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ORIGINAL ARTICLE

Pathology of MRI and second-look ultrasound detected multifocal breast cancer

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ABSTRACT

Introduction: Targeted second-look ultrasound (US) is often performed following MRI of the breast to determine if an MRI-detected lesion is visible on US and thus amenable to US-guided biopsy. This study aimed to assess the pathology of lesions detected and biopsied on the second-look US. In particular, for multifocal cancers, whether the pathology of additional lesions detected by second-look US is different to the index lesion.

Methods: Multicentre single-institution retrospective study of 300 consecutive cases of second-look US biopsies from August 2017 to April 2022 was performed, with their histopathology and imaging characteristics recorded. For multifocal cancers, Wilcoxon Signed Ranks Tests were used to compare differences between the index and additional lesions in the histopathology category (i.e., high-risk benign, precursor or malignant) and BRE grade.

Results: 69 multifocal cancers were detected. For the purposes of this study, additional lesions were considered more invasive if they were of a higher histopathological category or BRE grade, or demonstrated lymphovascular invasion when the primary lesion did not. 15/69 additional lesions were not seen on the initial mammogram/tomography or ultrasound, seen on subsequent MRI and second look US, and were less invasive than the index lesion. 3/69 additional lesions were more invasive than their index lesions. Wilcoxon Signed Ranks test showed additional lesions were of either similar or lesser invasiveness compared to index lesions ($z = -3.207$, $p = 0.001$) in the histopathological category, and the same or lower BRE grade ($z = -2.972$, $p = 0.003$).

Conclusion: In multifocal breast cancers, additional lesions detected on MRI and second-look US have the same or less invasive histopathology compared to the index lesion.

Abbreviations: US: ultrasound; MRI: magnetic resonance imaging; DCIS: ductal carcinoma in-situ; IC NST: invasive carcinoma no specific type; BRE grade: Bloom-Richardson-Elston grade; LCIS: lobular carcinoma in-situ; ER: oestrogen receptor; PR: progesterone receptor

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Introduction

Breast magnetic resonance imaging (MRI) is the most sensitive imaging modality for the detection of breast cancer [1,2]. However, MRI-guided biopsy is limited by its cost, availability and need for gadolinium-contrast administration [3]. Therefore, it has become a well-established practice that once a suspicious lesion is identified on MRI, a targeted second-look ultrasound (US) is then performed to determine if the lesion is actually visible on the US and thus amenable to US-guided biopsy [4–7]. In fact, Medicare rebate eligibility criteria for MRI-guided breast biopsies in Australia specifically require that an "ultrasound scan is performed immediately before … and confirms that the lesion is not amenable to biopsy guided by conventional imaging" [8]. At our institution, all lesions biopsied at time of second-look US also undergo a clip insertion and MRI clip view to determine if the US-biopsied lesion is concordant with a lesion of interest detected on MRI [9].

A large pooled meta-analysis by Spick et al. containing 2201 lesions, showed that the second-look US detection rate of lesions seen on MRI was markedly heterogeneous and ranged from 22.6% to 82.1% with an overall detection rate of 57.5%. The overall detection rate of malignancy was 2% to 51%, and US is more likely to detect the lesion if it is malignant and if the lesion was seen on MRI as a "mass" with enhancement rather than non-mass enhancement [4,10]. Thus, second-look US and biopsy are useful adjuncts to assessing lesions detected on MRI, but a negative second-look US does not negate the need for a subsequent MRI-guided biopsy [4,11–13]. If an MRI-detected lesion is also seen on second-look US, and undergoes US-guided biopsy with clip insertion, concordance with the MRI-detected lesion of interest on post-clip MRI can range from 74% to 87% [14,15].

In terms of histopathology, 79% of malignant lesions and 52% of benign lesions seen on MRI are also seen on US [4]. A detailed pathological description of the malignancy is essential in guiding the multidisciplinary management of the patient, whether it be adjuvant and neoadjuvant chemoradiotherapy or surgical options [16,17]. Multifocal cancer is

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especially important to consider, as local staging with breast MRI can detect additional disease and thus alter management in 16% of patients [18–20]. Multifocal cancers may have a negative impact on prognosis and are related to higher locoregional and distant relapse and need to be considered when planning treatments [21,22].

However, whilst the pathology of MRI-detected breast lesions as well as lesions subsequently detected on second-look US has been previously studied [23–25], to our knowledge, there have been no studies which assess the histopathology of additional lesions in multifocal breast cancer compared to the initially detected malignancy.

The aim of our study is to assess the pathology of lesions detected and biopsied on second-look ultrasound following MRI. In particular, for multifocal cancers, whether the pathology of additional lesions is different to that of the index lesion. Additionally, consideration was given to the size of MRI-detected lesions compared to their US correlates.

Methods

Patient selection

A retrospective search from August 2017 to April 2022 for the "MRI Clip View" label was performed through a radiology network in Victoria, Australia, in order to identify potential cases of second-look US biopsies. Ethics approval was obtained through the Cancer Council of Victoria (HREC 2302). Individual consent for each patient was waived via the ethics committee given the low-risk nature of this retrospective study.

Cases were included if they had a diagnostic MRI, followed by a second-look US and US-guided biopsy with clip insertion, and then MRI clip view to determine if the lesion(s) biopsied under US was concordant with the lesion(s) identified on MRI. MRI clip views must have had an axial T1 sequence, with optional additional axial STIR or T1 fat-saturated sequences. Cases were excluded if the pathology of the index or additional malignancy was not available, if the diagnostic MRI or second-look US was unavailable, or if the biopsy was performed under a modality other than the US (e.g., stereotactic guidance). Using this criteria, 89 patients were excluded. The scope of this study also does not include cases where the lesions were seen on MRI but not seen on second-look ultrasound and then had an MRI-guided biopsy.

300 consecutive cases of second-look US biopsies were identified from August 2017 to April 2022. The following information for each biopsy was collected: patient age, breast density, location and side of lesion, whether the lesion was seen on US or mammogram prior to MRI, size of the lesion on MRI, whether lesion was described as a mass or non-mass enhancement on MRI, size of the lesion seen and subsequently biopsied under US, whether the lesion biopsied on second-look US was concordant with the lesion seen on MRI, and the histopathology. MRIs were all requested by treating breast surgeons and indications included screening, cases where multifocal breast cancer had already been identified on US or mammography/tomography, and where results of conventional imaging were discordant with clinical findings. As is routine practice in the radiology network, second-look US was performed by experienced breast sonographers who used high-frequency probes (18 MHz or higher) targeted to the region of interest seen on MRI. Breast landmarks (e.g., distance from nipple, depth from skin, relationship to contours of the parenchyma) and lesion size/contour were used to assess whether a lesion seen in the US could be concordant with that seen on MRI.

The histopathology of the lesions was classified as benign (e.g., fibroadenoma), precursor (e.g., ductal carcinoma in-situ (DCIS)), or malignant (e.g., invasive carcinoma no special type (IC NST)). For precursor and malignant lesions, their oestrogen, progesterone, and Her-2 receptor status was recorded, as well as any lymphovascular invasion. The Bloom-Richardson-Elston (BRE) grade for malignant lesions was recorded, and Ki-67 percentage was also recorded when available. Ki-67 was not always performed for malignancies, particularly in older samples. Any malignancy diagnosed on biopsy or surgery within the 6 months prior to the MRI and second-look US biopsy was also recorded. Histopathology results were obtained from various pathology providers and their pathologists, as per the treating surgeon's preference[1].

Malignancy was considered multifocal if two or more precursor or malignant lesions were identified within 6 months of each other. No specific distinction was made between multifocal and multicentric breast cancer, as no surgical specimens were available to definitively distinguish between them. The index lesion was defined as the first lesion confirmed on biopsy or surgical specimen, the lesion seen on US or mammogram prior to MRI being performed, or the largest lesion if multiple lesions were seen simultaneously on US, mammogram or MRI. Lesions were considered separate if their margins were separate on MRI, regardless of the distance between them. The histopathology for each index and additional malignancy/precursor was recorded, and the location of and distance between the index and additional lesions was also measured.

For the purposes of this study, the additional lesion was considered to be less "invasive" than the index lesion if it had a lower BRE grade, no lymphovascular invasion compared to the presence of lymphovascular invasion in the index lesion, or was a precursor lesion compared to a malignant index lesion (e.g., DCIS additional and invasive carcinoma index lesion). Her-2 status was not considered when assessing invasiveness as it was not available for all specimens.

Statistical analyses

IBM SPSS statistics version 28 was used for statistical analyses. Descriptive statistics were performed for lesions that were concordant between US biopsy and MRI in the following categories: age, breast density, whether the lesion had been previously visualised on US or mammogram/

[1]Treating surgeons often prescribe their preferred pathology provider, where biopsy samples are sent. This choice is based on which pathology provider attends the treating surgeon's multi-disciplinary treatment meetings.

tomography, mass or non-mass enhancement on MRI, size of the lesion on MRI and size at US biopsy, and their histopathological characteristics.

For multifocal cancers, additional statistical analyses were performed to assess for differences in pathology between the index and additional lesions. Wilcoxon Signed Ranks Tests was used to compare differences between the index and additional lesions in the histopathology category (i.e., benign, precursor or malignant) and BRE grade. McNemar's test was used to assess for any significant differences in lymphovascular invasion between the index and additional lesions.

Additionally, consideration was given to the size of MRI-detected lesions compared to their US correlates. Wilcoxon Signed Ranks Test was also used to compare differences in size between the lesions when detected on MRI and at time of second-look US and biopsy.

Statistical significance was set at a threshold of p-value <0.05.

Results

Concordant lesions

Of the 300 consecutive cases of second-look US biopsies that were identified from August 2017 to April 2022, 271/300 (90.3%) US biopsied lesions were concordant with the lesion seen on MRI. All 271 concordant lesions were in patients who were female, with a mean age of 51 (standard deviation 11, range 23 to 87) at the time of second-look US-guided biopsy. The density of the breasts based on MRI was BIRADS A for 17, B for 42, C for 100 and D for 111 of the lesions; and one patient had had a mastectomy. 151/271 of the lesions had not been previously seen on other modalities (i.e., either mammogram/tomography, US or both), 89/271 had been seen previously and 31/271 lesions had not been previously assessed with either mammogram/tomography or ultrasound. On MRI, 205/271 lesions had been described as a mass and 66/271 of the lesions had been described as non-mass enhancement. The median size of the lesions on MRI was 13 mm (range 3 to 121 mm), and median size of lesions on second-look ultrasound at time of biopsy was 10 mm (range 3 to 78 mm).

Biopsies were considered in histopathological categories i.e., benign, precursor or malignant). Note that the histopathology of any particular lesion could contain benign, precursor and malignant components simultaneously e.g., lesions could have IC NST and DCIS within the same biopsy sample. 130/271 lesions were entirely benign, the highest histopathological category of 24/271 lesions was a precursor lesion, and the highest histopathological category of 117/271 lesions was a malignancy.

132 lesions had a benign component. The most common benign histology were fibroadenoma ($n=27$), benign breast parenchyma ($n=24$), intraductal papilloma ($n=19$), fibrocystic change ($n=11$) and sclerosing adenosis ($n=11$). Of note are the high risk benign lesions including atypical ductal hyperplasia ($n=1$), atypical lobular hyperplasia ($n=1$), complex sclerosing lesion ($n=6$), flat epithelial atypia ($n=1$), intraductal papilloma ($n=19$) and phyllodes ($n=1$).

60 lesions were in the precursor histopathological category and 117 lesions were in the malignant histopathological category these are outlined in Table 1. Of the lesions containing DCIS, 7 were low grade, 28 were intermediate grade and 20 were high grade. Of the malignant lesions, 16 were BRE grade 1, 68 were grade 2, and 32 were grade 3. The receptor status for the precursor and malignant lesions was as follows: oestrogen receptor (ER) negative 26, ER+ 4, ER++ 9, ER+++ 96; progesterone receptor (PR) negative 33, PR+ 3, PR++15, PR+++82; Her-2 receptor negative 104, Her-2 receptorpositive 24. For the malignant lesions, lymphovascular invasion was present in 13 lesions, absent in 102 lesions, and possible but non-diagnostic in 1 lesion. Mean Ki-67 percentage for the malignant lesions was 23% (standard deviation 23%). Note that grade, Ki-67 and receptor status were not available for all lesions, particularly some of the older samples.

Note that the histopathology of any particular lesion could contain benign, precursor and malignant components simultaneously, and each component has been listed separately in this table.

Multifocal cancers

There were 69 lesions that were considered the additional lesions in multifocal cancer, and all of these US-biopsied lesions were concordant with their MRI-detected counterparts. The density of the breasts was BIRADS A for 2, B for 8, C for 30 and D for 29 of the lesions. 52/69 of the lesions had not been previously seen on other modalities (i.e., either mammogram/tomography, US or both), 16/69 had been seen previously and 1/69 lesions had not been previously assessed on either

Table 1. High risk benign, precursor and malignant lesions.

High Risk Benign Lesions	N=	Precursor Lesions	N=	Malignant Lesions	N=
Intraductal papilloma	19	DCIS	51	IC NST	91
Complex sclerosing lesion	6	LCIS	4	IC NST and mucinous carcinoma	1
Atypical ductal hyperplasia	1	Intraductal papilloma with DCIS	4	Invasive lobular carcinoma	19
Flat epithelial atypia	1	DCIS and LCIS	1	Invasive mucinous carcinoma	2
Phyllodes	1			Invasive papillary carcinoma	1
				Invasive tubular carcinoma	1
				Invasive carcinoma with mixed ductal and lobular features	1
				Invasive carcinoma with mixed ductal and lobular features, IC NST, and micropapillary carcinoma	1

DCIS: ductal carcinoma in-situ, LCIS: lobular carcinoma in-situ, IC NST: invasive carcinoma no specific type.

Table 2. Less invasive additional lesions seen on MRI and Second-Look ultrasound but not initial mammogram/US.

Index lesion	Additional lesion
DCIS (intermediate grade)	Atypical ductal hyperplasia
IC NST (grade 2), DCIS (intermediate grade)	IC NST (grade 1), DCIS and LCIS (intermediate grade)
IC NST (grade 2), DCIS (intermediate grade)	IC NST (grade 2), DCIS (low grade)
IC NST (grade 2)	IC NST (grade 1)
IC NST (grade 2)	DCIS (high grade)
IC NST (grade 2)	IC NST (grade 1), DCIS (low grade)
Invasive mucinous carcinoma (grade 2)	Papilloma with DCIS (intermediate grade)
IC NST (grade 3), DCIS (high grade)	DCIS (intermediate grade)[a]
	DCIS (intermediate grade)[a]
IC NST (grade 3), DCIS (high grade)	DCIS (high grade)[b]
	DCIS (high grade)[b]
IC NST (grade 3)	DCIS (high grade)
IC NST (grade 3)	Invasive lobular carcinoma (grade 2), LCIS
IC NST (grade 3)	IC NST (grade 1), DCIS (intermediate grade)[c]
	Invasive carcinoma with mixed ductal and lobular features (grade 2), DCIS (intermediate grade)[c]

IC NST: invasive carcinoma no specific type, DCIS: ductal carcinoma in-situ, LCIS: lobular carcinoma in-situ.
[a,b,c]multiple additional lesions with same index lesion.

Table 3. More invasive additional lesions.

Index lesion	More Invasive Additional lesion	Other Additional Lesions in Same Breast
DCIS (intermediate grade)	IC NST (grade 3)	Atypical ductal hyperplasia
IC NST (grade 3), without lymphovascular invasion	IC NST (grade 3) with lymphovascular invasion	IC NST (grade 3), without lymphovascular invasion
IC NST (grade 3), without lymphovascular invasion	Invasive carcinoma with mixed ductal and lobular features, IC NST, and micropapillary carcinoma (grade 3) with lymphovascular invasion, DCIS (intermediate grade)	IC NST (grade 1), DCIS (intermediate grade)[a] Invasive carcinoma with mixed ductal and lobular features (grade 2), DCIS (intermediate grade)[a]

[a]Multiple additional lesions with same index lesion.

mammogram/tomography or ultrasound. On MRI, 51/69 lesions had been described as a mass and 18/69 of the lesions had been described as non-mass enhancement. The mean size of the lesions on MRI was 23 mm (standard deviation 21 mm, range 4 to 121 mm), and the mean size of the lesions on second-look ultrasound at the time of biopsy was 10 mm (standard deviation 7.4 mm, 4 to 50 mm).

When compared to the index malignancy, 40/69 lesions were of the same pathology and 29/69 were of a different pathology. 25/69 additional lesions were less invasive and 4/69 additional lesions were more invasive than the index lesion.

15/69 additional lesions were not seen on the initial mammogram/tomography or ultrasound, then seen on subsequent MRI and second look US and were also less invasive than the index lesion. These lesions and their index lesions are described in Table 2 below.

3/69 additional lesions were more invasive than their index lesions in the same breast and not seen on initial mammogram/tomography or ultrasound, and are outlined in Table 3 below. Interestingly, all of these were associated with other additional lesions in the same breast which were not seen on initial mammogram/tomography and ultrasound, and had the same or less invasive pathology. Breast density was BIRADS C or D for all three patients.

11/69 additional lesions were seen on the same modalities as their index lesions, but the additional lesion was less invasive than the index lesion. 20/69 additional lesions were not seen on initial mammogram/tomography or ultrasound, and then seen on subsequent MRI and second look US, but had the same pathology as the index lesion. 9/69 additional lesions were seen on the same modalities as their index lesions i.e., either all seen on initial mammogram/tomography and US as well as MRI, or all seen only on MRI and second look US, and the additional and index lesions were of the same pathology. 11/69 additional lesions were in the contralateral breast to their index lesion, and this included lesions that were seen on initial mammogram/tomography or ultrasound as well as those which were not previously seen.

Statistical comparisons

When assessing for differences in histopathology category (i.e., high-risk benign, precursor or malignant) in multifocal cancers, Wilcoxon Signed Ranks test showed that additional lesions were of either similar or lesser invasiveness compared to index lesions ($z = -3.207$, $p = 0.001$). For malignant lesions, Wilcoxon Signed Ranks test showed that additional lesions were of either the same or lower BRE grade compared to index lesions ($z = -2.972$, $p = 0.003$). McNemar's test did not demonstrate a statistically significant difference in lymphovascular invasion status between the malignant index and additional lesions ($p = 0.289$). For the multifocal cancers, the Wilcoxon Signed Ranks test demonstrated that the same lesion tended to measure larger on MRI than the US ($z = -6.615$, $p < 0.001$).

Discussion

We have demonstrated that in multifocal breast cancers, additional lesions that are detected on MRI and second-look US, but not initial mammogram/tomography/US, tend to have the same or less invasive histopathology compared to

the index focus detected on initial mammogram/tomography/US. This is statistically significant on Wilcoxon Signed Ranks Tests for both histolopathology category (i.e., high risk benign, precursor or malignant) as well BRE grade of malignant lesions. The findings have implications for surgical and neoadjuvant chemoradiotherapy planning, especially given that multifocal cancers are known to have poorer survival compared to unifocal cancers [21,22]. Histological studies of multifocal cancers have demonstrated that breast cancers rarely vary in their molecular subtype [26], and it is reassuring that the additional lesions detected on MRI and second-look US biopsy are generally also of similar or less invasive pathology. Although, there has been a previous study correlating the histopathology of multifocal cancers on US and MRI [25], our study is the first to describe a second-look US for MRI-detected lesions.

It is interesting to note that of the three additional lesions that were more invasive than their index lesion, all of them were associated with other additional lesions in the same breast which were not seen on initial mammogram/tomography and ultrasound, and had the same or less invasive pathology. Two out of the three lesions were also seen as non-mass enhancement on MRI. This may reflect the "field effect" concept in cancer presentation, where there are cellular and molecular alterations and susceptibility for malignancy over a large area, but focal progression can depend on diverse etiological factors [27].

Our concordance rate of 90.3% for second-look US lesions to their MRI correlates, is higher than the 74% to 87% described in previous studies [14,15]. This is probably due to local institutional practices, since if the likelihood of concordance on the second-look US is not considered high, then US-guided biopsy is usually not performed and MRI-guided biopsy is selected instead due to easy accessibility. Additionally, our subspecialised breast imaging departments have experienced breast radiologists and sonographers working together.

The proportion of benign (130/271, 48%), precursor (24/271, 9%), and malignant lesions (117/271, 43%) seen on MRI and second-look US biopsy is within the expected limits. Previous studies have demonstrated malignancy detection rates of between 2 and 51% [4]. MRI measurement of the same lesion being larger than the measured size on US is also expected, given that previous studies have found that US underestimates the true histopathological size of cancers [28,29].

Due to the retrospective nature of the study, we were limited by the lack of surgical specimens to compare core biopsy histopathological results against. Additionally, not all histopathological information was available, and there may be slight selection bias for palpable index lesions as most unavailable data was from externally referred screening patients; however, this should not affect the detection or pathology of additional lesions which are the target of this study.

Conclusion

In multifocal breast cancers, additional lesions which are detected on MRI and second-look US tend to have the same or less invasive histopathology compared to the index lesion. This is reassuring and could have implications for treatment planning.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

Data collected is stored in a Excel spreadsheet securely held by the first author, and is available if required.

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