]

In a retrospective chart analysis of 252 patients with IDC, Kijima et al.[34] evaluated US accuracy in the prediction of lymph node metastases. US was observed to accurately detect lymph node disease in 75% of the cases.[34] Other studies have estimated that pre-operative axillary lymph node imaging has a sensitivity (TPR) of 50.0% to 61.3%, TNR of 21.5% to 75.0%, FNR of 25.0% to 78.5% and FPR of 38.7% to 50.0%.[69,74] Comparatively, Alvarez et al.[36] performed a literature review to estimate the recorded accuracy of US detection of axillary lymph nodes metastases in IBC patients. In studies examining palpable and non-palpable axillary lymph nodes, where nodes >5 mm were deemed as positive, US was reported to have a sensitivity (TPR) of 66.1% to 72.7% and specificity (TNR) of 44.1% to 97.9% for the detection of axillary lymph nodes metastases.[36] When lymph node morphology was used to determine positivity, US sensitivity (TPR) and specificity (TNR) for axillary lymph node metastases ranged from 54.7% to 92.3% and 80.4% to 97.1%.[36] For studies that included only non-palpable lymph nodes, specificity (TNR) and sensitivity (TPR) ranged from 48.8% to 87.1% and 55.6% to 97.3%, respectively, when positivity was based on lymph node size (>5mm) and visibility.[36] When lymph node morphology was used to determine positivity, US displayed a sensitivity (TPR) of 26.4% to 75.9% and a specificity (TNR) of 88.4% to 98.1%.[36] Overall, axillary sonography has moderate sensitivity and fairly good specificity for diagnosing axillary lymph node disease in IBC patients.[34,36,69,74]

Following imaging, CNB is frequently performed to obtain a tumour sample for preliminary histologic diagnosis. As a result, the accuracy and reliability of CNB diagnoses are essential to ensure pre-operative patient management is well-informed and all potential

malignancies are detected.[31,46,50,53] Several large scale studies have reported that the degree of accuracy and sensitivity of CNB routinely falls within the recommended standards for CNB as a diagnostic tool.[2,21,42,43,44,50,54] For instance, CNB has been documented to have a sensitivity (TPR) of 71% to 100% in the detection of malignancy.[31,42,53,75] Concordance between CNB and surgical excision findings has been reported to range from 91 to 100%.[53] Moreover, CNB has been estimated to produce adequate tissue samples to achieve accurate diagnosis in 97.5 % to 100% of patients.[46,51,75] Simon et al.[75] retrospectively reviewed CNB findings from 71 breast lesion cases, reporting a 95% sensitivity (TPR) and 98% specificity (TNR).[75] Additionally, CNB was found to have a 95% PPV, 98% NPV, and overall accuracy of 97%.[75] In a review of 3226 core biopsies from imaging detected breast tumours, Andreu et al.[31] observed a sensitivity (TPR) of 90.8% and specificity (TNR) of 83.8%. Ultimately, benign tumours appear to be reliably and definitively distinguished from malignant lesions on CNB, allowing for subsequent therapeutic decisions to be made appropriately.[31]

In contrast, other studies have calculated the rate of breast malignancy underestimation on pathologic evaluation of CNB specimens to be anywhere from 0% to 100%.[21,22,24,56] For example, in a retrospective review of 758 patients who underwent breast CNB procedures, Houssami et al.[43] reported a malignancy underestimation rate of 27.7% from CNB. Jakate et al.[76] assessed concordance between CNB and surgical excision diagnoses of papillary lesions.[76] CNB diagnoses were noted to have been altered on final surgical excision in 21.5% of cases.[76] Variability in the observed rate of malignancy underestimation from CNB samples is likely due to the varied methodology, imaging and clinical information used by researchers to draw conclusions.[47]

CNB can not only be used to identify breast malignancy but also to evaluate histologic prognostic factors of IBC, such as histologic type and grade.[2,43,45,52,53,56] Studies have reported differing rates of concordance between histologic type determined on CNB compared to subsequent surgical excision specimens, ranging from 73.6% to 100%.[46,50,53,54,75] For instance, Badoual et al.[46] examined concordance between histologic prognostic factors evaluated from CNB and surgical excision specimens in a retrospective review of 110 breast tumour cases. The majority of histologic type discord was observed in tumours determined to be ILC or mixed IDC/ILC.[46] Notably, histologic type is most accurately predicted on CNB when a single histologic type is present such as IDC, ILC or MC.[53]

Similarly, a wide range of concordance, between 59% and 95%, have been reported in studies examining agreement of tumour grade determined from CNB and surgical excision.[50,52,53,54,56] Harris et al.[50] retrospectively reviewed 500 IBC cases and observed a statistically significant correlation ($R = 0.58$, p-value = <0.001) between histologic grade reported on CNB and excision of IBC. Histologic grade overestimation and underestimation on CNB accounted for 8% and 25% of discordant cases, respectively.[50] A high rate of CNB and excision specimen grade agreement, 84%, was observed between patients with grade 3 IBCs.[50] Motamedolshariati et al.[54] reviewed CNB and tumour excision pathology reports of 30 IBC patients and found 20% were upgraded and 13.3% were downgraded on final excision.[54] In a retrospective review of 1010 IBC cases, Badoual et al.[46] identified underestimation of tumour grade on CNB in 6.5% of cases and overestimation in 20.4% of cases.[46]

There are several diagnostic problems and challenges associated with CNB.[45] CNB often only provides a limited and fragmented sample of lesions, many of which are heterogenous and not entirely represented in the small sample.[45] The lack of uninvolved tissue surrounding the

lesion in CNB samples does not permit the pathologist to examine the tumour edge, which can be essential for diagnoses and accurate tumour grading.[2,45,53] Discrepancies in the histologic features reported from CNB and the corresponding surgical excision may be the result of inadequate and partial tumour sampling from CNB.[2,12,21,46,49,50,53,54] Adequate pathologic evaluation of CNB samples can also be compromised by artifacts created from the procedure and tissue processing.[18,45] Gauze, rough tissue handing, tissue cautery/freezing, and the use of vacuum-assisted core biopsy techniques can create uniquely patterned artifacts and disrupt the epithelial cell layer, all of which can complicate pathologic interpretation.[18,45] Variability in CNB interpretation further contributes to discordance between CNB and surgical excision histologic findings.[43] Histologic diagnoses can have variable reproducibility, particularly for lesions in which histologic changes are borderline.[43] The challenge of accurately and consistently reporting borderline changes may cause discordance between CNB and surgical excision conclusions.[43]

Several steps can be used to limit the likelihood of a false negative diagnosis including, optimizing lesion targeting, imaging and histologic finding correlation, and follow-up mammography to ensure missed malignancies are rapidly identified.[22] Chiefly, image guidance can significantly reduce the likelihood of inadequate CNB sampling.[2,21,24,43] Larger needle gauge and number of cores have been associated with greater concordance in the histologic findings reported from CNB and the corresponding surgical excision.[12,21,43,46,47,50] However, most centres have achieved accurate and satisfactory diagnosis of breast lesions using smaller US-guided CNB techniques.[50]

CHAPTER 3. RESEARCH OBJECTIVES

As illustrated above, several researchers have performed retrospective chart reviews of breast carcinoma patients and identified various associations between the diagnostic conclusions made from the evaluation of breast tumours on imaging and pathology.[43,44,47] Various investigators have noted both agreement and disagreement between the histologic findings and diagnoses made from breast CNB and surgical excision specimens.[2,12,43,44,46,47,48,49,58,65] Ultimately, the findings of these research studies resulted in the identification of inaccuracies in the assessment and diagnosis of breast carcinoma patients on imaging and pathology.[12,43,44,47,48,58,65] Moreover, many researchers were able to provide recommendations for alterations in diagnostic protocols to limit errors and enhance the accuracy of breast carcinoma diagnosis.[12,43,44,47,48,58,65]

Based on previous reports of associations between imaging and CNB findings compared to the corresponding excision in the literature, we expect to identify and define associations between these variables within the high risk population of breast carcinoma patients from Manitoba, Canada. Moreover, the ability of several researchers to translate such findings into conclusions and recommendations for diagnostic protocols suggests that the findings of this practicum could serve as tools to guide the clinical evaluation of breast carcinoma patients. This research practicum aims to perform a retrospective review of pathology reports and US-guided breast CNB histology breast requisition forms of IBC patients in Manitoba, Canada, to determine the level of agreement between findings reported from the evaluation of IBC patients using imaging, US-guided CNB and surgical excision specimens. More specifically, the research objectives of the practicum are as follows:

1. To evaluate the diagnostic accuracy of breast imaging in comparison to corresponding pathologic evaluation.
2. To further investigate and identify sources of discordance between findings reported on breast imaging and pathology.
3. To assess the diagnostic accuracy of CNB in the assessment of breast tumour histologic grade and histologic type.
4. To further examine and outline sources of discordance between pathologic features reported from breast CNB compared to corresponding surgical excision specimens.

CHAPTER 4. MATERIALS AND METHODS

Institutional approval of the project was granted by the University of Manitoba Health Research Ethics Board (# HS24062/H2020:314). A retrospective case review was performed on 266 adult female invasive breast carcinoma patients, 18 years of age or older, seen between 2018-2019 in Manitoba, Canada. Patient case records were obtained using CoPath, the pathology laboratory information system used in Shared Health Manitoba pathology laboratories in Manitoba, Canada. CNB and surgical excision specimen pathology reports and breast CNB histology breast requisition forms of the breast tumour patients were extracted from the CoPath laboratory information system by performing a search using the keywords “breast”, “bx”, “core biopsy” “lumpectomy”, and “mastectomy”. Cases were only included if the breast tumour was examined by imaging with subsequent pathologic review of CNB and surgical excision specimens, including lumpectomies and mastectomies, of the tumour. Patients were excluded if they had undergone neoadjuvant chemo/radio/endocrine therapy. The principal investigator

reviewed the patient case records retrieved from this search to extract relevant imaging and histologic data.

Clinical patient information including age, gender, type of imaging (ultrasound and/or mammography), biopsy type (ultrasound-guided core biopsy), surgical excision type (lumpectomy or mastectomy), tumour type (benign, suspicious or malignant), and history of neoadjuvant therapy (yes or no) were abstracted. Breast CNB histology requisition forms and imaging reports completed after mammography and/or US of the IBC patients were reviewed from which the following findings from imaging were recorded: size of tumour on imaging, suspicion of tumour on imaging (low, intermediate or high), BI-RADS score (0, 1, 2, 3, 4A, 4B, 4C, 5 or 6) and presence of axillary adenopathy (yes or no).

Pathology reports for breast CNBs performed on the IBC patients after diagnostic imaging were reviewed, and the following histological findings were extracted: histology (benign or malignant), histologic type and Nottingham histologic grade (1, 2, 3, or grading deferred to surgical excision). Similarly, pathology reports for corresponding surgical excision specimens from IBC patients evaluated after biopsy were also reviewed, and the following findings were recorded: histology (benign or malignant), histologic type, Nottingham histologic grade (1, 2, or 3), tumour size, presence of lymph node metastases (yes or no), and primary tumour (T) stage (T0, T1mi, T1a, T1b, T1c, T2, T3, T4a, T4b, T4c, or T4d).

To assess the diagnostic accuracy of imaging, concordance between the following features on imaging and pathology was evaluated:

1. Suspicion on imaging and tumour type on CNB.
2. Suspicion on imaging and tumour type on surgical excision.
3. BI-RADS score and tumour type on CNB.

4. BI-RADS score and tumour type on surgical excision.
5. Tumour size on imaging and surgical excision.
6. Primary tumour (T) stage on imaging and surgical excision.
7. Axillary adenopathy on imaging and presence of lymph node metastases on surgical excision.

Similarly, the diagnostic accuracy of CNB was assessed by measuring concordance between histologic grade and histologic type reported on biopsy and surgical excision. Rates of concordance and discordance were calculated for all comparisons. The effect of the following tumour characteristics, as determined on pathologic evaluation of final surgical excision, on the degree of concordance was assessed: histologic type (IDC vs other carcinomas), Nottingham histologic grade (1, 2 vs 3), and tumour size (≤2 cm vs>2 cm).

Concordance between suspicion on imaging and tumour type was defined as one of the following observations: (1) low suspicion on imaging with benign histology on pathology or (2) high suspicion on imaging with malignant histology. Discordance between suspicion on imaging and tumour histology was further categorized as either minor or major. Minor discordance was defined as reported intermediate suspicion on imaging with either benign or malignant histology on pathology. Major discordance was defined as one of the following observations: (1) low suspicion on imaging with malignant histology on pathology or (2) high suspicion on imaging with benign histology on pathology. Concordance between BI-RADS score and tumour type was defined as one of the following observations: (1) BI-RADS score ≤3 with benign histology on pathology or (2) BI-RADS score ≥4 with malignant histology on pathology. Discordance of reported BI-RADS score and tumour histology was defined as either of the following observations: (1) BI-RADS score ≤3 with malignant histology on pathology or (2) BI-RADS

score ≥4 with benign histology on pathology. Furthermore, TPR, TNR, FNR, FPR, and PPV of both suspicion on imaging and BI-RADS scores as predictors of malignancy on CNB and surgical excision were calculated to further quantify the accuracy of IBC detection on imaging.

The degree of concordance between tumour size reported on imaging and surgical excision pathology was categorized as concordance, minor discordance or major discordance. Concordance included cases where the same tumour size was reported on both imaging and pathology. Minor discordance was defined as a tumour size difference on imaging and pathology of ±5 mm. Major discordance was defined as a difference in tumour size on imaging and pathology >5 mm. Primary tumour (T) stage on imaging was assigned to each case by study personnel, based on the tumour size and chest wall/skin involvement as indicated on the imaging. Concordance was defined as the designation of the same primary tumour (T) stage on both imaging and surgical excision pathology. Discordance was defined as the observation of different primary tumour (T) classification on imaging and pathology.

The degree of concordance between the imaging and pathologic evaluation of lymph node metastases was categorized as concordant or discordant. Concordance was defined as the observation of axillary adenopathy on imaging and positive lymph nodes on pathologic assessment. Discordance was defined as one of the following observations: (1) axillary adenopathy reported on imaging with negative lymph nodes on pathology, or (2) no report of axillary adenopathy on imaging with positive lymph nodes on pathology. Additionally, TPR, TNR, FNR, FPR, PPV and NPV were calculated to further quantify the diagnostic accuracy of imaging in the detection of lymph node tumour metastases.

The observation of the same histologic grade and histologic type on both CNB and subsequent surgical excision was defined as concordance. Any difference in the histologic grade and histologic type determined on CNB and surgical excision was deemed discordant.

Data were analyzed by performing crosstabulations, two-tailed FFH exact tests, and Pearson correlation analysis using SPSS Statistics software. A p-value of ≤ 0.05 was regarded as statistically significant.

CHAPTER 5. RESULTS

5.1. Invasive breast carcinoma patient characteristics

Clinical characteristics of the IBC patients included in the study are presented in Table 5.1 and included: age, gender, type of imaging, biopsy type, type of surgical excision, tumour type on final diagnosis, and history of neoadjuvant therapy. All of the patients were female with a median age of 66 and age range of 28 to 90. Each patient had undergone both mammography and US assessment followed by US-guided CNB. Of the 266 patients, 183 (69%) had received lumpectomies and 83 (31%) had received mastectomies for their surgical excision procedures. Every patient was identified to have a malignant tumour type as their final diagnosis. None of the 266 patients had a reported history of neoadjuvant therapy prior to their surgical excision procedures.

Table 5.1. Clinical characteristics of invasive breast carcinoma patients

Clinical characteristic	**Number (n)**	**Percentage (%)**
Age		
<40	7	3
40-60	78	29
>60	181	68
Gender		
Female	266	100
Male	0	0
Type of imaging		
Mammography	266	100
Ultrasound	266	100
Biopsy type		
Ultrasound-guided core biopsy	266	100
Type of surgical excision		
Lumpectomy	183	69
Mastectomy	83	31
Tumour type on final diagnosis		
Benign	0	0
Suspicious	0	0
Malignant	266	100
Neoadjuvant therapy		
Yes	0	0
No	266	100

5.2. Concordance between suspicion on imaging and tumour type on pathology

As summarized in Figure 5.1, suspicion reported on imaging was found to be reasonably accurate in predicting the presence of malignancy CNB for the majority of IDC cases included in our study. Chiefly, malignant histology was identified on CNB in 100% (227) of cases with high suspicion on imaging. However, malignant histology was also reported from CNB in 100% (3) of cases with low suspicion and 97% (35) of cases with intermediate suspicion on imaging. Benign histology on CNB was exclusively associated with intermediate suspicion on imaging, accounting for 3% (1) of cases in the category. The overall degree of concordance identified

upon comparison of the reported level of suspicion on imaging and tumour type from CNB of IBC patients is depicted in Figure 5.2. Concordance was demonstrated in 227 (86%) of the 266 IBC cases examined. Minor and major discordances were noted in 35 (13%) and 3 (1%) cases, respectively. Likelihood of concordance was not observed to be significantly correlated with the following factors: tumour size (p = 0.163), histologic type (p = 0.556) or histologic grade (p = 0.056) (Table 5.2). A TPR of 86%, TNR of 100%, FPR of 0%, FNR of 14%, and PPV of 100% were measured for suspicion on imaging as a predictor of malignancy on CNB.

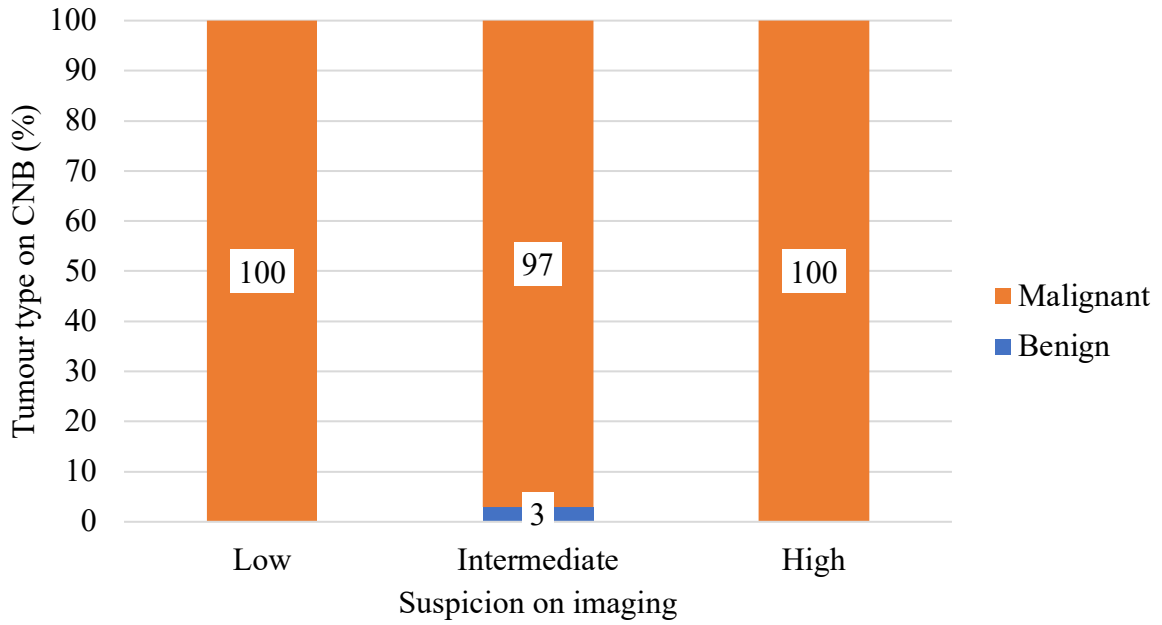

Figure 5.1. Correlation of suspicion on imaging and tumour type reported on CNB, n = 266.

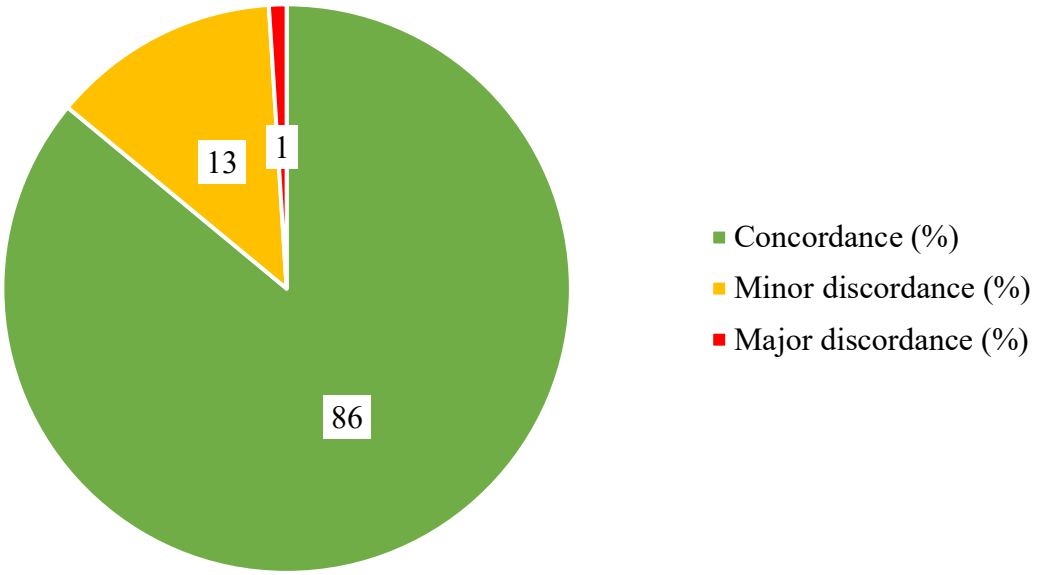

Figure 5.2. Degree of concordance between suspicion on imaging and tumour type reported on CNB, n = 266.

Table 5.2. Factors that did not significantly affect concordance of suspicion on imaging and tumour type on CNB, n = 266.

Factor	**p-value**
Tumour size (≤2 cm or >2 cm)	0.163
Histologic type (IDC or other carcinomas)	0.556
Histologic grade (1, 2 or 3)	0.056

Similarly, level of suspicion on imaging predicted the presence of malignancy on surgical excision pathology of IBC patients with decent accuracy (Figure 5.3). Most notably, malignant histology was identified on surgical excision in 100% (227) of cases with high suspicion on imaging. However, malignant histology was also reported on surgical excision in 100% (3) of cases with low suspicion and 100% (36) of cases with intermediate suspicion on imaging. No benign tumours were identified from surgical excision pathology of the IDC cases included in this study. The degree of concordance calculated from the comparison of suspicion on imaging

and tumour type on surgical excision pathology is illustrated in Figure 5.4. Of the 266 IBC cases included, concordance was noted in 227 cases (85%). Minor discordance was present in 36 (14%) cases and 3 cases (1%) displayed major discordance. Tumour size (p = 0.163), histologic type (p = 0.556) and histologic grade (p = 0.056) had no significant effect on the likelihood of concordance (Table 5.3). Overall, suspicion on imaging as a predictor of malignancy on surgical excision was calculated to have a TPR of 85%, FNR of 15%, and PPV of 100%. TNR and FPR could not be defined for this predictor due to the absence of true negative and false positive results in the study dataset.

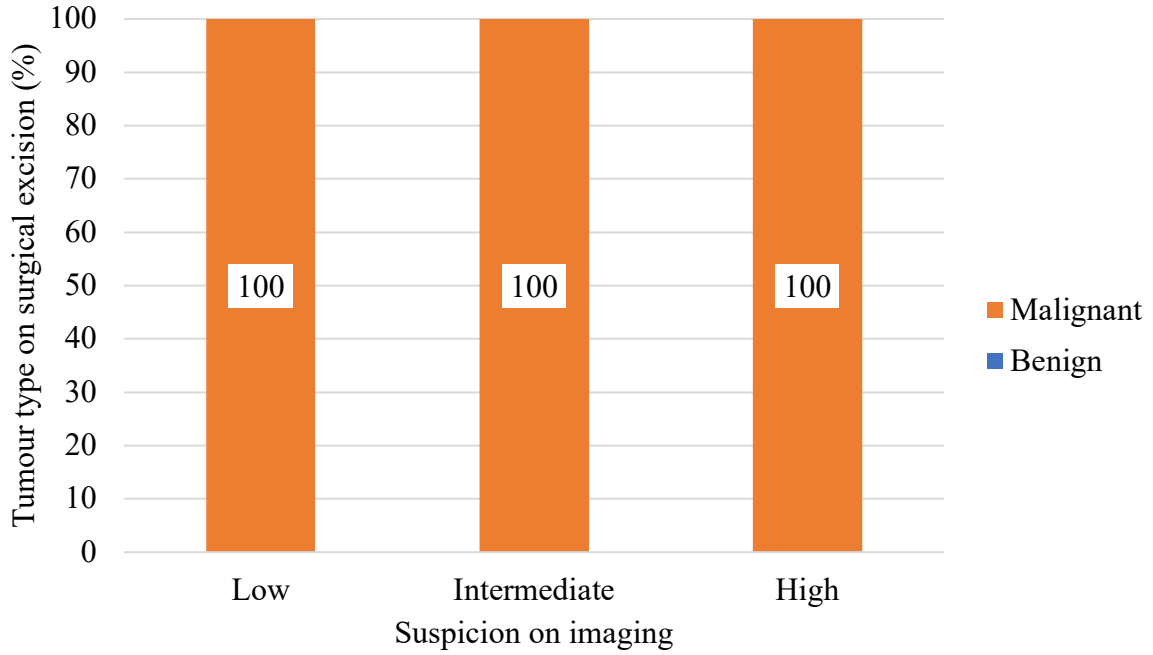

Figure 5.3. Correlation of suspicion on imaging and tumour type reported on surgical excision, n = 266.

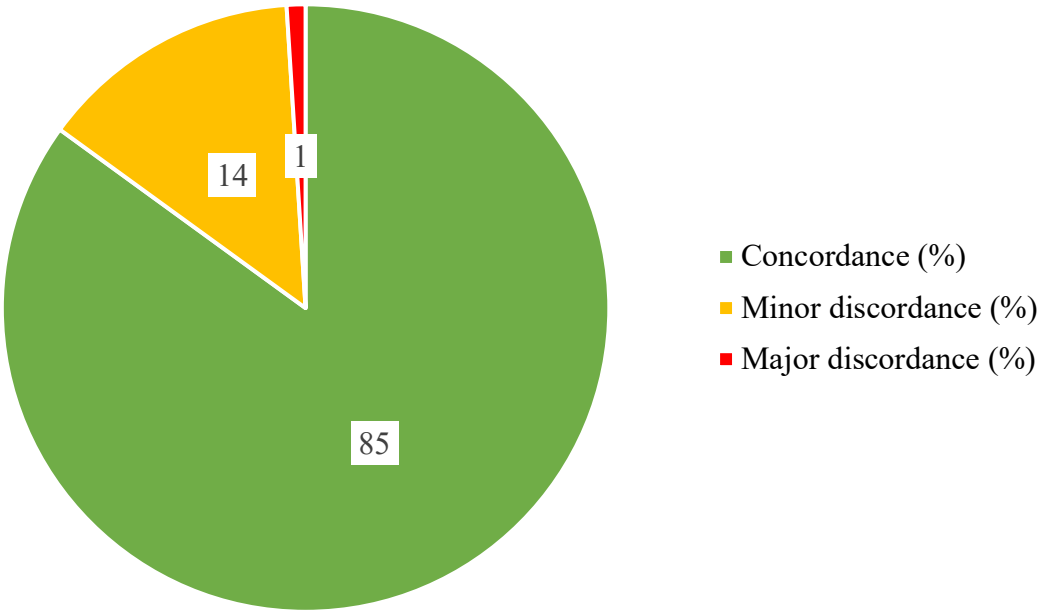

Figure 5.4. Degree of concordance between suspicion on imaging and tumour type reported on surgical excision, n = 266.

Table 5.3. Factors that did not significantly affect concordance of suspicion on imaging and tumour type on surgical excision, n = 266.

Factor	**p-value**
Tumour size (≤2 cm or >2 cm)	0.163
Histologic type (IDC or other carcinomas)	0.556
Histologic grade (1, 2 or 3)	0.056

5.3. Concordance between BI-RADS score and tumour type on pathology

BI-RADS scores were reported following imaging in only 101 of the 266 IBC cases included in the retrospective review. Of those reported, BI-RADS scores were limited to those ranging from categories 4 to 6. As shown in Figures 5.5 and 5.7, BI-RADS score assigned on imaging correctly predicted the presence of malignancy on patient CNB and surgical excision specimens. More specifically, malignant histology was identified on CNB and surgical excision

in 100% (5) of BI-RADS 4A, 100% (7) of BI-RADS 4B, 100% (8) of BI-RADS 4C, 100% (80) of BI-RADS 5 and 100% (1) of BI-RADS 6 lesions. Benign histology was not recorded on CNB or surgical excision pathology in any of the cases in which BI-RADS scores were reported. In short, concordance was exhibited in all 101 (100%) of the IBC cases included in the study. Discordances were not observed. As a result, the effect of tumour size, histologic type and grade on the likelihood of concordance could not be evaluated with the study dataset. A TPR of 100%, FNR of 0%, and PPV of 100% were measured for BI-RADS score as a predictor of malignant histology on CNB and surgical excision, however these numbers are suggested based on our retrospective approach. Due to the lack of true negative and false positive results in the study dataset, TNR and FPR could not be defined.

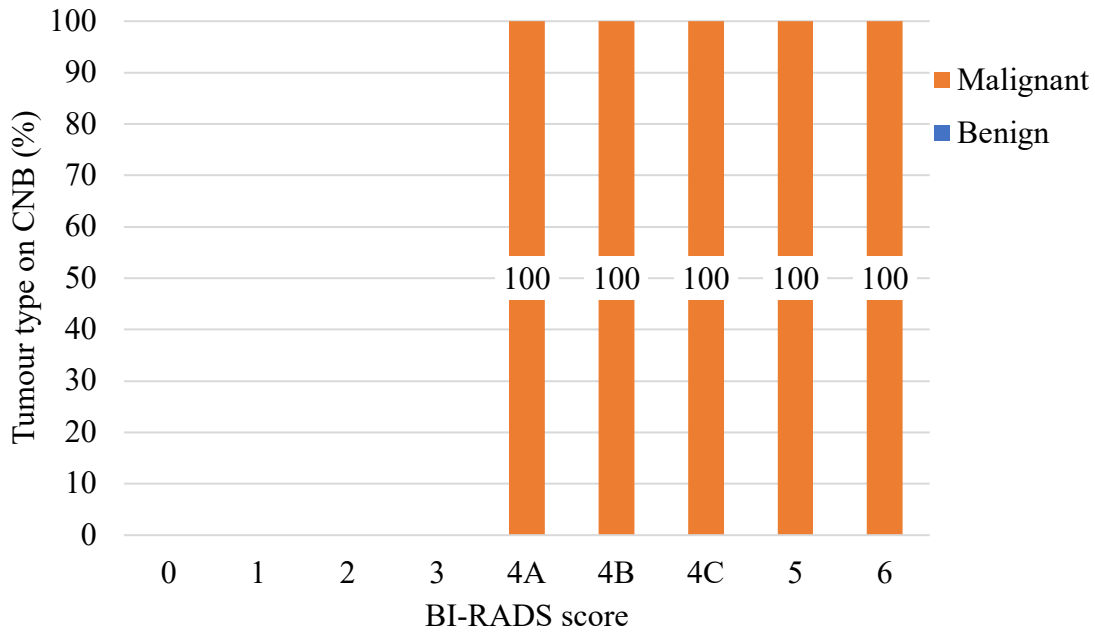

Figure 5.5. Correlation of BI-RADS score and tumour type reported on CNB, n = 101.

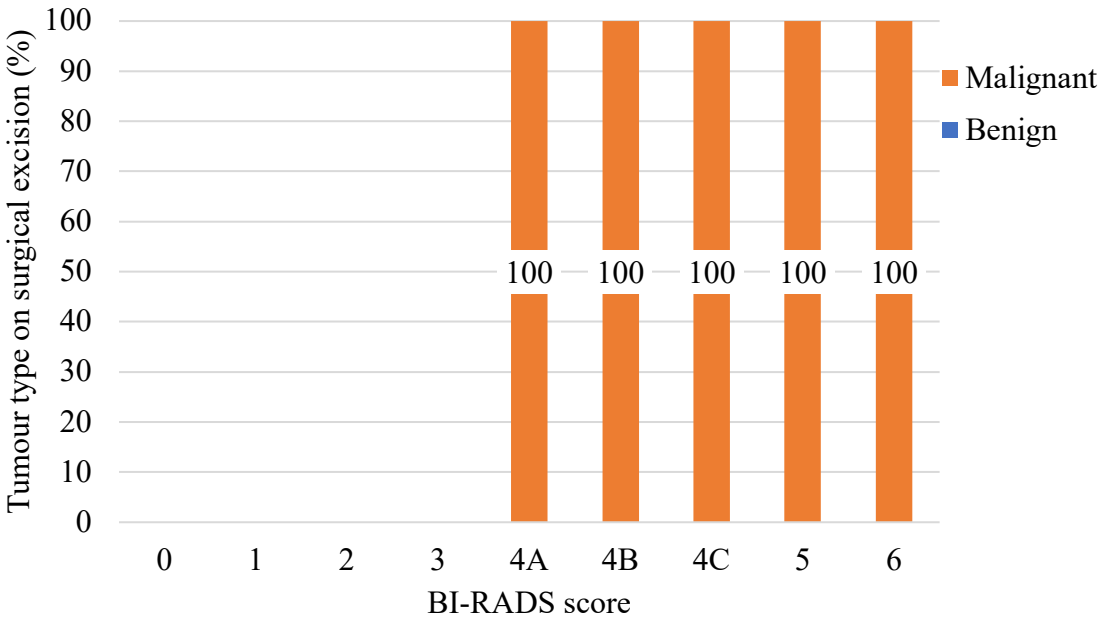

Figure 5.6. Correlation of BI-RADS score and tumour type reported on surgical excision, n = 101.

5.4. Cases with major discordance between imaging and tumour type on pathology

The imaging and pathology findings of the 3 IBC cases in which major discordance was observed between suspicion on imaging and tumour type on pathology are summarized in Table 5.4. In the cases with major discordances, low suspicion was reported on imaging with malignant histology identified on subsequent CNB and surgical excision specimens. However, BI-RADS scores indicative of suspicion for malignancy by the radiologist, including categories 4A (2 cases) and 5 (1 case), were found to have been assigned to all 3 cases on imaging. Additional comments were provided on imaging for 2 cases with major discrepancies and included the following suspected diagnoses: query sebaceous cyst and suspect complex cyst.

Table 5.4. Summary of imaging and pathology findings in cases with major discordance between imaging and tumour type on surgical excision.

Suspicion on imaging	Tumour type		BI-RADS score	Additional comments on imaging
	Biopsy	Excision		
Low	M	M	4A	None
Low	M	M	5	Query sebaceous cyst
Low	M	M	4A	Suspect complex cyst

M – malignant.

5.5. Cases with minor discordance between imaging and tumour type on pathology

Table 5.5. outlines the findings identified on imaging and pathology cases that displayed minor discordance between suspicion on imaging and tumour type on pathology. Intermediate suspicion on imaging was reported in association with malignant tumour type on CNB and/or surgical excision for each of the 35 cases that displayed minor discordances. BI-RADS scores were provided on imaging in 14 of these cases and included BI-RADS categories 4A (3 cases), 4B (7 cases) and 4C (4 cases). All of which indicate the presence of imaging features suspicious for malignancy. Additional comments were provided on imaging in 23 cases with minor discrepancies, the majority of which included the following statements: query fibroadenoma (11 cases), query carcinoma/malignancy (10 cases), indeterminate mass/complex lesion (4 cases), query papilloma (1 case), query lymphoma (1 case), query atypical cells (1 case), query complex cyst (1 case), suspected phyllodes (1 case), poor margins (1 case), difficulty localizing lesion (1 case), inadequate sample (1 case), and/or previous excision (1 case). Notably, three cases with intermediate suspicion on imaging were found to have additional comments that only listed "query fibroadenoma", a benign breast lesion, as a presumptive diagnosis.

Table 5.5. Summary of imaging and pathology findings in cases with minor discordance between imaging and tumour type on surgical excision.

Suspicion on imaging	Tumour type		BI-RADS score	Additional comments on imaging
	Biopsy	Excision		
Intermediate	M	M	NR	Suspect phyllodes, history of phyllodes
Intermediate	B	M	NR	Inadequate sample
Intermediate	M	M	4B	None
Intermediate	M	M	NR	Indeterminate complex lesion
Intermediate	M	M	NR	Query FA
Intermediate	M	M	NR	Query FA vs CA vs complex cyst
Intermediate	M	M	NR	Query multifocal CA
Intermediate	M	M	NR	Query FA
Intermediate	M	M	NR	Query FA vs CA, previous benign FNA, increase in size
Intermediate	M	M	NR	Query FA
Intermediate	M	M	NR	Query FA vs CA
Intermediate	M	M	NR	Difficult to localize on US
Intermediate	M	M	NR	Query malignancy
Intermediate	M	M	NR	Query CA
Intermediate	M	M	NR	Query FA vs papilloma vs circumscribed CA vs atypical cells
Intermediate	M	M	NR	None
Intermediate	M	M	4A	Indeterminate mass
Intermediate	M	M	NR	Query FA vs CA
Intermediate	M	M	NR	Poor margins
Intermediate	M	M	NR	Query FA
Intermediate	M	M	NR	Query FA vs CA
Intermediate	M	M	NR	Indeterminate complex lesion
Intermediate	M	M	NR	Query malignancy vs lymphoma, indeterminate solid lesion
Intermediate	M	M	4B	None
Intermediate	M	M	4B	None
Intermediate	M	M	4B	None
Intermediate	M	M	4C	None
Intermediate	M	M	4C	Previous excision
Intermediate	M	M	4B	None
Intermediate	M	M	4B	None
Intermediate	M	M	4B	None
Intermediate	M	M	4C	None
Intermediate	M	M	4A	None
Intermediate	M	M	4C	Query FA vs CA
Intermediate	M	M	4A	None

B – benign; CA – carcinoma; FA – fibroadenoma; NR – not reported; M – malignant.

5.6. Concordance of tumour size on imaging and surgical excision

Tumour size measured on both imaging and surgical excision pathology was reported in 265 of the 266 IBC cases included in the study. A significant moderate correlation, with a Pearson's correlation coefficient of 0.475 ($p = <0.001$), was measured between imaging and surgical excision tumour size (Figure 5.7). As demonstrated in Figure 5.8, concordance between tumour size on imaging and surgical excision pathology was identified in 22 (8%) cases. Minor discordances (size discrepancies of ±5mm) were noted in 147 (56%) cases, of which 38 were overestimated and 109 were underestimated in size on imaging. Ninety-six (36%) cases displayed major discordances (size discrepancies of >5mm), resulting in overestimation and underestimation of size on imaging in 20 and 76 cases, respectively. A significantly higher rate of concordance, 12% (18) of tumours ≤2 cm vs. 3% (4) tumours > 2 cm, was observed for tumours with a final pathologic tumour size of ≤2 cm compared to those >2 cm, $p = 0.007$ (Figure 5.9). Histologic type ($p = 0.266$) and grade ($p = 0.281$) had no significant effect on the likelihood of concordance between tumour size measured on imaging and pathology (Table 5.6).

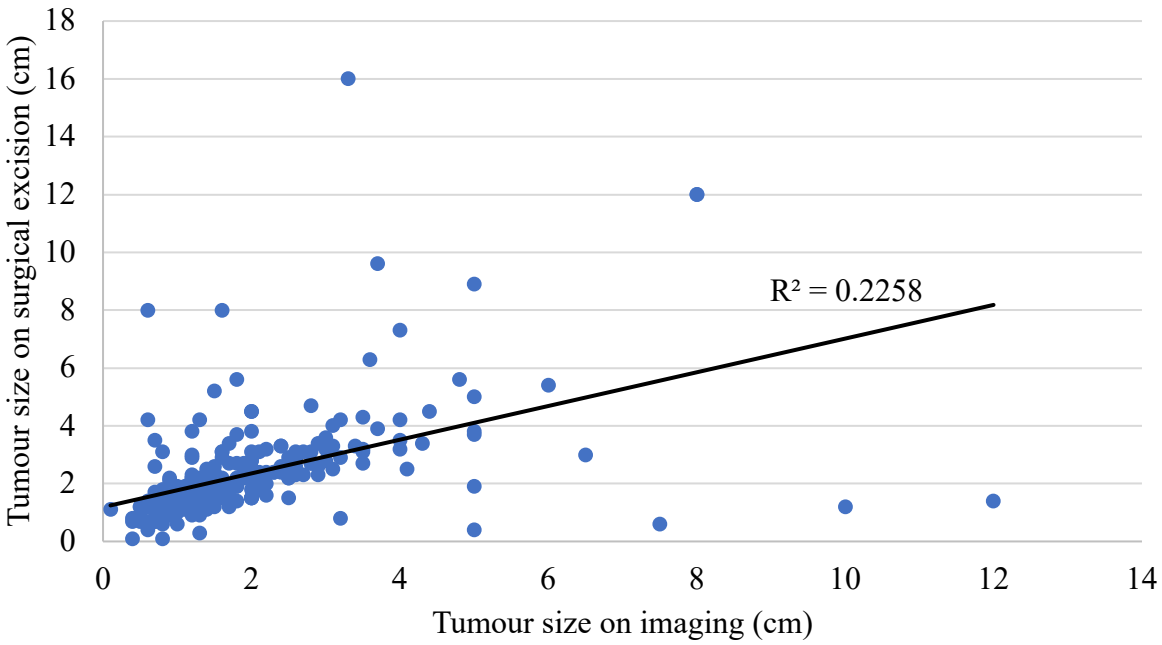

Figure 5.7. Correlation of tumour size on imaging and surgical excision, n = 265, p-value = <0.001 .

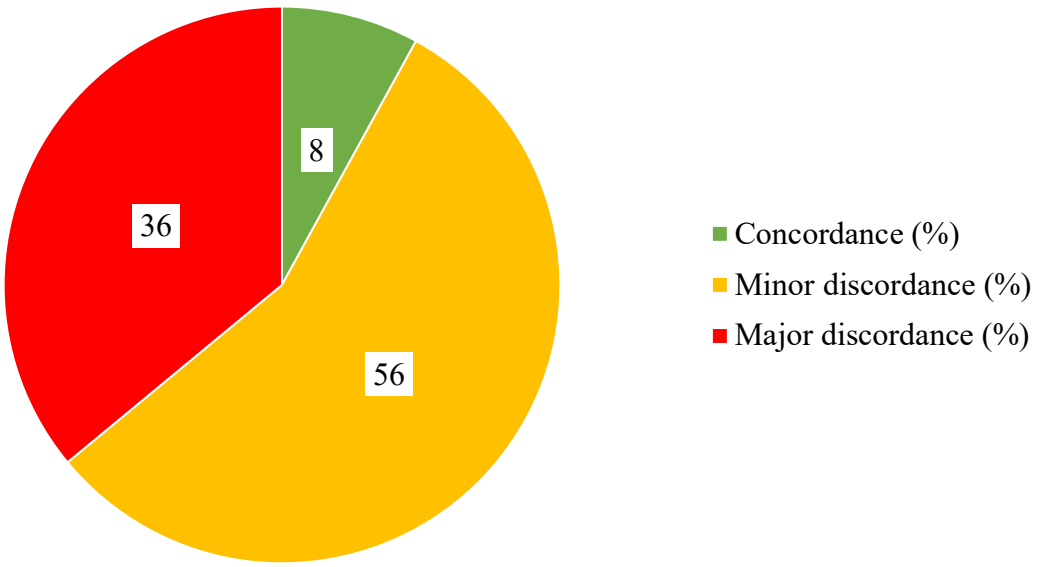

Figure 5.8. Degree of concordance of tumour size on imaging and surgical excision, n = 265.

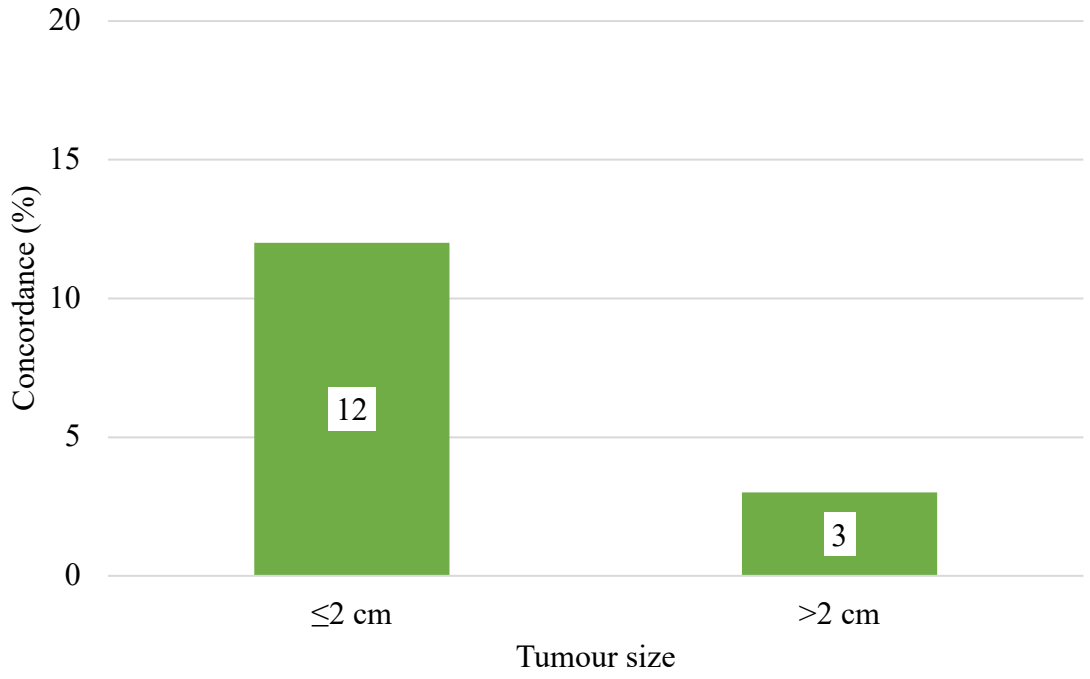

Figure 5.9. Effect of tumour size on concordance of tumour size on imaging and surgical excision, n = 265, p-value = 0.007.

Table 5.6. Factors that did not significantly affect concordance of tumour size on imaging and surgical excision, n = 265.

Factor	**p-value**
Histologic grade (1, 2 or 3)	0.281
Histologic type (IDC or other carcinomas)	0.266

5.7. Concordance of primary tumour (T) stage on imaging and surgical excision

Primary tumour (T) stages were assigned from imaging and surgical excision pathology in 265 of the 266 IBC cases examined. Of those assigned, primary tumour (T) stages included those ranging from categories T1mi to T3. As illustrated in Figure 5.10, the primary tumour (T) stage on imaging and pathology were significantly correlated (p = 0.001). Primary tumour (T)

stage on imaging was concordant with the corresponding surgical excision in 21 (36%) T1b tumours, 67 (54%) T1c tumours, 50 (76%) T2 tumours, and 2 (22%) T3 tumours. Discordant primary tumour (T) stage was identified in 1 (100%) T1mi tumour, 8 (100%) T1a tumours, 37 (64%) T1b tumours, 56 (46%) T1c tumours, 16 (26%) T2 tumours, and 7 (78%) T3 tumours. Overall, primary tumour (T) stage was concordant in 140 (53%) and discordant in 125 (47%) of cases (Figure 5.11). Discordance resulted in upstaging of 101 (81%) tumours and downstaging of 23 (19%) tumours on final surgical excision (Figure 5.12).

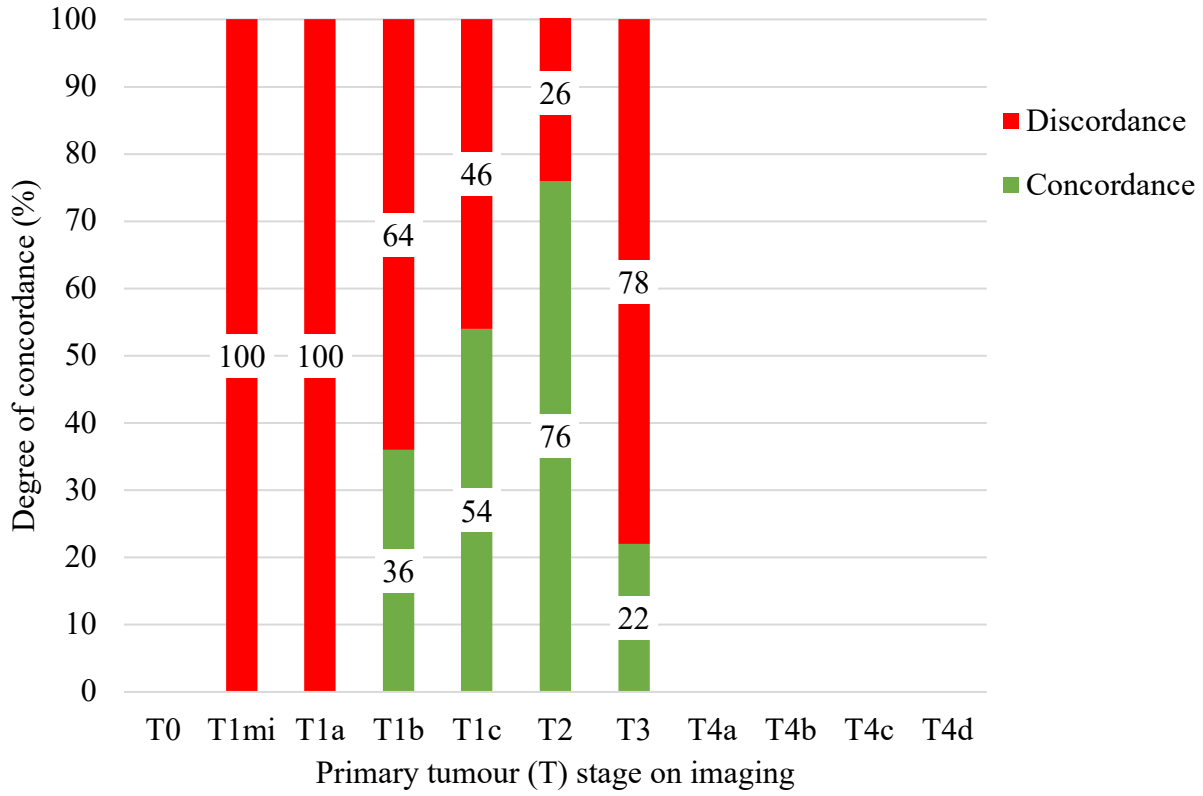

Figure 5.10. Correlation of primary tumour (T) stage on imaging and surgical excision, n = 265, p-value = <0.001.

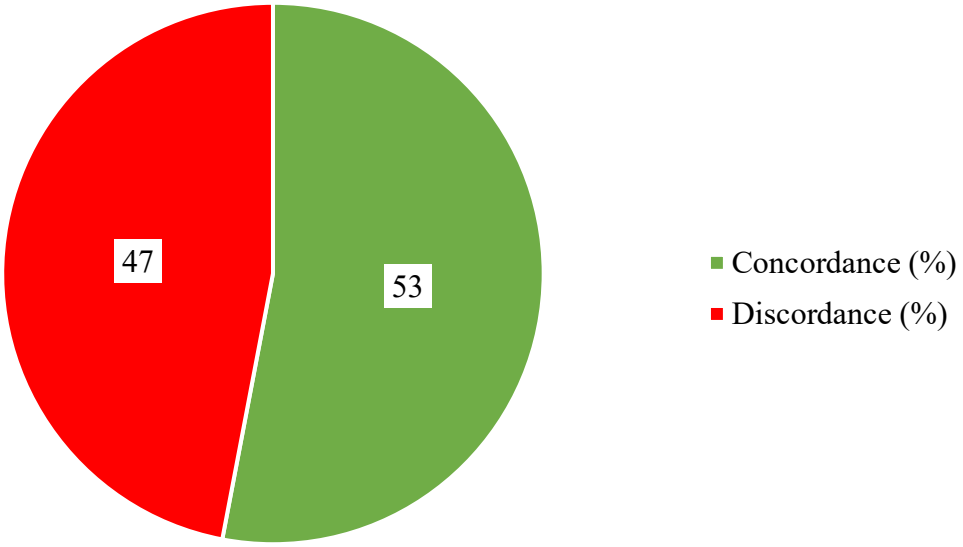

Figure 5.11. Degree of concordance of primary tumour (T) stage on imaging and surgical excision, n = 265.

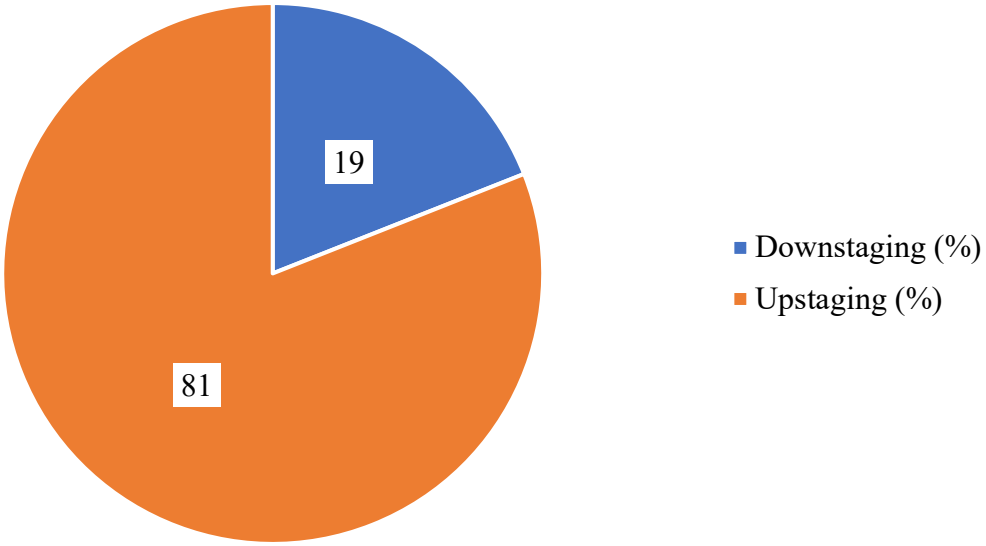

Figure 5.12. Type of alteration in primary tumour (T) stage reported on pathologic review of surgical excision compared to imaging in cases with discordance, n = 124.

As significantly higher proportion of IDC tumours, 58% (122 cases), displayed concordance between imaging and pathology primary tumour (T) stage compared to other histologic types, 34% (18 cases) (p = 0.003) (Figure 5.13). Additionally, the concordance rate was found to be significantly higher, 59% (87) of tumours ≤2 cm vs 45% (53) tumours >2 cm, for tumours with a final pathologic size of ≤2 cm as compared to those >2 cm (p = 0.014) (Figure 5.14). Final tumour histologic grade (p = 0.336) had no significant effect on the likelihood of concordance (Table 5.7).

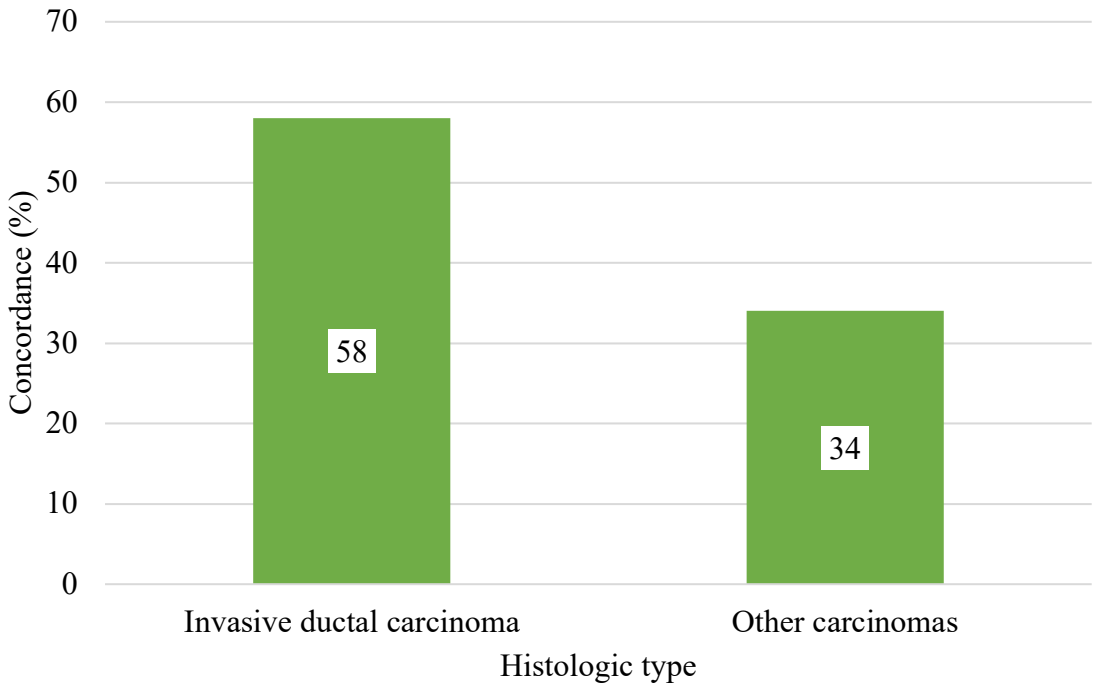

Figure 5.13. Effect of histologic type on concordance of primary tumour (T) stage on imaging and surgical excision, n = 265, p-value = 0.003.

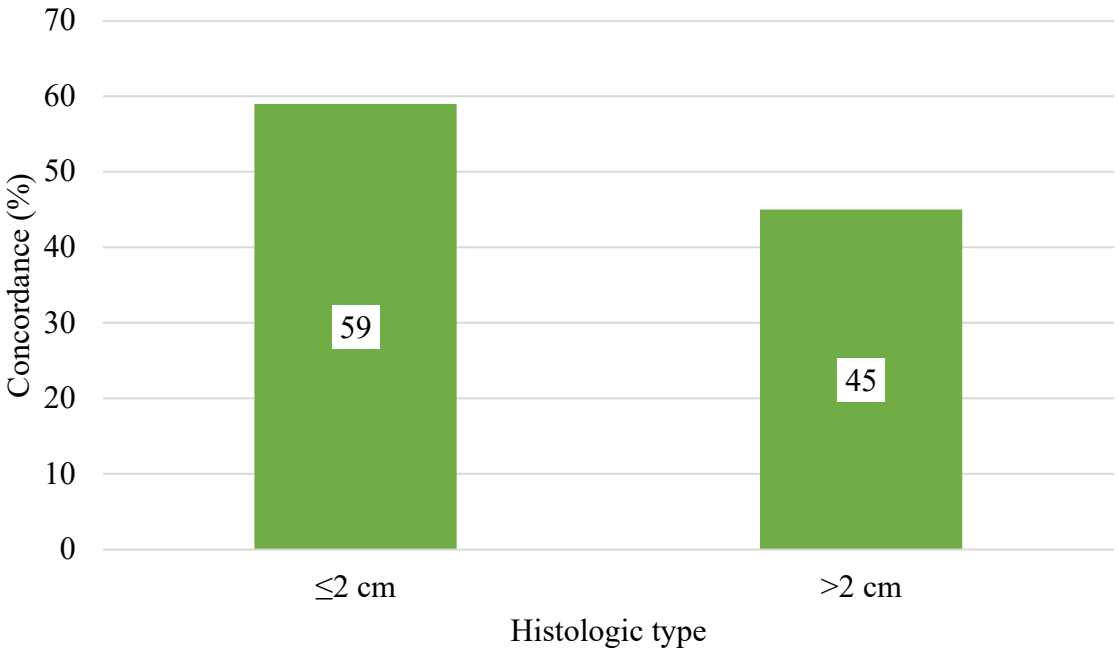

Figure 5.14. Effect of tumour size on concordance of primary tumour (T) stage on imaging and surgical excision, n = 265, p-value = 0.014.

Table 5.7. Factors that did not significantly affect concordance of primary tumour (T) stage on imaging and surgical excision, n = 265.

Factor	**p-value**
Histologic grade (1, 2 or 3)	0.336

5.8. Concordance of presence of lymph node metastases on imaging and surgical excision

Axillary adenopathy identified on imaging was significantly associated with the detection of lymph node metastases on surgical excision pathology (p = <0.001). Of the cases with axillary adenopathy identified on imaging, 20 (65%) had histologically confirmed lymph node metastases on surgical excision and 11 (35%) did not. In patients with no report of axillary adenopathy on imaging, lymph node metastases were not identified in 178 (76%) cases but were detected in 57

(24%) cases on pathology (Figure 5.15). Figure 5.16 outlines the degree of concordance measured upon comparison of axillary adenopathy detected on imaging and lymph node status identified on surgical excision pathology. Of the 266 IBC cases reviewed, concordance was noted in 198 (74%). Discordance was present in 68 (26%) cases. Concordance was determined to be significantly higher, 80% (119) of tumours ≤2 cm vs 67% (79) of tumours >2 cm, for tumours with a final pathologic size of ≤2 cm compared to those >2 cm (p = 0.009) (Figure 5.17). Tumour histologic type (p = 0.500) and histologic grade (p = 0.143) had no significant effect on the likelihood of concordance (Table 5.8). Overall, axillary adenopathy on imaging as a predictor of axillary lymph node metastases on pathology was calculated to have a TPR of 26%, TNR of 94%, FPR of 6%, FNR of 74%, PPV of 65% and NPV of 76%.

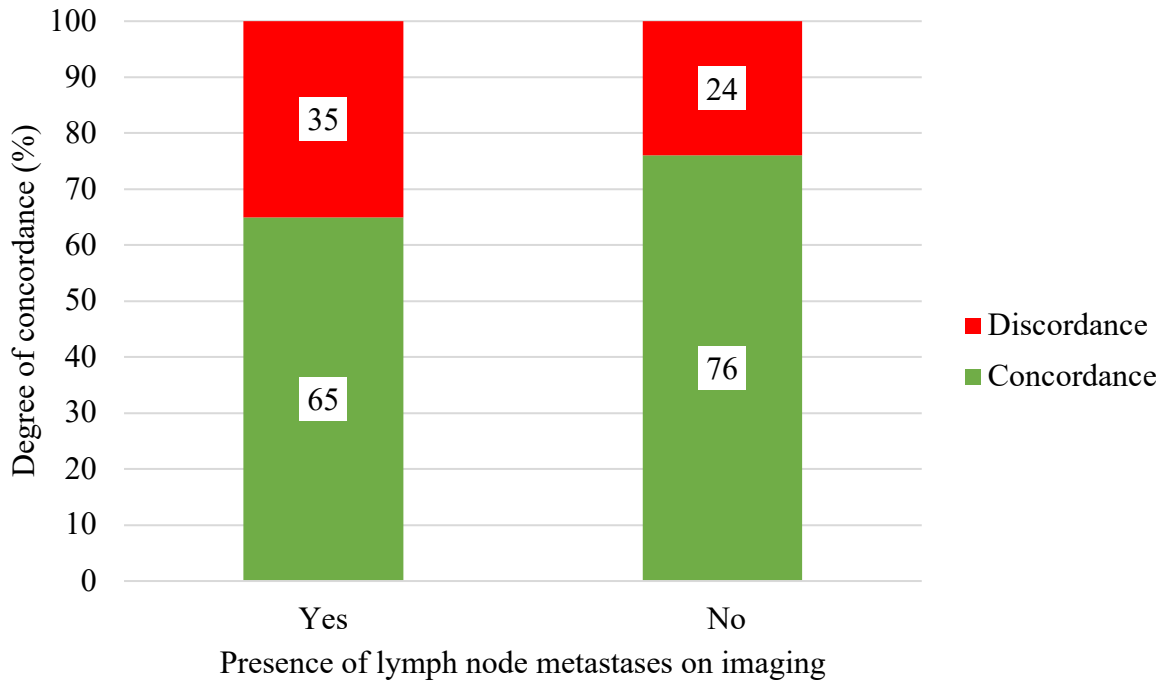

Figure 5.15. Correlation of axillary adenopathy on imaging and presence of lymph node metastases on surgical excision, n = 266, p-value = <0.001.

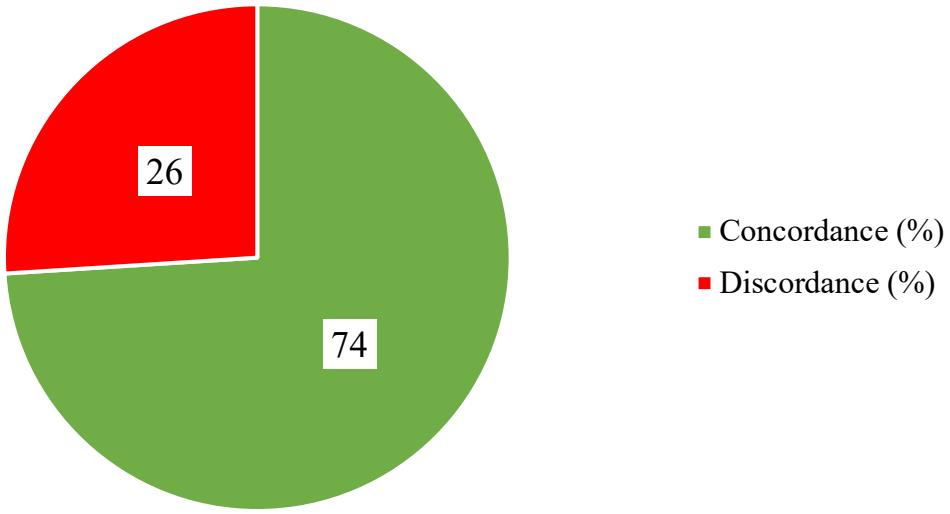

Figure 5.16. Concordance of axillary adenopathy on imaging and presence of lymph node metastases on surgical excision, n = 266.

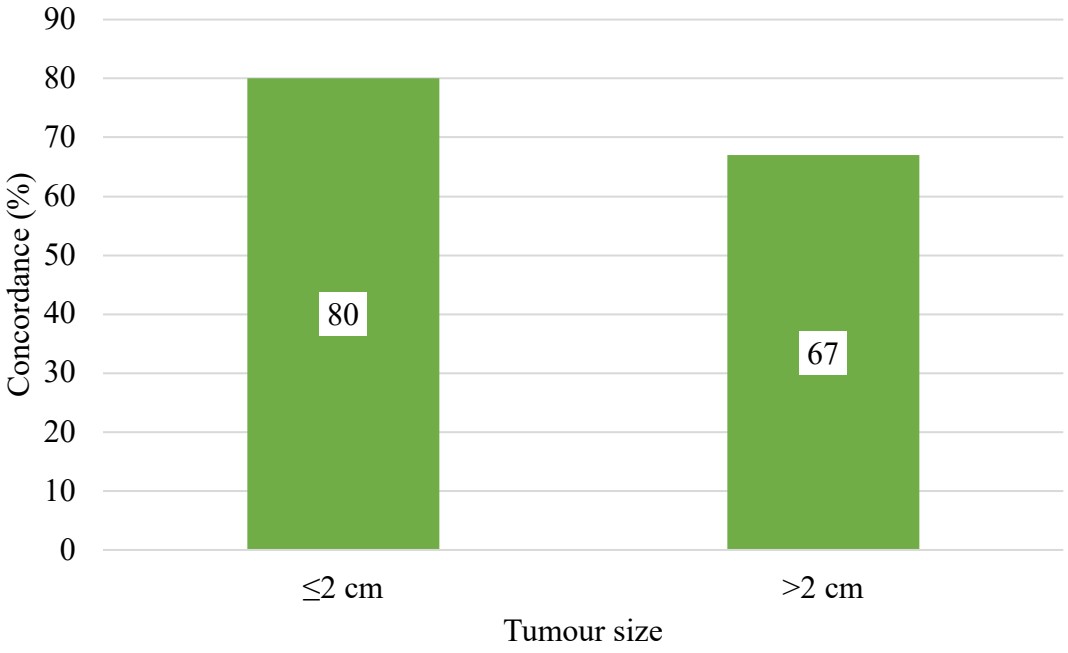

Figure 5.17. Effect of tumour size on concordance of axillary adenopathy on imaging and presence of lymph node metastases on surgical excision, n = 266, p-value = 0.009.

Table 5.8. Factors that did not significantly affect concordance of axillary adenopathy on imaging and presence of lymph node metastases on surgical excision, n = 266.

Factor	p-value
Histologic type (IDC or other carcinomas)	0.500
Histologic grade (1, 2 or 3)	0.143

5.9. Concordance of histologic grade on CNB and surgical excision

Tumour histologic grade was reported upon pathologic assessment of both CNB and surgical excision in 237 of the IBC cases included in the study. IBC histologic grading on CNB was deferred to surgical excision in 29 cases. A significant correlation was identified between tumour grade determined on CNB and the corresponding surgical excision (p = <0.001) (Figure 5.18). Concordance of CNB and surgical excision histologic grade was observed in 27 (29%) grade 1 tumours, 98 (65%) grade 2 tumours, and 40 (83%) grade 3 tumours. Discordance was noted in 11 (29%) grade 1 tumours, 53 (35%) grade 2 tumours, and 8 (17%) grade 3 tumours. In total, CNB and surgical excision tumour grade were concordant in 165 (62%) and discordant in 101 (28%) IBC cases (Figure 5.19). Discordance resulted in the downgrading of 31 (43%) and upgrading of 41 (57%) tumours (Figure 5.20). The rate of concordance was significantly higher for grade 2 tumours, 84% (98), compared to grade 1 and 3 tumours, 53% (27) and 57% (40) respectively (p = <0.001) (Figure 5.21). Histologic type (p = 0.855) and tumour size (p = 0.249) had no significant effect on concordance (Table 5.9).

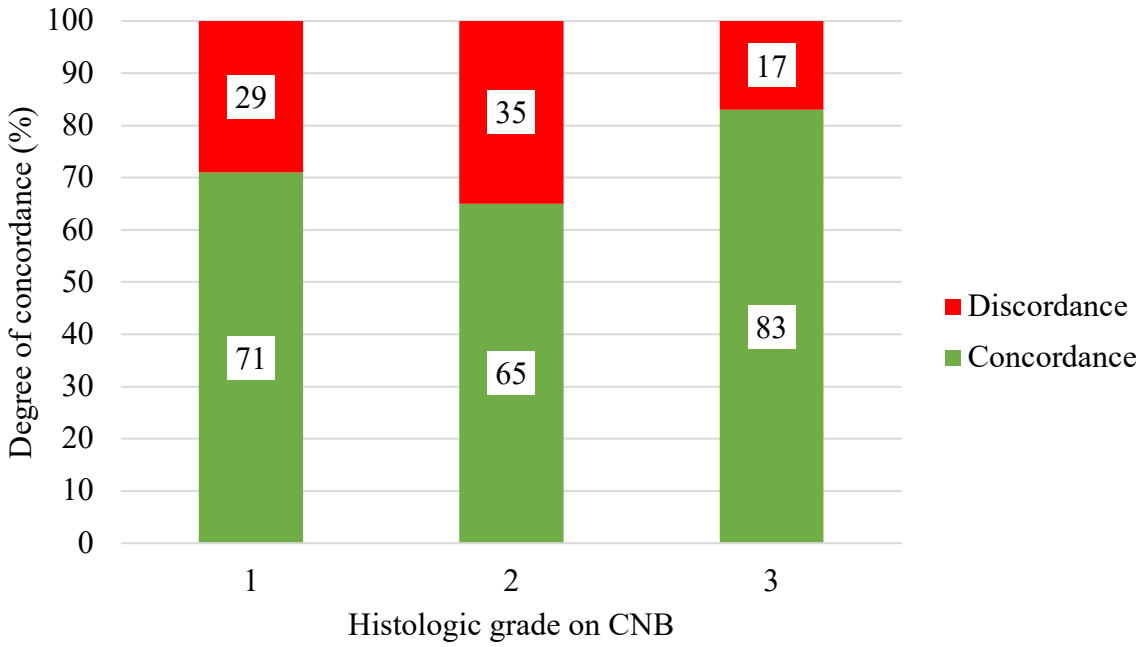

Figure 5.18. Correlation of histologic grade on CNB and subsequent surgical excision, n = 237, p-value = <0.001.

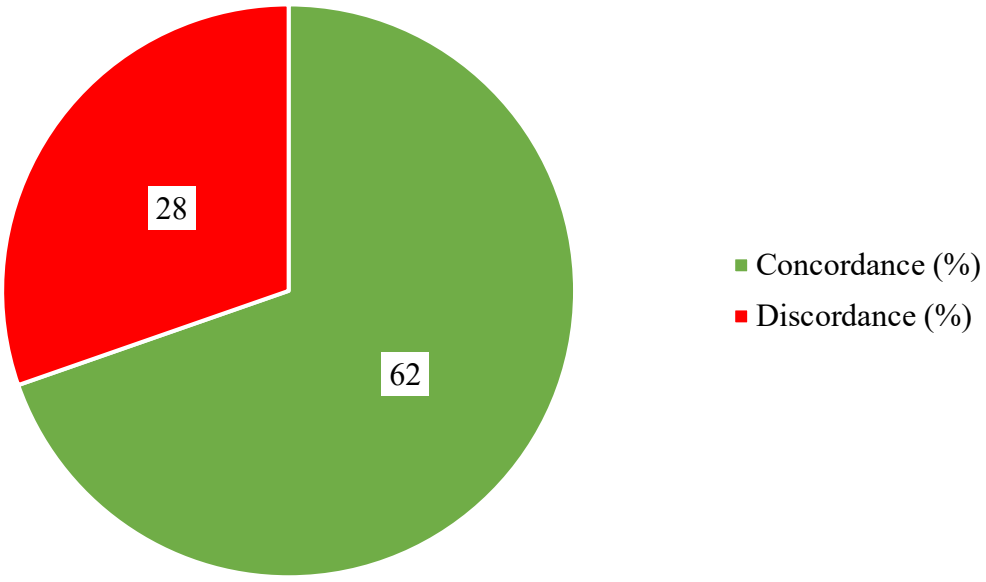

Figure 5.19. Concordance of histologic grade on CNB and subsequent surgical excision, n = 266, p-value = <0.001

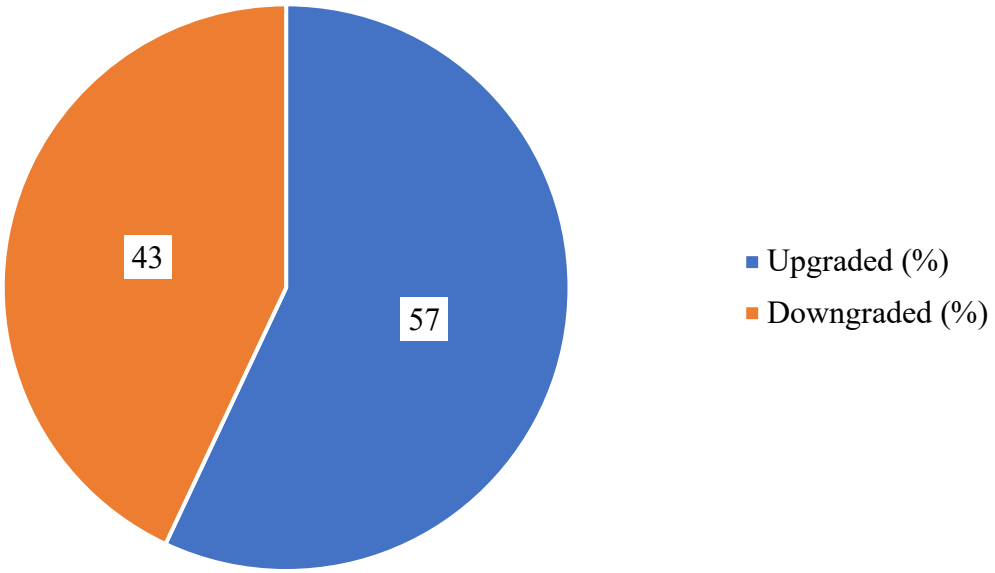

Figure 5.20. Type of alteration in histologic grade reported on pathological review of surgical excision compared to CNB in cases with discordance, n = 72.

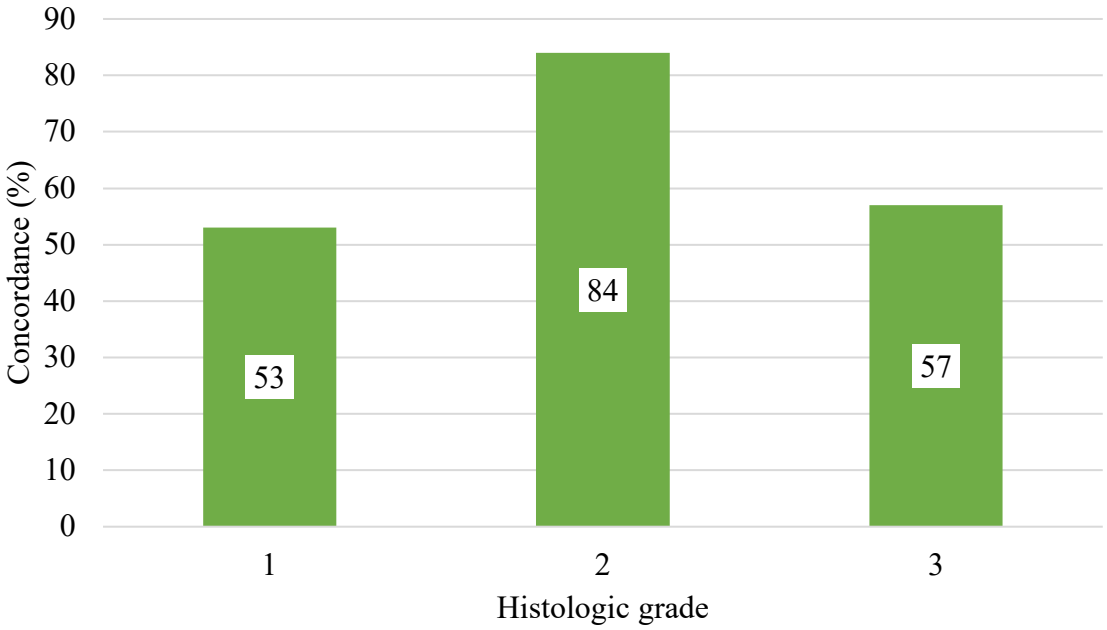

Figure 5.21. Effect of histologic grade on concordance of histologic grade reported on core biopsy and subsequent surgical excision, n = 237, p-value = <0.001.
Table 5.9. Factors that did not significantly affect concordance of histologic grade on CNB and surgical excision, n= 237.

Factor	p-value
Tumour size (≤2cm or >2cm)	0.249
Histologic type (IDC or other carcinomas)	0.855

5.10. Concordance of histologic type on CNB and surgical excision

Our data analysis revealed that CNB accurately predicted the presence of malignancy on surgical excision in 99.6% (265) of the 266 IBC cases included in the study cohort. Benign tissue was identified on CNB in one patient revealed to have an IDC tumour on evaluation of the subsequent surgical excision. Notably, suspicion of an inadequate sample had been reported following the US-guided CNB procedure in this particular case. Therefore, the missed IDC case is likely the result of a CNB sampling error.

As shown in Figure 5.22, tumour histologic type reported on CNB and surgical excision were found to be significantly correlated (p = <0.001). Histologic type identified on CNB was concordant with the corresponding surgical excision in 185 (88%) IDC tumours, 11 (39%) ILC tumours, 1 (11%) mixed IDC/ILC tumour, 9 (90%) MC tumours, 2 (67%) IMPC tumours, 1 (50%) MCB tumour, 0 (0%) IMC tumours, and 1 (50%) SCC tumour. Discordant CNB and surgical excision histologic type were noted in cases with the following final diagnoses: 26 (12%) IDC cases, 28 (61%) ILC cases, 10 (89%) mixed IDC/ILC cases, 1 (10%) MC case, 1 (33%) IMPC cases, 1 (50%) MCB case, 1 (100%) IMC case, and 1 (50%) SCC case. Overall, histologic type reported from CNB and surgical excision were concordant in 210 (79%) and discordant in 56 (21%) patients (Figure 5.23). Concordance was significantly higher for IDC tumours, 80% (185 case), in comparison other histologic types, 78% (25 cases) (p = <0.001). Concordance was not found to be significantly influenced by final pathologic tumour size (p = 0.763) or histologic grade (p = 0.227) (Table 5.10).

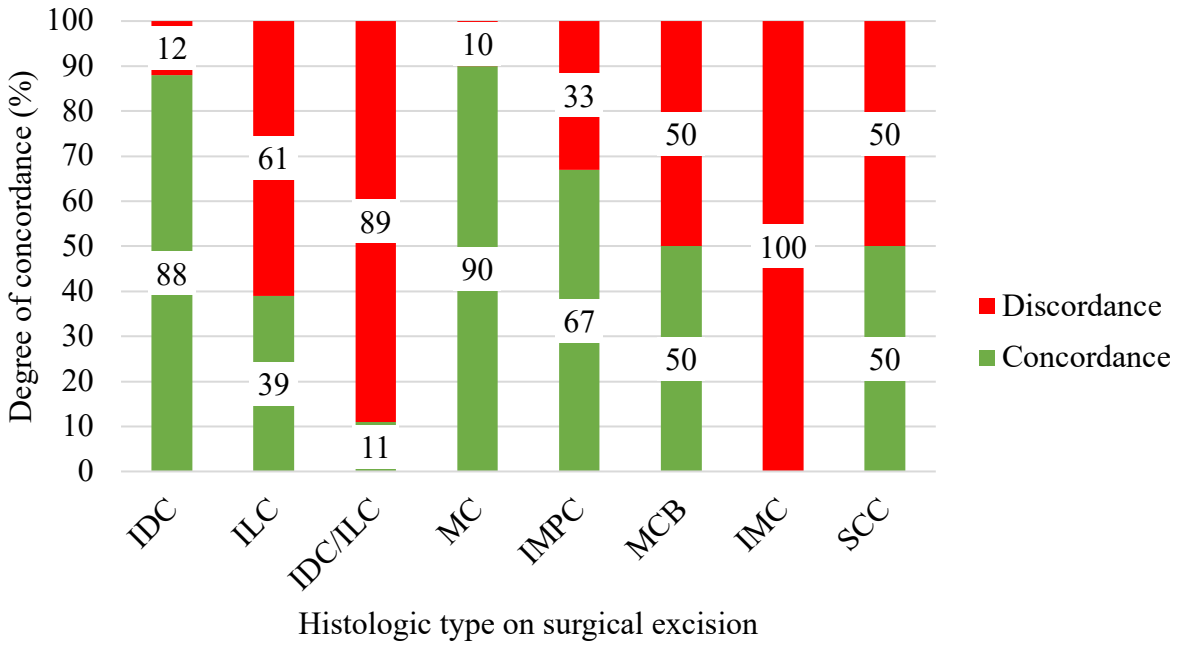

Figure 5.22. Correlation of histologic type on CNB and subsequent surgical excision, n = 266, p-value = <0.001.

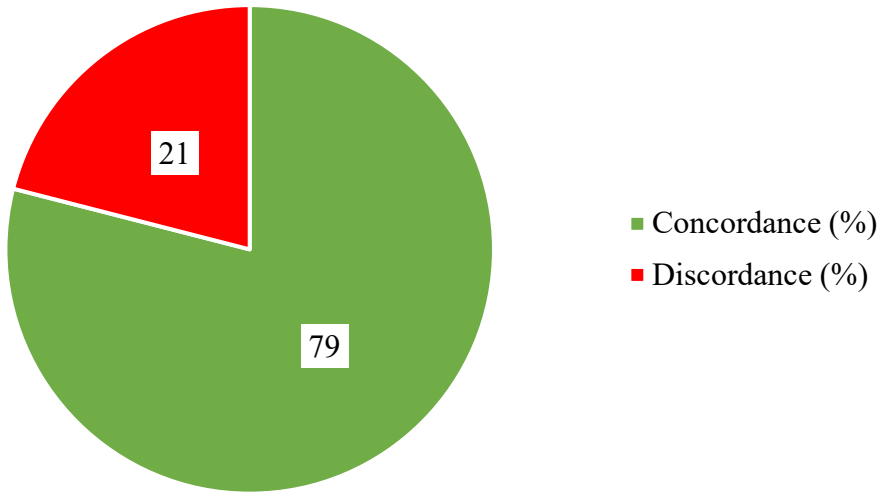

Figure 5.23. Concordance of histologic type on CNB and subsequent surgical excision, n = 266.

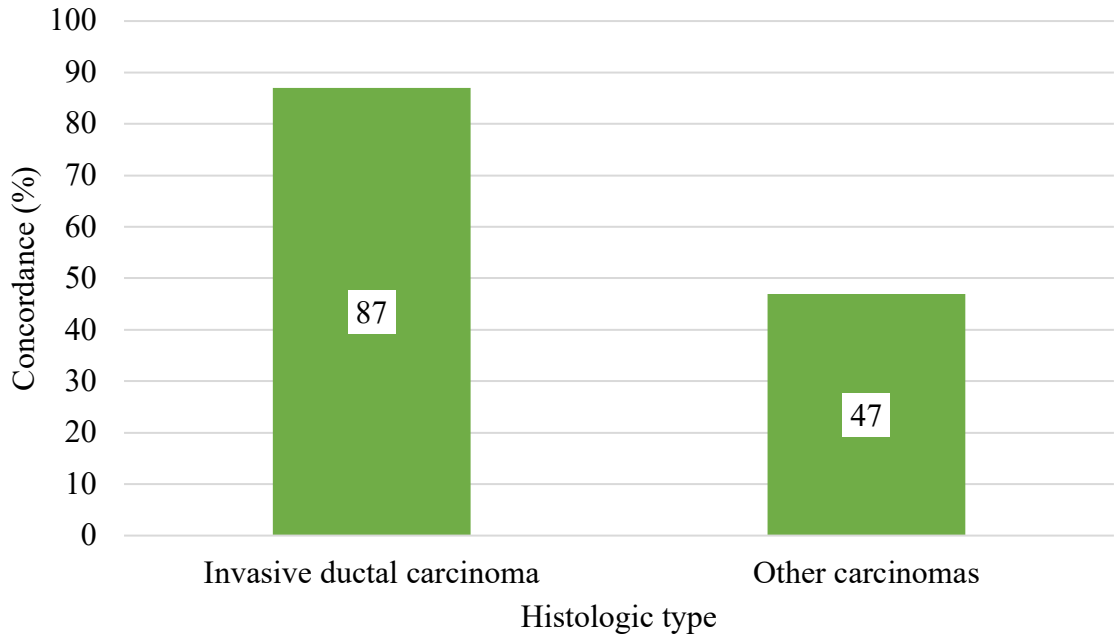

Figure 5.24. Effect of histologic type on concordance of histologic type reported on CNB and subsequent surgical excision, n = 266, p-value = <0.001.

Table 5.10. Factors that did not significantly affect concordance of histologic type on CNB and surgical excision, n= 266.

Factor	**p-value**
Tumour size (≤2cm or >2cm)	0.763
Histologic grade (1, 2 or 3)	0.227

CHAPTER 6. DISCUSSION

6.1. Diagnostic accuracy of breast imaging

Screening programs allow for the early detection and conservative treatment of breast carcinoma, thereby improving patient prognosis.[5,9,10] However, breast screening can also lead to false-positive screening results, patient overdiagnosis and the performance of unnecessary procedures and treatment.[11,39] As a result, accurate and reliable breast screening using diagnostic

imaging is essential.[11] Moreover, histologic features identified on subsequent breast tumour pathology should provide a reasonable explanation for the features reported on imaging.[21] Concordance of imaging and pathology findings indicates an extremely low risk of undetected or underdiagnosed breast carcinoma.[2] Conversely, discordance between imaging and pathology findings would indicate the need for repeat evaluation.[2] There is considerable variation in the accuracy and reliability of breast screening published in the literature.[25,27] Breast imaging has previously been found to have a sensitivity (TPR) of 97.6% to 98.4%, FPR of 20.0% to 50.0%, FNR of 0.3% to 15.0%, PPV of 93.3% and NPV of 98.4%.[55,60, 73] The CPAC recommends screening programs aim for a PPV of ≥5%.[13] Similar findings were identified in the results of this current study. Diagnostic imaging suspicion as a predictor of malignancy on CNB was observed to have a PPV of 100%, TPR of 86%, TNR of 100%, FNR of 15%, and FPR of 0%. Comparatively, a TPR of 85%, FNR of 15%, and PPV of 100% were measured for suspicion indicated on imaging as a predictor of malignancy on final surgical excision. Previous studies have reported imaging and pathology discordance in anywhere from 0.3% to 24.0% of cases evaluated.[6,30,55] Similarly, in our study CNB and surgical excision pathology were discordant with suspicion on imaging in 14% (38) and 15% (39) of cases, respectively. Suspicion on imaging was concordant with CNB pathology in 86% (227) cases and surgical excision in 85% (227) of cases. Likelihood of concordance was not found to be significantly affected by any of the following tumour features: final pathologic size ($p = 0.163$), histologic type ($p = 0.556$) or histologic grade ($p = 0.056$). To the best of our knowledge, the effect of these variables on imaging suspicion and tumour pathology concordance have not previously been examined.

Discordance between imaging and pathology findings may be attributed to several factors. Firstly, the nature of interval imaging can result in increased inter-observer variability

due to its production of a unique series of images that allow the clinician to view different features with more or less certainty.[16] Secondly, reliable imaging interpretation can be complicated by differences in technical parameters of the equipment, clinician experience and training, and patient characteristics such as patient age, breast size, tissue density and lesion location.[14,16] Due to the high susceptibility of imaging interpretation to inter- and intra-observer variability, biopsy of all solid masses even in the absence of suspicious features is often recommended.[16]

Most of the discordances (35 cases) between imaging suspicion and pathology identified in the study were minor and resulted from the reporting of intermediate suspicion on imaging followed by the identification of malignancy on histology. A small portion of discordances (3 case) were major and found to be due to the designation of low suspicion on imaging with malignant histology on subsequent pathology. However, in every case with discordance (39 cases) wherein BI-RADS scores were also provided (14 cases), the BI-RADS categories assigned indicated imaging features suspicious of malignancy (BI-RADS 4A, 4B, 4C and 5) and were concordant with the final pathologic diagnosis. In most cases with discordance, additional comments provided “query carcinoma/malignancy” as a presumptive diagnosis (12 cases) or described suspicious imaging features (6 cases), including indeterminate mass or poorly defined margins. Additionally, several discordant cases (8 cases) provided suspected differential diagnoses of carcinoma/malignancy versus benign lesions such as fibroadenoma, papilloma or complex cysts. However, several cases (3 cases) were noted to have “query fibroadenoma”, a benign breast lesion, as the only presumptive diagnosis provided in additional comments on imaging. The observation of benign histology on CNB in association with intermediate suspicion on imaging in one discordant case is likely due to inaccurate tumour targeting as the sample was

reported to be inadequate following imaging. These findings suggest that even in the presence of discordance between the level of suspicion indicated on imaging and tumour pathology, the presence of suspicious imaging features and the possibility of malignancy were still clearly indicated with additional comments or BI-RADS scores in imaging reports for all but three of the cases in the study cohort. Overall, the results of this study suggest that imaging can detect breast carcinoma with reasonable accuracy and reliability.

BIRADS categorization was implemented to standardize diagnostic imaging interpretation to improve breast cancer screening.[28] However, even after its implementation, inter- and intra-observer variability in breast imaging interpretation remain.[6] For instance, researchers have observed a concordance rate of 99.7% between BI-RADS scores and pathology diagnoses.[6] Moreover, BI-RADS classification has been previously reported to have a TPR of 97.6, FNR of 0.3% to 0.8%, PPV of 90.9% and NPV of 99.7%.[6,55] The results of this study revealed a marginally higher concordance rate of 100% (101 cases) and found no significant discordance between BI-RADS score and tumour pathology of IBC patients. BI-RADS score as a predictor of malignant histology on both CNB and surgical excision was calculated to have a TPR of 100%, FNR of 0%, and PPV of 100%. Even though our data suggests that BI-RADS has been applied with high accuracy in Manitoba, it should be noted that BI-RADS scores were only reported in 101 of the 266 cases examined. The high level of concordance observed in this study may be the result of BI-RADS scores being more frequently reported for breast lesions with obviously malignant features but omitted for lesions with ambiguous features that cannot be easily categorized.

6.2. Staging accuracy of breast imaging

Patient treatment and surgical management are highly dependent on tumour size and stage.[14,15,67,68] Therefore, accurate measurement and staging of breast tumours on imaging can significantly impact patient care. Variable imaging and pathologic tumour size concordance rates, ranging from 40% to 77% have been recorded in the literature.[68,77] Additionally, discordance rates have been reported to range from 39% to 71%.[68,77] This is likely the result of differences in the definition of size concordance in each study. For example, several studies permitted size differences within ±2 mm and ±5 mm to be considered as concordant.[68,77] In the present study, imaging and pathology tumour size was exactly concordant in only 8% and discordant in 92% of IBC cases examined. Markedly, discrepancies in size were minor (≤5 mm) in 56% and major (>5 mm) in 36% of cases. Discordance was deemed to have resulted from overestimating and underestimating tumour size on imaging in 22% and 70% of cases, respectively. Conversely, tumour stage determined on imaging and pathology were found to be significantly correlated ($p = 0.001$), have a higher concordance rate (53%) and lower discordance rate (47%). Final pathologic assessment resulted in the upstaging of 81% and downstaging of 19% of tumours with discordance. In comparison, Hamza et al.[68] identified discordance of tumour size ≤2 mm and ≤5 mm in 40.4% and 66.5% of IBC cases included in their retrospective review. Exact concordance of tumour size on imaging and pathology was only noted in 9.6% of cases examined.[68] Discordance rates between imaging and pathologic tumour stage were found to be marginally lower at 40.1%, of which 14.5% overestimated and 25.6% underestimated tumour stage.[68] Golshan et al.[67] found size discrepancies within 1 mm in 24.0% to 27.0% of patients, 1.1-1.5mm in 45.0% to 48.0% of patients, 5.1-10 mm in 14.0% to 14.0% of patients, 10.1-20 mm in 6.0% to 9.0% of patients, and >20 mm in 5.0% to 6.0% of patients.[67] Several studies examining

concordance of imaging and pathology tumour measurement have recorded significant correlations with a variable degree of strength and Pearson's R coefficients ranging from 0.480 to 0.920.[67,68,78,79,80,81] A moderate significant correlation, with a Pearson's R coefficient of 0.475 ($p = <0.001$), was observed in the present study.

Several studies have reported that larger tumour size is associated with decreased concordance between the tumour size measured on imaging and pathology.[12,14,68,82] More specifically, Hamza et al.[68] observed significantly higher concordance in tumour measurements when their final pathologic size was ≤2 cm (51.1%) than cases with a final pathologic size >2 cm (19.7%).[68] Tumour size measured on imaging has also been noted to be significantly more likely to correlate with pathology in T1 tumours compared to higher stage tumours.[67] In the current study, a significantly higher rate of tumour size concordance was observed in those with a final pathologic size of ≤2 cm (12% of tumours ≤2 cm vs 3% of tumours >2 cm, $p = 0.007$). Similarly, imaging and pathologic tumour stage concordance was found to be significantly higher in tumours with a final pathologic size of ≤2 cm (≤2 cm tumours: 59% vs>2 cm tumours: 45%, $p = 0.014$). Generally, smaller tumours are more circumscribed than those of larger caliber, contributing to a higher degree of concordance in tumours ≤2 cm.[68] Unfortunately, tumour size concordance is more critical for larger tumours as size determined on imaging is more relevant to the pathologist in cases with larger breast tumours.[5,68] Even though microscopic measurement is frequently used to determine tumour size, pathologists are more often reliant on imaging measurement in cases where tumours are too large to be accurately sized on microscopy.[68]

Others have postulated that diffuse tumour infiltration patterns, associated architectural distortion and carcinoma in situ contribute to the higher degree of measurement discordance in larger tumours.[14,15,17,67,68] This hypothesis is supported by the significantly greater likelihood of

tumour size underestimation upon imaging of special type IBCs, which are more often associated with diffuse infiltration patterns, recorded in several other studies.[14,15,17,67,82] Conversely, other research did not find any significant effect of histologic type on the likelihood of imaging and pathologic size concordance.[14] Moreover, this study was unable to reveal any significant effect of histologic type ($p = 0.281$) or grade ($p = 0.266$) on the probability of tumour size concordance. However, our study findings did reveal a significantly higher level of imaging and pathology tumour stage agreement in tumours with IDC histologic type on final pathologic assessment (IDC tumours: 58% vs other carcinomas: 34%, $p = 0.003$). We also evaluated the effect of final tumour grade on the likelihood of tumour stage concordance but did not identify any significant difference ($p = 0.336$).

Discordances in tumour size and stage may also arise from individual differences in imaging interpretation, such as whether the practitioner includes the hyperechoic margin of the tumour in their measurement.[14,83,84] The presence of several features on US, including acoustic attenuation, blurred margins and infiltrative vasculature, can also contribute to inaccuracies in tumour size determined on imaging.[14,68] Similarly, greater breast tissue density has been linked to a higher degree of discordance between tumour measurement on imaging and pathology.[14] Another study found evidence to suggest that greater delay between the date of diagnostic imaging and subsequent surgical procedure significantly increases the likelihood of discordance between tumour size on imaging and pathology. Hamza et al.[68] postulated that this is likely due to progressive changes in tumour size, which become noticeable when there are delays between the two assessment modalities.[68] As we did not examine these variables, some of the observed discordances in our study may be attributed to these factors. MRI has sometimes been reported to more accurately reveal tumour size compared to other imaging techniques. However, modalities

such as US and mammography are more widely accessible.[15,85,86,87,88] Alternatively, the use of multiple modalities has been shown to reduce the number of incorrectly staged tumours on diagnostic imaging and is therefore recommended whenever feasible.[67]

Treatment planning is also significantly impacted by IBC patient lymph node status.[34] Pre-operative lymph node assessment and staging is often achieved using diagnostic imaging modalities, including US, CT and MRI.[24,34] Although the identification of axillary adenopathy on imaging was found to be significantly correlated with the presence of axillary lymph node metastases on pathology in this study ($p = <0.001$), lymph node status determined from these evaluations was recorded to be concordant in only 74% of cases. Diagnostic imaging as a screening tool for axillary lymph node involvement was calculated to have a TPR of 26%, TNR of 94%, FPR of 6%, FNR of 6%, PPV of 65% and NPV of 76%. Conversely, tumour histologic type ($p = 0.500$) and grade ($p = 0.143$) were not found to impact the likelihood of concordance significantly. Several studies have compared diagnostic imaging and pathologic assessment of axillary lymph node disease in IBC patients.[34,36,69,74] Moreover, the reported accuracy of imaging detection of lymph node metastases varies widely. Kijima et al.[34] found that imaging could accurately predict the presence of lymph node metastases in 75% of IBC cases included in their retrospective study. Similarly, other researchers have identified a sensitivity (TPR) of 50.0% to 61.3%, TNR of 21.5% to 75.0%, FNR of 25.0% to 78.5% and FPR of 38.7% to 50.0% for pre-operative imaging in the evaluation of axillary lymph node disease.[69,74] In a literature review performed by Alvarez et al.[36] ultrasonography has been previously observed to have a sensitivity (TPR) ranging from 66.1% to 72.7% and specificity (TNR) of 44.1% to 97.9% for axillary lymph node metastases.

This current study also noted that a significantly higher proportion of tumours with a final pathologic size of ≤2 cm displayed concordance between lymph nodes status reported from imaging and pathology, compared to those >2 cm (tumours ≤2 cm: 80% vs tumours >2 cm: 67%, p = 0.009). Conversely, tumour histologic type (p = 0.500) and grade (p = 0.143) were not found to significantly impact the likelihood of concordance. Few studies have examined the relationship of tumour features on the likelihood of concordance between imaging and pathologic assessment of lymph node status.[37] Mainiero et al.[37] assessed the effect of tumour size on US axillary lymph node assessment sensitivity. Higher sensitivity was associated with increasing primary tumour size.[37] Variability in the criteria employed to classify abnormal axillary lymph nodes may contribute to the wide range of sensitivity and accuracy of lymph node metastases detection on imaging.[69] Notably, multiple studies have determined that diagnostic imaging has a higher sensitivity for lymph node metastases when morphologic criteria, including cortical thickening, transverse node diameter and absence of hilum, are used to distinguish suspicious lymph nodes.[35,36,37] Therefore, the implementation of the aforementioned morphologic criteria is suggested as it may improve imaging accuracy in the assessment of IBC patients for lymph node involvement.[36]

In summary, the reasonably high FNR observed in this study and reported in others highlights that pre-operative axillary assessment still requires improvement to better detect node-positive IBC patients.[69] In general, imaging is not recommended to be employed as the sole method to determine lymph node status pre-operatively.[36] US-guided lymph node biopsy can be performed on sonographically suspicious lymph nodes to provide additional confirmation of node-positive disease as it has been observed to increase specificity up to 100%.[36,69]

Additionally, SLNB is still recommended as the gold standard to assess the need for axillary dissection due to the prevalence of false-negative results on imaging.[36]

6.3. Diagnostic and grading accuracy of breast CNB

The chief aim of CNB is to provide a sample of breast lesion tissue for histologic diagnosis pre-operatively.[18,45,46,47,50,55] According to the literature, histologic diagnosis obtained from CNB and excision have a high degree of concordance.[21,44,54] For instance, breast CNB has been recorded to have a sensitivity for malignancy ranging from 71.0% to 100.0%.[42,46,53,75] In contrast, other studies have reported malignancy underestimation rates on CNB that range from 0.1% to 100%.[21,24,43,56,75,89] By comparison, CNB was found to accurately detect malignancy on surgical excision in 99.6% of IBC patients in this study. Benign histology was noted on CNB in one patient that was later diagnosed with IDC on surgical excision. Importantly, suspicion of inadequate sampling was identified during the US-guided CNB procedure performed on the patient. Therefore, the missed IDC case is likely the result of CNB sampling error.

CNB can not only be used to identify malignancy but also to assess additional prognostic features of IBC such as histologic type and grade.[2,24,45,46,47,50,52,53,54,56] This prognostic information can be used to guide surgical and neoadjuvant therapy planning.[24,54] Therefore, inaccuracies in the assessment of carcinoma histologic type and grade can significantly impact patient care. For example, failure to identify aggressive high grade tumours with poor prognoses or histologic types associated with diffuse infiltrative patterns, such as ILC, could prevent IBC patients from being appropriately assessed as candidates for neoadjuvant therapy or more aggressive surgical interventions.[50]

Previous research suggests that CNB samples provide sufficient tissue to determine histologic grade with reasonable accuracy.[52] Histologic grade on CNB and final surgical excision have been reported to be significantly correlated ($p = <0.001$) with concordance estimated to range from 59.0% to 95.0%.[12,46,50,52,53,54,56] In the present study, histologic grade provided on CNB and surgical excision was also significantly correlated ($p = <0.001$). Reported tumour grade concordance and discordance rates were found to fall in the midrange of that in the literature at 62.0% and 28.0%, respectively. Of the cases with discordance, 43.0% were downgraded and 57.0% were upgraded on excision. Other studies have observed grade overestimation in 8.0% to 20.4% and underestimation in 6.5% to 25% to CNBs.[46,54,76] However, histologic grade was only reported upon pathologic assessment in 89.0% of CNBs included in this study and was deferred to surgical excision in 29 cases. A similar rate of tumour grading deferral (15%) was recorded in a study by Badoual et al.[46] and was attributed to insufficient tumour sampling on biopsy. In our assessment, a significantly higher rate of histologic grade agreement was noted in grade 2 tumours (84%) compared to grade 1 (53%) and grade 3 (57%) tumours ($p = <0.001$). Conversely, tumour grade concordance has been reported to be the highest among grade 3 IBCs in most published literature.[46,50,53] Histologic type ($p = 0.855$) and tumour size ($p = 0.249$) had no significant impact on the likelihood of agreement between tumour grade on CNB and surgical excision.

Current literature indicates CNB can preliminarily assess histologic type with sufficient accuracy and reliability.[52] Histologic type identified on CNB has been found to be concordant with the surgical excision in 73.6% to 100%.[44,46,50,52,53,54,75] By comparison, our data analysis revealed a significant association between histologic type identified on CNB and the corresponding surgical excision ($p = <0.001$). The concordance and discordance rates of the

histologic type reported from these two specimens were 79% and 21%, respectively. A significantly higher rate of agreement was observed in patients with IDC tumours (80%) in comparison to other carcinoma histologic types (22%) ($p = <0.001$). Other researchers have identified similar observations.[46,50,52,53,75] Badoual et al.[46], Harris et al.[50] and Ellis et al.[52] observed the majority of histologic type discordance in patients with special type IBC. Final pathologic tumour size ($p = 0.763$) and histologic grade ($p = 0.227$) were found to have no significant effect on the likelihood of concordance. No previous research examining the impact of histologic type and tumour size on concordance of both histologic grade and histologic type were identified in the literature.

Several factors contribute to the persistent but minimal disagreement observed between histologic features on CNB and surgical excision. Firstly, CNB provides limited and fragmented lesion material, complicating pathologists' ability to distinguish benign, malignant, non-invasive and invasive breast lesions.[12,44] Minimal sampling can also limit the accuracy of mitotic counts required for tumour grading, thereby resulting in frequent underestimation of grade.[49,50,54] Secondly, sampling error is a large contributor to underestimation of malignancy and tumour grade from CNB.[21,43,49,53,54] Undersampling also appears to be a major source of discordant histologic type on CNB.[50] Particularly in IDC, ILC and mixed IDC/ILC tumours that display both features of ductal and non-ductal carcinomas, making them particularly difficult to differentiate in small CNB samples.[50] Overall, greater size, number and quality of CNB samples is associated with greater diagnostic reliability.[12,21,43,46,47,50] Fortunately, CNB provides several advantages as a diagnostic tool, including its low cost, easy use, allowance for repeat biopsy and minimally invasive nature.[42,46,47] Ultimately, CNB can reduce unnecessary surgery, treatment costs and can be the final required procedure in up to 90% of patients.[24,31,51,52,53,54,55]

6.4. Limitations of the study

There are several limitations associated with the current study. The study method consisted of a retrospective chart review. Therefore, it relies upon patient data entered into the CoPath laboratory information system that was not collected for research according to predetermined standards specific to the study. As such, several variables that were evaluated in the study were found not to have been recorded in the database at all in some cases. Additionally, the sample size of the study was fairly small (n = 266). A small sample size may limit the generalizability of the study conclusions, particularly for variables in which data was not reported in all patient charts.

Our study was unable to examine the accuracy of several significant IBC patient histologic prognostic factors such as tumour hormone receptor status and lymphovascular invasion, as they are not consistently evaluated on CNB. Similarly, this study exclusively examined IBC patients and did not include those with benign final diagnoses. As a result, the evaluated screening modalities' NPV and accuracy in the diagnoses of benign breast lesions cannot be determined using the study data.

The generalization of our findings is also limited due to our selective examination of IBC patients from the specific geographic region of Manitoba, Canada. Furthermore, patient cases included in the study cohort were identified using consecutive non-probability sampling. Although consecutive sampling can provide a relatively representative sample of the study's target population, female IBC patients in Manitoba, Canada, it is possible that the patient population at the time of sampling may not be representative.

6.5. Future directions of study

The limitations identified in this study provide guidance for possible future directions of research. For instance, the inclusion of patients with final diagnoses of benign breast lesions in future study would provide further insight into the diagnostic accuracy of breast cancer screening in Manitoba, Canada, in assessing benign breast pathologies. Additionally, to enhance the generalizability of research findings, additional study with a larger sample size and probability sampling should be performed.

Several factors that have been previously reported in the literature to influence the accuracy of breast carcinoma screening were not examined in the study. For example, Jakate et al.[76] identified a higher rate of CNB diagnostic accuracy when breast pathologists rather than non-breast pathologists performed pathology review. Similarly, the accuracy of tumour measurement on imaging is negatively correlated with age, breast density, and increased delay between imaging and subsequent tumour removal.[67] Further investigation of the impact of these factors on the accuracy of breast carcinoma screening can help identify additional sources of the diagnostic discordances observed in this study. A future study examining concordance between tumour features reported on imaging and their subsequent gross morphology described on excision to assess the accuracy of breast imaging in the prediction of tumour morphologic features would also be beneficial.

CHAPTER 7. CONCLUSION

The main objective of this study was to evaluate the diagnostic and staging accuracy of breast imaging and CNB. In particular, we examined the level of agreement between diagnostic features reported pre-operatively on breast imaging and CNB compared to post-operatively on

surgical excision. In this retrospective study, 266 IBC patient cases from Manitoba, Canada, between 2018 to 2019 were reviewed. Pathologic diagnosis was concordant with suspicion on breast imaging in 85% to 86% and BI-RADS score in 100% of cases. A significant correlation ($R = 0.475$, $p = <0.001$) and concordance was found between imaging and pathologic tumour size and stage in 8% and 53% of patients. Tumour size concordance was greater in tumours ≤2 cm ($p = 0.007$). Alternatively, concordance of tumour stage was significantly higher in both IDC cases ($p = 0.003$) and tumours ≤2 cm ($p = 0.014$). Axillary lymph node status on imaging and pathology were also significantly correlated ($p = <0.001$) and concordant in 74% of cases. Lymph node status was significantly more likely to be concordant in tumours ≤2 cm ($p = 0.009$). Notably, breast carcinoma was accurately identified on CNB in 99.6% of patients. Histologic grade and type reported on CNB and surgical excision were significantly correlated ($p = <0.001$) and concordant in 62% and 79% of patients, respectively. Histologic grade displayed a higher degree of concordance in grade 2 tumours ($p = <0.001$), whereas histologic type was significantly more likely to be concordant in IDC patients ($p = <0.001$).

In summary, breast imaging and CNB of IBC patients in Manitoba, Canada, can detect and characterize malignancy with sufficient accuracy and reliability. IBC patient prognosis and effective clinical management are reliant on adequate breast carcinoma screening and diagnosis. However, the considerable variation in the degree of concordance between pre-operative and post-operative IBC tumour diagnosis and assessment reported in the literature suggest that the interpretation of breast imaging and CNB is highly subjective and susceptible to inter-observer variability. Fortunately, awareness of factors affecting concordance between pre-operative and post-operative IBC patient diagnostic reporting can help inform patient treatment and surgical planning.

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